An Investigation of the Neurobiology of Psychogenic Non-Epileptic Seizures

Finian O'Brien

The Royal College of Surgeons in Ireland, finobrien@rcsi.com
An Investigation of the Neurobiology of Psychogenic Non-Epileptic Seizures

Dr. Finian M. O’Brien
MB, BCh, BAO, MRCPsych, MSc, HDip.

A thesis submitted to the Royal College of Surgeons in Ireland
in fulfilment of the requirement for the degree of Doctor of Philosophy

Department of Psychiatry,
Royal College of Surgeons in Ireland, in collaboration with the
Department of Neuroscience, Trinity College Dublin

2018

Research Supervisors
Professor Kieran Murphy
Professor Hugh Garavan
Professor Norman Delanty
Dr Gillian Fortune
“There’s no art to find the mind’s construction in the face”

Taken from Macbeth, by William Shakespeare
Declaration

I declare that this thesis, which I submit to the RCSI for examination in consideration of the award of a higher degree, Doctor of Philosophy, is my own personal effort. In every case where content presented is the result of input or data from a related collaborative research programme, this is duly acknowledged in the text so that it is possible to ascertain how much of the work is my own. I have not previously obtained a degree in the RCSI or elsewhere on the basis of this work. In addition, I have taken reasonable care to ensure that this work is original and, to the best of my knowledge does not breach copyright law and has not been taken from other sources except where such work has been cited and acknowledged within the text.

Signed:

Student Number : 05010276

Date: 30th April 2017.
# Table of Contents

Declaration .................................................................................................................. 2

Table of Contents ........................................................................................................ 3

Glossary ....................................................................................................................... 13

Definition of Key Terms ............................................................................................ 20

List of Figures .............................................................................................................. 22

List of Tables ............................................................................................................... 25

Summary of Thesis ...................................................................................................... 30

Acknowledgements ..................................................................................................... 32

Dedication .................................................................................................................... 35

## Chapter 1. Introduction ......................................................................................... 36

The Neurobiology of Conversion Disorders ............................................................. 36

1.0 General Introduction ............................................................................................ 36

1.1 Definition of Psychogenic Neurological Disorders (PNDs) .............................. 37

1.2 Clinical Presentation and Neurological Diagnosis of PNDs ............................... 38

1.3 Psychiatric Diagnosis in relation to PNDs ......................................................... 46

1.4 Subtypes of Conversion Disorder (CD) .......................................................... 50

1.5 Epidemiology of CD ......................................................................................... 52

1.6 Barriers to epidemiological research of CD ..................................................... 53

1.7 Psychiatric aspects of CD relating to co-morbidity ............................................. 54

1.8 Conversion disorder, stress and life events ....................................................... 55

1.9 CD and dissociation ......................................................................................... 56

1.10 CD and emotional processing ...................................................................... 58

1.11 Neuropsychological aspects of CD ................................................................. 58

1.12 Neurophysiological aspects of CD ................................................................. 60

1.12.1 Neurophysiological findings relating to arousal and trauma ......................... 61
catalepsy (Figure 1.5). Therefore, at present, diagnosis largely relies on the exclusion of a diagnosis of epilepsy and through vEEG in particular. ----89
2.5.1 Design and methodology of the study

2.6 Methodology relating to the psychiatric and neuropsychological investigations of patients with PNES

2.6.1 Design and Methodology of the study

2.6.2 Settings for study

2.6.3 Inclusion and exclusion criteria

2.6.4 Recruitment: strategy and process

2.6.5 Assessment schedule

2.6.6 Self-report questionnaires

2.6.6.1 Beck Depression Inventory, version 2 (BDI-II)

2.6.6.2 Beck Anxiety Inventory (BAI)

2.6.6.3 Dissociative Experiences Scale, version 2 (DES II)

2.6.6.4 Toronto Alexithymia Scale, 20 question version (TAS-20)

2.6.6.5 The Coping Inventory for Stressful Situations (CISS)

2.6.6.6 Life Events Checklist (LEC)

2.6.6.7 Personality Assessment Inventory (PAI)

2.6.6.8 General Health Questionnaire (GHQ)

2.6.6.9 Edinburgh Handedness Inventory (EHI)

2.6.7 Meeting with participant to review questionnaires and carry out psychiatric and neuropsychological assessment

2.6.8 General review of self-report questionnaires

2.6.9 Semi-structured psychiatric assessment

2.6.10 Neuropsychological assessment

2.6.10.1 Wechsler Test of Adult Reading (WTAR)

2.6.10.2 Wechsler’s Abbreviated Scale of Intelligence (WASI)

2.6.10.3 The Medical Symptom Validity Test (MSVT)

2.6.10.4 The Cambridge Neuropsychological Test Automated Battery (CANTAB)
2.6.11 Testing procedures for all participants ————148

2.7 Methodology relating to the neuroimaging investigations of patients with PNES ————150

2.7.0 Technical background to the neuroimaging methods used in this thesis ————150

2.7.1 Introduction: The utilisation of neuroimaging methods in investigating the neurobiology of psychiatric disorders ————150

2.7.2 Neuroimaging modalities used in this study ————152

2.7.2.1 Structural magnetic resonance imaging (sMRI) ————153

2.7.2.2 Diffusion Tensor imaging (DTI) ————160

2.7.2.3 Functional Neuroimaging (fMRI) ————175

2.7.3 Methodology used relating to the sMRI and DTI studies of patients with PNES in this thesis ————192

2.7.3.1 MRI and DTI Scanning protocols ————192

2.7.3.2 Pre-processing of sMRI and DTI data ————193

2.7.3.3 VBM data processing and analysis ————193

2.7.4 Methodology used relating to the fMRI studies of PNES in this thesis ————196

2.7.4.1 fMRI Scanning protocol ————196

2.7.4.2 fMRI data processing and analysis ————200

Chapter 3: ................................................................................................................201

Study 1 ................................................................................................................201

The prevalence of PNES in the epilepsy monitoring unit of an Irish tertiary referral centre for epilepsy ————201

3.1 Setting for Study ————201

3.2 Referral process to the epilepsy monitoring unit (EMU) ————201

3.3 Role of the EMU ————202

3.4 Objectives of the Study ————204

3.5 Methodology of the Study ————206
3.6 Results relating to general neuropsychiatric assessment of patients attending the Epilepsy Monitoring Unit (EMU) 206

3.7 Diagnostic information and demographic data relating to the patients who underwent EMU assessment 206

3.8 Management of patients after diagnosis with PNES 209

3.9 Presentation of the diagnosis of PNES & immediate follow-up as an EMU inpatient: the prevailing modus operandi and pathway to care 210

3.10 Results of follow-up of patients diagnosed with PNES in the EMU 212

3.11 Discussion 213

Chapter 4: 218

Study 2 218

Psychiatric and neuropsychological profiles of patients with psychogenic non-epileptic seizures 218

4.1 Summary of chapter 218

4.2 Aims and hypotheses 219

4.3 Methods 220

4.4 Data preparation and statistical analysis 220

4.5 Results 221

4.5.1 Clinical data 222

4.5.2 Results of psychometric assessment 223

4.5.3 Results of CANTAB neuropsychological battery assessment 226

4.6 Discussion 226

Chapter 5: 234

Study 3 234

Investigation of brain structure and integrity using voxel-based morphometry and diffusion tensor imaging in patients with PNES 234

5.1 Summary of chapter 234

5.2 Aims and hypotheses 235
5.3 Methods..................................................................................................................236
5.4 Data preparation and statistical analysis.................................................................236
5.5 Results......................................................................................................................238
5.5.1 Demographic Data..............................................................................................238
5.5.2 Neuroimaging Results.......................................................................................240
5.6 Discussion...............................................................................................................245

Chapter 6: ......................................................................................................................254
Study 4 .........................................................................................................................254
An fMRI study of implicit (unconscious) emotional processing in patients with PNES.................................................................................................................................254
6.1 Summary of chapter...............................................................................................254
6.2 Aims and hypotheses..............................................................................................256
6.3 Methods..................................................................................................................256
6.4 Data preparation and statistical analysis...............................................................257
6.4.1 Methods of analysis of CISS coping style........................................................257
6.4.2 Methods of analysis of alexithymia (TAS-20) scores.......................................258
6.4.3 fMRI behavioural data analysis.........................................................................259
6.4.4 fMRI activation data analysis.............................................................................259
   6.4.4.1 Methods of analysis used to determine if there are differences between PNES and healthy-control groups in response to the fMRI task (implicit EFE processing).........................................................................................260
6.4.4.2 Methods of analysis used to determine if the fMRI task activates similar brain regions in each group during the processing of neutral faces..............................................................................................................261
6.4.4.3 Methods of analysis used to determine if there are between-group differences in brain activations to emotional expression and intensity in those regions (from question no. 2) found to be activated by neutral face-processing in both patient and control groups..................................................................................262
6.4.4.4 Analysis of relationships between fMRI activation data and clinical and demographical variables

6.5 Results

6.5.1 Results of analyses of demographic and clinical measures

6.5.2 Results of analyses of neuropsychological data

6.5.3 Results of analyses of fMRI data

6.5.3.1 Behavioural data results:

6.5.3.2 Implicit EFE processing results:

6.6 Discussion

6.6.1 Comment on Psychometric and Neuropsychological findings

6.6.2 Comment on behavioural data findings

6.6.3 Comment on fMRI findings

6.6.4 Limitations

6.6.5 Conclusions

Chapter 7: General Discussion

7.1 Summary of main findings from this project in relation to each hypothesis

7.1.1 Hypothesis 1: People with PNES will represent a significant proportion of those who attend Beaumont Hospital with treatment-resistant epilepsy and there will be challenges in providing follow-up treatment

7.1.2 Hypothesis 2: People with PNES will have significant co-morbidity with other psychiatric conditions, particularly those which involve anxiety and depression, and will have significant levels of emotional dysregulation and dissociative conversion symptoms

7.1.3 Hypothesis 3: People with PNES will be significantly impaired relative to healthy controls on performance of executive functioning tasks, particularly those relating to attention and working memory
7.1.4 Hypothesis 4: People with PNES will show abnormalities of brain structure, particularly affecting regions associated with cortico-subcortical motor loops.

7.1.5 Hypothesis 5: People with PNES will have abnormalities in unconscious (implicit) processing of emotion.

7.2 Contemporary models of the pathogenesis of PNES and implications of the findings of this thesis for improving our understanding of this condition.

7.2.1 Psychological models of psychomotor conversion disorders, including PNES.

7.2.2 Neurobiological models of psychomotor conversion disorders, including PNES.

7.2.3 Towards a revised model of PNES: how do the findings from this study enhance our understanding of the neurobiology of this condition?

7.2.3.1 Characteristics of patients in this study: a sample of interest in the research of PNES?

7.2.3.2 Relating our findings to contemporary hypothetical models of psychogenic movement disorders, including PNES.

7.2.3.3 Implications of these findings: towards an updated model of PNES.

7.2.3.4 Stress reactivity in PNES: a unifying hypothesis?

7.3 Future research studies that could potentially improve the understanding and treatment of PNES.

7.4 Concluding comments.

REFERENCES.

APPENDIX A: Study ethics documentation, information sheets, consent forms and scanning sheets.

APPENDIX B: Supplementary data for chapter 3 results.

APPENDIX C:
# Glossary

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>3D</td>
<td>Three Dimensional</td>
</tr>
<tr>
<td>ACC</td>
<td>Anterior Cingulate Cortex</td>
</tr>
<tr>
<td>AD</td>
<td>Axial Diffusivity</td>
</tr>
<tr>
<td>ADC</td>
<td>Apparent Diffusion Coefficient</td>
</tr>
<tr>
<td>AFNI</td>
<td>Analysis of Functional Neuroimages</td>
</tr>
<tr>
<td>AGG</td>
<td>Aggression (scale on PAI)</td>
</tr>
<tr>
<td>AHR</td>
<td>Amygdala-Hippocampal Region</td>
</tr>
<tr>
<td>AIR</td>
<td>Automated Image Registration</td>
</tr>
<tr>
<td>ALC</td>
<td>Alcohol Problems (scale on PAI)</td>
</tr>
<tr>
<td>ANCOVA</td>
<td>Analysis of Covariance</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Analysis of Variance</td>
</tr>
<tr>
<td>ANT</td>
<td>Antisocial Features (scale on PAI)</td>
</tr>
<tr>
<td>ANX</td>
<td>Anxiety (scale on PAI)</td>
</tr>
<tr>
<td>APA</td>
<td>American Psychiatric Association</td>
</tr>
<tr>
<td>ARD</td>
<td>Anxiety Related Disorders (scale on PAI)</td>
</tr>
<tr>
<td>ASTMT</td>
<td>Amsterdam Short-Term Memory Test</td>
</tr>
<tr>
<td>AvPD</td>
<td>Avoidant Personality Disorder</td>
</tr>
<tr>
<td>BA</td>
<td>Brodmann's Area</td>
</tr>
<tr>
<td>BAI</td>
<td>Beck Anxiety Inventory</td>
</tr>
<tr>
<td>BDI-II</td>
<td>Beck Depression Inventory, version 2</td>
</tr>
<tr>
<td>BE</td>
<td>Between Errors</td>
</tr>
<tr>
<td>BET</td>
<td>Brain Extraction Tool</td>
</tr>
<tr>
<td>BG</td>
<td>Basal Ganglia</td>
</tr>
<tr>
<td>BH</td>
<td>Beaumont Hospital</td>
</tr>
<tr>
<td>BOLD</td>
<td>Blood Oxygen Level Dependent</td>
</tr>
<tr>
<td>BOR</td>
<td>Borderline Features (scale on PAI)</td>
</tr>
<tr>
<td>BPD</td>
<td>Borderline Personality Disorder</td>
</tr>
<tr>
<td>CANTAB</td>
<td>Cambridge Neuropsychological Test Automated Battery</td>
</tr>
<tr>
<td>CAT or CT</td>
<td>Computerised Axial Tomography</td>
</tr>
<tr>
<td>CBT</td>
<td>Cognitive Behavioural Therapy</td>
</tr>
<tr>
<td>CCN</td>
<td>Cognitive Control Network</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>CD</td>
<td>Conversion Disorder</td>
</tr>
<tr>
<td>CER</td>
<td>Cerebellum</td>
</tr>
<tr>
<td>CGD</td>
<td>Correct Gender Discrimination</td>
</tr>
<tr>
<td>CISS</td>
<td>The Coping Inventory for Stressful Situations</td>
</tr>
<tr>
<td>CMHT</td>
<td>Community Mental Health Team</td>
</tr>
<tr>
<td>CN</td>
<td>Caudate Nucleus</td>
</tr>
<tr>
<td>CNS</td>
<td>Consistency Variable</td>
</tr>
<tr>
<td>CR</td>
<td>Corona Radiata</td>
</tr>
<tr>
<td>CSF</td>
<td>Cerebrospinal Fluid</td>
</tr>
<tr>
<td>CUH</td>
<td>Cork University Hospital</td>
</tr>
<tr>
<td>CUL</td>
<td>Culmen (Cerebellum)</td>
</tr>
<tr>
<td>DEN</td>
<td>Dentate (Cerebellum)</td>
</tr>
<tr>
<td>DEP</td>
<td>Depression (scale on PAI)</td>
</tr>
<tr>
<td>DES-II</td>
<td>Dissociative Experiences Scale, version 2</td>
</tr>
<tr>
<td>DFT</td>
<td>Directed Forgetting Task</td>
</tr>
<tr>
<td>DICOM</td>
<td>Digital Imaging &amp; Communication in Medicine</td>
</tr>
<tr>
<td>DLPFC</td>
<td>Dorso-Lateral Prefrontal Cortex</td>
</tr>
<tr>
<td>DMN</td>
<td>Default Mode Network</td>
</tr>
<tr>
<td>DOM</td>
<td>Dominance (scale on PAI)</td>
</tr>
<tr>
<td>DR</td>
<td>Delayed Recognition Memory</td>
</tr>
<tr>
<td>DRG</td>
<td>Drug Problems (scale on PAI)</td>
</tr>
<tr>
<td>DSM 4</td>
<td>Diagnostic and Statistical Manual of Mental Disorders, version 4</td>
</tr>
<tr>
<td>DFT</td>
<td>Directed Forgetting Task</td>
</tr>
<tr>
<td>DTI</td>
<td>Diffusion Tensor Imaging</td>
</tr>
<tr>
<td>EC</td>
<td>External Capsule</td>
</tr>
<tr>
<td>EEG</td>
<td>Electroencephalograph</td>
</tr>
<tr>
<td>EFE</td>
<td>Emotional Facial Expression</td>
</tr>
<tr>
<td>EHI</td>
<td>Edinburgh Handedness Inventory</td>
</tr>
<tr>
<td>EMG</td>
<td>Electromyogram</td>
</tr>
<tr>
<td>EMU</td>
<td>Epilepsy Monitoring Unit</td>
</tr>
<tr>
<td>EPI</td>
<td>Echo Planar Imaging</td>
</tr>
<tr>
<td>ETL</td>
<td>Echo Train Length</td>
</tr>
<tr>
<td>FA</td>
<td>Fractional Anisotropy</td>
</tr>
<tr>
<td>FAST</td>
<td>fMRI Artefact Rejection &amp; Sleep Scoring Toolbox</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>FDR</td>
<td>False Discovery Rate</td>
</tr>
<tr>
<td>FDT</td>
<td>FMRIB's Diffusion Toolbox</td>
</tr>
<tr>
<td>FFG</td>
<td>Fusiform Gyrus</td>
</tr>
<tr>
<td>FLAIR</td>
<td>Fluid Attenuated Inversion Recovery</td>
</tr>
<tr>
<td>FLIRT</td>
<td>FMRIB's Linear Image Registration Tool</td>
</tr>
<tr>
<td>FM</td>
<td>Forceps Major</td>
</tr>
<tr>
<td>fMRI</td>
<td>Functional Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>FMRIB</td>
<td>Functional Magnetic Resonance Imaging Brain</td>
</tr>
<tr>
<td>FNIRT</td>
<td>FMRIB's Nonlinear Image Registration Tool</td>
</tr>
<tr>
<td>FOV</td>
<td>Field of View</td>
</tr>
<tr>
<td>FPC</td>
<td>First Principal Component</td>
</tr>
<tr>
<td>FR</td>
<td>Free Recall</td>
</tr>
<tr>
<td>FSE</td>
<td>Fast Spin Echo</td>
</tr>
<tr>
<td>FSIQ</td>
<td>Full Scale Intelligence Quotient</td>
</tr>
<tr>
<td>FSL</td>
<td>FMRIB Software Library</td>
</tr>
<tr>
<td>FSS</td>
<td>Functional Somatic Symptoms</td>
</tr>
<tr>
<td>FWER</td>
<td>Family Wise Error Rate</td>
</tr>
<tr>
<td>GABA</td>
<td>Gamma Amino Butyric Acid</td>
</tr>
<tr>
<td>GDT</td>
<td>Gender Discrimination Task</td>
</tr>
<tr>
<td>GHQ</td>
<td>General Health Questionnaire</td>
</tr>
<tr>
<td>GLM</td>
<td>General Linear Model</td>
</tr>
<tr>
<td>GM</td>
<td>Grey Matter</td>
</tr>
<tr>
<td>GCR</td>
<td>Glucocorticoid Receptors</td>
</tr>
<tr>
<td>GRF</td>
<td>Gaussian Random Field Theory</td>
</tr>
<tr>
<td>HC</td>
<td>Healthy Control</td>
</tr>
<tr>
<td>HPA</td>
<td>Hypothalamic-Pituitary-Adrenal Axis</td>
</tr>
<tr>
<td>HPD</td>
<td>Histrionic Personality Disorder</td>
</tr>
<tr>
<td>HRF</td>
<td>Haemodynamic Response Function</td>
</tr>
<tr>
<td>IC</td>
<td>Internal Capsule</td>
</tr>
<tr>
<td>ICD-10</td>
<td>International Statistical Classification of Diseases &amp; Related Health Problems, version 10</td>
</tr>
<tr>
<td>IED</td>
<td>Intra Extra Dimensional Shift Test (CANTAB)</td>
</tr>
<tr>
<td>IFG</td>
<td>Inferior Frontal Gyrus</td>
</tr>
<tr>
<td>IFO</td>
<td>Inferior Fronto Occipital Tract</td>
</tr>
<tr>
<td>ILF</td>
<td>Inferior Longitudinal Fasciculus</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>INC</td>
<td>Inconsistency (scale on PAI)</td>
</tr>
<tr>
<td>INF</td>
<td>Infrequency (scale on PAI)</td>
</tr>
<tr>
<td>Ins</td>
<td>Insula</td>
</tr>
<tr>
<td>IOG</td>
<td>Inferior Occipital Gyrus</td>
</tr>
<tr>
<td>IPL</td>
<td>Inferior Parietal Lobule</td>
</tr>
<tr>
<td>IQ</td>
<td>Intelligence Quotient</td>
</tr>
<tr>
<td>IR</td>
<td>Immediate Recognition Memory</td>
</tr>
<tr>
<td>ITG</td>
<td>Inferior Temporal Gyrus</td>
</tr>
<tr>
<td>LEC</td>
<td>Life Events Checklist</td>
</tr>
<tr>
<td>LG</td>
<td>Lingual Gyrus</td>
</tr>
<tr>
<td>LSDI</td>
<td>Line Scan Diffusion Imaging</td>
</tr>
<tr>
<td>MAN</td>
<td>Mania (scale on PAI)</td>
</tr>
<tr>
<td>MCR</td>
<td>Mineralocorticoid Receptors</td>
</tr>
<tr>
<td>MD</td>
<td>Mean Diffusivity</td>
</tr>
<tr>
<td>MDT</td>
<td>Multidisciplinary Team</td>
</tr>
<tr>
<td>MEG</td>
<td>Magnetoencephalography</td>
</tr>
<tr>
<td>MFG</td>
<td>Middle Frontal Gyrus</td>
</tr>
<tr>
<td>MITT</td>
<td>Mean Initial Thinking Time (SOC CANTAB test)</td>
</tr>
<tr>
<td>MMI</td>
<td>Molecular Medicine Ireland</td>
</tr>
<tr>
<td>MMPI</td>
<td>Minnesota Multiphasic Personality Inventory</td>
</tr>
<tr>
<td>MNI</td>
<td>Montreal Neurological Institute of McGill University Health Centre</td>
</tr>
<tr>
<td>MOG</td>
<td>Middle Occipital Gyrus</td>
</tr>
<tr>
<td>MOT</td>
<td>The Motor Screening Test (CANTAB)</td>
</tr>
<tr>
<td>MPFC</td>
<td>Medial Prefrontal Cortex</td>
</tr>
<tr>
<td>MPRAGE</td>
<td>Magnetisation Prepared Rapid Gradient Echo</td>
</tr>
<tr>
<td>MR</td>
<td>Magnetic Resonance</td>
</tr>
<tr>
<td>MRT</td>
<td>Mean Reaction Time</td>
</tr>
<tr>
<td>MSVT</td>
<td>Medical Symptom Validity Test</td>
</tr>
<tr>
<td>MTG</td>
<td>Middle Temporal Gyrus</td>
</tr>
<tr>
<td>M1</td>
<td>Primary Motor Cortex</td>
</tr>
<tr>
<td>Nifti</td>
<td>Neuroimaging Informatics Technology Initiative</td>
</tr>
<tr>
<td>NIM</td>
<td>Negative Impression Management (scale on PAI)</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear Magnetic Resonance</td>
</tr>
<tr>
<td>NNLS</td>
<td>Nonlinear Least Squares</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>NON</td>
<td>Nonsupport (scale on PAI)</td>
</tr>
<tr>
<td>NPV</td>
<td>Negative Predictive Value</td>
</tr>
<tr>
<td>OCPD</td>
<td>Obsessive Compulsive (Anankastic) Personality Disorder</td>
</tr>
<tr>
<td>OFC</td>
<td>Orbito-Frontal Cortex</td>
</tr>
<tr>
<td>OG</td>
<td>Occipital Gyrus</td>
</tr>
<tr>
<td>OLS</td>
<td>Ordinary Least Squares</td>
</tr>
<tr>
<td>PA</td>
<td>Paired Associates</td>
</tr>
<tr>
<td>PAG</td>
<td>Peri-acqueductal Grey Matter</td>
</tr>
<tr>
<td>PAI</td>
<td>Personality Assessment Inventory</td>
</tr>
<tr>
<td>PAR</td>
<td>Paranoia (scale on PAI)</td>
</tr>
<tr>
<td>PC</td>
<td>Precuneus</td>
</tr>
<tr>
<td>PCA</td>
<td>Principal Components Analysis</td>
</tr>
<tr>
<td>PCC</td>
<td>Posterior Cingulate Cortex</td>
</tr>
<tr>
<td>PET</td>
<td>Positron Emission Tomography</td>
</tr>
<tr>
<td>PFC</td>
<td>Prefrontal Cortex</td>
</tr>
<tr>
<td>PHG</td>
<td>Para-Hippocampal Gyrus</td>
</tr>
<tr>
<td>PIM</td>
<td>Positive Impression Management (scale on PAI)</td>
</tr>
<tr>
<td>PIQ</td>
<td>Performance Intelligence Quotient</td>
</tr>
<tr>
<td>PMC</td>
<td>Primary Motor Cortex</td>
</tr>
<tr>
<td>PMD</td>
<td>Psychogenic Movement Disorder</td>
</tr>
<tr>
<td>PND</td>
<td>Psychogenic Neurological Disorder</td>
</tr>
<tr>
<td>PNES</td>
<td>Psychogenic Non Epileptic Seizures</td>
</tr>
<tr>
<td>PosCG</td>
<td>Post Central Gyrus</td>
</tr>
<tr>
<td>PPD</td>
<td>Paranoid Personality Disorder</td>
</tr>
<tr>
<td>PPV</td>
<td>Positive Predictive Value</td>
</tr>
<tr>
<td>PrCG</td>
<td>Pre Central Gyrus</td>
</tr>
<tr>
<td>PTSD</td>
<td>Post Traumatic Stress Disorder</td>
</tr>
<tr>
<td>RCSI</td>
<td>Royal College of Surgeons in Ireland</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised Control Trial</td>
</tr>
<tr>
<td>RD</td>
<td>Radial Diffusivity</td>
</tr>
<tr>
<td>RESTORE</td>
<td>Robust Estimation of Tensors by Outlier Rejection</td>
</tr>
<tr>
<td>RF</td>
<td>Radio frequency</td>
</tr>
<tr>
<td>RFT</td>
<td>Random Field Theory</td>
</tr>
<tr>
<td>RHI</td>
<td>Rubber Hand Illusion Task</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>ROI</td>
<td>Region of Interest</td>
</tr>
<tr>
<td>RTS</td>
<td>Response to Task Stimuli</td>
</tr>
<tr>
<td>RVP</td>
<td>Rapid Visual Processing Test (CANTAB)</td>
</tr>
<tr>
<td>RXR</td>
<td>Treatment Rejection (scale on PAI)</td>
</tr>
<tr>
<td>SCID</td>
<td>Structured Clinical Interview for DSM 4</td>
</tr>
<tr>
<td>SCID 1</td>
<td>Structured Clinical Interview for DSM 4, Axis 1 Disorders</td>
</tr>
<tr>
<td>SCID 2</td>
<td>Structured Clinical Interview for DSM 4, Axis 2 Disorders</td>
</tr>
<tr>
<td>SCZ</td>
<td>Schizophrenia (scale on PAI)</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>SDT</td>
<td>Signal Detection Theory</td>
</tr>
<tr>
<td>SE</td>
<td>Spin Echo</td>
</tr>
<tr>
<td>SEM</td>
<td>Scanning Electron Microscope</td>
</tr>
<tr>
<td>SENSE</td>
<td>SENSitivity Encoding</td>
</tr>
<tr>
<td>SFG</td>
<td>Superior Frontal Gyrus</td>
</tr>
<tr>
<td>SIMEX</td>
<td>Simulation &amp; Extrapolation Statistical Approach</td>
</tr>
<tr>
<td>SLF</td>
<td>Superior Longitudinal Fasciculus</td>
</tr>
<tr>
<td>SMA</td>
<td>Supplementary Motor Area</td>
</tr>
<tr>
<td>sMRI</td>
<td>Structural Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>SNR</td>
<td>Signal to Noise Ratio</td>
</tr>
<tr>
<td>SOC</td>
<td>The Stockings of Cambridge Test (CANTAB)</td>
</tr>
<tr>
<td>SOM</td>
<td>Somatic Complaints (scale on PAI)</td>
</tr>
<tr>
<td>SPECT</td>
<td>Single Photon Emission Computed Tomography</td>
</tr>
<tr>
<td>SPGR</td>
<td>Spoiled Gradient Recalled Echo</td>
</tr>
<tr>
<td>SPSS</td>
<td>Statistical Package for the Social Sciences</td>
</tr>
<tr>
<td>SPI</td>
<td>Suicide Potential Index (scale on PAI)</td>
</tr>
<tr>
<td>SPL</td>
<td>Superior Parietal Lobule</td>
</tr>
<tr>
<td>SPM</td>
<td>Statistical Parametric Mapping</td>
</tr>
<tr>
<td>SR</td>
<td>Spatial Resolution</td>
</tr>
<tr>
<td>STEAM</td>
<td>Stimulated Echo Acquisition Mode</td>
</tr>
<tr>
<td>STG</td>
<td>Superior Temporal Gyrus</td>
</tr>
<tr>
<td>Str</td>
<td>Stress Reactivity</td>
</tr>
<tr>
<td>STR</td>
<td>Stress (scale on PAI)</td>
</tr>
<tr>
<td>StS</td>
<td>Stress Sensitivity</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>SUI</td>
<td>Suicidal Ideation (scale on PAI)</td>
</tr>
<tr>
<td>SvD</td>
<td>Simple Visual Discrimination</td>
</tr>
<tr>
<td>SvDR</td>
<td>Simple Visual Discrimination Reversal</td>
</tr>
<tr>
<td>SWM</td>
<td>Spatial Working Memory Test (CANTAB)</td>
</tr>
<tr>
<td>TAS-20</td>
<td>Toronto Alexithymia Scale, 20 question version</td>
</tr>
<tr>
<td>TBSS</td>
<td>Tract-Based Spatial Statistics</td>
</tr>
<tr>
<td>TCD</td>
<td>Trinity College Dublin</td>
</tr>
<tr>
<td>TCIN</td>
<td>Trinity Centre for Cognitive Neuroscience</td>
</tr>
<tr>
<td>TEc</td>
<td>Echo Time</td>
</tr>
<tr>
<td>TE</td>
<td>Total Errors</td>
</tr>
<tr>
<td>TFCE</td>
<td>Threshold For Cluster Enhancement</td>
</tr>
<tr>
<td>Thal</td>
<td>Thalamus</td>
</tr>
<tr>
<td>TMS</td>
<td>Transcranial Magnetic Stimulation</td>
</tr>
<tr>
<td>TOMM</td>
<td>Test of Memory Malingering</td>
</tr>
<tr>
<td>TPJ</td>
<td>Temporo-Parietal Junction</td>
</tr>
<tr>
<td>TR</td>
<td>Repetition Time</td>
</tr>
<tr>
<td>TRRes</td>
<td>Temporal Resolution</td>
</tr>
<tr>
<td>UF</td>
<td>Uncinate Fasciculus</td>
</tr>
<tr>
<td>VBA</td>
<td>Voxel Based Analysis</td>
</tr>
<tr>
<td>VBM</td>
<td>Voxel Based Morphometry</td>
</tr>
<tr>
<td>vEEG</td>
<td>Video Electroencephalogram</td>
</tr>
<tr>
<td>VIQ</td>
<td>Verbal Intelligence Quotient</td>
</tr>
<tr>
<td>VLPFC</td>
<td>Ventro-Lateral Prefrontal Cortex</td>
</tr>
<tr>
<td>VMPFC</td>
<td>Ventro-Medial Prefrontal Cortex</td>
</tr>
<tr>
<td>VPS</td>
<td>Views per Segment</td>
</tr>
<tr>
<td>WAIS III</td>
<td>Wechsler Adult Intelligence Scale, version 3</td>
</tr>
<tr>
<td>WASI</td>
<td>Wechsler Abbreviated Scale of Intelligence</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organisation</td>
</tr>
<tr>
<td>WLS</td>
<td>Weighted Linear Least Squares</td>
</tr>
<tr>
<td>WM</td>
<td>White Matter</td>
</tr>
<tr>
<td>WMT</td>
<td>Word Memory Test</td>
</tr>
<tr>
<td>WRM</td>
<td>Warmth (scale on PAI)</td>
</tr>
<tr>
<td>WTAR</td>
<td>Wechsler Test of Adult Reading</td>
</tr>
</tbody>
</table>
Definition of Key Terms

(as they will be applied in this thesis)

Co-morbidity: is the presence of one or more additional disorders that are present concomitantly with the primary disease or disorder.

Conversion disorder: a psychiatric condition in which a patient presents with symptoms and signs of a physical disorder that is not explained by a neurological disease or other medical condition, and the expression of which is not under voluntary control. The term is taken to traditionally infer an unconscious etiology involving stress, and is now classified under the umbrella term “functional neurological disorder”.

Functional neurological disorder: a disorder which involves presentation of neurological (sensory or motor) dysfunction but which is not caused or explained by neurological disease. The term does not refer to possible causation of such disorders.

(The) Mind: the collection of unconscious and conscious mental events and capabilities of a person relating to will, perception, thinking, reasoning, and feeling.

Neurological disorder: is any discernibly recognisable physical disorder or disease of the central and peripheral nervous system.

Organic brain disease/disorder: is a syndrome or disorder of mental function whose cause is considered to be physiological or physical rather than from a (dys)function of the mind.

Physical treatment: is a treatment applied to the body and/or brain that is not related to pharmacological or psychotherapeutic application.
Psychiatric disorder: is a behavioural or mental pattern of symptoms and signs that causes significant distress and/or impairment of personal functioning, and which is not discernibly due to a primary organic disease.

Psychogenic: an adjective that refers to something having a psychological, rather than a physical, etiology or cause.

Psychogenic non-epileptic seizures: are events resembling epileptic seizures, but which lack electrophysiological brain correlates, and where the associated movements are presumed to have psychological or psychopathological causation.

Psychological: refers to something that is arising in or affecting the mind and related to the mental and emotional state of the person.

Psychological treatment: is a treatment for psychological problems in which a therapist and a patient interact and/or work together, with the aim of understanding the patients problems and bringing about a change in their way of thinking and behaviour to overcome problems in desired ways. This type of treatment may also involve a healing process from mental distress.
List of Figures

1.1 Classification of Psychogenic Neurological Disorders 38
1.2 Clinical features in conversion disorders affecting movement suggestive of psychogenic aetiology 41
1.3 DSM-5 criteria for somatic symptom disorder 47
1.4 DSM-5 criteria for conversion disorder 48
1.5 Some differential diagnoses of seizure-like events 89
1.6 Summary of volumetric and resting-state connectivity (FC) findings of neuroimaging studies in psychogenic non-epileptic seizures compared with healthy controls 104
2.1 Pathway for recruitment of patients with PNES 122
2.2 Pathway for recruitment of healthy control participants 123
2.3 The Motor Screening Test (MOT) 139
2.4 The Stockings of Cambridge test (SOC) (CANTAB) 141
2.5 The Spatial Working Memory Test (SWM) (CANTAB) 143
2.6 The Intra / Extra-dimensional Shift Test (IED) (CANTAB) 145
2.7 The Rapid Visual Processing Test (RVP) (CANTAB) 147
2.8 How neuroimaging research has helped to develop neurobiological models of mental disorder 151
2.9 The influence of an external magnetic field on proton alignment 154
2.10 The principle of DTI and contrast generation 163
<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.1</td>
<td>Significant voxel-based morphometry (VBM) findings in Temporal Lobe region of interest (ROI)</td>
<td>239</td>
</tr>
<tr>
<td>5.2</td>
<td>Significant diffusion tensor imaging (DTI) findings from the ROI Mask Analysis</td>
<td>242</td>
</tr>
<tr>
<td>6.1</td>
<td>Mean response times to all EFE stimuli during the fMRI face-processing task in PNES and healthy-control groups</td>
<td>272</td>
</tr>
<tr>
<td>6.2</td>
<td>Total errors committed during the fMRI face processing task in PNES and healthy-control groups</td>
<td>273</td>
</tr>
<tr>
<td>7.1</td>
<td>Brown and Reuber’s hypothesised sequence of events in PNES, focusing on “how” rather than “why” PNES arise</td>
<td>333</td>
</tr>
<tr>
<td>7.2</td>
<td>Possible neural networks involved in psychogenic movement disorders</td>
<td>334</td>
</tr>
<tr>
<td>7.3</td>
<td>Baslet’s hypothetical model for pathogenesis of psychogenic non-epileptic seizures</td>
<td>338</td>
</tr>
<tr>
<td>7.4</td>
<td>Hypothetical neurobiological model of psychogenic non-epileptic seizures showing major connections of motor cortex and interactions between areas found to be abnormal in the neuroimaging studies of this condition in this thesis</td>
<td>342</td>
</tr>
<tr>
<td>7.5</td>
<td>Illustration of the hypothalamic-pituitary-adrenal (HPA) axis in humans</td>
<td>337</td>
</tr>
</tbody>
</table>
## List of Tables

1.1 Historical and examination findings included in published diagnostic criteria for functional disorders .......................... 39

1.2 Review of semiological features from vEEG studies that can help differentiate PNES from epilepsy ..................... 93

2.1 Personality Assessment Inventory scales and sub-scales .......................................................... 128

2.2 Description of WASI index subtests ......................................................................................... 134

2.3 The CANTAB tests that were administered ago all participants .................................................. 138

2.4 Order of test administration to all participants (both those with PNES and healthy controls) ......................... 149

2.5 Common software tools available for DTI processing ............................................................... 170

3.1 Results of video electroencephalography (vEEG) and neurological assessment of patients in the EMU .......... 207

3.2 Referrals of patients diagnosed with PNES for follow-up after discharge from EMU ...................... 213

4.1 Selected demographic data for participants .................................................................................. 222

4.2 Results showing variables that predicted group status .............................................................. 224

4.3 Results of CANTAB neuropsychological assessment analysis covarying for FSIQ ......................... 225

4.4 Results of nonparametric correlation analysis between demographic, psychometric and neuropsychological variables found to differ between-groups, within the group with PNES .......................................................... 227
5.1 Demographic data .......................................................... 238
5.2 All ROI analysis FDR results. ........................................ 241
5.3 Results of partial correlation analysis between neuroimaging findings and relevant demographic and psychometric variables .......................................................... 243
5.4 Results of partial correlation analysis between neuroimaging findings and relevant neuropsychological data .......................................................... 244
6.1 Demographic and clinical characteristics of PNES and healthy control groups .......................................................... 265
6.2 Patients’ length of time suffering with PNES and average frequency of seizure-like events .......................................................... 266
6.3 Correlations between endorsement of an abnormal coping style and relevant psychometric variables in PNES and healthy control groups .......................................................... 267
6.4 Results of binary logistical regression analysis comparing patient and control groups on CANTAB test performance (controlling for effects of FSIQ) .......................................................... 269
6.5 Results of general linear model analysis comparing patient and healthy control groups on fMRI task-related behavioural performance .......................................................... 271
6.6 Correlations between behavioural and psychometric variables that predicted PNES group status .......................................................... 274
6.7 Brain regions showing uniformly lower task-related BOLD signal changes to the set of faces showing fear in the patients with PNES compared with healthy controls .......................................................... 275
6.8 Brain regions showing uniformly lower task-related BOLD signal changes to the set of faces showing disgust in the patients with PNES compared with healthy controls .......................................................... 276
6.9 Brain regions showing uniformly lower task-related BOLD signal changes to the set of faces showing fear in the patients with PNES compared with healthy controls.

6.10 Results of post-hoc analysis of those brain-activation clusters that failed to show a significant between-group difference to the neutral face condition.

6.11 Brain-activation clusters that failed to show a significant between-group difference to the neutral face condition but showed between-group differences at 50% intensity after removing the effects of neutral activation.

6.12 Table showing the overlap clusters for all emotions for the HC group only.

6.13 Table showing the overlap clusters for all emotions for the PNES group only.

6.14 Table showing the overlap between face-processing for neutral vs the null hypothesis consistent across all three emotional stimuli and combined across both groups.

6.15 Table showing brain regions in which there was a differential activation between patients with PNES and healthy controls and derived from the common regions of activation during the neutral, versus the baseline condition.

6.16a Results of PCA of fMRI measures to EFEs showing fear.

6.16b Results of regression model of fear showing interaction effects.

6.16c Results of regression model of fear showing main effects.

6.16d Results of regression model of fear showing intensity.

6.17a Results of PCA of fMRI measures to EFEs showing disgust.
6.17b Results of regression model of disgust showing interaction effects

6.17c Results of regression model of disgust showing main effects

6.17d Results of regression model of disgust showing intensity

6.18a Results of PCA of fMRI measures to EFEs showing sadness

6.18b Results of regression model of sadness showing interaction effects

6.18c Results of regression model of sadness showing main effects

6.18d Results of regression model of sadness showing intensity

6.19a Fear PCA fMRI, adjusting for psychometric and clinical variables that predicted group status

6.19b Disgust PCA fMRI, adjusting for psychometric and clinical variables that predicted group status

6.19c Sadness PCA fMRI, adjusting for psychometric and clinical variables that predicted group status

6.20 Results of regression model analysis investigating the relationship between mean response time to facial stimuli and fMRI activations

6.21 Results of regression model analysis investigating the relationship between total errors committed during the implicit face-processing task and fMRI activations

6.22 Results of regression model analysis investigating the relationship between spatial working memory performance (total errors) and fMRI activations

7.1 The main psychological models of PNES: key strengths and limitations
Summary of Thesis

**Background:** Psychogenic non-epileptic seizures (PNES) are paroxysmal episodes of seizure-like behaviour that superficially resemble epileptic events, but lack EEG correlates of epilepsy. Diagnosis is often delayed and the condition is associated with significant impairments of general functioning. At the time that this project was commenced there were few neuropsychological studies of PNES and the neural correlates of this condition were unknown.

**Aims:** This project aimed to firstly, examine the prevalence and management of PNES in an Irish epilepsy monitoring unit (EMU) and secondly to examine neuropsychiatric, neuropsychological, structural and functional neuroimaging correlates of adults with PNES.

**Methods:** Standardised assessments and cognitive test batteries were used to assess psychiatric and neuropsychological functioning of patients with PNES and a matched healthy-control group. All participants underwent structural neuroimaging, diffusion tensor imaging and a functional neuroimaging task involving implicit face processing. Only those who passed a test of effort were included. Data analysis controlled for known potential confounders, including differences in intelligence.

**Results:** Patients with PNES were found to score significantly higher on measures of stress, alexithymia and multiple dissociative-conversion indices. In addition they demonstrated abnormal spatial working memory performance, even after controlling for between-group differences in FSIQ. ROI analyses of the sMRI and DTI data showed that patients had reduced grey matter in a region comprising left middle and inferior temporal gyrus, and abnormal integrity of white matter tracts involving forceps major (FM), thalamus, and especially the superior longitudinal fasciculus (SLF), but these findings did not survive statistical correction for group differences in FSIQ (which was not taken into account in the previous studies). Analysis of the fMRI data demonstrated that patients with PNES exhibited an abnormally reduced functional response to the
implicit face-processing task, in regions known to be involved in face-processing, socio-emotional processing and movement.

**Conclusions:** The fMRI findings demonstrated that patients with PNES have abnormal functioning of brain regions that subserve cognitive, emotional, face-processing, and movement processes. Patients with PNES had relatively reduced grey matter volumes in an area of the left temporal lobe known to be involved in semantic memory and language (MTG), face-processing (ITG), and multimodal sensory-integration (MTG and ITG). In addition, patients had relatively increased fractional anisotropy in white matter tracts involving the left fronto-temporal region [comprising left superior longitudinal fasciculus (SLF) forceps major (FM)] and thalamus, tracts that are involved in integration of motor, sensory and visual functioning, inter-hemispheric connectivity, and regulation of consciousness, transmission of sensory and motor output and intentional movement, respectively. The changes observed may represent an abnormal maturation process of white matter. However, both sMRI and DTI findings were not statistically significant between-groups after controlling for the effects of differences in FSIQ.

Some of the neuroimaging findings were related to clinical indices associated with PNES, with a focus on physical and sensory symptoms related to conversion disorder being a particularly prominent association. These findings have important implications for our current understanding of the neurobiology of PNES. Future studies are necessary to replicate these findings with larger sample sizes and to delineate the processes underlying abnormal emotional processing in PNES.
Acknowledgements

I would like to express my sincere gratitude to all those who took the time to participate in this research project, especially those who had to travel significant distances and endure a lengthy assessment process. I would like to thank particularly those who suffer from psychogenic non-epileptic seizures for your support and involvement, and hope that the work that I have carried out with your participation will help advance and improve the understanding and treatment of your condition.

A huge thank you to Molecular Medicine Ireland (MMI) for their educational support and funding that enabled me to carry out this project as part of my clinician-scientist fellowship in neuropsychiatry. I am very grateful and proud to have been associated with the first group of scholars to receive the MMI research training scholarship.

There are a number of people without whom this project could not have progressed to completion. Firstly, I would like to sincerely thank my principal supervisor, Professor Kieran Murphy, for his consistent help and guidance from the first time I raised the idea of doing this project, through the years of planning and execution of the studies, to completion of the thesis. His calm and positive support throughout times that varied from exciting to intensely challenging was invaluable and is, and will be, forever appreciated. In addition, I am very grateful to my co-supervisors Dr Gillian Fortune and Professor Norman Delanty who were very supportive of my efforts to make this project a success. Gillian, your input on the effort task was prophetic! In particular, thank you Professor Hugh Garavan for being my neuroimaging supervisor, and in particular for supervising an analysis when we were separated geographically across different time-zones and continents. This was not easy to co-ordinate with conflicting schedules, and could not have been completed without your support.

My particular and heartfelt thanks to my colleague Dr. Erik O’Hanlon, whose indispensible help and assistance across timezones and continents with the neuroimaging analysis was instrumental in helping me to complete this project.
An especially big thanks goes to Dr Patrick Dicker and Professor Ronan Conroy for your invaluable assistance and advice on statistical matters. Your enthusiasm to ensure the study design and analysis was as robust as possible was very inspiring and I learned a lot from you both. I will never forget your kindness, Professor Conroy, in meeting me on a cold winter’s day just before Christmas 2016 when you were clearly unwell but determined to help.

I would like to thank my former neuroimaging colleagues in Trinity College Dublin (including Dr Brendan Behan, Dr Adam Stone and Sojo Joseph) for helping me carry out and complete the neuroimaging studies. Thank you also to my colleague in liaison psychiatry, Dr Eugene Cassidy (Cork University Hospital), who was a great help to me in helping me to recruit suitable candidates and in general, throughout the project.

Thank you also to the Royal College of Surgeons in Ireland for supporting this project and thesis. I would like to convey my appreciation to Professor Niamh Moran, head of the school of postgraduate studies for her understanding and support in helping me to complete this thesis. Also, an especially big thank you to Professor Hannah McGee and Professor Kevin Nolan of the Royal College of Surgeons in Ireland for all your positive words of encouragement and practical support.

I would like to sincerely thank my family, particularly my parents Edward and Briege, who have encouraged me tirelessly throughout my career and who have always been irreplaceable supports in my life. Words are not sufficient to convey my eternal gratitude for being there to support me in every possible way you could.

To my friend Mark whose family home has always offered a warm welcome and respite from work! Thank you Mark.

Finally, I would like to convey sincere appreciation to my darling wife Fanta, who has been a rock of love, understanding and support for me throughout the duration of this project. To my children, who have had to put up with Dada “working”, I love you very much and look forward to more time together. Now
that this thesis is completed, you have no idea how much I am looking forward to some (relatively) undisturbed family days out now with you and our children, Caelfhionn, Lorcan and Brendan.
Dedication

I would like to dedicate this thesis to the memories of my dear friend Sean Cooney, and my cousin Michael Darker, who both passed-away during the period of my preparing this thesis. Sean was a close friend and support since childhood who not only played guitar with me during “downtime” from the thesis and was an able barista, but also both participated in this study as a healthy control and designed a presentation-program to help me exhibit my initial results in a beautiful format at a national conference. Sadly, Sean passed away in 2014 at a young age, from an incurable illness, leaving behind a void that will never be filled.

Michael was a dear cousin of mine who passed away in 2009, but who always met each day with a sense of humour, kindness and compassion for others, and a zest for life, especially manifested in his love for dancing and singing. He is also in my thoughts constantly.

They both leave behind treasured memories to those that knew them, of a life well-lived during the time they had.

Suaimhneas síoraí dá n-anamnacha
Finian.
Chapter 1. Introduction

The Neurobiology of Conversion Disorders

1.0 General Introduction

It is not uncommon for patients to present to physicians with neurological symptoms that have no obvious medical explanation. Since ancient times, various terms have been used to describe these medically-unexplained symptoms (Cottencin, 2014). For example, “hysteria” was a term applied to medically unexplained symptoms in women, according to early medical literature, and it implied conceptualisation of a link between such manifestations and the uterus. In the late nineteenth century, the idea that such disorders could result from a dichotomy between conscious and unconscious processes, termed “dissociation”, was proposed by Janet, and probably influenced Sigmund Freud's subsequent theory of “conversion” (Spiegel et al., 2011). Freud wrote several books on this subject and proposed that such symptoms of neurological dysfunction, occurring in the absence of organic lesions in the nervous system, resulted from transformation of a psychological conflict into physical symptoms, secondary to repression in the unconscious mind (Freud and Breur, 1895). The term “conversion” largely replaced “hysteria”, and remains in use to this day within psychiatric classification systems of such disorders. In recent decades, other terms have been applied to symptoms without discernible organic cause. For example, the term “psychogenic” describes disorders that have no known underlying structural or neuro-chemical pathology but instead are attributable to psychological or psychiatric processes (Hinson et al., 2006). These disorders are also referred to in the literature variably as “medically unexplained symptoms” (suggesting that a medical explanation may be found in the future), and “non-organic” (suggesting there is no underlying pathology) (Edwards and Bhatia, 2012). However, apart from the commonly-used term “psychogenic disorders”, that of “functional disorders” is probably the other most often-applied nomenclature by physicians for these
disorders, and broadly refers to the conceptualisation that there is abnormal functioning of the affected system combined with non-demonstration of underlying structural pathology. Moreover, “functional” could also be interpreted as broadly applying to neurological disorders not considered to be psychogenic, such as headache (Edwards and Bhatia, 2012). There is currently a debate in the scientific literature as to which of these latter two terms should be most appropriately applied to conversion disorders (Edwards and Bhatia, 2012; Vuilleumier, 2014).

Many medically-unexplained neurological symptoms such as sensory loss, blindness, atasia-abasia, amnesia, paralysis, movement disorders and non-epileptic seizures, are considered to be psychogenic in origin. However, as yet, the mechanisms by which these symptoms manifest are unknown. This thesis focuses on psychogenic non-epileptic seizures (PNES), which medically presents as a psychogenic neurological disorder but is classified psychiatrically as a conversion disorder. In this chapter, I will provide a broad description of the current classification of psychogenic neurological symptoms both medically and psychiatrically, and review the epidemiology, presentation and approach to diagnosis of conversion disorders. I will also describe what is known about the socioeconomic burden and outcome of these disorders and the prevailing recommended approach to their management. I will then review relevant study findings relating to contemporary knowledge of the underlying pathophysiology of these disorders, referring to relevant neuropsychological and neuroimaging studies in that process. Finally, in a subsequent section, I will describe the current scientific literature in relation to the epidemiology and behavioural, neurophysiological and neuroanatomical phenotype of PNES specifically.

1.1 Definition of Psychogenic Neurological Disorders (PNDs)

Psychogenic neurological disorders (PNDs) are disorders which present with neurological symptoms that do not relate to discernible underlying neurological disease, but rather are thought to manifest secondary to psychiatric or
psychological disturbance (Mehta et al., 2013; Gelauff et al., 2014). These include psychogenic non-epileptic seizures (PNES) (Figure 1.1).

Figure 1.1 Classification of Psychogenic Neurological Disorders.

1.2 Clinical Presentation and Neurological Diagnosis of PNDs
Patients can attend medical practitioners with any type of psychogenic involuntary movement and the clinical features and associated phenomena often present in atypical, mixed and variable ways (Hallett, 2006). However, the most common forms encountered in clinical practice are psychogenic non-epileptic seizures, weakness or paresis, tremor, dystonia, myoclonus, gait abnormalities and parkinsonism (Edwards and Bhatia, 2012).

Table 1.1 Historical and examination findings included in published diagnostic criteria for functional disorders (Espay, 2015).

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Clinically definite</th>
<th>Clinically probable</th>
<th>Clinically possible</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fahn and Williams [1, 2]</td>
<td>Documented or clinically established; incongruent or inconsistent plus ≥1 of</td>
<td>1. Distractibility</td>
<td>Obvious emotional disturbance</td>
</tr>
<tr>
<td></td>
<td>1. Other false signs</td>
<td>2. Other false signs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Multiple somatosensations</td>
<td>3. Multiple somatosensations</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Obvious psychiatric disturbance</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4. Distractibility</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5. Deliberate slowness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shill and Gerber [3]</td>
<td>Proven or primary criteria</td>
<td>Example of probable (all 4)</td>
<td>Example of possible (all 5)</td>
</tr>
<tr>
<td></td>
<td>1. Excessive pain or fatigue</td>
<td>1. Excessive pain or fatigue</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Previous exposure to a disease model</td>
<td>2. Multiple somatosensations</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Potential for secondary gain</td>
<td>3. Obvious psychiatric disturbance</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Secondary criteria</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1. Multiple somatosensations</td>
<td>Not endorsed</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(other than pain and fatigue)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Obvious psychiatric disturbance</td>
<td>Not endorsed</td>
<td></td>
</tr>
<tr>
<td>Gupta and Lang [4-6]</td>
<td>Documented (as per F&amp;W) or clinically established plus other features (as per F&amp;W) or clinically established minus other features (i.e., unequivocal clinical features of FMD, incompatible with organic disease, without the other features required by the F&amp;W criteria)</td>
<td>Not endorsed</td>
<td></td>
</tr>
</tbody>
</table>

Traditionally, the decision to classify neurological symptoms as being of psychogenic origin was made after discernible neurological pathology that could explain the presentation was excluded through medical assessment and investigation (Lang et al., 2006). However, there has been a very significant
growth of clinical and investigative research in this area over the last decade, and this has led to the recent establishment of diagnostic guidelines aiming to improve diagnostic accuracy and management of these disorders (De Paola et al., 2014). Currently, psychogenic neurological disorders are identified usually by specialist neurologists and on the basis that full clinical history, examination and appropriate investigations confirm that the clinical presentation is principally inconsistent and incongruent with current classifications of neurological illness.

Several different neurological classification systems for diagnosing psychogenic neurological disorders have been in use by neurologists for some time, including criteria outlined by Fahn & Williams (Williams et al., 2005; Shill and Gerber 2006), and extended upon by Gupta & Lang (Gupta and Lang, 2009). In the main, these systems have traditionally approached the definition and diagnosis of psychogenic neurological disorders through criteria relating to incompatibility of the presenting features with neurological pathology, in combination with an association with “obvious psychiatric disturbance”. There are a number of published diagnostic criteria guidelines for neurological classification of psychogenic neurological disorders (Table 1.1). The Fahn & Williams criteria, for example, were originally designed to diagnose psychogenic (functional) dystonia, but subsequently the same criteria were extended to guide diagnosis of all psychogenic neurological disorders, as it was assumed that these general criteria would apply similarly in all cases (Espay and Lang, 2015).

Traditionally, several clinical features were highlighted as evidence supportive of a psychogenic presentation, regardless of the individual phenomenology of the neurological disorder, including sudden onset and/or rapid progression of symptoms, symptom inconsistency, marked variability in symptom presentation, change in phenomenology over time, sudden recurrences or complete remissions of symptoms, distractibility of the patient during clinical exam, and a history of other symptoms considered to be psychogenic (functional) in nature (Fahn and Williams, 1988; Edwards and Bhatia, 2012) (Figure 1.2). However, over recent years, research studies in this area have highlighted several pitfalls of approaching the diagnosis using criteria that rely heavily on features that may not be directly related to the
characteristics of the motor or sensory disturbance itself. For example, a sudden appearance of the clinical feature was purported to provide greater support for the presence of a psychogenic symptom, although this can also occur with some organic disorders (Morgante et al., 2012). Conversely, more recent evidence suggests that psychogenic features may appear slowly and progress over time (Gupta and Lang, 2009). Similarly, it is now well-recognised that psychological or psychiatric disturbances are often co-morbid with, or arise from, many organic disorders (Kranick et al., 2011) and conversely, may be absent or not obvious in cases of psychogenic neurological disorder (Edwards et al., 2014). In addition, inter-rater reliability studies relating to diagnosis of psychogenic neurological disorders have reported findings suggesting that neurologists have traditionally tended to over-estimate the significance of overt psychological or psychiatric disturbance in patients, features that can occur co-morbidly with neurological or other physical illnesses (Morgante et al., 2012, Morgante et al., 2013). Moreover, phenomenological signs are often different within and between psychogenic neurological disorders (Espay and Lang, 2015). Additional problems with definition include how psychogenic

<table>
<thead>
<tr>
<th>Clinical features in conversion disorders affecting movement suggestive of psychogenic aetiology.</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Abrupt onset</td>
</tr>
<tr>
<td>• Paroxysmal movement disorder</td>
</tr>
<tr>
<td>• Bizarre movement</td>
</tr>
<tr>
<td>• Deliberate slowness of movement</td>
</tr>
<tr>
<td>• Movement or sensory deficit attenuated by patient’s attention to it and reduced by distraction from it</td>
</tr>
<tr>
<td>• Variability and inconsistency of findings between presentations</td>
</tr>
<tr>
<td>• Incongruous movements and sensory features</td>
</tr>
<tr>
<td>• Response to placebo, suggestion</td>
</tr>
<tr>
<td>• Spontaneous remissions</td>
</tr>
<tr>
<td>• Association with other functional neurological disorders</td>
</tr>
</tbody>
</table>
neurological disorders are classified when there are definite neurological conditions present co-morbidly (Morgan et al., 2004).

Overall, such research has supported the need for a change in diagnostic approach to these disorders, and over recent years acknowledgement of these findings has led to a general acceptance among neurologists that formulating a diagnosis as being of psychogenic origin can only be made reliably by active demonstration of typical “positive” features during clinical assessment, rather than on the basis of exclusion of neurological disease or of the identification of emotional or psychosocial factors in the particular case (Espay and Lang, 2015; Lehn et al., 2016). It has also been recognised that diagnostic criteria that offer certainty at a “probable” or “possible” level, as in the cases of the approach suggested by the Fahn & Williams, Shill & Gerber, and Gupta & Lang diagnostic criteria classification systems, are less helpful to the clinician than having a number of highly reliable, clear and incongruent clinical features for a particular psychogenic neurological disorder that, when present, provide sufficient evidence for a definitive diagnosis (Carson et al., 2012; Cottencin et al., 2014; Espay and Lang, 2015; Lehn et al., 2016).

An important study by Daum and colleagues (Daum et al., 2014) provided a systematic review of the scientific literature to examine sensitivity and specificity, where available, of “positive” bedside-examination signs suggestive of a psychogenic (functional) disorder. The authors included signs pertinent to many psychogenic neurological disorders that involve disturbances of the senses or movement. However, although they did not study signs for PNES specifically, they concluded that 9 positive signs relating to psychogenic movement disorders were validated, comprising 7 motor and 2 gait-related signs. Importantly, these signs were also reported to have reasonable inter-rater reliability (Daum et al., 2014). These were as follows:

**Sensory Related Clinical Signs**

1. Midline splitting of the sensory deficit: this sign is positive if the patient reports sensory loss of half of the body (with face, torso, limb involvement) with splitting of experienced sensation exactly through the midline of the body.

   The differential diagnosis is small thalamic lesions. This sign was found to
have an estimated specificity of 93%; sensitivity of 20%; a positive predictive value (PPV) of 40% and a negative predictive value (NPV) of 82%.

2. Splitting of vibration sense: this sign is based on the fact that vibration is perceived mainly through bone conduction so that, when tested by placing a tuning fork on either side of the forehead or sternum, the vibration should be perceived similarly on both sides. This sign is considered to reflect psychogenic sensory loss if the patient reports difference in perceived sensation over one side of these specific bony areas. This sign was found to have an estimated specificity of 14%; sensitivity of 95%; a PPV of 22% and a NPV of 92% and had methodological limitations relating to consistency of application by examiners.

3. Non-anatomical sensory loss: this sign relates to the patient reporting sensory losses so that the pattern does not conform to recognised dermatomal patterns of sensory innervation. This sign was found to have an estimated specificity of 100%; sensitivity of 74%; a PPV of 100% and a NPV of 79%.

4. Inconsistent or changing pattern of sensory loss: this sign also relates to the patient reporting sensory losses so that the pattern does not conform to recognised dermatomal patterns of sensory innervation. It was found to have an estimated specificity of 70%; sensitivity of 79%; a PPV of 61% and a NPV of 85%. Parietal lesions may also produce sensory testing, affecting the specificity of this sign for psychogenic sensory loss.

5. Systematic failure: this is where patients perform poorer than chance on a task involving sensory discrimination (e.g., when asked to tell examiner if manipulated placement of their toe is upwards or downwards). This sign was found to have an estimated specificity of 100%; sensitivity of 8.7%; a PPV of 100% and a NPV of 100%.

Motor Related Signs
1. Hoover sign: this sign is based on the assumption that when a limb flexes, the contralateral limb performs a simultaneous reflex extension. It is positive
where there is weakness of voluntary hip-extension while at the same time there is normal involuntary hip-extension during contralateral hip-flexion against resistance. This is assessed in two stages:

Hip extension: first, with the patient supine, the examiner places one hand under each of the patient's heels. The patient is asked to press their heels down forcefully. In organic hemiplegia, downward pressure will be felt from the normal leg but not from the weak leg. Hip flexion: Secondly, after performing the above step, the examiner removes his hand from under the normal leg and places it on top of that leg and asks the patient to raise their leg against resistance from his hand. It would be expected that no added pressure will be felt by the hand under the weak leg. If the patient is asked to raise the weak leg against gravity, downward pressure will be felt under the normal leg. This sign was found to have an estimated specificity of 99%; sensitivity of 94%; a PPV of 99% and a NPV of 96%.

2. Abductor Sign: this sign is based on the same principle as the Hoover sign, in that when a limb flexes, there is a simultaneous reflex extension movement in the contralateral limb. Firstly, the patient is asked to lie supine and the examiner places his hands on the lateral surfaces of both leg abductors. Then, the examiner tells the patient to abduct each leg while he/she opposes this movement with his hands. The leg contralateral to the abducted one shows opposite actions for organic paresis and non organic paresis i.e., when the paretic leg is abducted, the “normal” leg stays fixed in organic paresis, but moves in the hyper-adducting direction in a non-organic paresis. The sign is negative if the paretic leg moves in adduction and is positive if the paretic leg stays in position. This sign was found to have an estimated specificity of 100%; sensitivity of 100%; a PPV of 100% and a NPV of 100%.

3. Abductor finger sign: This test involves asking the patient to carry out abduction finger movements of one hand against resistance of the examiner for 2 mins, with a maximal sustained contraction being performed to detect synkinetic abduction finger movements of the contralateral hand. There are synkinetic abstraction finger movements of the contralateral “paretic” hand in psychogenic paresis but no movement of same with neurologically mediated
paresis. This sign was found to have an estimated specificity of 100%; sensitivity of 100%; a PPV of 100% and a NPV of 100%.

4. Spinal injuries centre test: in this test, with the patient in the supine position, the examiner asks them to lift up their knees so that their legs are positively placed in a flexed posture. If this is not possible to complete by the patient, the examiner lifts them up. The sign is positive if the patient then keeps their legs up without further help from the examiner, and negative if the leg drops in an abduction movement. This sign was found to have an estimated specificity of 98%; sensitivity of 100%; a PPV of 93% and a NPV of 100%.

5. Collapsing/give-way weakness sign: for this test to be positive, it is observed that either the patient's limb collapses from a normal position with a light touch from the examiner, or a normal strength is developed and then suddenly gives way so that the limb “collapses”. It relies on the examiner’s subjective interpretation of strength of the limb movement. This sign has been reported to have an estimated specificity of 97%; sensitivity of 63%; a PPV of 96% and a NPV of 65%.

6. Co-contraction sign: this sign is based on the fact that during the movement of voluntarily contracting an agonist muscle, there is simultaneous contraction of an antagonist muscle. This sign can be observed either during testing of muscle strength by the examiner or with a surface electromyogram. The test is positive if it is observed that during a voluntary agonist movement, there is simultaneous contraction of the antagonist, resulting in little or no movement from that limb. This sign has been reported to have an estimated specificity of 100%; sensitivity of 17%; a PPV of 67% and a NPV of 75%.

Gait Related Signs

1. Dragging-monoplegic gait: in this sign, instead of performance of a leg circumduction, the leg is dragged at the hip, behind the body. This sign was found to have an estimated specificity of 100%; sensitivity of 8.4%; a PPV of 100% and a NPV of 32%.
2. Chair test: The examiner asks the patient to push a swivel chair on wheels. The sign is positive if the patient propels the chair better than when they are walking. This sign was estimated to have a specificity of 100%; sensitivity of 89%; PPV of 100% and a NPV of 90%.

Since Daum et al. published their review, several studies have reported new clinical tests to assist clinicians in positively identifying some psychogenic neurological disorders (Lehn et al., 2016). For example, reaction time may help in assessing psychogenic dystonia and accelerometry may help identify psychogenic tremor affecting the head (Parees et al., 2014; Ramos and Hallett, 2014). However, the sensitivity, specificity and relevant predictive values of these assessments will require further elucidation over time.

### 1.3 Psychiatric Diagnosis in relation to PNDs

Psychogenic neurological disorders are classified psychiatrically as mental and behavioural disorders according to the two internationally-recognised psychiatric diagnostic systems. The International Statistical Classification of Diseases and Related Health Problems (ICD-10) system is a medical classification guideline published by the World Health Organisation (WHO), and includes diagnostic criteria for psychiatric disorder (WHO, 1993). Secondly, the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) is the standard classification of mental disorders used by mental health professionals in the United States of America, and is published by the American Psychiatric Association (APA, 2013).

The vast majority of psychogenic neurological disorders are reported by patients as being involuntary, and most fulfil criteria consistent with a diagnosis of dissociative (conversion) disorder according to ICD-10, or conversion (functional neurological symptom) disorder according to DSM-5. Both these terms are used to describe a condition in which patients present with neurological symptoms that are inconsistent with a neurological disease, but are not due to factitious disorder or malingering.
A factitious disorder is a condition in which a person acts as if they have an illness by deliberately producing, feigning, or exaggerating symptoms (ref DSM-5). However the presentation of a person presenting with factitious disorder differs from that of malingering in that, in the former, the person has an ingrained, unreasonable attachment to the idea of being ill or acting as the caretaker of another ill person, while in malingering, the person engages in fabricating or exaggerating the symptoms of mental or physical disorders for personal gain. In the latter disorder, personal gain may relate to financial compensation, avoiding responsibilities, duties or punishments, or simply to attract attention or sympathy. In both factitious disorder and malingering, abnormal movements are produced voluntarily. However, in practice, such cases are rare and seldom encountered clinically (Ellenstein et al., 2011).

According to ICD-10, most psychogenic neurological disorders can be classified under the heading of dissociative (conversion) disorders.

The common themes that are shared by dissociative or conversion disorders are a “partial or complete loss of the normal integration between memories of
the past, awareness of identity and immediate sensations, and control of bodily movements”. Moreover, it is presumed that in dissociative (conversion) disorders, the individual has an impaired ability to exercise a conscious and selective control with respect to the deficit or abnormal action. In addition, these disorders are presumed to be psychogenic in origin, being “associated closely in time with traumatic events, insoluble and intolerable problems, or disturbed relationships” (WHO, 1993).

In contrast, according to the recently revised DSM-5 guidelines, psychogenic neurological disorders are classified under the general heading of somatic symptom disorders, replacing their previous inclusion under the heading of “somatoform disorders” (APA, 2013) (Figure 1.3).

This significant change involved removing the previous criterion that a particular psychological cause needed to be identified in making this diagnosis, and this was replaced by a more general criterion that the symptoms cause significant distress and/or disability in normal life. These revisions were mainly motivated by the facts that, firstly, psychological factors are often difficult to identify with a degree of certainty in such cases; secondly, where identified, it is difficult to presume a significant degree of association of the psychological factors with the clinical symptoms; and thirdly, requiring identification of obvious psychological factors that are acting on the patient’s unconscious is unreliable, subjective and
difficult and inconsistent with the prevailing neuro-scientific view of these disorders (Vuilleumier, 2014).

Somatic symptom disorders, including psychogenic neurological disorders, are characterised by somatic symptoms that have been present for at least six months, are either very distressing or result in significant disruption of functioning, and are associated with excessive and disproportionate thoughts, feelings and behaviours in relation to these symptoms. The terms “Conversion disorder”, “functional neurological symptom disorder” or “psychogenic”, including psychogenic movement disorders (PMDs), are included under this classification, and mean that the symptoms have a psychological basis and possibly occur secondary to a recent or remote stressor (APA, 2013). The revised DSM-5 criteria for conversion disorder also removed both the requirement for a discernible recent psychological stressor and for exclusion of feigning, and replaced them with importance of demonstrating positive physical signs to back-up the diagnosis (Figure 1.4). There is also an inference in DSM-5 that these disorders may involve abnormalities in brain function (Kanaan, 2016).

A notable difference between these approaches to classification is that a diagnosis of somatic symptom disorder does not require that the somatic symptoms are medically unexplained, so that symptoms may or may not be associated with another medical condition. This criterion is a new addition to the DSM-5 classification of this group of disorders, and its inclusion has produced considerable controversy among patient advocacy groups, psychiatrists and academic researchers, with claims that this term is ambiguous and causes confusion for users of this system. Furthermore, there are concerns that it will allow clinicians to apply a psychiatric diagnostic label to people who are understandably psychologically affected by distressing medical illnesses, and that it will also make inclusion criteria for academic studies of conversion disorder less clear than prior to this revised edition of the classification (Lehn et al., 2016).

The ICD-10 and DSM-5 classification systems differ in terms of criteria applicable to psychiatric diagnosis of psychogenic neurological disorders,
especially relating to potential factors involved in etiology, and reflect different cultural ideologies and organisation of health systems. However, periodic revisions of criteria also take into account developments in our understanding of these disorders. For example, whereas traditional diagnostic criteria reflected theories of dissociative (conversion) disorder etiology, such as Freudian theory, the use of modern research methods to investigate neurological processes, has led to an increased neurobiological understanding of these disorders. The methods that have particularly revolutionised our ability to understand neurophysiological processes of psychiatric disorder include neuroimaging. The research relating to neuroimaging of conversion disorder and PNES will be discussed later in this chapter.

1.4 Subtypes of Conversion Disorder (CD)

Conversion disorders are currently classified under rather specific headings, according to the presenting symptom and are outlined below in terms of how common they are clinically encountered, in descending order:

**Psychogenic non-epileptic seizures**: these are characterised by abnormal paroxysmal movements of the body resembling epileptic seizures, which may include generalised shaking of the limbs, impaired consciousness, and sudden unresponsiveness. However, clinical and electroencephalograph (EEG) features are inconsistent with epilepsy. This disorder is the focus of this thesis and will be described in greater detail later in this chapter.

**Psychogenic weakness and paresis**: the most common presentation of these conversion symptoms is that of unilateral weakness or paresis, but this kind of impairment can affect just one or both limbs (Stone et al., 2010). Dissociative symptoms, anxiety or physical injury to the affected limb often precedes onset (Stone and Edwards, 2012). The patient may also report feeling that the affected limb doesn't “belong” to them or may present as appearing indifferent to their dysfunction (Reuber et al., 2003a).
Psychogenic movement disorders: these include, in order of most prevalence within this group, tremor (accounting for at least 50% of these patients), dystonia (25%), myoclonus (found in 20-25%), gait disturbance (6-11%), with psychogenic parkinsonism, chorea and tics being rarely reported (Kirsch and Mink, 2004; Bhatia and Schneider, 2007; Edwards and Bhatia, 2012).

Psychogenic speech disorders: the most common psychogenic symptom of speech is dysphonia, which typically presents as hoarseness or whispering. Other psychogenic speech presentations include intermittent slurred speech, telegraphic speech (typified by omission of definite articles and conjunctions in sentence formation), stuttering, mutism and foreign accent syndrome (Binder et al., 2012; Daum et al., 2014).

Psychogenic sensory disorders: paraesthesias (sensory loss or anaesthesia) are common conversion disorder symptoms (Sharpe et al., 2011), and are often associated with other conversion symptoms such as weakness or pain (Stone et al., 2009).

Psychogenic cogniform disorders: although cognitive symptoms are strictly not classified under conversion disorder, it is argued that they present commonly in conversion disorder patients and should be classified under this heading (Delis and Wetter, 2007). These include impairments of concentration and memory, fluency, speed of response and other features such as difficulty finding words and mixing up words when talking (Pennington et al., 2015). In addition amnesia may present as a conversion disorder or part of another conversion disorder (such as psychogenic non epileptic seizures or motor conversion disorder) (Stone et al., 2009; Staniloiu and Markowitsch, 2014).

Finally, it is quite common to find considerable overlap between the different psychogenic disorder subtypes (Crimlisk et al., 1998) with one study reporting mixed symptoms in 35% of conversion disorder cases (Roelofs et al., 2005) and another reporting that on average, affected patients present with 2.5 symptoms from different subtypes (Sharpe et al., 2011).
1.5 Epidemiology of CD

Psychogenic neurological disorders (PNDs) are common in medical practice. Two studies carried out in the UK reported consistent results in that 30% of new patients were rated as having symptoms 'not at all' or only 'somewhat explained' by 'organic disease' (Stone et al., 2009, Stone et al., 2010b). PNDs relating to movement abnormalities have been reported to account for 16% of new cases and overall, 2-3% of patients presenting to specialist neurological clinics (Factor et al., 1995; Stone et al., 2010b). The estimated prevalence of conversion disorder derived from community studies ranges from 0.004 to 0.2% (Carson et al., 2012) and overall in clinical settings, from 2-6% (Perkin et al., 1989; Stone et al., 2010b). The reported incidence rates of conversion disorder, including PNDs, is believed to be more relatively consistent, within the range of 4 to 22 cases per 100,000 population, per annum (Stefansson et al., 1976; Akagi and House, 2001).

Conversion disorder has been reported to be more prevalent in people of relatively lower socio-economic status and in those from rural communities (Hales et al., 2008). Other epidemiological associations are poor educational status, low “psychological mindedness” and a past history of physical or sexual abuse (Hales et al., 2008; Singh and Lee, 1997; Roelofs et al., 2002a).

Most studies have found that the majority of patients with conversion disorder are women, with a female to male ratio of 2-10:1. The reasons for this significant difference, generally, in gender association are unclear. However, this gender ratio may be different in PNES. The average age of onset ranges from 37 to 50 years of age (Factor et al., 1995; Williams et al., 1995). Conversion disorder tends to be more prevalent in young adults (Nowak and Fink, 2009). However, it may also present in children (Schwingenschuh et al., 2008) and the elderly (Factor et al., 1995) although this is uncommon.

Conversion disorders have been found to be associated with neurological abnormality (Lempert et al., 1990a). Conversely, patients with neurological disorders and hemispheric dysfunction have been reported to have a greater
incidence of conversion disorders (Ney et al., 1996). Conversion disorder has also been reported to be triggered by neurological illnesses (Crimlisk et al., 1998) and physical injury (Stone et al., 2009).

### 1.6 Barriers to epidemiological research of CD

It is widely accepted that there are several barriers to epidemiological research of conversion disorders (Edwards and Bhatia, 2012). Firstly, there are several approaches to case definition. For example, according to DSM-5, conversion disorder is classified as a functional neurological disorder, whose criteria comprise: 1. The patient has at least one symptom of altered voluntary motor or sensory function; 2. There is evidence from clinical findings of incompatibility between the presenting symptoms and formally recognised neurological and medical conditions; 3. The presenting symptom-deficit is not better explained by another medical or mental disorder; 4. The symptom-deficit causes clinically-significant distress to the patient, or impairment in functioning (including social, occupational, personal, etc), or would be deemed to require medical assessment (American Psychiatric Association, 2013). On the other hand, ICD-10 classifies conversion disorder under the heading: “Dissociative and conversion disorders”, whose case-definition is subtly different, i.e., “a disorder whose predominant feature is a loss or alteration in physical functioning that suggests a physical disorder but that is actually a direct expression of a psychological conflict or need…, without an organic cause” (WHO, 1993). The second definition presumes there is an identifiable psychological conflict or need, which may in practice be very difficult to either reliably identify or relate to the presenting symptoms. Therefore, on the one hand, some authors may identify psychogenic movement disorders (PMDs) as clinical cases of patients that present with neurological symptoms but who have no discernible pathophysiological correlates. On the other hand, to improve definition of case-ness, the psychogenic factors could be further operationalised. However, this approach could be too stringent to include all presentations that may in fact be psychogenic in nature.
Often in these types of situations, clinicians face the difficulty of misdiagnosing the patient, a fear that is particularly highlighted by an often-quoted study from the 1960s which reported that one-third of patients who were initially diagnosed as having a conversion disorder were subsequently found to have an organic illness on follow-up (Slater and Glithero, 1965). However, a more recent meta-analysis established that misdiagnosis of conversion disorder, including psychogenic neurological disorder, is approximately 4% (Stone et al., 2005), a rate which is more broadly consistent with that found with misdiagnosis of other psychiatric or neurological illnesses (Aybek et al., 2008). Furthermore, that study also reported that the rate of misdiagnosis was unaffected by the introduction and availability of clinical neuroimaging (Stone et al., 2005). Nevertheless, commentators have pointed out that the main reasons for failure to accurately classify cases are likely the result of applying different definitions and methods for identifying cases and, simply, clinician-error (Carson et al., 2012). It is noteworthy that neurologists have described patients with conversion disorders as the “most difficult to help” and that they view these conditions as relatively “unlikeable” (Carson et al., 2012), which may reflect the challenges posed by these disorders in terms of clinician’s personal confidence in the diagnosis and subsequent management of the situation.

1.7 Psychiatric aspects of CD relating to co-morbidity

Conversion disorder in general has been found to be highly associated with other psychiatric disorders, with overall rates of 30-90% co-morbidity being reported, including co-presentation with other dissociative disorders (Crimlisk et al., 1998; Lempert and Schmidt, 1990b; Sar et al., 2004; Gelauff et al., 2014). Depression, generalised anxiety disorder and panic disorder have been found to be much more prevalent in conversion disorder than in the general population or neurological populations (Carson et al., 2011). Personality disorders, particularly those of emotionally-unstable (borderline), histrionic and narcissistic types have also been reported to be frequently co-morbid with conversion disorders (Crimlisk et al., 1998; Stone et al., 2004a).
The data in relation to co-morbidity of PMDs in particular, appears more robust than for other forms of conversion disorder. For example, taking studies that met criteria for inclusion for a systematic review, anxiety disorders have been found in 17-42% and affective disorder (principally depression) in 19-71% of people with psychogenic movement disorders (Gelauff et al., 2014). Conversion disorders have been diagnosed in approximately 70-75% of those with PMDs. The same authors have also reported some limited data from their studies with respect to their experience of malingering and factitious disorder. Malingering was reported in 1 patient out of a case sample of 24 (4%) in one study and in 2 out of a sample size of 83 (2%) with PMD; while the prevalence of factitious disorder in those studies was 2 (8%) and 0 (0%), respectively (Williams et al., 1995; Munhoz et al., 2011).

Co-morbidity of conversion disorder with neurological disease is a relatively frequent occurrence, with reported prevalence rates of 12-17% co-morbidity of neurological illness, in people with conversion disorder affecting movement. One of these papers highlighted that organic tremor was most often present, with dystonia, dyskinesia and Parkinson’s disease being also noted to a lesser extent (Kim et al., 1999). Finally, a study of 103 patients presenting with fixed dystonia (a neurological movement disorder in which abnormal fixed postures occur following repetitive or continually sustained muscle contractions) specifically reported that 38 (37%) met criteria for psychogenic dystonia, 29% had somatisation disorder, and 24% fulfilled criteria for both disorders (Schrag et al., 2004).

It has been noted that people who develop conversion disorders are relatively more likely to have had a prior history of psychiatric disorders, including emotional disorder, and medically unexplained symptoms, such as fatigue and pain (Sar et al., 2004; Stone et al., 2013).

1.8 Conversion disorder, stress and life events
Historically, the association of stress and life events with dissociative conversion disorder is inherent in the diagnostic criteria. Indeed, psychological factors including interpersonal conflict, trauma and stress have been broadly associated (WHO, 1992; APA, 2013). However, these may not be readily apparent. Moreover, even when reported, the association of stress and life events with the development of conversion disorder is not a specific finding. For example, several epidemiological studies have highlighted that risk factors for conversion disorder (including PNDs) are similar to those associated with depressive and anxiety disorder (Roelofs et al., 2005). Studies have also found that such factors do not discriminate conversion disorder from people with neurological disorder or healthy controls (such as seizures in epilepsy) (Testa et al., 2012; Maurer et al., 2015). Nevertheless, generally, there is a well-reported increase in frequency of life-events near the time of onset of conversion disorder (Roelofs and Spinhoven, 2007), and the severity of conversion disorder symptoms has been associated with a comparatively greater frequency of early and later life events (Roelofs et al., 2005; Bowman, 1993). Moreover, people with conversion disorder, specifically involving psychogenic motor weakness and psychogenic non-epileptic seizures (PNES), have been reported to be less likely to attribute their symptoms to stress than people with neurological illness (Stone et al., 2004a; Stone et al., 2010a).

### 1.9 CD and dissociation

Dissociation has been most often defined as a mechanism underlying dissociative or conversion disorders, and describes psychopathological processes that can alter an individual’s level of awareness of themselves and their surroundings, and the integration of relevant sensory, cognitive, and motor experiences (Carson et al., 2012). This concept of dissociation largely arose from the work of Pierre Janet and others in the nineteenth century. For example, Pierre Janet, through a series of experiments, demonstrated that dissociative phenomena form what was considered to be a psychological defence response against overwhelming traumatic or stressful experiences (Van der Hart and Horst, 1989), and for the next hundred years, dissociation
was largely considered to represent a unitary model incorporating various psychological and physical phenomena (Brown, 2006). The “Dissociative Experiences Scale” (DES) (Bernstein and Putnam, 1986) was created to measure quantitative differences in the degree of dissociation experienced between-individuals, and was based on this unitary model. However, investigations of the degree of dissociation experienced by people with different categories of conversion or somatic symptom disorders have produced inconsistent results. For example, different profiles have been observed that have been influenced by such factors as the type of dissociative disorder, the presence of organicity (e.g., epilepsy), the type of abuse suffered and trauma exposure (Reuber et al., 2003a; Goldstein and Mellers, 2006; Goldstein and Mellers, 2012). Overall, the available evidence would suggest that dissociation on its own, as measured by the DES, is not a reliable discriminator of conversion disorder subtypes, nor does it reliably discriminate psychogenic versus organic disorders.

More recently, the unitary concept of dissociation has been challenged by reviews of research evidence, so that a number of authors have suggested a model of dissociation in which at least two categories of dissociative phenomena that have distinct definitions, mechanisms and treatment can be clearly distinguished. These categories include “detachment” and “compartmentalisation” (Cardena, 1994; Holmes et al., 2005; Brown, 2006), where detachment has been defined as “an altered state of consciousness characterised by a sense of separation (detachment) from aspects of everyday experience”, and involving phenomenal descriptions such as an alteration or absence of emotional experience and a “dream-like state” (Holmes et al., 2005); and where compartmentalisation has been defined as involving a (reversible) “deficit in the ability to deliberately control processes or actions that would normally be amenable to such control” which cannot be overcome wilfully, and yet “the apparently disrupted functions are operating normally and continue to influence cognition, emotion and action” (Brown, 2006). Under this revised conceptualisation of dissociation, both detachment and compartmentalisation are proposed to have different mechanisms of action (see Brown, 2006), and dispute the “one size fits all” approach to assessment of dissociation by the DES. Instead, the authors suggest that measurement of these discrete categories is a better approach to case-definition and that further research,
including neuroimaging studies, could be very helpful in examining the neurobiological basis of these phenomena. However, since then, no dissociation assessment tool has been developed that discriminates experiences according to these concepts. In any case, there is little doubt that dissociation is a crucial marker of psychobiological health. For example, there is compelling evidence that dissociation is developmentally linked with the fundamental bio-psycho-social process of attachment behaviour, and attachment behaviour is the single best predictor of psychological health status in the adult that can be measured reliably in childhood (Putnam, 2009). Also, people with high dissociation scores are more likely to have an elevated baseline stress response (Putnam, 2009). Therefore, although the DES and it’s updates (DES 2) has been the most widely used measure of dissociation in research and clinical practice since 1986, the development of assessment tools that discriminate between categories of dissociation will be useful in reliably examining biological (including neurobiological) correlates of these phenomena.

1.10 CD and emotional processing

Alexithymia is a personality trait characterised by deficits in emotional regulation and has been measured in some subtypes of conversion disorder, but analysis of findings in these studies have been hampered by the presence of affective disorders, which confounds interpretation (Tojek et al., 2000; Bewley et al., 2005). In addition, most studies relating to emotional processing of conversion disorder have related to PNES, and therefore will be discussed later in this chapter under the relevant heading.

1.11 Neuropsychological aspects of CD

As previously outlined, the first models of conversion disorder were guided by Freud’s conceptualisation that such symptoms resulted from an unconscious
process involving the repression of aversive, stressful thoughts and emotions (Vuilleumier, 2014). Some of the earliest investigators of conversion disorder observed similarities between symptoms produced under hypnosis and conversion symptoms, and examined potential associations between both phenomena. For example, suggestibility to hypnosis was compared between people with a history of conversion disorder and healthy controls without a history of such manifestations, and found to be higher in the former group (Roelofs et al., 2002b). Furthermore, hypnotic suggestion has been reported to change or remit conversion symptoms in some affected individuals (Lemonnier and Aiiliaire, 1995; Moene et al., 1998). However, these observations have been challenged by inconsistent findings between similar studies and because no test relating to malingering was applied to such experiments; therefore raising questions about assessment validity and that feigning could have been a relevant confounder of reported results (Kanaan, 2010).

Several studies have reported findings suggestive of potential neuropsychological dysfunction in conversion disorder. For example, one of the earliest such studies used the Paired Associates Test and Guessing Technique to examine cognitive functioning of a group of 17 patients diagnosed with mixed conversion disorder (mainly related to motor weakness), and of a control group comprising people with other psychiatric disorders, and reported relative episodic memory deficits in the patient group (Bendefeldt et al., 1976). A subsequent study also utilised the Paired Associations Test, in addition to a Trail Making Test, to examine neuropsychological functioning in 10 patients diagnosed with conversion disorder (comprising mixed subtypes) and 10 depressed patients, and reported relatively greater frontal lobe and non-dominant hemisphere dysfunction in the former group (Flor-Henry et al., 1981). Another interesting study around that period observed that people with conversion blindness performed either better or worse than chance on visual recognition tasks, indicating that their choices were visually guided even if they were not consciously aware of seeing (Sackheim et al., 1979). This early research provided preliminary evidence that people diagnosed with conversion disorder could have neuro-cognitive abnormalities, but studies were limited by small sample-size and choice of control groups, which were insufficient to reliably generalise results. However, a more recent study investigated
executive and memory functioning in 21 patients with conversion disorder of motor subtype in comparison with a larger healthy-control group (Brown et al., 2014). The authors employed a directed forgetting task (DFT) using words with varying emotional valence to investigate memory suppression, and reported deficits in auditory-verbal memory and executive functioning, the latter being driven mainly by differences in IQ and affective symptoms. In addition, there were no significant differences observed between groups on DFT performance, although there was a trend of impaired performance in the patient group, so that memory suppression was not found to be significantly altered in conversion disorder in this study.

These studies have limitations in methodology, relating principally to having small sample sizes, and being insufficiently powered to detect clinically significant differences between groups. Moreover, with the exception of a number of studies relating to psychogenic non-epileptic seizures (which will be discussed separately later in this chapter), there has been a dearth of neuropsychological studies relating to other conversion disorder subtypes, so that further studies are needed to elucidate if and how neuropsychological functioning is affected in conversion disorder.

1.12 Neurophysiological aspects of CD

An early model of conversion disorder proposed that conversion symptoms resulted from dysfunctional attentional mechanisms secondary to increased corticofugal inhibition of afferent stimulation (Ludwig, 1972). However, although an initial case-report reported reduced somatosensory–evoked potentials from the affected limb in conversion disorder (Hernandez Peon et al., 1963), subsequent investigations failed to reliably reproduce this finding so that normal evoked responses are considered typical of conversion disorder (Sierra and Berrios, 1999).

Several studies have investigated the P300 component of event-related responses in people with conversion disorder. The P300 wave is a positive deflection in the human event-related potential. In one study, patients were
asked to report their awareness of sensory stimuli applied to their hands while undergoing EEG recording and healthy patients were asked to deliberately feign a lack of awareness on one side (Lorenz et al., 1998). A P300 response was observed in feigners, but not patients. These findings provided preliminary evidence that this test is quantitatively different in people with sensory conversion disorder compared with people who deliberately feign sensory symptoms (malingering).

Generally, basic neurophysiological measures of perceptual processing and response utilising visual, auditory, somatosensory or motor evoked potentials are normal in conversion disorder, so that these scientific investigations may help to establish the diagnosis in comparison with gross organic causation (Vuilleumier, 2014). However, more refined measures of discriminative abilities or in relation to complex task experiments have found some abnormal alterations in this group, and described below.

1.12.1 Neurophysiological findings relating to arousal and trauma

An early study of skin resistance reported that patients with mixed conversion disorder symptoms had higher baseline arousal levels and abnormally reduced adjustment of their skin-conductance to repetitive auditory stimulation (Lader and Sartorius, 1968). A subsequent study found similar findings in patients with remitted mixed conversion symptoms (Horvath et al., 1980). These findings suggest that in conversion disorder and in people who are at risk of developing conversion symptoms, there may be greater arousal or failure to modulate and inhibit physiological response to a familiar sensory stimulus (Voon et al., 2010a). Other studies have similarly extended findings of abnormally increased baseline arousal in some people with conversion disorder, using skin conductance tests. For example, a greater startle response to both positive and negative affective stimuli has been reported in psychogenic movement disorder (Seignourel et al., 2007). Therefore, overall, patients with mixed features of
conversion disorder appear to have greater arousal while the disorder is active. In addition, a history of exposure to traumatic life events, including childhood sexual abuse, may also play a role in the modulation of baseline cortisol levels and processing of threat response (Roelofs et al., 2005).

1.12.2 Neurophysiological findings relating to self-monitoring, sensory attenuation, attention and self-agency

The phenomenon of interoception relates to the perception and awareness of sensations related to physiological processes in the body, and is believed to be important in emotional processing (Craig, 2002; Teodoro and Edwards, 2016). People with conversion disorder of motor type have been found to have lower awareness of their heart-beat than healthy controls, a finding that has been found in people with emotional disorder such as depression (Pollatos et al., 2009; Demartini et al., 2014a; Riccardi et al., 2016). Subsequently, as a result of these findings, other studies have investigated the sense of body-ownership in people with conversion disorders of motor and movement subtypes, but results showed that in both experiments, using a “rubber-hand illusion” task (RHI), indicated no impairment of this sense of self (Reinersmann et al., 2013; Demartini et al., 2016).

Sensory attenuation relates to the physiological phenomenon of reduction in perceived intensity of self-generated stimuli, and is a proposed measure of the process that categorises movement as self-generated or occurring involuntarily (also referred-to as self-agency) (Teodoro and Edwards, 2016; Lehn et al., 2016). A number of studies have studied this sense of agency for movements in people with conversion disorder. For example, one study explored sensory attenuation utilising a force-matching task, and reported differences from healthy controls in their overestimation of forceful pressure to skin (Parees et al., 2014). Another investigated median nerve stimulation at rest in people with psychogenic movement disorder, and found a lack of attenuation in the N20 and
N30 amplitudes of sensory-evoked potentials at the onset of self-paced movement (Macerollo et al., 2015). Both study findings suggest that people with conversion disorders have abnormal sensory attenuation and probably have impaired sense of agency. Sensory attenuation therefore appears to be a promising biomarker for conversion disorder, at least with respect to motor symptoms.

Further neurophysiological studies investigating the role of attention and self-agency in conversion disorder have suggested that firstly, the attention of the patient to symptoms may play a significant role in manifestation of their disorder (Parees et al., 2012; Lehn et al., 2016) and secondly, that patients with psychogenic motor disorder perform poorly on highly predictable tasks because their attention shifts and becomes focused on a mode of processing that impairs movement control (Parees et al., 2013). The authors of the latter study also found that movement of people with psychogenic motor symptoms becomes normal when these attentional processes are disengaged, such as if they are distracted by unintentional movement.

Research studies that have specifically investigated secondary somatosensory cortex function in people with sensory conversion symptoms utilising magnetoencephalography (MEG) have not reported abnormality, suggesting that altered processing in patients with conversion disorder much occur elsewhere (Harvey et al., 2006). However, a recent study compared MEG activity between patients with mixed conversion disorder symptoms (including motor symptoms) and healthy controls, during an emotion-regulation task, and found relatively impaired fronto-cortical, but enhanced sensorimotor modulation activity in those with conversion disorder (Fiess et al., 2015). This finding suggested that people with conversion disorder have reduced cognitive control associated with a “conversion” of negative emotions into negative somatic sensations. However, further studies are required to determine if these findings are replicated.
1.12.3 Neurophysiological findings relating to involuntariness of movement

Studies involving combined electroencephalogram (EEG) and electromyogram (EMG) analysis have found that 86% of patients with conversion disorder have evidence of pre-motor planning of volitional movement, before an involuntary jerk, but 58% did not demonstrate this sign before a voluntary movement. The authors suggested that these findings indicate that people with conversion disorder have disordered perception of whether a movement is voluntary or involuntary (Van der Salm et al., 2012). Furthermore, other studies have found that similar to voluntary movement generation, abnormal movements in motor conversion disorder are affected by entrainment and distraction, but that patients lack a sense of control for the abnormal involuntary movements, a failure of "self-agency" and an impaired feeling of intention before movement (Edwards et al., 2011; Kranick et al., 2013). Another series of recent studies of fixed dystonia analysed dynamic responses of the affected limbs to a set of forced postural-disturbance (perturbation) and found that the control groups, but not the motor conversion disorder group, actively gave way to the imposed forced postural changes. This effectively meant that the patients with conversion disorder actively resisted a forced postural task, and the authors suggested that overall, findings from their studies indicated that patients with conversion disorder of this subtype have deregulation of inhibitory force feedback (Munts et al., 2011; Mugge et al., 2012; Mugge et al., 2016).

1.13 Neuroimaging studies of CD

Neuroimaging techniques can help develop potential models of conversion disorder by examining neural structure and function and identifying potential neural correlates.
1.13.1 Structural neuroimaging studies of CD

Findings from structural magnetic resonance imaging (sMRI) studies have indicated that exposure to stress is associated with structural alterations in brain anatomy (McEwen, 2001). Further, those regions found to be particularly vulnerable to alteration by stress are the hippocampus and amygdala of the limbic system, which work closely in modulating neural activation during emotional processing and memory tasks (McEwen and Magarinos, 2001; Richter-Levin, 2004), and the prefrontal cortex, which plays an important role in working memory and executive functioning (McEwen, 2004). However, while it is not yet known whether structures specifically implicated in the stress response are abnormal in conversion disorder, there is some evidence to suggest that patients with conversion disorder have underlying structural brain abnormalities. As previously described earlier in this chapter, there has been some evidence to suggest conversion disorders are associated with neurological abnormality (Lempert et al., 1990a), and conversely, there is a greater incidence of conversion disorders in patients with pre-existing neurological abnormality (Ney et al., 1998). Therefore, early evidence indicated that there may be structural brain abnormalities in people with conversion disorder.

In recent years, three structural magnetic resonance imaging (sMRI) studies of conversion disorder have been published (excluding those for psychogenic non-epileptic seizures). The first such study, published in 2006, examined regional brain volumes in 10 female patients with conversion disorder of motor subtype and 10 healthy controls, and reported significantly smaller thalamic volumes, with relatively greater reduction on the right side, in the patient group (Atmaca et al., 2006). A subsequent sMRI study of conversion disorder, also of motor subtype, utilised a region-of-interest analysis approach to measure brain volumes of basal ganglia, thalamus and amygdala in 14 patients and 31 healthy controls (Nicholson et al., 2014), and found comparatively smaller volumes of thalamus in the patient group. However, in contrast with the findings of Atmaca and colleagues, they reported significant volumetric differences affecting left, but not right thalamus. While the reasons for the differences in results of both studies are unknown, it is likely that differences in sample characteristics,
methodology and analysis influenced results. For example, the second study corrected their volumetric analysis for intracranial volume, while the former study did not.

A recently published sMRI study used manual-tracing methods to measure pituitary volumes specifically in 20 females with conversion disorder (of mixed subtypes, the majority comprising patients with psychogenic non-epileptic seizures) and matched controls, and reported significantly reduced volumes bilaterally in the patient group (Atmaca et al., 2016).

Overall, these three sMRI studies suggest that there are brain abnormalities in people with conversion disorder, affecting structures known to be associated with relaying and integrating motor output (in the case of the thalamus), and the regulation of fear and anxiety (pituitary gland’s control of the hypothalamic–pituitary–adrenal axis). No other structural neuroimaging studies of conversion disorder have been published to-date (with the exception of a small number of studies of psychogenic non-epileptic seizures specifically, which will be outlined separately, later in this chapter).

1.13.2 Functional neuroimaging studies of CD

The use of functional neuroimaging as a flexible, non-invasive tool to examine neurobiological correlates of neurological and psychiatric disorders, has been the single most significant contributory factor to the rapid increase in research of conversion disorder over the last twenty years, and the last decade in particular. These methods have rapidly advanced our scientific knowledge of structural and functional neuroanatomy, and has allowed testing of theories of altered functioning of brain networks in different disorders, through investigating brain activation patterns of patients with neurological or psychiatric disorder, and those of healthy control groups. Such comparisons can reveal sites of abnormality and help elucidate mechanisms of symptom manifestation (Weiller et al., 2006). I will summarise findings of the most important functional neuroimaging studies to-date, that have helped develop current models of understanding of the neurobiological underpinnings of conversion disorder.
Early theories relating to the neurobiology of conversion disorders were developed, not on empirical evidence, but on speculation based on contemporary models of the nervous system (Vuilleumier, 2014). One theory formulated by Pavlov, proposed that cortical centres based mainly in the frontal lobe, had an inhibitory function on emotional arousal arising from subcortical regions, and that conversion symptoms could therefore manifest as the result of a strong arousal response increasing inhibition of other neurological pathways involving motor and sensory function (Pavlov, 1933). More recently, theories relating to active inhibition of these processes, (including cognitive processes), preventing them from being incorporated into conscious awareness, have been proposed (Sackheim et al., 1979; Oakley, 1999; Bell et al., 2011). Other authors developed theories based on older pathogenic models of hysteria, and proposed that conversion symptoms could occur if there was activation of primitive defence mechanisms under conditions of trauma or stress (Whitlock, 1967; Nijenhuis et al., 2004).

1.13.2.1 Functional studies relating to arousal and trauma-processing in people with CD

According to theories of conversion disorder (CD), stressful life-events trigger symptom production in vulnerable patients (WHO, 1992; APA, 2013). Several studies have investigated these associations using functional magnetic resonance imaging (fMRI) techniques.

Neurophysiological studies of CD have reported greater arousal in patients compared with healthy controls, and several studies have compared these patterns. For example, the influence of arousal on brain functioning was compared between 16 patients with motor subtype CD and a healthy control group, by examining implicit (unconscious) emotional processing through exposing participants to faces demonstrating positive and negative emotions, while carrying out a gender identification task during fMRI (Voon et al., 2010a). The authors found significantly greater arousal in the patient group, associated with increased activity between amygdala and supplementary motor area (SMA).
regions. Similarly, a recent study by Aybek and colleagues of implicit emotional processing comparing sad and fearful faces with neutral faces found relatively increased activity of left amygdala in the motor subtype CD group in response to the negative emotional faces, that was associated with a hyper-sensitisation response, rather than that of habituation, over time (Aybek et al., 2015). The authors also observed significantly increased activity in peri-aqueductal gray (PAG) matter and frontal regions involving premotor and supplementary motor areas, dorsolateral prefrontal cortex and cingulate cortex (Aybek et al., 2015). Taken together, these findings indicated that findings of abnormal emotional regulation is linked with motor dysfunction in CD.

Another group of researchers investigated brain functioning in 12 patients with motor subtype CD using an interesting experimental paradigm. They identified stressful events from the patient’s histories that they believed could have been associated with onset of conversion symptoms (which was ascribed a “severe” threat but a control-condition), and also classified specific events for which development of such symptoms could help the patient avoid distressing consequences (ascribed an “escape” experimental condition) (Aybek et al., 2014). They then asked the patients to recall those specific threatening events during fMRI scanning. They found that, in comparison with the healthy control group (HC), those with CD had significant differences in neural activation patterns, so that there was increased activity of the SMA and temporo-parietal junction (TPJ) on the right side, while on the left side, activity was relatively increased in the left dorsolateral prefrontal cortex (DLPFC), and decreased in the left hippocampus region. They reported that “escape” events were associated with longer reaction times and were perceived by patients as less upsetting than the “severe” control events. This finding suggested that the CD group processed threatening events differently, and was interpreted as representing potential DLPFC “top down” disruption in recall of unwanted memories, consistent with the Freudian concept of “repression”. In addition, activation was comparatively reduced in right inferior frontal cortex but enhanced in regions involving amygdala and motor areas (involving SMA and cerebellum), findings considered to represent vulnerability factors for development of conversion disorder, as they were present in patients across the whole experiment. This finding was also consistent with that of Voon and
colleagues, whereby arousal of patients with motor subtype CD was associated with greater limbic-motor region interactions during conditions of arousal (Voon et al., 2010a). Nevertheless, studies involving other motor symptoms of conversion disorder have not reproduced such findings. For example, a single-case fMRI study of CD motor type affecting speech (mutism) found that after recovery of symptoms, (but not during active mutism), reduced connectivity with amygdala and increased connectivity between inferior frontal gyrus (IFG) and anterior cingulate cortex (ACC) was observed (Bryant and Das, 2012). This pattern suggested that in the “active” state of the conversion disorder, there was impaired connectivity between speech networks and those that regulate anxiety. These differences in findings may reflect differences in subtype of CD.

1.13.2.2 Functional studies relating to sensory and cognitive conversion symptoms

A number of studies have examined conversion symptoms relating to impairment of somatosensory function (Malis-Gagnon et al., 2003; Ghaffar et al., 2006), visual function (Werring et al., 2004; Schoenfeld et al., 2011; Becker et al., 2013) and memory (Markowitsch, 2003; Fujiwara et al., 2004; Thomaas-Anterion et al., 2010) but for the most part have found reduced activations in brain regions known to be involved normally in functioning of the respective modality. However, changes involving hypo- or hyper-activation of other brain regions [for example, ACC, prefrontal cortex (PFC), insula, basal ganglia (BG), thalamus], were generally observed, but with no clear definitive pattern. However, a more recent case-study involving psychogenic visual loss found that in the active state (but not after recovery) there were selective increases in ventromedial prefrontal cortex (VMPFC) activity and associated coupling with the occipital region, a pattern of fronto-limbic activity that has been reproduced in another study involving psychogenic pain (Malis-Gagnon et al., 2003).
1.13.2.3 Functional studies relating to motor conversion symptoms

Studies of CD of motor subtype have examined theories of inhibition or pre-motor planning of movements. For example, an early single-case study of a female with left leg conversion paralysis reported that when the patient was asked to try to move her affected limb, there was no neural activation of primary motor cortex (PMC), but increased activation of right orbito-frontal cortex (OFC) and right ACC (Marshall et al., 1997). The authors proposed that these findings reflected the presence of an inhibitory effect by prefrontal regions on execution of movement.

Studies involving healthy control groups who were asked to “feign” paralysis or be subjected to hypnotic suggestion have demonstrated interesting comparisons. For example, the earliest such study of hypnotic paralysis found OFC and ACC activations during attempts to move the “affected” limb (Halligan et al., 2000), similar to findings in the conversion paralysis case (Marshall et al., 1997). However, a subsequent study that compared brain activations between patients hypnotised to believe they had limb paralysis, and controls asked to feign paralysis, found greater ACC and SMA activations during movement, but no abnormalities in the OFC, in the hypnosis group (Deeley et al., 2013). The findings from these studies suggest that CD of motor subtype may share similar inhibitory mechanisms on movement regions with those in operation during hypnosis, particularly relating to the ACC, whose role has been proposed to also involve attentional functions, including action-monitoring (Voon, 2014).

One of the earliest functional neuroimaging studies of motor conversion symptoms utilised positron emission tomography (PET), a functional imaging technique, to observe metabolic processes in the brains of 3 men presenting with arm-weakness and compared results with deliberate feigners of the relevant limb impairments. The authors reported distinct patterns of regional blood-flow between those with CD and feigners during movement of the relevant limb, so that there was decreased left dorsolateral prefrontal cortex (DLPFC) activity in those with CD, compared with a finding of right DLPFC hypo-function in the control group, regardless of laterality of the CD deficit.
(Spence et al., 2000). They postulated that these findings in CD provided preliminary evidence of impaired preparation of action, higher-order control of motor functioning, or both. A subsequent study of CD of motor subtype demonstrated that during preparation to move, patients with CD showed reduced activity in the SMA but increased amygdala and insula activity, on comparison with that of healthy controls. There was also decreased connectivity between SMA and amygdala regions in CD on comparison of voluntary versus cued movements, indicating possible impairment of higher-order processes involved in selecting actions relating to voluntary movement (Voon et al., 2011).

Another fMRI study utilised a modified Go/NoGo paradigm to investigate brain activity during action, including functions relating to motor intention, execution and inhibition of movement (Cojan et al., 2009a). The study only involved 2 patients with left-sided motor CD so that findings are limited by small numbers of participants. Nevertheless, the authors reported findings indicating normal motor preparation (involving contralateral PMC), but a comparative loss of motor activation in right motor cortex at the time of attempts to move the affected limb. The same authors also compared functioning relating to inhibition of movement in motor CD using the same paradigm (Cojan et al., 2009a; Cojan et al., 2009b). They found that in healthy controls, cancelling a prepared movement by either hand activated a network known to be involved in motor inhibition and cognitive control, comprising right inferior frontal gyrus (IFG) and right inferior parietal lobule (IPL) (Cojan et al., 2009b; Aron et al., 2003; Xue et al., 2008). In comparison, those with motor CD had normal activation of those structures on the contralateral side, but no such activation on the affected side, suggesting that the impaired motor execution with the affected hand was not related to active voluntary inhibition. However, it was observed that activation occurred in the precuneus and ventromedial prefrontal cortex (VMPFC) regions of those with motor CD, but not in healthy controls regardless of whether they feigned impairment or not. Precuneus activation has been found to particularly relate to autobiographical memory tasks, involving sensory images and tasks relating to focusing on self-perspective (Cavanna and Trimble, 2006), free choices of motor action (Soon et al., 2008) and self-agency judgements (Farrer and Frith, 2002). Activations of VMPFC have been postulated to relate to emotionally relevant information about the self (Moran et al., 2009), and also
including self-judgement (D’Argembeau et al., 2008; Jenkins et al., 2008; Schneider et al., 2008), introspection on personal emotions (Johnson et al., 2002; Macrae et al., 2004; Piguet et al., 2013) and recall of emotional information from memory (Sterpenich et al., 2007; D’Argembeau et al., 2008). An interesting single-photon emission computed tomography (SPECT) imaging study examined brain activity in 7 patients with unilateral motor CD at rest and during bilateral proprioceptive stimulation, firstly, when their symptoms were active, and subsequently, after their symptoms resolved a number of months later (Vuilleumier et al., 2001). Proprioceptive stimulation activated corresponding sensorimotor cortical areas appropriately during active motor symptoms but demonstrated abnormalities in cortico-subcortical motor-loops involving thalamus and BG of the contralateral hemisphere. These changes were also found to be directly associated with activity levels in VMPFC. However, the abnormalities were not evident on repeat of the scanning after resolution of symptoms, implicating impaired functioning of the respective cortico-subcortical motor loops in active-state motor CD.

1.13.2.4 Functional studies relating to involuntariness of movement

Evidence of impaired self-agency (subjective perception that the motor conversion symptoms are outside an affected person’s control) has been previously demonstrated by neurophysiological studies of CD, outlined earlier in this chapter. Self-agency has also been investigated by a fMRI study, in which brain activations of 8 patients with CD of movement subtype (conversion tremor) were compared with mimicked tremor activity (Voon et al., 2010b). The authors reported reduced activity, in patients, at the right TPJ, and a relative decrease in functional connectivity was noted between this region and regions implicated in sensory-feedback pathways (comprising sensorimotor cortices and cerebellar vermis), and limbic areas (comprising ventral striatum and ventral ACC). The right TPJ is implicated in activity relating to comparing internal predictions with actual external events so that it has been proposed to be involved in processes such as self-agency and attention (Decety and Lamm, 2007). A recent study of motor CD, with a larger sample size reported similar
findings (Maurer et al., 2016). Therefore, the reduction in TPJ activity observed in these studies may mean that patients with motor CD have an abnormal internal predictive process, that lead to their perception that their movements are outside of their control (Voon, 2014).

1.13.2.5 Functional studies relating to self-monitoring

Self-monitoring refers to the capacity to observe and reflect on one’s thinking and behaviour. Activity involving self-monitoring has been previously associated with a brain circuit called the default mode network (DMN), a network of interacting brain regions known to have activity highly correlated with each other and distinct from other networks in the brain, and including the medial PFC, posterior cingulate cortex (PCC), and the IPL (Culpepper, 2015). Some studies have specifically investigated self-monitoring correlates with brain activity in people with CD, following observations of dysfunctional PFC activity in affected patients. For example, De Lange and colleagues demonstrated that unconsciously inducing motor imagery relating to the limb affected in motor CD, resulted in comparative selective activation of the superior temporal cortex and the VMPFC regions. This finding suggested an enhanced self-monitoring process was correlated with these regions (De Lange et al., 2007). Cojan and colleagues found greater functional connectivity between right motor cortex and VMPFC, precuneus, and PCC in conversion motor paralysis, indicated that internal self-representations may influence motor activity (Cojan et al., 2009a). A subsequent study by the same authors of hypnosis-induced paralysis, found parallels with precuneus-motor cortex activity patterns in motor CD, but no evidence of abnormal activation of motor intention or motor inhibition in the hypnosis group (Cojan et al., 2009b). These findings were proposed to implicate that suggestion might mediate motor behaviour in people with CD through activation of self-monitoring processes (Voon, 2014).

1.14.0 Management of CD
1.14.1 General Approach to Presentation of CD Diagnosis and Management Plan

The management of conversion disorder is complicated by the fact that, once diagnosed, it can be challenging to explain the presenting symptomatology to the patient, in terms of highlighting positive investigative findings that are specific for conversion disorder, and offering a clear neurobiological explanation for the patient’s symptoms. In addition, there is a limited research base on which management decisions can be made with confidence (Edwards and Bhatia, 2012; Gelauff et al., 2014). Traditionally, many people with conversion disorders have come away from the initial diagnostic explanation confused, having interpreted the explanations offered as meaning that there is nothing working with them physically but that the problem “is all in your head” (Cottencin, 2014).

The often recommended first therapeutic steps in a successful first-line treatment approach are effective communication of the diagnosis and explanation of symptoms in a way that is rational and understandable to the patient, so as to create a therapeutic alliance moving forwards (Stone et al., 2011; Edwards and Bhatia, 2012; Stone and Edwards, 2012). It is important that the initial therapeutic approach to management after diagnosis is considered carefully, especially as studies have found that rapid improvement in conversion symptoms can occur after during an inpatient period of feedback of diagnosis and psychoeducation, a process that may include tentative exploration of the individual’s coping style and possible etiological factors (Duncan et al., 2011).

It has been proposed by some authors that, when a conversion disorder has been diagnosed, a multidisciplinary approach to management is preferable, so that for example, the ideal situation would be that a combined consultation occur, where the relevant specialist neurologist and psychiatrist are present with the patient and their family at the time that the diagnostic explanation and recommended management plan is provided (Cottencin et al., 2007; Cottencin, 2014). This approach would help to promote the idea that a positive, holistic,
supportive and shared interdisciplinary model of care operates in that healthcare facility between different healthcare professionals and between healthcare professionals and their patients. In addition, where identified, co-morbid psychiatric illness (the most frequent being depressive or anxiety disorder) should be treated (Stonnington et al., 2006).

In many specialist neurological units, neurologists, neuropsychiatry, neuropsychology and allied professionals are presented to patients attending the service as being members of a combined multi-disciplinary team which may be expected to be involved in an individual’s patients care, so that there is standard multidisciplinary assessment in neurology facilities, including psychiatric assessment, as standard protocol (such as in some specialist epilepsy monitoring units), or as required (O’Brien et al., 2009). This structure helps promote the idea that meeting a psychiatrist or a psychologist during an admission or healthcare visit to neurology (or vice versa) is socially acceptable, rather than it being in some way pejorative or seen as a dis-affirmation of a patient’s experience. Such approaches help to reduce stigma in general towards mental health issues and promote a positive holistic environment in which the physical and mental aspects of a patient’s health are recognised as important by the medical professional and seen by the patient as such.

Depending on the type of setting that the relevant healthcare is provided, the presentation of the diagnosis of conversion disorder and relevant recommended management plan could be held for example, during a multidisciplinary ward round or scheduled multidisciplinary case-conference. However, having such a joint meeting may not be feasible in many facilities, being largely dependent on how the healthcare service is organised. In those situations, it has been recommended that the neurologist first meets with the patient, provides feedback on their diagnostic opinion and explains the problem, including discussing and clarifying particular symptoms that have no discernible biological correlates. Firstly, the neurologist explains that specialist psychiatrist input will be required to help the patient with their symptoms. Secondly, the patient attends a joint neurology-psychiatry consultation to hold a discussion on how they may help the patient recover. A suggested approach to this type of multidisciplinary meeting is outlined below. Thirdly, after the joint consultation, the neurology and psychiatry teams discuss the consultation and their
impressions of the interview, including sharing of observations, both clinical (including possible overt signs of mental illness such as depression), and in terms of the therapeutic relationship. They then form a pragmatic joint-management plan, agreeing their roles and what further treatments and follow-up may be offered.

The shared-consultation or neurology-psychiatry multidisciplinary approach has many advantages including improved communication between professional colleagues, and between medical professionals, patients and their families. It also helps to promote a shared understanding of mind-body issues among all involved and a recognition of the patients experience of symptoms within such a formulation. Moreover, this approach may improve prognosis by treating co-morbid psychiatric disorders, and improving the chances of compliance with follow-up. On the other hand, there may be disadvantages to this process, including that a patient may feel being overwhelmed or unhappy to attend a joint consultation or a multidisciplinary case conference, referring instead a sequential consultation model (Cottencin, 2014).

The approach to how diagnosis and management of the relevant conversion disorder is communicated is crucially important (Stone et al., 2011). The attitude of the multidisciplinary teams involved, in particular, to psychosomatic presentations is important here, as negative attitudes by medical professionals can re-inforce symptoms (Stephenson and Price, 2006). Ideally, these issues should be discussed by the specialists involved in the care of the patient, and a meeting strategy agreed, in advance of meeting the patient for this purpose. When different members of the multidisciplinary team are involved, it is important that the explanation of diagnosis is consistent.

A suggested approach may be that, firstly, the neurologist explains the problem and the results of their assessment to the patient and their family, in front of the psychiatrist. It is important to highlight positive ways in which the diagnosis has been made rather than the earlier often-used explanation that all relevant investigations have been negative (Edwards and Bhatia, 2012). It is also important to reassure the patient and their families of the absence of somatic disorders, where relevant (Cottencin et al., 2007; Reuber and Elger, 2003b). Secondly, questions from the patient are facilitated and answered, during which time the psychiatrist can act as mediator. The language used by the medical
professionals should avoid medical jargon and refer to relevant mind-body interactions. It is important to provide a rational model for the patients and their family to understand the particular physical symptoms (Edwards and Bhatia, 2012). The psychiatrist can subsequently help to redefine the symptoms in terms of psychopathological language framed simply and in an understandable manner for the layperson. Some authors have suggested that the consultation also includes the neurologist and psychiatrist writing a joint letter to their general practitioner in front of the patient, which in their experience helps improve the transparency and validity of the process for the patient, in a situation where the patient may feel that doctors may refer to them and their symptoms in a negative or pejorative way (Cottencin, 2014).

Nevertheless, even if these steps are carried out carefully and tactfully, it is not unsurprising that the patient may feel they and their symptoms are not being taken seriously by the medical professionals involved, and may react in this situation with a rejection of the diagnosis, the proposed model of explanation, and the pro-offered management approach (which will include psychiatric and psychological specialist input) (Cottencin, 2014). This can occur particularly as, by definition, patients with psychosomatic presentations often have (at least initially) difficulty recognising associations between their personal psychological issues, including stress, and somatic or neurological symptoms (Stone et al., 2004a). Therefore, doctors should not, during the initial stage of presentation of diagnosis and recommended management plan, explore potential psychological issues in depth with patients. It has been found that it is often not easy for patients to suddenly start to openly talk with doctors about their own psychological issues, life events and stress in these situations (Morell-Dubois et al., 2008). It is more appropriate that these type of conversations are supervised by the relevant mental health professional, and particularly by the psychiatrist, in subsequent consultations. Nevertheless, several research studies have demonstrated that explanation of the diagnosis and provision of psycho-education about the disorder during inpatient care can lead to symptom-resolution, at least in the short-term (Barsky et al., 2004).

It is important to note that patients who do not accept the diagnosis and explanation for their conversion disorder are unlikely to benefit from moving to second-line treatments, so that in these cases, the treating team should, as
much as possible, provide the relevant information and information resources for the patient to reflect on, and offer the opportunity for clarification and discussion at a later stage.

1.14.2.0 Specific Treatments for CD

Treatment can be offered to those who accept the diagnosis and wish to engage in treatment.

1.14.2.1 Pharmacological Treatment of CD

The evidence base for the effectiveness of treatments in conversion disorder (apart from PNES) is very limited (Gelauff et al., 2014). Although there is some evidence for example, that pharmacotherapy, particularly antidepressants, may be of benefit in treatment of conversion disorder, particularly symptoms involving psychogenic weakness and blackouts (LaFrance et al., 2010), a recent systemic review of factors affecting prognosis of conversion disorder, trials of treatment with antidepressant medications and levodopa (a dopamine agonist used in Parkinson’s disease) were not associated with better outcome.

1.14.2.2 Psychological Treatments of CD

A number of psychological treatments for conversion disorder have been studied. A systemic review found that studies were generally underpowered and that psychological treatments involving hypnosis and suggestion were not associated with better outcomes (Gelauff et al., 2014). They reported that, overall, 49% of the patients involved in these interventional studies, (including pharmacological treatments), had the same or worse symptoms on follow-up. There have been a number of other psychological studies pertinent to conversion disorder that either were not included in Gelauff et al.’s review, or were carried out since it was carried-out. Firstly, a randomised-controlled trial
(RCT) of a professionally-supervised 4 session self-programme based on cognitive behavioural therapy (CBT), included emphasis on psychoeducation of 127 participants in relation to their psychogenic neurological symptoms, and was found to improve participant’s perception of their health-related quality of life over the short-term follow-up and their symptoms over a longer term (Sharpe et al., 2011).

A 6 month study examining the effects of a psychodynamic psychotherapy intervention on psychogenic movement disorders was recently published (Kompoliti et al., 2014). The authors found no significant main effect for treatment. However, they reported difficulty in recruiting patients from a defined case register of psychogenic movement disorders, and further, the attrition rate of participants during the study was high (35%), leading to the study being underpowered.

Lastly, a small study examined the effects of liaison psychiatry involvement in 23 cases of psychogenic neurological symptoms, and reported positive results of this support on symptom severity and hospital attendance (Hubschmid et al., 2015).

Family therapy is recommended in general for treatment of psychiatric conditions in which disordered or unhelpful family dynamics may influence presentation and exacerbation of an individual’s psychiatric condition. Similarly, it has been proposed as an appropriate intervention for patients with conversion disorder who may benefit from an assessment of their family functioning in relation to communication styles, family roles and approach to problem solving and stress-management. Family therapy has been reported to help improve conversion symptoms where relevant, according to a review of such studies (Stonnington et al., 2006).

### 1.14.2.3 Specialised Physiotherapy and Biofeedback for CD

Specialised physiotherapy has been proposed to have an important role in the management of conversion disorder, particularly where the psychogenic symptoms relate to movement or weakness (Lehn et al., 2016; Nielsen et al., 2015a). Physiotherapy consultation and management helps the
multidisciplinary team re-inforce the idea, through education of the patient, that the mind and body interact in such conditions and that physiotherapy is one of a number of positive health management strategies that try to address psychogenic deficits holistically (e.g., where the patient is unable to move a limb in psychogenic paresis). This is not novel and physical rehabilitation has traditionally formed part of the management strategy recommended by psychiatrists to treat psychogenic neurological symptoms and psychogenic motor disorders in particular, over many years. Nevertheless, until recently, there have been few trials on which to base treatment decisions (Edwards and Bhatia, 2012).

However, several trials of physiotherapy have been found to produce positive benefits in people with psychogenic neurological symptoms, particularly motor conversion disorder. For example, a 5-day multidisciplinary team (MDT) inpatient rehabilitation programme which included positive explanations of motor conversion disorder, but emphasised physical treatment, reported marked improvement in symptoms in 69% of the 60 participants immediately after completion, which were sustained over 2 years afterwards (McCormack et al., 2014). Another inpatient physiotherapy programme was the first RCT for people with psychogenic gait disorders and found that the 3-week physical and sports therapy programme had significant positive effects on symptoms that was sustained at 1-year follow-up (Jordbru et al., 2014). Following development of a consensus guideline on the nature of content and intensity of physiotherapy for motor conversion disorders, a research group developed a 5-day specialised physiotherapy programme for motor conversion disorder (excluding those with untreated co-morbid psychopathology and those with prominent pain and fatigue symptoms). This group of 47 people had a number of poor prognostic indicators, including a long duration of symptoms (5.5 years on average), previous physiotherapy with our benefit, and reliance on state benefits secondary to poor health. It included patient education according to a previously developed approach, exploration of how the (psychogenic) symptoms affected each patients own movement and posture, and then extended previous physiotherapy trials by helping participants improve or “retrain” their movement based on redirection of attention strategies, followed by development of a personal action plan to reinforce this learning and experience (Nielsen et al., 2015b). The authors reported that 65% of 47 patients with
chronic duration of motor conversion disorder were at least much improved at the end of a 5-day intervention, with 55% maintaining this positive outcome at 3 months. Nevertheless, other studies have shown that patients with conversion disorder have abnormal cognitive appraisal of symptom characteristics, including overestimating their severity (Ricciardi et al., 2015a) and that these perceptions can be modifiable through specialised biofeedback sessions in which patients are asked about their perceptions of their movement disorder, then receive feedback from others and via video-recordings and mirrors, while re-appraising their original perceptions (Nielsen et al., 2015a). Another biofeedback study evaluated the feasibility of using entrainment as a bedside therapeutic strategy in 10 patients with psychogenic tremor (Espay et al., 2014). Entrainment is the change or elimination of tremor as patients carry out a voluntary rhythmical movement by the unaffected limb, and is a key diagnostic hallmark of psychogenic tremor. In this novel study, participants were helped to retrain their tremor frequency using tactile and auditory external cueing and visual feedback on a computer screen with immediate benefits lasting up to 4 weeks in all patients. However, just 3 patients maintained their tremor free status by 6 months, with relapses in the others. Nevertheless, other studies have also demonstrated reversibility of psychogenic symptoms to the patient, either through non-electrical clinical techniques at the bedside (e.g., Hoover’s sign of psychogenic weakness) (Stone and Edwards, 2012) or therapeutic sedation (Stone et al., 2014a), have demonstrated short term positive results. However, the central problem with these techniques appears to be helping the patient to achieve long-term remission.

1.14.2.4 Multidisciplinary treatment of CD

Three recent studies have demonstrated that a MDT approach that comprised both physical (including occupational therapy) and psychological treatment (relating to CBT) for motor conversion disorder can have significant effects on outcome, even with patients who have enduring impairment of functioning (McCormack et al., 2014; Saifee et al., 2012; Demartini et al., 2014b). For example, one of these studies reported improvement in health related quality of life for two-thirds of the 66 patients who received it (Saifee et al., 2012).
1.14.2.5 Other Physical Treatments of CD

Therapeutic sedation with propofol has been used as a treatment in small groups of patients with conversion disorder, and has been found to have beneficial effects that were reported to persist at an average of 30 months on follow-up (Stone and Carson, 2015). However, it has not been studied extensively.

Similarly, abreaction is a therapeutic technique that involves interviewing patients who are lightly sedated having been administered an intravenous drug. It has been proposed that this procedure may assist patients to be more amenable to explanations of their conversion symptoms, which can lead to improvement. A meta-analysis of observational studies reported that 79% of participants recovered (Poole et al., 2010). However, this technique is rarely used and it would be important to establish a positive therapeutic relationship prior to such interventions.

Transcranial magnetic stimulation (TMS) is a noninvasive procedure that uses magnetic fields to stimulate nerve cells in the brain, and involves application of an electromagnet to the patients forehead which delivers a painless magnetic pulse. Its exact mechanism of action is not known. However, its applicability to treating conversion disorder has been investigated through a number of studies, including a systematic review (Jellinek et al., 1992; Chastan and Parain, 2010; Pollak et al., 2014). For example, one of these studies comprised a sample of 70 patients with recently diagnosed psychogenic weakness, and reported that a single 15-minute session of supra-motor threshold intensity TMS resulted in remission of symptoms for 89% of participants (Chastan and Parain, 2010). However, some obvious limitations of this study were that the participant group was heterogeneous (involving children and adults), the symptoms could have remitted without the effect being attributable to the TMS (given the short duration of symptoms), and there was no subsequent follow-up study to determine if benefits were maintained (Lehn et al., 2016). However, another recent study, treated a group of 24 patients with different types of psychogenic
movement disorder, and utilising low frequency TMS, reported that 75% of
patients improved by over 50%, and further, that benefits were sustained by a
median follow-up period of 19.8 months (Garcin et al., 2013). Therefore,
although results appear promising for this treatment, further studies are required
with this technique to determine efficacy and safety in conversion disorder and
indeed conversion disorders of different types (e.g., sensory conversion
disorder).

1.14.2.6 Questionable techniques in management of CD

It is recommended that techniques that involve deception, presentation of false
information or surgery are avoided, from an ethical point of view (Ataoglu et al.,
2003; Shapiro and Teasell, 2004).

In summary, there are no evidence-based medication treatments recommended
for conversion disorder (psychogenic neurological disorders) *per se*, unless the
patient requires medication treatment for a co-morbid psychiatric condition.
There is evolving evidence for positive effects of psychological treatment,
particularly that based on CBT, and, in relation to motor conversion disorders,
for physical treatments such as occupational therapy and TMS. There is also
evidence that a multidisciplinary team involvement in treatment is beneficial.
However, the most significant research in recent years in terms of outcome has
been with the evaluation of physiotherapy as a treatment for motor conversion
disorders, which has demonstrated positive effects persisting in short-term
follow-up.

The neurobiological basis of the effectiveness of the psychosocial and physical
interventions in CD is unknown. However, the “scaffolding” theory of conversion
disorder proposes that there is a failure of inhibitory processing of threat-related
stimuli in PNES, so that explicit cognitive strategies that aim to positively
address such dysfunctional processing may help to reduce symptoms.
Similarly, physiotherapy and psychosocial interventions (e.g., psychoeducation,
multidisciplinary management of the patient in a consistent understanding
manner) may reduce the threat element (perceived by the patient) of the
abnormal processing that contributes to the physical and sensory manifestations of the CD.

In addition, according to this “scaffolding” model of CD, a number of neurotransmitters that mediate disturbed inhibitory processing (e.g., serotonin, noradrenaline, dopamine) may be abnormally regulated and could therefore possibly be treated by an intervention that regularises the neural functioning, including psychoactive medications or TMS (Brown and Reuber, 2016). However, no studies have specifically evaluated the metabolic correlates relating to this theory, so that until such research examines neurobiological correlates of conversion disorder at this level, it is unlikely that we can predict with confidence what patients may benefit from medication and what types of medication may be helpful in CD.

Overall, the development of effective treatments is hampered by the as yet unknown pathophysiological mechanism of these disorders. Therefore, further research is needed to clarify neurobiological mechanisms relating to pathogenesis and persistence of conversion disorder so that more specific treatments can be designed accordingly.

1.15 The Socio-Economic Burden of CD

No studies have specifically examined the socio-economic burden of conversion disorders as a whole. However, given that people with these disorders frequently present to healthcare facilities seeking diagnosis and treatment of their condition, a process which may include costly investigations, it would be unsurprising if these costs are high. Indeed, one UK study estimated the annual costs to society associated with medically-unexplained (somatisation) symptoms in the working-age population to be £18 billion (Bermingham et al., 2011), which was reported to be similar to those associated with dementia (Knapp et al., 2007).
1.16 Outcome Studies Relating to CD

Some studies have reported that initial diagnosis and associated first-line management of conversion disorder within the hospital setting can be associated with initial recovery rates of between 50 to 90% of patients, but that up to a quarter of these patients who do, relapse within a year (Barsky et al., 2004).

Long-term follow-up studies of conversion disorder are hampered by the manner of case definition and the organisational structure of the health service they present to, as previously outlined earlier in this chapter (Edwards and Bhatia, 2012). For example, people who may have brief or transient psychogenic neurological symptoms may not be diagnosed by the time they present to a specialist neurology clinic. Nevertheless, from the studies that have been carried out relating to follow-up of conversion disorder, outcome in general for affected patients generally is relatively poor (Gelauff et al., 2014).

In the most comprehensive paper on this subject, a recent systemic review of outcome studies for conversion disorders affecting movement, reported that the remission rate was low, with just over 21% of patients being completely symptom-free over a mean duration of follow-up of up to 7.4 years after diagnosis (Gelauff et al., 2014). Moreover, having the status of persisting or worsening of symptoms was held by an average of 40% of affected patients over that period of follow-up, with the relevant rate for specific disorders being 69% for dystonia, 66% for tremor, 44% for mixed movement disorders, 42% for muscular weakness, and 29% of those with mixed motor symptoms. The same study also reported that between 17-65% of patients with psychogenic movement disorders were at work on follow-up, so that the effects of this type of condition on an individual's work attendance was highly variable. In addition, high levels of disability, dependency and absence from work were observed. Another study showed that over a mean follow-up of 3.2 years, conversion disorder affecting movement persisted in 90% of patients and this finding was notably associated with those with other co-morbid mental illnesses, including depression, anxiety and personality disorders (Feinstein et al., 2001).
One retrospective study of 42 patients with different types of conversion symptoms (psychogenic weakness and sensory disturbances) found that 83% of patients continued to have persistent psychogenic symptoms after a median of 12 years, with multiple other physical symptoms including fatigue, myalgias, arthralgia and nausea being most frequently reported (Stone et al., 2003).

Several studies have reported that conversion disorder with sensory symptoms may have a better outcome (Stone et al., 2003; Toth, 2003) than that for movement disorders, including dystonia and tremor (Gelauff et al., 2014; Stone et al., 2003; Ibrahim et al., 2009).

Chronicity of symptoms and the presence of multiple symptoms have been reported to be a predictor of relatively poor outcome (Feinstein et al., 2001). Other predictors of poor outcome have been reported, including the presence of an expectation by the patient that they will not recover, and an attitude that symptoms are not attributable to psychological factors. In addition, having poor physical functioning (Stone et al., 2003) and the status of being in receipt of health-related financial support by the government at the time of diagnosis was also found to be a predictor of negative outcome (Sharpe et al., 2010). On the other hand, some studies have identified positive prognostic factors in patients presenting with conversion disorder, including a short duration of illness, positive perception of clinical treatment and the presence of psychiatric illness that is treatable, specifically depression or anxiety disorder (Jankovic et al., 2006; Thomas et al., 2006).

1.17 Background to psychogenic non-epileptic seizures (PNES)

In this section, I will review the conversion disorder subtype of psychogenic non-epileptic seizures (PNES). I will provide a description of the disorder and its epidemiology, current diagnostic process and associated issues, its associated burden to the individual and society and an outline of current treatment options and prognostic issues. Subsequently, I will review relevant
study findings relating to contemporary knowledge of etiological factors and mechanism of action of PNES, referring to relevant psychiatric, psychometric, neuropsychological and neuroimaging studies in that process.

1.18 Introduction to PNES

The term PNES describes paroxysmal episodes of seizure-like behaviour that typically include features of impaired consciousness or awareness, collapse and abnormal motor and sensory manifestations and that superficially resemble epileptic events, but lack EEG correlates of epilepsy (Brown and Reuber, 2016a). These disturbances are considered to have a psychological rather than a medical etiology (Goldstein and Mellers, 2012) so that the direction of treatment is significantly different to that of epilepsy. Therefore, making an accurate diagnosis and differentiation of PNES from epilepsy as soon as possible is important for the welfare of the patient.

1.19 Epidemiology of PNES

PNES are one of the three most common diagnoses made when patients present to clinicians with transient loss of consciousness (Malmgren et al., 2012) and are the most common medically unexplained (i.e., “functional”) symptom presenting to neurology centres (Stone et al., 2010b).

It is estimated that between 12-25% of patients attending neurology centres for treatment of epilepsy have PNES (Reuber et al., 2005a). Furthermore, PNES is the most frequent non-epileptic condition seen at epilepsy centres, being more common than physiological non-epileptic conditions, with an estimated prevalence of 2 to 33 per 100,000 (Benbadis and Allen-Hauser, 2000; Benbadis et al., 2004). Moreover, the prevalence of PNES is higher (20-30%) in that group of adult patients who are admitted to epilepsy monitoring units to help definitively characterise their seizures; a group whose seizures are usually
either refractory to treatment, clinically difficult to define or who may be undergoing work-up for potential epilepsy surgery.

Patients with PNES often have concurrent epilepsy, with studies reporting variable prevalence of epilepsy co-morbidity of approximately 5 to 30% of those with PNES (Benbadis et al., 2001). The presence of co-morbidity can make accurate characterisation within an affected patient clinically challenging (Benbadis and Allen-Hauser, 2000; Martin et al., 2003). Nevertheless, in cases of co-morbid PNES and epilepsy, accurate classification of the different semiologies is crucial to direct appropriate treatment to both conditions (LaFrance et al., 2013a).

The majority of patients with PNES are women by a ratio of 3 to 1, for reasons that are not clear (Goldstein and Mellers, 2012; Bodde et al., 2009). No clear gender-differences in clinical presentation or psychopathology of PNES have been reported. However, some authors hold speculative views that women differ from men in their vulnerability and response to various trauma (Rosenbaum, 2000).

PNES typically present in people aged between 20-30 years, with an average age of onset of 23 years old (Reuber and Elger, 2003b). PNES may also present in children as young as 4 years of age, although PNES in children is currently considered to have a different etiology and the research literature in this group is not as well-developed as that for adults (Reuber and Elger, 2003b; Dworetzky, 2015). Nevertheless, prevalence appears to increase with age, through adolescence (Smith, 2014).

1.20 Neurological diagnosis of PNES

At the current time, it is a clinical challenge to accurately distinguish PNES from epileptic seizures. There are no clinical signs of PNES that reliably and consistently exclude a diagnosis of epilepsy. On the other hand, there are no clinical signs unique to epilepsy, with the exception of co-occurring and
characteristic electroencephalographic abnormalities. PNES can manifest similarly to any type of seizure event and can particularly be confused with seizures arising from frontal lobe (Kanner et al., 1990).

PNES are diagnosed after neurological, medical, and video-EEG (vEEG) assessments confirm that the events are non-epileptic in nature and have no other physical explanations, such as, for example, cardiogenic syncope or catalepsy (Figure 1.5). Therefore, at present, diagnosis largely relies on the exclusion of a diagnosis of epilepsy and through vEEG in particular.

This assessment process involves clinical observation of the patient’s behaviour and capturing typical seizure-like events simultaneously with vEEG recordings of the relevant brain-wave activity.

VEEG protocols may include provocation tests, which are often used to try to shorten duration of vEEG monitoring. There are a variety of provocation techniques that can be employed, such as intravenous saline injection, photic stimulation, hyperventilation and suggestive interviewing. If used, it is

---

**Figure 1.5 Some differential diagnoses of seizure-like events.**
recommended that these tests should only be carried out with the patient’s informed consent (Gordon et al., 2014). It has been argued by some authors that these tests are more likely to provoke PNES rather than epileptic seizures, given that people with a positive test may be more suggestible (Benbadis, 2009a). In addition, the procedure has been associated with induction of isolated seizures, which have no clinical relevance, such as can occur after intoxication by anticonvulsant medications or general anaesthesia. Therefore, caution must be exercised to try to ensure that several typical seizure-like events experienced by the patient outside of the clinical environment are registered so that possible PNES-epileptic co-morbidity is assessed and outruled (Gordon et al., 2014). An important and prudent practice in this regard is “observer-validation”, in which the clinical team presents the recorded events to the patient and their family or caregivers in order to confirm that the recorded events during vEEG are consistent with the usual pattern of the patient’s seizures. Such a procedure is thought to be important to help identify false positive results for PNES, where these type of events are not typically experienced by the patient and may have only occurred under conditions of clinical observation or iatrogenic provocation (LaFrance et al., 2013a; Gordon et al., 2014).

A typical seizure-like event is defined as a PNES when there is no co-registered EEG evidence of epileptic discharges. This is generally believed to accurately diagnose PNES in approximately 90% of cases (Benbadis et al., 2009b).

Misclassification of PNES is more likely when diagnosis is based on observation of a single seizure-like event on vEEG or on history alone (Smith, 2014). For example, some simple and complex partial seizures of frontal lobe may not demonstrate epileptic discharges on vEEG (Gordon et al., 2014). Therefore, caution must be exercised that diagnosis is not reliant on vEEG alone as firstly, 10-20% of some epilepsies may not be detected by EEG, and secondly, inter-rater reliability examinations by clinicians differ for diagnosis (Benbadis et al., 2009b; Brown et al., 2011). Currently, the gold standard for making a “diagnosis with high confidence” of PNES, according to a recent consensus guideline by the International league Against Epilepsy Non-epileptic Seizures Task Force, is by taking a comprehensive patient history, and observing a typical seizure-like
event simultaneously co-registered with vEEG (LaFrance et al., 2013b). Diagnostic uncertainty is infrequent after this process is followed appropriately. Nevertheless, diagnosis is never definitive using current assessment methods.

1.21 Psychiatric diagnosis of PNES

PNES are generally classified as mental disorders according to current classification systems. The vast majority of PNES are reported by patients as being outside of their voluntary control, and most fulfill the diagnostic criteria consistent with dissociative (conversion) disorder (ICD-10) or conversion (functional neurological symptom) disorder (DSM-5); these are terms used to describe a condition in which patients present with neurological symptoms that are inconsistent with a neurological disease but are not due to malingering. PNES are currently interpreted as an involuntary response to emotional, physical, or social distress and to have a psychological origin (Brown et al., 2011; Smith, 2014). PNES should be differentiated from other psychiatric disorders such as panic disorder or post-traumatic stress disorder, for example, where features such as severe anxiety, impulse control difficulties and flashbacks may, in some cases, resemble PNES. Seizure-like events may also be produced by feigned behaviour but this is not considered a mental disorder (Reuber and Elger, 2003b; LaFrance et al., 2013b). An appropriate and thorough psychiatric assessment of such patients as soon as possible after diagnosis of PNES is important and many centres include psychiatric assessment as part of the admission protocol for all patients receiving epilepsy monitoring using vEEG, because of the high prevalence of psychiatric disorders in epilepsy and in people attending specialist epilepsy centres (O’Brien et al., 2009).

Diagnosis of PNES may be delayed for many reasons, including inadequate medical assessment and difficulties in accessing appropriate specialist neurological care & vEEG facilities. A large proportion of patients with PNES will have experienced seizure-like events for several years before a definitive diagnosis is made, with reported ranges of 1-38 years and mean latency...
periods of approximately 7 years being reported in countries considered to have well-developed health systems. However, delays in diagnosis of PNES can be considerably longer if the appropriate medical expertise and resources are not available (Ettinger et al., 1999; Reuber et al., 2002). In addition, physician factors, including lack of consideration of possible psychological causation for the seizure-like events, have also been reported to contribute to delay in diagnosis (Reuber et al., 2002; Reuber and Elger, 2003b).

Unfortunately, the current situation in most health systems is that most patients with PNES (and without epilepsy) are initially misdiagnosed as having epilepsy. Furthermore, over the subsequent period of time that the seizures continue to be inaccurately characterised, patients are treated with anti-convulsive medication and inappropriate medical interventions, thereby being exposed to iatrogenically-related harm, which may lead inadvertently to death in some cases. Moreover, failure to make the appropriate diagnosis means that affected people will not receive treatment that may help reduce PNES and improve their quality of life, thus prolonging morbidity associated with the condition (Reuber and Elger, 2003b).

1.22 Seizure-event semiology

The clinical manifestations of PNES closely resemble those of epileptic syndromes and, like epilepsy, present in many variations (Brown et al., 2011). Several studies have utilised cluster analysis of retrospective data to identify up to 6 subtypes of PNES, based on semiology of seizure-like events (Groppel et al., 2000; Hubsch et al., 2011; Seneviratne et al., 2012). Nevertheless, there is little known about how these subtypes relate to our understanding of the disorder and currently these findings have insufficient evidence base to be considered clinically useful in making an accurate diagnosis of PNES (Avbersek and Sisodiya, 2010; Brown et al., 2011).

Over the years, many studies have attempted to identify clinical features that reliably differentiate between PNES and epileptic events to try to diagnose
PNES as early as possible after manifestation. A recent review highlighted clinical signs that were established in vEEG studies to have over 90% specificity for PNES (Table 1.2) (Goldstein and Mellers, 2012). Those features that have been reported to be most predictive of diagnosis include eye closure, fluctuating course, post-ictal stertorous breathing, and a seizure-event duration of over 2 minutes (Azar et al., 2010; Goldstein and Mellers, 2012). Witnesses to typical seizure-like events are necessary to obtain collateral information about associated semiology. However, witness reports are not as reliable as direct review of video-recorded events by expert medical staff (Syed et al., 2008; Seneviratne et al., 2012). Nevertheless, some of these signs have since been questioned by a subsequent small study (Syed et al., 2011), so that for the

Table 1.2 Review of semiological features from vEEG studies that can help differentiate PNES from epilepsy (taken from Goldstein and Mellers, 2012).

<table>
<thead>
<tr>
<th>Signs with &gt;90% specificity</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long duration*</td>
<td>-</td>
</tr>
<tr>
<td>Closed eyes</td>
<td>52-96</td>
</tr>
<tr>
<td>Fluctuating course</td>
<td>47-88</td>
</tr>
<tr>
<td>Asynchronous movements**</td>
<td>9-56</td>
</tr>
<tr>
<td>Side to side head movements**</td>
<td>15-36</td>
</tr>
<tr>
<td>Pelvic thrusting**</td>
<td>7-44</td>
</tr>
<tr>
<td>Ictal weeping</td>
<td>4-37</td>
</tr>
<tr>
<td>Recall for period when apparently unconscious</td>
<td>63</td>
</tr>
<tr>
<td>(assessed post-ictally)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Signs with &gt;90% specificity for epilepsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stertorous breathing (convulsive seizures)</td>
</tr>
<tr>
<td>Occurrence from EEG-verified sleep</td>
</tr>
<tr>
<td>Post-ictal confusion</td>
</tr>
<tr>
<td>(assessed by examination)</td>
</tr>
</tbody>
</table>

* Long duration has been consistently demonstrated to be a useful discriminating sign, but its specificity and sensitivity cannot be calculated as varying definitions of long duration have been used. However, duration over 2 minutes is common in PNES but uncommon in epilepsy.

** Asynchronous movements, side to side head movements and pelvic thrusting are common in frontal and parietal (hypermotor) seizures and of low specificity in distinguishing these seizures from PNES.

vEEG, video electroencephalography; PNES, psychogenic non-epileptic seizures; EEG, electroencephalography.
moment, vEEG recording of “typical” seizure-like events remains the diagnostic intervention of choice in differentiating PNES from epilepsy.

1.23 Psychiatric aspects of PNES relating to co-morbidity

People with PNES are classified as having a dissociative or conversion disorder. However, the mechanisms by which this occurs is not yet understood and it is considered that intra-psychic distress is, in some way, converted into physical neurological symptoms (Goldstein and Mellers, 2012). In addition, more than 90% of patients with PNES have other psychiatric co-morbidity (Brown et al., 2011).

There is consistent evidence that, compared with people with epilepsy, those with PNES have higher levels of anxiety, depressive, somatisation, and conversion symptoms on personality assessment and a relatively high frequency of personality disorders (Reuber and Major, 2012). The most common co-morbid Axis 1 disorders are other dissociative disorders (22-91%), depressive disorders (57-85%), somatoform disorders (22-84%), anxiety disorders (11-50%) and post traumatic stress disorder (35-49%). In addition, 25-67% of patients are found to have co-morbid Axis 2 (i.e., personality) disorders, particularly those of “cluster B” type involving emotional dysregulation and impulse control problems that include borderline, narcissistic, histrionic and antisocial personality disorders (Galimberti et al, 2003; Reuber et al., 2009). Chronic anxiety has also been reported to be a consistent feature in PNES. Comorbidity of panic attacks in PNES has been reported to be more prevalent in adolescents relative to adults, raising the possibility that there may be an interactional relationship between panic disorder and age in PNES (Bodde et al., 2009). However, we do not know if the co-morbid psychiatric disorders are cause or effect of PNES or unrelated to PNES altogether (Bodde et al., 2009). Nevertheless, studies examining personality profiles of those with PNES, have identified several different clusters of pathological personality traits that may represent distinct groups (Reuber et al., 2004; Cragar et al., 2005; Bodde et al.,
2013). For example, one of these studies found that, based on personality profiles, affected patients may have normal or high levels of emotionality (termed “depressed neurotics” and “somatic defenders”, respectively) (Cragar et al., 2005). Another study described three factors that they found to be “essential” for subgroup classification: the history or not of overwhelming psychological trauma, the tendency to somatise in response to emotional overload and the presence of “novelty-seeking” personality traits (Bodde et al., 2011; Bodde et al., 2013). The meaning of these findings, in terms of understanding the underlying mechanisms of PNES remains elusive. Nevertheless, some authors have suggested that personality psychopathology profile research, combined with known etiological factors, can be utilised as a basis to develop psychological formulations to guide tailored treatment strategies for PNES (Brown et al., 2011; Bodde et al., 2013). Research on treatment efficacy based on such models of PNES is awaited.

1.24 PNES and stress

It has been proposed that people manifest PNES as a result of an as-yet-unknown psychophysiological process that occurs in response to stress. The manifestation of PNES has been associated with a range of interacting psychosocial stressors and there is increasing evidence that people with PNES have an abnormal response to stress (Brown and Reuber, 2016a). One study found that people with PNES manifest an abnormal baseline level of autonomic hypervigilance and a positive attentional bias in processing of potential social threats (Bakvis et al., 2009a). Follow-up studies by the same group reported that, compared with healthy control subjects, people with PNES have poorer memory performance under conditions of social distraction (Bakvis et al., 2010a; Bakvis et al., 2010b), suggesting that they have an abnormally increased stress response. In addition, several studies have reported significant variability in heart rates between people with epilepsy and those with PNES, both pre- and post-ictally, suggesting that those with PNES have
significantly high but different patterns of autonomic arousal patterns (Ponnusamy et al., 2011; Ponnusamy et al., 2012; Reinsberger et al., 2015).

1.25 PNES and life events

Some studies have examined patient’s experience of stressful life events in PNES but findings have been inconsistent. For example, one study found that in comparison with a group of people with epilepsy, those with PNES had a higher frequency of life events in the year before, but not in the immediate 3 month period leading to, onset of seizure-like events (Binzer et al., 2004). However, Testa et al. found no difference in frequency of recent or remote life-events or the reported distress associated with these events between people with PNES and epilepsy (Testa et al., 2012). Therefore, how life events relate to PNES manifestation remains unknown.

1.26 PNES and coping style

A number of studies have examined how people with PNES cope with stress. Several studies have reported a coping style characterised by hostility towards other people (Mokleby et al., 2002; Cragar et al., 2005). Other studies have examined defence mechanisms and coping. For example, one study found that people with PNES prefer to use denial and repression rather than problem solving to pro-actively solve problems (Jawad et al., 1995). Similarly, another found that in their sample, just over 30% had a greater tendency to cope using emotional expression, while just over 25% had a reduced tendency to problem solve and confront problems (Myers et al., 2013). Other research has indicated subgroups of people with PNES that are characterised by different coping profiles. For example, one study found two subgroups in people with PNES, one characterised by difficulties with emotional regulation; the other having comparatively normal emotional regulation but higher levels of depression and
somatization (Brown et al., 2013). An avoidant coping style has also been reported in subgroups of people with PNES (Frances et al., 1999; Goldstein et al., 2000; Cronje and Pretorius, 2013), and in one study, explicit anxiety was associated with experiential avoidance (Dimaro et al., 2014). Therefore, overall, these studies indicate that people with PNES utilise different maladaptive coping strategies to deal with unpleasant emotions. Further research on the strategies used and research aimed at determining biological underpinnings of PNES may help to formulate potential mechanisms of PNES and improve our understanding of how PNES manifest.

1.27 PNES and dissociation

Dissociation is defined as a disruption in the normally integrated functions of identity, consciousness, perceptions of the environment and memory and is considered by many to be a mechanism by which the self can avoid emotional distress by altering conscious experience (Bodde et al., 2009). Dissociation has been proposed to be a common underlying mechanism for PNES (Baslet, 2011) on the basis of evidence suggesting that many patients with PNES have reported dissociative symptoms (Brown and Reuber, 2016a). It has been found to be higher in those who have experienced post-traumatic stress disorder (Lanius et al., 2002) and in people with PNES who have suffered trauma, particularly sexual abuse (Bowman and Markand, 1996). However, a recent review of dissociation studies found that the degree of dissociation in PNES is broadly comparable to that found in some other psychiatric disorders, especially depression and that levels are generally lower than those required to diagnose a possible dissociative-disorder (Brown and Reuber, 2016a). On the other hand, the largest of such studies found no significant differences in dissociation scores between PNES and epilepsy patients (Alper et al., 1997).
1.28 PNES and emotional processing

People with PNES may have deficits in emotional processing. One study found that compared with healthy controls, people with PNES describe their emotions as more damaging and overwhelming and have a tendency to control anxious and unhappy reactions, but not anger, to situations (Urbanek et al., 2014). Another recent study reported significantly high emotion processing deficits in comparison with patients with healthy controls (Novakova et al., 2015).

We and others have reported high rates of alexithymia, a personality trait characterised by deficits in emotional recognition and processing, in people with PNES (Baslet, 2011; Dineen et al., 2001). Rates of alexithymia in PNES have generally varied from approximately 33% to as high as 90.5% (Brown and Reuber, 2016a), with rates in the 30-40% range found to be comparable with those with epilepsy and other medical conditions (Taylor et al., 1997). The reason for these discrepancies in rate are unknown but thought to reflect the heterogeneous presentation of PNES and sample differences (Brown and Reuber, 2016a). Other research has indicated that alexithymia has been associated with seizure-like event frequency in PNES and that people with PNES have a poorer understanding of their emotions (Urbanek et al., 2014). The meaning of these findings in terms of understanding the mechanism of PNES remains elusive. Nevertheless, there are clear indications of deficits in emotional processing in this group. However, similar to dissociation, the neurobiological underpinnings of this feature remains unknown.

1.29 Neuropsychological aspects of PNES

People with PNES may have differences in neuro-cognitive functioning (Reuber and Major, 2012). Some of the earliest studies compared performance on neuropsychological testing between groups of people with PNES, epilepsy, and mixed PNES and epilepsy. However, results from those studies were inconsistent. For example, people with PNES were reported to perform better (Cragar et al., 2002), worse, or no different (Black et al., 2010; Turner et al.,
2010; Turner et al., 2011) on a range of tests compared to people with epilepsy. Those studies that found abnormal results in PNES reported deficits in executive functioning, working memory and attention, in particular (Strutt et al., 2011). Inhibitory processing has not been shown to be abnormal in PNES, even after stress induction (Bakvis et al., 2009b; Almis et al., 2013). The findings of subsequent studies have suggested that neuropsychological deficits reported previously in PNES research were indicative of factors such as emotional disturbance, personality disturbance, and suboptimal motivation (Binder and Salinsky, 2007). Since then, suboptimal effort during neuropsychological testing, in particular, has been highlighted as a frequent finding in people with PNES compared with patients with epilepsy and associated with poor neuropsychological performance (Strutt, 2011). Therefore, it is possible that in those early studies, variable levels of effort between participants contributed to inconsistent neuropsychological findings.

Several studies have evaluated indices of suboptimal performance of patients with PNES on neuropsychological testing. Bakvis and colleagues used the Amsterdam Short-Term Memory Test (ASTMT) to examine effort and compared patients with PNES and a healthy control group on performance of a specific working memory test under baseline and stressful conditions (Bakvis et al., 2010a). Their findings indicated a general deficit of attention in the PNES group. However, although the authors used one index of symptomatology (SCL-90-R) and one neuropsychological test, the intelligence quotients of participants were not controlled for with formal assessment and this potential confounder may have affected results.

Locke and colleagues examined the relationship of composite indicators of neuropathology, psychopathology, and effort to neuropsychological results in patients with epilepsy and PNES and found that patients with PNES had relatively higher cortisol stress responses and impaired cognitive integrative functioning (Locke et al., 2006). They recorded participants' scores on the Test of Memory Malingering (TOMM) but did not directly compare groups on this measure. The sample included patients with neurological abnormality, but patients were not formally psychiatrically assessed, and affective symptoms were not measured. A notable finding was a significant relationship between effort and scores on all cognitive domains apart from executive functioning. In
addition, neuropathology was related to memory functioning performance in both groups. A further study compared neuropsychological functioning of women with PNES with that of people with epilepsy, including scores on the TOMM (Strutt et al., 2011). The authors excluded participants who failed the TOMM from the analysis. They reported no abnormal neuro-cognitive findings in the group with PNES using normative data for the tests and found that the group with PNES generally outperformed the group with epilepsy.

In summary, these findings suggest that people with PNES have abnormalities of neuro-cognitive and emotional processing. However, there is convincing evidence that neuropsychological performance in PNES is affected by variables such as neuropathology, psychopathology, stress, and performance effort. While Strutt and colleagues reported impaired neuropsychological functioning while controlling for effort in women with PNES only, the generalisability of these results is unclear (Strutt et al., 2011). Moreover, the results of prior studies have to be interpreted cautiously because of differences in sampling and methods of psychiatric, psychometric, and neuropsychological test assessments and analyses.

1.30 Face-processing studies of PNES

By time of writing, six neuropsychological studies have examined how patients with PNES respond to emotional faces under various conditions (Roberts et al., 2012; Pick et al., 2016; Schonenberg et al., 2015, Bakvis et al., 2009a, b; Bakvis et al., 2010a; Bakvis et al., 2011), of which just one investigated preconscious responses to positive and negative emotional facial expressions (EFEs) (Bakvis et al., 2009b).

Several studies have investigated explicit (conscious) aspects of face processing in PNES. On the one hand, some have reported evidence of a differential response to EFEs in PNES. For example, Bakvis and colleagues found that the working memory performance of patients with PNES was significantly more vulnerable to face distractors (involving happy, angry and...
neutral faces) than that of healthy controls. Furthermore, they found that this effect was not related to anxiety and depressive symptoms or behavioural task performance (response time), and postulated that their findings indicated that patients with PNES have difficulties inhibiting irrelevant socio-emotional stimuli (Bakvis et al., 2010b). A later study published by this group investigated responses to an approach and avoidance task in patients with PNES and healthy controls, involving their evaluation of emotional valence of angry and happy faces and indicating affect-congruence by making arm movements (Bakvis et al., 2011). They found that patients with PNES demonstrated a relatively slower approach to angry faces, which was associated with basal pre-task serum cortisol levels, indicating a relatively increased avoidance tendency in PNES. Moreover, one study compared the explicit emotional responses to affective pictures of a group of eighteen patients with PNES, with those of seizure-free control groups that were scored as either high or low for the presence of post-traumatic stress symptoms (PTS) (Roberts et al., 2012). The authors found that patients with PNES reported more emotional intensity to neutral pictures than the low or high-PTS groups, more emotional intensity to pleasant pictures in the low-PTS group, and less positive emotional behaviour to pleasant pictures than the high-PTS group. In addition, those with PNES reported greater emotional dysregulation and demonstrated a relatively reduced respiratory sinus arrhythmia than the low-PTS but not the high-PTS group (Roberts et al., 2012).

These studies provided preliminary evidence of altered face-processing in PNES that may be associated with abnormal stress regulation and affect emotional-cognitive functioning. On the other hand, a recent study by Pick and colleagues reported that patients with PNES were less accurate at explicitly identifying faces, irrespective of the relevant emotional expression (involving fear, sadness, disgust, happiness, anger and neutral expressions) compared with healthy controls, although both groups had comparable accuracy on judging emotional intensities (Pick et al., 2016). This result appears to suggest a basic disturbance of explicit face processing in PNES.

Finally, Schoenberg and colleagues investigated both subjective experience of emotion and detection of emotional expression in patients with PNES and healthy controls, using a computerised movie showing EFEs that slowly
morphed from neutral expression to one of six emotions (fear, disgust, sadness, surprise anger, happiness) (Schonenberg et al., 2016). They found no differences in recognition of emotions or in task error-rates. However, although their findings would appear to be inconsistent with the other studies reporting disturbed explicit face processing in PNES, their objective and corresponding methodology was quite different to those earlier studies. For example, studies have shown of a differential brain response to facial stimuli presented over a shorter versus a longer period of time (Trautmann-Lengsfeld et al., 2013), and in the latter study, they compared group responses to faces slowly changing from a neutral to an emotional expression in each case, which took place over a considerably longer period of time (500ms) in comparison to the earlier studies (approximately 100ms). Also, results were not controlled for anxiety or depression scores. These differences in methodology likely accounted for differences in findings between-studies, at least partially. Nevertheless, their findings helped to extend knowledge of how patients with PNES respond to social cues involving faces, by providing preliminary evidence that they detect subtle changes in changing emotional expression within a normal range of ability. Overall, these studies indicate that patients with PNES have differences from healthy controls in explicit processing of human EFEs, that these differences may be associated with stress-regulation and cognitive disturbances, but that their perception of emotional-intensity and subtleties in changes of expressions may be relatively intact if the face is being viewed over a slightly longer period of time.

Just one neuropsychological study has examined implicit (unconscious) face processing in PNES. The authors employed a masked pictorial emotional Stroop task to examine preconscious attentional processing of neutral, happy and angry faces, and a computerised Stroop colour-word task to compare attentional processing of neutral stimuli, and compared responses between nineteen patients with PNES and twenty matched healthy-controls, both at baseline and under stressful conditions (Bakvis et al., 2009b). They reported evidence for alterations in preconscious allocation of attention towards angry (but not neutral or happy faces) at baseline, but not under stress, for the group with PNES only, and that selective attention for neutral stimuli was unaffected in
patients with PNES. Further, patients, but not controls, performed less accurately in both tasks at baseline versus under-stress. The authors interpreted these findings as evidence that patients with PNES allocated relatively greater attention preconsciously to social threat stimuli.

1.31 Neuroimaging studies of PNES

PNES is considered a motor conversion disorder in which psychogenic events occur intermittently, yet the condition can follow a chronic course (Reuber, 2009). To date, there have been a number of fMRI studies of PNES that have found abnormal brain activation patterns indicative of disturbed connectivity between neural networks involved in emotion, executive control and movement (Van der Kruijs et al., 2011; Ding et al., 2013; Ding et al., 2014; Van der Kruijs et al., 2014; Li et al., 2015a; Li et al., 2015b). However, no fMRI study has examined neural correlates of emotional (face) processing in PNES.

There has been just four published structural neuroimaging studies to-date that have investigated brain structure in PNES specifically. Labate et al. compared structural integrity of brain between twenty people with PNES and forty age- and gender-matched controls utilising voxel-based morphometry (VBM) and cortical thickness analysis of whole brain and reported abnormal cortical atrophy of motor and pre-motor regions in the right hemisphere and bilateral cerebellum (Labate et al., 2012). Hernando et al. used DTI to specifically investigate the uncinate fasciculus (UF), in eight people with PNES and age- and gender-matched controls, and reported relatively leftward asymmetry of this tract (Hernando et al., 2015). In contrast, the same investigative group examined whole brain white matter integrity using tract-based spatial statistics (TBSS), in sixteen people with PNES and age- and gender-matched controls, and reported significantly higher fractional anisotropy (FA) values in left hemisphere regions of UF, superior temporal gyrus (STG), corona radiata (CR), internal capsule (IC) and external capsule (EC) (Lee et al., 2015). Finally, Ding et al. utilised both fMRI and diffusion tensor imaging (DTI) of brain to construct
functional connectivity networks in seventeen people with PNES and twenty controls and reported altered topological organisation in PNES, suggesting abnormal coalescence (Ding et al., 2013) (Figure 1.6).

**1.32 Management of PNES**

The general approach to management of conversion disorders, in relation to involvement of the multidisciplinary team and presentation of the diagnosis of psychogenic-non-epileptic seizures, should be followed as outlined earlier in this chapter. Specific treatments that have been evaluated with respect to psychogenic non-epileptic seizures are now outlined.

---

Figure 1.6 Summary of volumetric and resting-state connectivity (FC) findings of neuroimaging studies in psychogenic non-epileptic seizures compared with healthy controls.

The left panel shows peak coordinates of cortical thickness and voxel-based morphometry studies (Labate et al., 2012; Ristic et al., 2015), while the right panel displays peak coordinates of abnormal resting-state FC (Van der Kruijs et al., 2012; Ding et al., 2014; Li et al., 2015a; Li et al., 2015b). Blue circles indicate decrease, and red circles indicate increase in the respective measures. Cerebellar and basal ganglia foci and seed region coordinates are not shown here (Perez and LaFrance, 2016).
The vast majority of the scientific literature on PNES relates to research on semiology, psychiatric co-morbidity and neuropsychological assessment and with a more recent focus on examining the neurobiological underpinnings of this disorder. These studies have been aimed principally at forming a scientific understanding of the characteristics of the disorder in order to aid as early a diagnosis as possible. However, although there is a widely recognised need to develop relevant treatments for PNES, comparatively less research has focused on this area (Smith, 2014).

Several open label studies examining the effect of medication in reducing PNES event frequency have been carried out (particularly involving different types of antidepressants and benzodiazepines, including sertraline, venlafaxine and diazepam) (LaFrance et al., 2010). However, these trials were small and there is currently an insufficient evidence-base to recommend any medication to treat PNES (Smith, 2014).

Psychotherapy is considered to be the most appropriate approach to treating PNES (Mayor et al., 2011). The most studied psychotherapeutic intervention has been CBT, and some studies, including a RCT, have demonstrated promising results of its effect on reducing PNES events and improving quality of life (Rusch et al., 2001; Goldstein et al., 2004; LaFrance et al., 2009; Goldstein et al., 2010; LaFrance et al., 2014). It is noteworthy that despite models of treatment differing between CBT trials, positive results were reported for the CBT approach.

Nevertheless, long term follow-up data sufficient to confirm effectiveness of these approaches is not available as yet. Similarly, several studies examining the effectiveness of psychodynamic therapy have reported positive results, including one study which provided positive long-term outcome data (Barry et al., 2008; Mayor et al., 2010). However, despite preliminary data suggesting effectiveness of these psychological therapies, recommendations about treatment preferences are limited due to lack of adequately powered RCTs (Smith, 2014).
1.33 The socio-economic burden of PNES

Healthcare costs associated with PNES are high. People with PNES who have not been appropriately diagnosed, frequently present at healthcare facilities for assessment and treatment of their condition, including that of acute events. Patients with PNES are more likely than those with epilepsy to develop seizures, leading to relatively greater emergency presentations to hospital (Reuber et al., 2005a). In addition, frequent admissions to hospital are common as are moves between specialists and different types of care provider (Ahmedani et al., 2013). There are associated costs of these presentations, as well as unnecessary and often invasive, expensive medical procedures. Studies carried out in the United States indicate that the financial cost of misdiagnosis runs to hundreds of thousands of dollars, once indirect costs of loss of employment and other productivity for patients and carers are taken into consideration (Martin et al., 2003; Reuber and Elger, 2003b).

1.34 Outcome studies of PNES

Treatment delay is associated with poor psychosocial outcomes and poor overall quality of life for those with PNES. During the time that patients are treated by doctors and society as if they have intractable epilepsy, they are conventionally unable to drive and are often very restricted in terms of employment options, general productivity and social independence. They are also more likely to be dependent on carers and social and disability benefits (Reuber et al., 2002; Reuber et al., 2005a). However, many studies have highlighted findings that once an appropriate diagnosis is made, the frequency of PNES events for a significant proportion of patients reduces and may cease, although reported rates for each are variable (Ahmedani et al., 2013). For example, retrospective studies have reported that the rate of cessation of PNES after communication of diagnosis, and without further intervention, ranges from 16-38% of patients (LaFrance et al., 2013a; O’Sullivan et al., 2007; McKenzie et al., 2010). Evidence appears to suggest that most people who become PNES
event-free after communication of diagnosis only, do so almost immediately after an appropriate explanation of the condition (McKenzie et al., 2010).

In financial terms the cost of undiagnosed PNES to healthcare systems may equate to the costs of managing treatment-resistant epilepsy over a lifetime (Gene-Cos and Ring, 2005), and a 1998 study estimated this cost to the United States to be up to $920 million per year (Martin et al., 1998). In addition, there are significant socio-economic costs to the patient with PNES, their families and society at large, as a result of the associated loss of productivity, employment income, and dependence on available financial and social supports (Reuber, 2008; Dickinson and Looper, 2012).

However, once patients have a PNES diagnosis, there tends to be a drastic reduction in their utilisation of all types of healthcare facilities (Razvi et al., 2012; LaFrance et al., 2013a). For example, one small study reported a reduction of over 50% in health-care costs associated with attendance, admission, investigations and treatment of patients with PNES once diagnosis was made (Jirsch et al., 2011). Another more recent study demonstrated very significant reductions in costs associated primarily with reduction in neurology care and inpatient stays, that remained even after psychiatric care costs, subsequent to PNES diagnosis, were taken into account (Ahmedani et al., 2013).

On the other hand, there may be inadvertent adverse consequences to diagnosis and explanation of PNES to the patient. Some studies have reported worsening of other mental health conditions and persistence or increase in seizure frequency. The reasons for these findings are unknown but some authors have suggested that engagement of patients in follow-up treatment may be compromised if the patient feels angry or unclear after the pro-offered explanation of their condition (Thompson et al., 2009; LaFrance et al., 2013a). This finding has highlighted the importance of specialists adopting a positive strategy in how they communicate the diagnosis of PNES to patient and caregivers, so that this process represents a crucial and effective first step in the therapeutic management of people newly diagnosed with PNES (LaFrance et al., 2013a).
Factors affecting persistence of PNES have been reported to include a history of abuse and the presence of co-morbid depressive illness and/or personality disorder (Kanner et al., 1999). Other negative prognostic factors include poor coping and communication skills, no identifiable or acute psychological trauma preceding PNES onset, high dependance on socio-economic supports, positive or dramatic motor features and concomitant epilepsy (Bodde et al., 2009). It has been considered that in general, the underlying psychological disorder and, in particular, negative personality factors may represent one of the most significant associations with outcome (Reuber and Elger, 2003b; Reuber et al., 2003c; Bodde et al., 2009).

On the other hand positive prognostic factors for cessation of PNES events include relatively recent onset and early diagnosis of PNES, being female, higher intelligence (IQ) and education level, higher social status, continued-employment status and positive social network. Other factors associated with more positive outcome include a lack of dependence on disability and other relevant welfare-assistance, an absence of a history of abuse and no clinical features of co-morbid depressive illness, anxiety disorder and personality disorder (particularly that of borderline type) (Bodde et al., 2009; LaFrance et al., 2013a). In addition, scores on the higher order personality dimension of “inhibitedness” has been reported to be an important outcome predictor, representing the individual’s degree of self-disclosure and restricted affective expression of positive emotions. Low scores on inhibitedness has been found to indicate a better prognosis and vice versa (Bodde et al., 2009).

It has been reported that PNES often recur once the patient returns to their usual environment after diagnosis, especially if stressors identified as potential contributors to their PNES remain relevant; this tends to particularly occur for symbolic or post-traumatic related PNES (Reuber et al., 2003b).

Long-term follow-up studies of PNES tend to report quite pessimistic outcomes in terms of personal burden and seizure outcome. For example, one study reported that more than 70% of patients with PNES continued to experience seizure-like events 4 years after diagnosis was made (Reuber and Elger, 2003b) and this and other studies have reported frequency of seizures
persisting subsequently in 25-40% (Reuber and Elger, 2003b; O'Sullivan et al., 2007; McKenzie et al., 2010). Unemployment and dependence on available social supports remain high. For example, one study reported that unemployment levels in PNES (47%) were double that of patients with epilepsy and that over 25% were living in someone else’s home (O’Sullivan et al., 2007). Another found that although some people with PNES (whose seizures ceased) returned to work, they continued to receive social welfare support (McKenzie et al., 2010). On the other hand, resolution of PNES has been associated with employment and good health (Ettinger et al., 1999).

1.35 Summary

Functional neurological disorders involving involuntary impairment of sensory or motor function are classified psychiatrically as dissociative (conversion) disorders (CDs). CDs can be sub-classified based on the type of presenting neurological impairment and in order of most prevalence comprise PNES, psychogenic weakness and paresis, psychogenic motor disorders, psychogenic speech disorders, psychogenic sensory disorders and psychogenic cogniform disorders. CDs are common presentations to medical settings but are challenging and costly to identify, often taking multiple investigations and several years to diagnose. Although there are some validated clinical signs that can help identify CD, none can readily identify all subtypes of CD with confidence.

CDs have high levels of co-morbidity with both neurological disorders and other psychiatric conditions, the latter including other dissociative disorders, affective disorders and personality disorders. In general, management involves positive and effective communication of diagnosis, and the best evidence for treatment involves physiotherapy programmes for motor CD subtype in particular. However, there is little evidence to support pharmacological interventions, psychological interventions and other physical treatments for all CDs at this time.

Epidemiological studies are impeded by issues relating to definition of CD cases and structure of health services. However, in general the long-term outcome for
those with CD is poor and represents a high socio-economic burden, with the presence of factors such as multiple symptoms and chronicity of symptoms representing poor prognostic indicators.

There have been relatively few neuropsychological studies of CD, in comparison with other psychiatric disorders, but studies from the last 10 years in particular suggest that in CD there are deficits in executive functioning and memory, driven mainly by differences in IQ and affective symptoms. Neurophysiological studies have reported relatively high baseline arousal levels and people with CD have also been reported to have reduced awareness of heart beat and abnormal sensory attenuation. Furthermore, there is neurophysiological evidence that affected patients may focus and shift attention onto their symptoms and may employ a mode of processing that impairs movement control. Moreover, the results of some studies have suggested that people with CD may have disordered perception of whether a movement is voluntary or not, associated with deregulation of inhibitory force feedback.

Few structural neuroimaging studies of CD have been published to-date, and have studied CD of motor subtype in particular. Findings have implicated thalamic and pituitary volume abnormalities. In contrast, functional neuroimaging studies of conversion disorder have found evidence of abnormal activation of brain regions involving the limbic system and sensori-motor cortices (Mehta et al., 2013). However, neuroimaging findings in conversion disorder have been generally inconsistent. The reasons for these disparate findings is unknown but likely to be contributed to by methodological factors such as small and heterogeneous study samples involving different types of conversion motor symptoms or involving contrived models of conversion disorder (Browning et al., 2011). Nevertheless, these neuroimaging findings have led to hypotheses that in conversion disorder, fronto-limbic regions impair or inhibit motor areas and that modulation of motor networks occurs by emotional or attentional processes.

PNES are the most common functional symptoms presenting to neurology centres and this condition is associated with high socio-economical burden for affected patients, their caregivers and society in general. Healthcare utilisation
costs are high and patients are exposed to inappropriate interventions and treatments before definitive diagnosis is made. Treatments are limited and insufficiently validated and long-term outcomes are currently poor in terms of remission of PNES, general health status, productivity and quality of life.

Researchers of PNES have long-recognised that diagnosing PNES as early as possible after manifestation is a crucial step in trying to establish a pathway to better outcomes, and this approach is backed up by the findings of remission of PNES in a proportion of people after explanation of diagnosis. However, invariably there are barriers to accessing vEEG monitoring facilities in most countries including inadequate provision of multidisciplinary neurology teams and specialist epilepsy monitoring units to meet population needs, and the fact that vEEG is expensive, time consuming and requires a team with specialist expertise to manage these units. For these reasons, early diagnosis using conventional best practice may not be a realistic goal at present within many healthcare services. The recognition of these challenges has led to a research focus on attempting to diagnose PNES using other methods apart from vEEG monitoring. With increasing recognition that timely diagnosis of this condition can have very significant positive effects on outcome, healthcare and social care utilisation and associated costs, the last decade in particular has been characterised by intensification of research efforts to try to understand the neurobiological underpinnings of PNES, to be better able to diagnose and treat it.

There is growing evidence from psychometric studies to suggest that people with PNES have an abnormally increased biological response to stress, utilise maladaptive coping mechanisms and have deficits in human-face and emotional processing. In addition, neuropsychological studies of PNES have reported deficits in executive functioning, working memory and attention, but these findings have been proposed to reflect factors such as emotional disturbance and suboptimal motivation.

Functional neuroimaging studies of PNES have reported abnormal brain activations indicating dysfunctional connectivity between neural networks known to be involved in regulation of movement, emotions and executive control, while
structural neuroimaging studies have reported evidence of abnormal cortical atrophy of motor and premotor regions and disturbed integrity of white matter tracts linking prefrontal and subcortical pathways. Overall, these studies provide evidence suggesting altered brain structure and function in people with PNES. Specifically, these findings suggest that PNES may develop within a context of alternated brain networks involved in sensorimotor function (e.g., premotor regions & pre-and post-central gyri), emotional regulation (e.g., cingulate cortices, insula, OFC), cognitive control [e.g., prefrontal cortex (PFC), cingulate cortices] and multimodal integrative functioning (e.g., cingulate gyrus, precuneus, posterior parietal cortex). Nevertheless, results have been inconsistent between-studies and interpretation of neuroimaging findings has been challenging. The reasons for these disparate findings are unknown. However, possible influences on results include differences in sample characteristics, given that most previous neuroimaging studies have not assessed both their PNES and control groups to include psychometric, psychiatric and neuropsychological data, so that clinical variables could have affected results. Other possible reasons for these disparate findings include differences in methodology, including disparate analytical techniques and interpretation of data.

Therefore, there is growing evidence from psychometric, neuropsychological and neuroimaging studies of a neurobiological model of conversion disorder. However, neuropsychological research of PNES has generally not assessed, controlled-for or accounted-for variables known to influence performance on neuropsychological tests such as effort and FSIQ, in their study designs. In addition, although a number of studies have employed neuroimaging techniques to investigate PNES specifically, none to-date have utilised combined structural neuroimaging modalities or examined neural correlates of emotional processing. I believed that I could design a project that could help develop understanding of the neurobiological basis of PNES by firstly, examining the prevalence of PNES in our own tertiary care referral centre for epilepsy (Beaumont Hospital, Dublin); secondly, examine neuropsychological functioning in PNES taking account of the limitations of previous research; thirdly, utilise complementary neuroimaging methods to examine brain structure in PNES and, fourthly, examine neural correlates of emotional-processing in
people with PNES. I will outline the aims and hypotheses of this research project and provide details of the methodology used in Chapter 2.
Chapter 2. General Methodology

2.1 General Methodology

The purpose of this chapter is firstly, to describe how the research protocol for this thesis was developed, secondly, to outline the relevant aims and hypotheses tested, and thirdly, to provide details of the methodology applied to each of the five studies of PNES. The following order will apply: the chapter will begin with an outline of the role of the candidate and the respective supervisors in the genesis and conduct of this project. Then, the methodology used for the preliminary study of prevalence and management of PNES in Beaumont Hospital will be described, followed by an outline of the study design in relation to the investigations of the neurobiology of PNES. Background information on the materials will be provided where appropriate (e.g., in relation to the questionnaires, the computerised neuropsychological tests and the neuroimaging techniques).

2.2 Role of the candidate in this project and the development and supervision of this thesis

I, with the support of my principal supervisor Professor Kieran Murphy (Department of Psychiatry, RCSI), prepared and submitted an application for research funding for this project to Molecular Medicine Ireland (MMI) in its inaugural initiative to award clinician-scientist fellowships in Ireland. A national competition was held to receive project submissions, and after selection of appropriate studies, an interview process was held to choose those who would receive MMI fellowships. This project was one of just 12 studies (and one of just two studies involving research in psychiatry) that were awarded funding by the MMI adjudication panel that particular year.
During the development stage of the project, I presented the research protocol to the Trinity Centre for Cognitive Neuroscience (TCIN) academic group, and to peer-group academic meetings of the Department of Psychiatry, Royal College of Surgeons in Ireland (RCSI). The oral feedback from these meetings helped to refine the final research protocol for the project.

I conducted the literature reviews throughout the project that informed the development of the experimental measures, plans of analysis and interpretation of results. I prepared and submitted the documentation for ethical approval from the respective centres, and, after ethical approval was received, I advertised the project to potential participants, sought consent as appropriate and conducted all the assessments and neuroimaging sessions with participants throughout this study. I carried out analysis and interpretation of data, with the assistance of those named as collaborators and supervisors, and wrote up this thesis myself.

Apart from my principal supervisor, I was mentored by a team including Professor Hugh Garavan TCIN, Trinity College Dublin), Professor Norman Delanty (Department of Neurology, Beaumont Hospital) and Dr Gillian Fortune (Department of Psychology, Beaumont Hospital). Additional support was provided by both Dr Brendan Behan and Dr Adam Stone from the TCIN neuroimaging group, and by Dr Erik O’Hanlon in particular, from the Department of Psychiatry, RCSI’s neuroimaging group. Professor Ronan Conroy and Dr Patrick Dicker provided assistance for the statistical design and analysis of the study and checked all associated statistical analyses.

Dr Gillian Fortune supervised and trained me in the use and interpretation of the relevant neuropsychological assessments and ensured that the inter-rater reliability of assessment results was appropriate and of a satisfactory standard.

Professor Kieran Murphy supervised the prevalence study, the neuropsychological profiling study, and was overall supervisor for the project and thesis. Professor Hugh Garavan supervised all the neuroimaging studies.
2.3 Aims and Hypotheses of this thesis

The aims of this research project were:

a) To investigate the prevalence and management of PNES in a tertiary referral hospital for neurology,

b) to examine psychiatric and neuropsychological functioning in a group of adults with PNES compared with a healthy control group,

c) to examine brain structure and functioning (specifically, unconscious emotional processing) of adults with PNES compared with a healthy control group using multimodal neuroimaging.

The thesis project comprised 4 main studies: study 1 would investigate the prevalence and management of PNES in people attending the epilepsy monitoring unit of Beaumont Hospital. This study would be the first to examine the prevalence and management of PNES in a major neurology centre in Ireland. Studies 2, 3 and 4 followed the first study and involved the same sample of patients and healthy controls who all underwent the exact same psychometric and neuropsychological assessment before receiving multimodal neuroimaging assessment. Specifically, study 2 would investigate and compare psychiatric, neuropsychological and neurocognitive functioning in adults with PNES and healthy controls, while studies 3 and 4 would investigate neurobiological correlates of PNES using multimodal neuroimaging assessment. Further, study 3 would examine and compare brain structure in adults with PNES and healthy controls, utilising two complementary neuroimaging modalities; and study 4 would investigate and compare unconscious (implicit) emotional processing in adults with PNES and healthy controls. The following key hypotheses would be tested:

1. Hypothesis 1: People with PNES will represent a significant proportion of those who attend Beaumont Hospital with treatment-resistant epilepsy and there will be challenges in providing follow-up treatment to this group. This hypothesis would be tested by study 1.
2. Hypothesis 2: People with PNES will have significant levels of emotional dysregulation and dissociative conversion symptoms and share co-morbidity with other psychiatric conditions, particularly those which involve affective dysfunction, such as anxiety and depression. This hypothesis would be tested by study 2.

3. Hypothesis 3: People with PNES will be significantly impaired relative to healthy controls on performance of executive functioning tasks, particularly those relating to attention and working memory. This hypothesis would be tested by study 2.

4. Hypothesis 4: People with PNES will show abnormalities of brain structure, particularly affecting regions associated with cortico-subcortical motor loops. This hypothesis would be tested by study 3.

5. Hypothesis 5: People with PNES will have abnormalities in unconscious (implicit) processing of emotion. This hypothesis would be tested by study 4.

2.4 Plan of investigation and study participants

It was envisaged that study 1 would help to determine the prevalence of PNES in a tertiary care neurology population in Beaumont Hospital, a training hospital of the Royal College of Surgeons, at which the candidate was employed at the time. This study would provide an estimate of the numbers of patients that have been diagnosed with PNES in the service over the respective period. It would also involve creating a clinical database of patients diagnosed with PNES which could be updated on an ongoing basis as patients were medically and psychiatrically classified.

After completion of study 1, patients identified from this clinical database of patients with PNES and who met criteria for inclusion in Studies 2, 3 and 4 were
approached to register their interest in participation in the studies pertaining to this thesis.

2.5 Design and Methodology of Study 1: The prevalence of PNES in the epilepsy monitoring unit of an Irish tertiary referral centre for epilepsy

2.5.1 Design and methodology of the study

The EMU keeps a case register of all patients who have been admitted for epilepsy monitoring and records a brief summary of patient’s details, treating consultant, date of admission, duration of admission, whether seizures occurred during admission, the classification of these seizures, diagnosis and follow-up plan.

This study was a retrospective audit of clinical case data. The case register for all those patients who were admitted to BH’s EMU over a retrospective and continuous 3-year period (2003-5) was examined retrospectively. Patients who had seizure-events captured during EMU admission which were classified as psychogenic non-epileptic seizures (PNES) were noted, including those who also had co-morbid epilepsy. The unique medical record identification number for each patient was noted and the charts of all those who had been admitted to the EMU over that time and diagnosed with PNES were retrieved from the hospital’s medical records department. Appropriate data relating to referral, assessment and management of each patient by the neurology, neuropsychiatry and neuropsychology services was gathered, and it was noted if admitted patients completed EMU assessment and recommended follow-up during that admission. The following information was collated in each case: relevant demographic data (age, gender, where they live in the country), clinical data relating to their diagnosis of PNES (when admitted and diagnosed with PNES, whether their PNES were co-morbid or not with epilepsy, mental illness or developmental disability), and data relating to how their care was managed in
the immediate period after they received a diagnosis of PNES, was also gathered.

The data collected was entered into an electronic database set up for this study and analysed using the Statistical Package for the Social Sciences version 17.0 (SPSS-Incorporated, 2007).

There were a number of specific questions to be addressed that would test the hypothesis for study 1:

1. How many patients were admitted to the EMU over the respective period?
2. Of those admitted, how many had seizure-events classified as being PNES?
3. How many patients diagnosed with PNES had co-morbid epilepsy?
4. Were all patients diagnosed with PNES managed in a clear and consistent manner?
5. Did patients who were diagnosed with PNES receive specialised psychiatric and psychological follow-up?
6. Could management and follow-up of patients diagnosed with PNES be improved?

2.6 Methodology relating to the psychiatric and neuropsychological investigations of patients with PNES

The following methodology relates to studies 2, 3 and 4 in this thesis and firstly provides a description of the settings for the studies, the recruitment process, and the psychiatric, psychometric, and neuropsychological assessment of all participants included in these studies. The same pool of participants was used in all three studies.
2.6.1 Design and Methodology of the study

This study was a cross-sectional case-control designed study.

2.6.2 Settings for study

This multi-site study was conducted at the academic centres of RCSI and Trinity College Dublin (TCD) and the clinical centres of BH and Cork University Hospital (CUH). Ethical approval for the studies was provided initially by the Beaumont Hospital medical research ethics committee (Protocol no: 08/47), and then subsequently after review of the same protocol by both the Trinity College Dublin School of Psychology Research Ethics Committee, and University College Cork’s Clinical Research Ethics Committee of the Cork Teaching Hospitals (Relevant ethical approval and associated documents are provided in Appendix A).

2.6.3 Inclusion and exclusion criteria

Inclusion criteria for the PNES group included: (i) that all patients had previously received comprehensive neurological examination comprising physical assessment, structural neuroimaging, and vEEG monitoring. Moreover, all patients met the gold standard for “diagnosis with high confidence” of PNES according to a recent consensus guideline, where the diagnosis is made on the basis of both patient history and a typical seizure-like event is observed, simultaneously co-registered with EEG (LaFrance et al., 2013b); (ii) if they had been diagnosed with psychogenic non-epileptic seizures after capture of a typical seizure-like event on vEEG monitoring; (iii) if they had experienced multiple seizure-like events; (iv) if neurological and structural magnetic
resonance imaging (sMRI) examinations excluded demonstrable neurological abnormality; (v) the patient had not been taking anticonvulsant medication three months prior to participation in the study; (vi) aged between 18 and 60 years.

Exclusion criteria for the PNES group included: (i) patients diagnosed with PNES while under the age of 18 years; (ii) a history of co-morbid neurological or endocrine disorder; (iii) having an intellectual disability; (iv) a history of difficulties in reading or writing; (v) a history of experiencing major psychiatric illness including psychotic disorder or substance abuse.

Healthy controls: inclusion criteria for the control group included: (i) being currently physically and mentally healthy; (ii) Sufficiently familiar with the use of the English language to be able to complete the neuropsychological assessments and facial emotion task.

Exclusion criteria included (i) having a history of neurological disorder, brain injury, or endocrine disorder; (ii) having a history of major psychiatric illness including psychotic disorder, or substance abuse; (iii) having a history of intellectual disability; (iv) having a history of difficulties in reading or writing; (v) being aged between 18 and 60 years.

Healthy control participants were matched for gender and age with the PNES group.

2.6.4 Recruitment: strategy and process

Psychogenic non-epileptic seizures group

Patients who had been diagnosed with PNES without co-morbid epilepsy (through EMU admission and vEEG classification of typical seizure-like events) in the three years before and during the period of this study were identified from relevant EMU clinical case-registers at BH and CUH, and invited by letter to participate in this research project (Figure 2.1). Of forty adults identified from
case registers as having PNES, twenty met the criteria for inclusion in the study and agreed to participate.

Clinical data were gathered from a combination of participants' self-report and hospital and primary physician medical records.

**Healthy-control group**

Healthy-control participants were recruited on-site through poster advertisement and webmail advertisement at BH, TCD and RCSI, and by writing to people who
had previously participated in research projects at the relevant academic centres and whose contact details were available on research registers (Figure 2.2). The finalised healthy control sample comprised 25 adults.

Once a potential participant expressed an interest in being involved in the project, I discussed the project with them over the phone. If the person wished to participate, a pack containing self-report questionnaires was posted to them and a mutually convenient time and the venue were agreed upon to review their responses and carry out the assessment schedule. Then, at this appointment, written informed consent (see Appendix A) from the participant was obtained. All volunteers from both groups were assessed at TCIN.
All potential participants received information leaflets and consent forms before taking part. These documents explained the reasons for the study and why we needed volunteers to participate, what they could expect from involvement and describe what they would expect in the assessment sessions (see Appendix A). Once initial contact was made with patients, they were then contacted by telephone and had the opportunity to ask further questions about the study. All participants provided written informed consent for involvement in the study. Once consent was obtained, participants were invited to undergo the psychiatric and neuropsychological assessment and the neuroimaging at Trinity College Dublin’s Institute for Neuroscience (TCIN).

Patient volunteers were not paid for involvement in the study, but relevant travel expenses for participation were reimbursed. Healthy control volunteers were paid 20 euros for their time involved in completing participation, and associated travel expenses to attend assessments were reimbursed. Healthy-control volunteers were also offered a picture of their brains which would be sourced from their individual scans. Each participant spent a total of between 3 hours and 4 hours participating in the assessment process, which took place at the neuroimaging research centre at TCIN.

2.6.5 Assessment schedule

Firstly, all participants were posted a package containing the self-report questionnaires and a map with detailed directions to the TCIN. They were asked to complete all the self-report questionnaires before attending their appointment for the psychiatric and neuropsychological assessment.

2.6.6 Self-report questionnaires

The following self-report questionnaires were completed by all participants:
2.6.6.1 Beck Depression Inventory, version 2 (BDI-II)
The BDI-II is a 21-item self-report scale. It measures the person's experience of depressive symptoms within the previous two weeks. It has good internal consistency with a co-efficient alpha of 0.91 in an outpatient population, and reliably discriminates patients with clinical depression from patients without clinical depression (Beck et al., 1996). It takes approximately 5 minutes to complete.

2.6.6.2 Beck Anxiety Inventory (BAI)
The BAI is a 21-item self-report scale, and measures the person's experience of anxiety symptoms within the previous month. The instrument has excellent internal consistency with a co-efficient alpha of 0.92, and has high test-retest reliability (r=0.75). It reliably discriminates people with anxiety disorders from people without anxiety disorders (Beck and Steer, 1990). It takes approximately 5 minutes to complete.

2.6.6.3 Dissociative Experiences Scale, version 2 (DES II)
The DES II is a 28-item self-report questionnaire that has been designed to assess current dissociative experiences. Responses are provided through an 11-point multiple-choice format that ranges from 0% to 100%. Internal consistency of the DES has been shown to be quite high and it has demonstrated excellent convergent validity (r=0.96) and high correlation co-efficient scores (0.85 to 0.95) (Ellason et al., 1994). It takes approximately 10 minutes to complete.

2.6.6.4 Toronto Alexithymia Scale, 20 question version (TAS-20)
This instrument assesses deficiency in understanding, processing, or describing emotions. It has demonstrated high inter-rater reliability and validity (Taylor et al., 1985). It takes approximately 5 minutes to complete.
2.6.6.5 The Coping Inventory for Stressful Situations (CISS)

The CISS is a 48-item self-report measure that is used to assess the preferred coping style of the individual and the relationship between their coping style and their personality (Endler and Parker, 1994). It asks respondents to indicate how much they engage in various coping activities during a stressful situation by employing a Likert scale ranging from 1 (not at all) to 5 (very much). The CISS comprises three 16-item scales assessing emotion-oriented coping (emotion scale), task-orientated coping (task scale) and avoidance (avoidance scale). The avoidance scale can also be divided into separate distraction (8 items) and social (5 items) scales. It takes approximately 10 minutes to complete.

2.6.6.6 Life Events Checklist (LEC)

The LEC is a 17-item, self-report measure that screens for potentially traumatic events in a respondent's lifetime. The LEC has demonstrated high convergent validity with measures assessing varying levels of exposure to potentially traumatic events and psychopathology known to relate to traumatic exposure. It has also shown a mean kappa for all items of 0.61 and a retest correlation of $r = .82, p < .001$ (Gray et al., 2004). It takes approximately 5 minutes to complete.

2.6.6.7 Personality Assessment Inventory (PAI)

The PAI is a self-report, objective measure of adult personality that assesses psychopathological syndromes and provides information relevant to clinical diagnosis and screening for psychopathology (Table 2.1) (Morey, 2007). It has independent scales that provide a measurement of symptoms, according to the Diagnostic and Statistical Manual version 4 (DSM-4), treatment considerations, the respondent's interpersonal style and test-response behaviours. It is completed by the participant and has 344 items that are answered using a 4-point Likert scale. The PAI has a low reading level (grade 4) and no item overlap across scales for improving discriminant validity. It has 22 full scales that are comprised of 4 validity scales, 11 clinical scales, 5 treatment considerations scales and 2 interpersonal scales.
The 4 validity scales (inconsistency, infrequency, negative impression management, and positive impression management) that measure the respondent's approach to the test, including screening for exaggerated or false responses and defensiveness, clinical scales corresponding to psychiatric diagnostic categories, treatment factor scales and dimensional assessment of personality functioning. Inconsistency (INC) measures respondent consistency of responses, with high scores suggesting inattentive or inconsistent responding. Infrequency (INF) measures random responding and indifference on the part of the participant, with increasing scores indicating more atypical responses until high scores indicate invalid reporting. Negative impression management (NIM) measures the degree to which the respondent appears to be creating a negative impression of themselves (“fake bad”), with increasing scores indicating exaggeration and high scores indicating malingering to a cut-off point of invalidity. Positive impression management (PIM) measures the respondents tendency to create a positive impression of themselves (“fake good”), with increasing scores indicating the person is portraying themselves as being relatively free from common faults to a cut-off-point for invalidity.

There are 11 clinical scales, 9 of which have sub-scales (see Table 2.1, below), and these are: Somatic Complaints (SOM), Anxiety (ANX), Anxiety-Related Disorders (ARD), Depression (DEP), Mania (MAN), Paranoia (PAR), Schizophrenia (SCZ), Borderline Features (BOR), Antisocial Features (ANT), Alcohol Problems (ALC) and Drug Problems (DRG). The five treatment consideration scales are: Aggression (AGG), Suicidal Ideation (SUI), Stress (STR), Nonsupport (NON), and Treatment Rejection (RXR). The two interpersonal scales are: Dominance (DOM) and Warmth (WRM).

The PAI also has 31 sub-scales under 10 of the full scale categories. The sub-scales comprise somatic complaints (conversion, somatisation, and health concerns), anxiety (cognitive, affective and physiological), anxiety-related disorders (obsessive-compulsive, phobias, and traumatic stress), depression (cognitive, affective, and physiological), mania (activity level, grandiosity, and irritability), paranoia (hyper-vigilance, persecution, and resentment), schizophrenia (psychotic experiences, social detachment, and thought disorder), borderline features (affective instability, identity problems, negative relationships, and self-harm), antisocial features (antisocial behaviours,
### Table 2.1 Personality Assessment Inventory scales and sub-scales

<table>
<thead>
<tr>
<th>Scale/Subscale</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somatic Complaints (SOM)</td>
<td>Measures concerns with health matters and somatic complaints that may be associated with somatization and conversion disorders.</td>
</tr>
<tr>
<td>Conversion (SOM-C)</td>
<td>Focuses on symptoms associated with conversion disorder such as sensory or motor dysfunctions.</td>
</tr>
<tr>
<td>Somatization (SOM-S)</td>
<td>Focuses on physical symptoms and complaints of ill health and fatigue.</td>
</tr>
<tr>
<td>Health Concerns (SOM-H)</td>
<td>Focuses on a preoccupation with health status and physical problems.</td>
</tr>
<tr>
<td>Anxiety (ANX)</td>
<td>Measures concerns with phenomenology and observable signs of anxiety.</td>
</tr>
<tr>
<td>Cognitive (ANX-C)</td>
<td>Focuses on ruminate worry and concern about issues that result in impaired concentration and attention.</td>
</tr>
<tr>
<td>Affective (ANX-A)</td>
<td>Focuses on the experience of tension, difficulty in relaxing, and the presence of fatigue as a result of high-perceived stress.</td>
</tr>
<tr>
<td>Physiological (ANX-P)</td>
<td>Focuses on overt physical signs of tension and stress (e.g., sweaty palms, shortness of breath).</td>
</tr>
<tr>
<td>Anxiety-Related Disorders (ARD)</td>
<td>Measures symptoms and behaviors related to specific anxiety disorders such as phobias, traumatic stress, and obsessive-compulsive symptoms.</td>
</tr>
<tr>
<td>Obsessive-Compulsive (ARD-O)</td>
<td>Focuses on intrusive thoughts or behaviors, rigidity, indecision, perfectionism, and affective constriction.</td>
</tr>
<tr>
<td>Phobia (ARD-P)</td>
<td>Focuses on common phobic fears such as social situations, public transportation, heights, or other specific objects.</td>
</tr>
<tr>
<td>Traumatic Stress (ARD-T)</td>
<td>Focuses on the experience of traumatic events that cause continuing distress and that are experienced as having left the adolescent changed or damaged in some way.</td>
</tr>
<tr>
<td>Depression (DEF)</td>
<td>Measures symptoms and phenomenology of depressive disorders.</td>
</tr>
<tr>
<td>Cognitive (DEF-C)</td>
<td>Focuses on thoughts of worthlessness, hopelessness, and personal failure, as well as indecisiveness and difficulties in concentration.</td>
</tr>
<tr>
<td>Affective (DEF-A)</td>
<td>Focuses on feelings of sadness, loss of interest in normal activities, and anhedonia.</td>
</tr>
<tr>
<td>Physiological (DEF-P)</td>
<td>Focuses on levels of physical functioning, activity, and energy, including disturbance(s) in sleep pattern and changes in appetite and/or weight loss.</td>
</tr>
<tr>
<td>Mania (MAN)</td>
<td>Measures affective, cognitive, and behavioral symptoms of mania and hypomania.</td>
</tr>
<tr>
<td>Activity Level (MAN-A)</td>
<td>Focuses on overinvolvement in a variety of activities in a somewhat disorganized manner and the experience of accelerated thought processes and behavior.</td>
</tr>
<tr>
<td>Grandiosity (MAN-G)</td>
<td>Focuses on inflated self-esteem, expansiveness, and the belief that one has special and unique skills or talents.</td>
</tr>
<tr>
<td>Irritability (MAN-I)</td>
<td>Focuses on the presence of strained relationships due to frustration with the inability or unwillingness of others to keep up with his or her plans, demands, and possibly unrealistic ideas.</td>
</tr>
<tr>
<td>Paranoia (PAR)</td>
<td>Measures symptoms of paranoid disorders and more enduring characteristics of paranoid personality.</td>
</tr>
<tr>
<td>Hypervigilance (PAR-H)</td>
<td>Focuses on suspiciousness and the tendency to monitor the environment for real or imagined slights by others.</td>
</tr>
<tr>
<td>Persecution (PAR-P)</td>
<td>Focuses on the beliefs that one has been treated inequitably and that there is a concerted effort among others to undermine one’s interests.</td>
</tr>
<tr>
<td>Resentment (PAR-R)</td>
<td>Focuses on bitterness and cynicism in interpersonal relationships, and a tendency to hold grudges and externalize blame for any misfortunes.</td>
</tr>
<tr>
<td>Schizophrenia (SCH)</td>
<td>Measures symptoms relevant to the broad spectrum of schizophrenic disorders.</td>
</tr>
<tr>
<td>Psychotic Experiences (SCH-P)</td>
<td>Focuses on the experiences of unusual perceptions and sensations, magical thinking, and/or other unusual ideas that may involve delusional beliefs.</td>
</tr>
<tr>
<td>Social Detachment (SCH-S)</td>
<td>Measures the extent to which a person is interested in supportive and empathic personal relationships. A bipolar dimension, with a dominant style at the high end and a submissive style at the low end.</td>
</tr>
<tr>
<td>Thought Disorder (SCH-T)</td>
<td>Focuses on confusion, concentration problems, and disorganization of thought processes.</td>
</tr>
<tr>
<td>Borderline Features (BOR)</td>
<td>Measures attributes indicative of a borderline level of personality functioning, including unstable and fluctuating interpersonal relations, impulsivity, affective lability and instability, and uncontrolled anger.</td>
</tr>
<tr>
<td>Affective Instability (BOR-A)</td>
<td>Focuses on emotional responsiveness, rapid mood changes, and poor emotional control.</td>
</tr>
<tr>
<td>Identity Problems (BOR-I)</td>
<td>Focuses on uncertainty about major life issues, feelings of emptiness and unfulfillment, and an absence of purpose.</td>
</tr>
<tr>
<td>Negative Relationships (BOR-N)</td>
<td>Focuses on history of ambivalent, intense relationships in which one has felt exploited and betrayed.</td>
</tr>
<tr>
<td>Self-Harm (BOR-S)</td>
<td>Measures the extent to which a person is controlling and independent in personal relationships. A bipolar dimension, with a dominant style at the high end and a submissive style at the low end.</td>
</tr>
<tr>
<td>Antisocial Features (ANT)</td>
<td>Focuses on lack of empathy or remorse and a generally exploitative approach to interpersonal relationships.</td>
</tr>
<tr>
<td>Antisocial Behaviors (ANT-A)</td>
<td>Focuses on history of antisocial acts and involvement in illegal activities.</td>
</tr>
<tr>
<td>Egocentricity (ANT-E)</td>
<td>Measures the extent to which a person is controlling and independent in personal relationships. A bipolar dimension, with a warm outgoing style at the high end and a cold, rejecting style at the low end.</td>
</tr>
<tr>
<td>Stimulus-Seeking (ANT-I)</td>
<td>Measures the extent to which a person is interested in supportive and empathic personal relationships. A bipolar dimension, with a warm outgoing style at the high end and a cold, rejecting style at the low end.</td>
</tr>
</tbody>
</table>
egocentricity, and stimulus seeking), and aggression (aggressive attitude, verbal aggression, and physical aggression).

Also, the PAI contains two primary measures that can be used in the assessment of suicidal risk, comprising the SUI scale, and the Suicide Potential Index (SPI). The SUI scale items are directly related to suicidal thoughts and behaviours, whereas the SUI functions as a measure of suicidal ideation rather than as a predictor index of suicide. The SUI scale helps to alert the clinician that the respondent should receive further evaluation and appropriate intervention as required, relating to their risk of suicide. On the other hand, the SPI scale comprises 20 features of the PAI profile that are considered essential risk-factors for completed suicide. These include such factors as severe psychic anxiety, poor impulse control, hopelessness, and worthlessness. The SPI is scored by counting the number of positive endorsements relating to these indices.

The PAI was developed with a construct-validation framework, under the rational quantitative model, in preference to using empirical or factor-analytic models, as this model often has reliability and validity scores that exceed those of scales developed by the latter methods.

A particular emphasis was placed on scale homogeneity, the use of multiple discriminative criteria in item selection, scale stability and external correlates. PAI profiles can be compared with both healthy and clinical populations, based on data from a United States of America census-matched normative sample of 1,000 community-dwelling adults matched by race, gender and age, a sample of 1,265 patients from 69 clinical centres and a college sample of 1,051 students. It has demonstrated excellent internal consistency (median alpha and test-retest correlations exceed .80 for the 22 scales), high convergent and discriminator validity, and correlates well with similar measures of personality and psychopathology (Morey, 2007). It takes approximately 50 minutes to complete.
2.6.6.8 General Health Questionnaire (GHQ)
The GHQ is a 28-item instrument that measures global functioning and was
developed to detect those likely to have, or be at risk of, developing psychiatric
disorders. It screens for problems such as depression, anxiety, somatic
symptoms, and social withdrawal. It has demonstrated high reliability
(coefficients of 0.78 to 0.95) in various studies (Goldberg and Hillier, 1979). It
takes approximately 10 minutes to complete.

2.6.6.9 Edinburgh Handedness Inventory (EHI)
The EHI is a validated measurement scale used to assess the dominance of a
person's right or left hand in their everyday activities and can be completed as
self-report or by observer assessment (Oldfield, 1971). It takes less than 2
minutes to complete.

2.6.7 Meeting with participant to review questionnaires
and carry out psychiatric and neuropsychological
assessment
All interviews for the psychiatric and neuropsychological assessments took
place at the TCIN research centre. Participants were welcomed and orientated
to the TCIN, before being brought to an examination room to continue their
evaluation.
All parents participating in the study underwent the study assessments in the
same order.

2.6.8 General review of self-report questionnaires
The candidate firstly reviewed the self-report questionnaires brought by the
participant. If the volunteer asked for clarification about items on the
questionnaires, these were addressed, and all questionnaires were completed by the participant, before proceeding. This procedure usually took less than 10 minutes.

2.6.9 Semi-structured psychiatric assessment

The candidate carried out a semi-structured psychiatric assessment with all participants (both PNES and healthy controls). This involved administration of the structured clinical interviews for DSM-4 for axis 1 and axis 2 disorders. All six sections of the SCID-I and all ten of the 10 DSM-4 personality disorders of the SCID-II were used to screen for psychopathology. The assessment also involved the gathering of information on participants’ medical and psychiatric histories, and of basic demographic information including age, gender, race, and the number of years spent in education.

The Structured Clinical Interviews for DSM 4 Disorders (SCID) (Ekselius et al., 1994; Steinberg et al., 1994; Pincus et al., 1996) are semi-structured and well-validated research interviews that are frequently used in psychiatric research with adult patients to assess for clinical diagnoses.

The SCID evaluation is primarily based on diagnostic criteria laid out in the Diagnostic and Statistical Manual 4th version (DSM-4) (American Psychiatric Association, 1994).

The SCID allows the interviewer to make DSM-4 axis-I psychiatric diagnoses (SCID-I) and DSM-4 Axis-II personality disorder diagnoses (SCID-II). The format involves taking an initial, brief overview detailing demographic information and education and work history. It then guides screening for periods of psychopathology and psychopathology during the past month and assesses current social functioning. Specific questions are asked of participants during this screening interview relating to psychiatric disorders, including mood disorders, anxiety disorders (panic disorder, agoraphobia without panic disorder, social phobia, specific phobia, obsessive-compulsive disorder, generalised anxiety disorder), post-traumatic stress disorder,
substance abuse (alcohol and drug use), and eating disorders. Screening for past and present suicidal behaviours is also carried out.

Symptoms in the screening interview are rated as either ‘not present’ or ‘present’, depending on their current and past severity. If symptoms are assessed as present, any of the specified modules relating to the reported symptom could be administered.

Additional clinical data in those with PNES, such as age at onset, age at diagnosis, frequency of seizures, prescribed psychotropic medication, and whether previously treated with cognitive behavioural therapy, were also gathered and cross-checked with data from patient’s medical records.

The SCID-II interview includes both interview and self-report data. It is a reliable instrument and has high internal consistency (Maffei et al., 1997) and inter-rater reliability (Maffei et al., 1997; Brooks et al., 1991).

The interviews can take up to 120 minutes to administer, where psychopathology is identified and assessed.

### 2.6.10 Neuropsychological assessment

Participants underwent the neuropsychological evaluations in the following order:

All participants completed the Wechsler Test of Adult Reading (WTAR) (to estimate an individual’s level of intellectual functioning before the onset of illness (Wechsler, 2001), followed by the Wechsler Abbreviated Scale of Intelligence (WASI) to ascertain a full-scale intelligence quotient (FSIQ) (Axelrod, 2002). There was then usually a 10-20 minute break before administration of the computerised Medical Symptom Validity Test (MSVT) to examine effort applied to assessment tasks (Green, 2004), followed immediately by administration of the Cambridge Automated CANTAB neuropsychological test battery. The WTAR, WASI, and MSVT assessments always occurred on the same day and immediately before the participant
underwent the CANTAB neuropsychological battery. Each participant spent approximately 4 hours participating in the evaluation process. The candidate (FOB) carried out all assessments. The researcher was trained by a senior clinical neuropsychologist (GF) in WTAR and WASI test administration and interpretation, and inter-rater reliability scores between both assessors on scoring the instruments were over 0.9.

2.6.10.1 Wechsler Test of Adult Reading (WTAR)

This assessment tool for older adolescents and adults is an effective method for predicting a person's pre-morbid or pre-injury level of intellectual functioning for individuals ages 16 to 89 years. This reading test is composed of a list of 50 words that have atypical translations from word-appearance to sound. The intent in using words with irregular pronunciations is to minimise the current ability of the client to apply standard pronunciation rules and assess previous learning of the word. The rationale for its capacity to measure pre-morbid intellectual functioning is that, in contrast with many mental and memory abilities, reading recognition is relatively stable in the presence of cognitive declines associated with healthy ageing or brain injury. The purpose of the WTAR is to allow an initial estimation of pre-morbid intellectual and memory abilities (assuming a normal development of reading skills before injury or cognitive decline), and not that it can be used to assess and diagnose developmental reading disorders. Administration of the WTAR takes less than 10 minutes and involves asking the client to read out loud 50 words. Pronunciations are provided on the record form for scoring accuracy; the total score is the number of words read correctly.

The WTAR can be interpreted using a large national norming sample carefully matched to the U.S. and U.K populations. Also, it provides demographic data to predict premorbid IQ in neuropsychological cases accurately, and, extensive clinical validity with group studies including Alzheimer's disease, Huntington's disease, Parkinson's disease, Korsakoff's syndrome and traumatic brain injury (Strauss and Spreen, 2006). WTAR performance also appears to remain stable in patients exerting suboptimal effort (Whitney et al., 2010).
2.6.10.2 Wechsler’s Abbreviated Scale of Intelligence (WASI)

Wechsler’s Abbreviated Scale of Intelligence (WASI) (Axelrod, 2002) is a measure of overall intellectual functioning and provides accurate estimates of Verbal, Performance and Full-Scale IQ (VIQ, PIQ and FSIQ, respectively). VIQ and PIQ scores are scored from parallel forms of Wechsler Adult Intelligence Scale (WAIS-III) sub-tests. VIQ is assessed using scores from the Similarities and Vocabulary sub-tests, and PIQ is derived from the Block Design and Matrix Reasoning subtests (Table 2.2). T-scores are derived from the raw score from each sub-test, and these are added to form VIQ and PIQ index scores. The FSIQ score is computed from the VIQ and PIQ scores. The WASI has a much shorter administration-time compared with the WAIS-III and was chosen for this study, for this reason. The WASI can be administered in 20-30 minutes. It takes about 10 minutes to score.

One researcher (FOB) carried out all assessments. The researcher was trained by a senior clinical neuropsychologist (GF) in neuropsychological test administration and interpretation of the WTAR and WASI, and the inter-rater reliability of test scoring between FOB and GF over a subsample of 5 assessments of each test was >.9.

Table 2.2 Description of WASI index subtests.

<table>
<thead>
<tr>
<th>Index</th>
<th>Subtest</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Performance IQ (PIQ)</td>
<td>Block Design</td>
<td>The participant uses red and white blocks to recreate a constructed picture in the stimulus book, within a specified time-limit.</td>
</tr>
<tr>
<td>Verbal IQ (VIQ)</td>
<td>Similarities</td>
<td>The participant is presented with two words that represent common concepts or objects and are asked to describe how they are similar.</td>
</tr>
<tr>
<td>Verbal IQ (VIQ)</td>
<td>Vocabulary</td>
<td>The examiner reads words aloud, and the participant is requested to provide definitions of that word or concept.</td>
</tr>
<tr>
<td>Performance IQ (PIQ)</td>
<td>Matrix Reasoning</td>
<td>The participant views an incomplete matrix and has to select the missing section from five possible options.</td>
</tr>
</tbody>
</table>
2.6.10.3 The Medical Symptom Validity Test (MSVT)

The MSVT examines effort applied to assessment tasks (Green, 2004). Firstly, the person undergoing the test is presented with ten simple word pairs representing everyday objects (e.g., a tennis-ball) on a computer-screen. These word pairs are presented over two trials. Secondly, there is computerised testing of various aspects of memory for the word pairs. The main types of memory tested are Immediate Recognition memory (IR) and Delayed Recognition memory (DR). Following the presentations, IR is tested. After a ten-minute delay, DR is tested, followed by a Paired-Associates trial (PA) where the first word of each pair is presented and the participant’s ability to recall the second word is then assessed. Lastly, there is a Free Recall trial (FR). The test calculates a consistency variable (CNS) relating to the participant’s consistency-of-recall across tasks, in addition to memory performance (Howe et al., 2007). Administration and scoring are automated.

The MSVT is cost efficient and fast as a verbal memory screen with built-in effort measures. In comparison with other symptom validity tests, it contains only four subtests and a 10-minute delay between IR and DR subtests.

The MSVT subtests differ from each other in their objective difficulty. For example, someone applying a good effort will score well on the subtests that are designed to be easy (although they may appear difficult), and will score less well on the more challenging subtests. However, a participant who applies a weak or inconsistent effort may score poorly on the tests that are designed to be easy and may fail to score as low as expected on more challenging tests.

At the end of the MSVT, the participant is asked to indicate if they made their best effort on the test they just completed. Their response (which is either yes or no) is recorded by the computer. If scores on the MSVT indicate an inconsistent or inadequate effort but the patient reported that they made their best effort, this profile is indicative of an inaccurate self-report of effort applied, and suggests possible exaggeration of symptoms of cognitive difficulty, and by extension, of other reported symptoms.
The MSVT is intended for use by health professionals who assess cognitive functioning and disability. The MSVT has been used with clinical samples and has demonstrated results similar to previous validation studies of other well-validated symptom validity scales (Howe et al., 2007). The test was 99% accurate in differentiating between good effort versus simulated memory impairment in a large Brazilian study.

The MSVT has demonstrated high sensitivity and specificity in differentiating good effort from simulated memory impairment in previous studies of clinical populations, where a potential incentive to perform poorly exists (Green et al., 2009). Only participants who passed the MSVT had their data included in the analyses.

2.6.10.4 The Cambridge Neuropsychological Test Automated Battery (CANTAB)

At the time this project commenced (2009), there were few published studies of neurocognitive functioning in PNES (See section 1.29). Therefore, this limited evidence-base and the prevailing theory of dissociative (conversion) disorder informed our choice of tasks chosen from the neurocognitive assessment battery, which was based on contemporary theories of the pathogenesis of PNES, but nevertheless exploratory in nature. The candidate wanted to assess and explore a range of neurocognitive domains and to employ tasks that were regarded as best practice in the assessment of attention and concentration, working memory, executive function and planning efficiency. The research group at the Department of Psychiatry, RCSI had experience using the CANTAB neuropsychological test battery, which comprised a set of evaluations that had previously demonstrated high validity and reliability in both healthy control and patient groups (see below) for those particular tasks. Therefore, the CANTAB was selected as the assessment tool of choice for this study.

The CANTAB is a computer-administered and visually presented (nonverbal) set of neuropsychological tests containing 22 neuropsychological tests in five cognitive domains: attention, visual memory, semantic/verbal memory, decision-
making and response control, and executive function (Fray et al., 1996a). These tasks particularly examine components of cognition known to be associated with frontal and medial temporal brain regions (Robbins et al., 1994), and the CANTAB battery has demonstrated a high degree of sensitivity in detecting brain dysfunction in these areas, including the amygdalo-hippocampal complex (Owen et al., 1996). Several subtests have been utilised and evaluated in human lesion and functional imaging studies (Roberts et al., 1988; Dias et al., 1996; Owen et al., 1996), thereby permitting inferences to be made about the underlying neural circuitry associated with the performance of these tasks. Also, the subtests are graded by difficulty, which allows their use across a wide age and diagnostic range (Robbins et al., 1994; Fray et al., 1996a; Fray and Robbins, 1996b; Luciana and Nelson, 1998). Detailed technical description of the tests may be found on the Cambridge Cognition’s website: http://www.cantab.com.

The CANTAB has been extensively validated for assessing brain–behaviour relationships in adult populations (Robbins et al., 1994), adults with psychiatric illness (e.g., Barnett et al., 2001; De Luca et al., 2003), including schizophrenia (Elliott et al., 1995), depressive disorder (Elliott et al., 1996; Porter et al., 2003), and neurogenerative disease (Pantelis et al., 1997; Rahman et al., 1999). It can be administered to people aged between 4-90 years.

There are some important implications for the user arising from the use of CANTAB. Firstly, access to CANTAB is limited by an expensive licence to use the computerised software. Secondly, the software is designed to run on the Microsoft Windows Operating System, and therefore practitioners have to upgrade the software of both their operating system and the CANTAB periodically, to incorporate relevant technological and scientific updates. Thirdly, a clinician is required to supervise every testing session to ensure that the participant understands the instructions, carries out the test as instructed and to pace each subtest. Therefore, the utilisation of the battery in clinical settings can be cumbersome and expensive. Further, the nature of stimulus presentation of, and participant responses to the CANTAB battery are exclusively nonverbal, thus limiting the conclusions that can be drawn from subtest performance. Lastly, there is limited flexibility to alter the structure of
and order of tests. For example, a subject can only move on to the next level or task in the battery when they have completed a certain number of levels (whether successfully or unsuccessfully).

There are also several positive user-friendly features of the CANTAB. Firstly, the computerised nature of the tests and the touch screen used in the assessment process are likely to assist participants to pay attention to the tasks, and to continue to engage and motivate them throughout the assessment (Luciana, 2003). Secondly, CANTAB involves standardised administration of tests and automated recording of participant responses, which would otherwise be difficult to accomplish by hand (Falconer et al., 2010). For example, the response-times of participants can be recorded with precision, to the millisecond, thus increasing the sensitivity of the test (Luciana, 2003).

The author used CANTABeclipse (Cambridge Cognition Ltd. 2005) software to assess performance of each participant on basic visual-motor functions, attention and fronto-striatal function (Intradimensional/Extradimensional Shift Task), sustained attention to compound stimuli (Rapid Visual Processing Task), planning efficiency and memory (Stockings of Cambridge Task), and executive functioning and memory (Spatial Working Memory Task). All tests were presented on a touch-screen tablet PC (Paceblade Slimbook P110 series). Sustained attention tasks were administered using a press pad (Cambridge Cognition 2-Button Press Pad Version 1.0). Table 2.3 provides a brief description of each test utilised in the study and images of test screens can be viewed in Appendix B.

<table>
<thead>
<tr>
<th>Test</th>
<th>Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOT</td>
<td>A screening test to measure accuracy of pointing and latency of response</td>
</tr>
<tr>
<td>BLC</td>
<td>A screening test to measure visual discrimination</td>
</tr>
<tr>
<td>SWM</td>
<td>Measures ability to preserve spatial information, including the use of heuristic memory strategies. A measure of executive functioning and sensitive to both spatial working memory capacity and strategy development</td>
</tr>
<tr>
<td>SOC</td>
<td>Measures executive functioning particularly planning and problem-solving</td>
</tr>
<tr>
<td>IED</td>
<td>Measures cognitive set-shifting</td>
</tr>
<tr>
<td>RVP</td>
<td>Measures sustained attention and inhibitory-control</td>
</tr>
</tbody>
</table>
CANTAB Tests used

The Motor Screening test (MOT) (CANTAB)

Purpose

The Motor Screening test (MOT) is common to all of the CANTAB test batteries. It is administered first, before any other CANTAB tests, as it introduces the subject to use of the touch-screen (Figure 2.3) and functions as a training procedure to ensure that participants can point accurately. The test screens for gross motor, visual and comprehension difficulties. It also measures speed and accuracy in carrying out the task, so that it provides an index of the subjects’ motor skills.

Administration
Subjects were asked to touch a flashing-cross as it appeared in different locations on the screen. After a demonstration of the correct way to touch the screen, using the forefinger of the dominant hand, the subject was then asked to point to the flashing-crosses as they appeared.

Measures studied

The test has two outcome measures: speed of response (mean latency) and accuracy of subject’s pointing (mean error).

The Stockings of Cambridge test (SOC) (CANTAB)

Purpose

The Stockings of Cambridge test (SOC) is a measure of visual planning (executive function). It comprises a spatial planning and problem-solving test and is sensitive to frontal lobe dysfunction. The SOC task provides independent assessments of planning time and a problem-solving measure.

Administration

The subjects were shown two displays containing three coloured balls (Figure 2.4). These displays resemble stacks of coloured balls held in stockings and suspended from a beam. The purpose of this visual arrangement is to assist subjects to readily understand some of the rules of the problems that involve 3-D concepts.
Subjects were asked to look at the top and bottom displays and requested to arrange the coloured balls so that those in the lower display correctly match the arrangement shown on top. Participants are also asked that for each new presentation, they do not perform any action until they are sure they can solve the arrangement. The test starts with one and two-move problems which are not included in the output measures. The level of difficulty increases so that subjects are asked to solve 3-, 4- and 5-move problems in the fewest moves they can. Both the time required to complete each problem and the number of steps needed to solve it, are recorded as measures of the subject’s planning abilities. Finally, after each block of planning tasks, there is a motor-control phase during which the subject just follows a sequence of ball movements matching those they made while solving the previous problems.

This task serves to allow more accurate measurement of planning time, by accounting for motor speed.
Measures studied

The SOC test has three outcome measures, including the number and percentage of correct trials and latency (speed of participant’s response).

**Spatial Working Memory (SWM) (CANTAB)**

**Purpose**

Spatial Working Memory (SWM) is a test that measures maintenance and update components of visuospatial working memory. This task requires the subject to retain spatial information and to manipulate remembered items in working memory. It is a self-ordered task, which also assesses heuristic strategy. The task demands high levels of self-organisation, self-monitoring and multi-tasking and, as such, it is sensitive to frontal lobe dysfunction (Owen et al., 1990).

**Administration**

A trial began with some coloured boxes displayed on the screen. Subjects had to find blue tokens hidden in “boxes” by process of elimination (Figure 2.5). The overall aim was that the participant had to find a blue ‘counter’ in each of the boxes and use them to fill up an empty column on the right-hand side of the screen. At any one time, there would be a single blue token hidden inside one of the boxes and subjects are required to search until they found it, at which point the next token would be hidden. Subjects are instructed that, for each presentation, they should not return to a box where they had previously found a token.
The SWM task increases in complexity, so that there are initially just three boxes presented on the screen (which serves as practice only, and is not measured), but the task increases to involve four, six and finally eight boxes.

Consequently, two types of search error are possible. Firstly, a subject may return to open a box in which a blue token has already been found during the same trial, and this comprises a 'between search' error. Secondly, a subject may return to a box that had been already opened and shown to be empty in the same search sequence, and this comprises a 'within search' error.

Subjects can search the boxes in any order, but for control purposes, the number of empty boxes visited (excluding errors), before a token was found is determined by the computer (Owen et al., 1996). As the task gets more complicated at 6- and 8-box levels, performance is enhanced by the use of a heuristic search strategy. The best strategy is to repeat the previously employed order of choices until a reinforced location is encountered, after which
time it is necessary to try a new location. The strategy score is calculated from
the frequency of starting searches from different boxes during each use: the
minimum score was 8 (1 for each stage), and the maximum was 56 (1 for each
search).

Measures studied

There are 24 outcome measures for SWM that include errors (touching boxes
that have been found to be empty, revisiting boxes that have previously been
found to contain a token), a measure of strategy, and latency measures.

Intra / Extra-dimensional Shift Test (IED) (CANTAB)

Purpose

The Intra / Extra-dimensional Shift Test (IED) is a test that assesses set
formation and attentional abilities at different levels of complexity to determine
whether basic cognitive processes are intact. It features visual discrimination,
attentional set formation, maintenance, shifting and flexibility of attention, and is
primarily sensitive to changes in the fronto-striatal areas of the brain. The task
consists of nine stages, during which the subject must learn to discriminate
between stimuli by trial and error.

Administration

Two artificial dimensions are used in the test: colour-filled shapes and white
lines. Simple stimuli are made up of just one of these dimensions (i.e., coloured
shapes), whereas compound stimuli are made up of white lines overlying colour
filled shapes (Figure 2.6).
Subjects progress through the test by satisfying a set of criterion of learning at each stage (i.e., six consecutive correct responses). However, if at any stage the subject fails to reach this criterion after fifty trials, the test terminates. The test starts with block 1, and the presentation of two coloured filled shapes. In the first stage, subjects have to learn a simple visual discrimination (SvD) between two coloured shapes, followed by a reversal trial, called simple visual discrimination reversal (SvDR). The subject must learn which of the shapes is correct by touching it and continue until the criterion is reached. In block 2, the rule is reversed, so that the previously incorrect shape becomes the correct shape. In block 3, an irrelevant dimension (consisting of white lines) is introduced. The white line is initially positioned beside the stimuli, but in block 4 it is super-imposed on the stimuli. The rule remains the same at this stage until the criterion is reached. The subject must learn that the newly introduced stimulus is irrelevant to the task and then reverse the learned discrimination as
before (i.e., a compound discrimination followed by a compound discrimination reversal).

However, in block 5 the rule is reversed within the original dimension. Notably, the second dimension (white line) is redundant at this stage. Once the subject has learned the compound discrimination, new shapes are introduced in block 6 still varying along the same two dimensions. Subjects are required to continue to attend to the previously relevant dimensions of shape and learn which of the two new shapes is correct; this is the intra-dimensional shift. Once the subject has completed a successful intra-dimensional shift, followed by a reversal in block 7, again the compound shapes are changed. In the block 8 stage, subjects are required to shift attention to the previously irrelevant dimension and learn which of the two illustrations in this dimension is now correct; this is the extra-dimensional shift. Finally, in block 9, the situations are again reversed.

Measures studied

The IED test has 18 outcome measures, that assess errors made during performance, and the numbers of trials and stages completed.

Rapid Visual Information Processing (RVP) (CANTAB)

Purpose

The Rapid Visual Information Processing test (RVP) measures sustained attention capacity (Sahakian et al., 1989). It also measures the subjects inhibitory control and response biases using Signal Detection Theory (SDT).
Administration

The participant looks at a white box in the centre of the screen in which the numbers 2-9 appear in pseudo-random order at a rate of one hundred digits per minute (Figure 2.7). The subject is asked to detect specific target sequences of numbers (e.g. 3-5-7, 1-2-3) and when a target sequence is identified, to register their response using the press pad. A practice session is done before the real test begins, during which the software assists the subject in identifying the target sequence (1-2-3 or 3-5-7) through a series of cues and prompts, which are gradually removed as the practice trial progresses. In clinical test mode (the mode used to assess adults), a subject must identify and respond to 3 target sequences (2-4-6, 3-5-7 and 4-6-8).

Measures studied
Seven outcome measures are calculated, comprising: (1) mean latency, the average time taken to respond with correct responses; (2) total misses (i.e., the number of occasions that the subject failed to respond); (3) probability of hits (i.e., the total times the subject responded correctly, divided by the sum of total hits and total misses); (4) total correct rejections (stimuli that were rightly rejected); (5) probability of false alarms (comprising the total number of times the subject responded inappropriately, divided by the sum of total false alarms and total correct rejections); (6) $A'$, a signal detection measure of sensitivity to the target, regardless of response tendency. It is a measure of discriminability, so that it assesses how well the subject could identify the objective overall (Chari, Shaw et al. 1996); (7) $B''$, a signal detection measure of the strength of trace required to elicit a response, so that it is a measure of response bias (Chari et al., 1996). The $A'$ measure ranges from 0 (no sensitivity) to 1 (perfect sensitivity or 100% detection), and $B''$ ranges from -1 to 1; with -1 indicating an extremely liberal response bias (i.e., responding “yes” to all stimuli) and 1 indicating a highly conservative response bias (i.e., the subject had a higher tendency to reject stimuli as targets). A score of 0 indicates no measurable response bias. The RVP task takes 4 minutes to administer.

2.6.11 Testing procedures for all participants

Testing procedures were the same for those with PNES and healthy controls (Table 2.4). The order of administration of the assessments for all participants (those with PNES and healthy controls) was the same. Each participant in the PNES and healthy control groups completed both psychiatric and neuropsychological assessments. These evaluations at TCIN took between 3-4 hours of actual testing time to complete. Due to the length of time involved and consequent concerns about fatigue, the psychiatric and neuropsychological assessments were separated by a break of 30 minutes. Also, within each assessment session (comprising on average of 90 minutes actual testing-time), there was a 10-minute break taken after each 45-minute testing period.
Table 2.4 Order of test administration to all participants (both those with PNES and healthy controls).

<table>
<thead>
<tr>
<th>Session</th>
<th>All participants PNES &amp; healthy-controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Meeting</td>
<td>Complete all self-report questionnaires</td>
</tr>
<tr>
<td>Session 1</td>
<td>Review of questionnaires</td>
</tr>
<tr>
<td></td>
<td>WTAR</td>
</tr>
<tr>
<td></td>
<td>WASI</td>
</tr>
<tr>
<td></td>
<td>SCID 1</td>
</tr>
<tr>
<td></td>
<td>SCID 2</td>
</tr>
<tr>
<td></td>
<td>15 minute break</td>
</tr>
<tr>
<td>Session 2</td>
<td>MSVT</td>
</tr>
<tr>
<td></td>
<td>CANTAB administration</td>
</tr>
<tr>
<td></td>
<td>Motor screening (MOT)</td>
</tr>
<tr>
<td></td>
<td>Big/Little Circle (BLC)</td>
</tr>
<tr>
<td></td>
<td>Stockings of Cambridge (SOC)</td>
</tr>
<tr>
<td></td>
<td>Spatial Working Memory(SWM)</td>
</tr>
<tr>
<td></td>
<td>Intra/Extradimensional Shift (IED)</td>
</tr>
<tr>
<td></td>
<td>Rapid Visual Processing (RVP)</td>
</tr>
<tr>
<td></td>
<td>60 minute break (lunch)</td>
</tr>
<tr>
<td></td>
<td>Neuroimaging</td>
</tr>
<tr>
<td></td>
<td>sMRI</td>
</tr>
<tr>
<td></td>
<td>DTI</td>
</tr>
<tr>
<td></td>
<td>fMRI</td>
</tr>
</tbody>
</table>

WTAR, Wechsler Test of Adult Reading; WASI, Wechsler Abbreviated Scale of Intelligence; SCID 1, Structured Clinical Interview for DSM-4 Axis 1 Disorders; SCID 2, Structured Clinical Interview for DSM-4 Axis 2 Disorders; MSVT, Medical Symptom Validity Test; CANTAB, Cambridge Neuropsychological Test Automated Battery; sMRI, structural magnetic resonance imaging; DTI, diffusion tensor imaging; fMRI, functional magnetic resonance imaging.

All participants were tested in TCIN and testing was carried out on a level surface in a quiet room.
2.7 Methodology relating to the neuroimaging investigations of patients with PNES

This section will outline the technical background to the neuroimaging methods used in this thesis and provide a description of the methodology used in relation to the data analysis and interpretation.

2.7.0 Technical background to the neuroimaging methods used in this thesis

2.7.1 Introduction: The utilisation of neuroimaging methods in investigating the neurobiology of psychiatric disorders

Until the mid-1970’s, the medical community believed that psychiatric illnesses had no neural correlates per se, and that mental disorders evolved and persisted through psychosocial and other influences. However, the finding by Johnstone and colleagues in 1976 that people with schizophrenia had relatively enlarged cerebral ventricles challenged those views and heralded an evolution of the scientific examination of neurobiological influences and processes associated with mental disorders (Johnstone et al., 1976; Linden, 2012).

In the early 1970s, a researcher called Michael Merzenich was carrying out experiments to prove his hypothesis that brain structure and organisation was specialised and compartmentalised for specific skills. However, he found the opposite (i.e., that the brain demonstrated highly neuroplastic behaviour in response to learning or changes in its environment). Since then, his findings have been replicated so that it is now generally accepted that the human brain can adapt and change in response to multiple factors. These include
hormones, neurotransmitters, growth factors, and pharmaceutical agents, and neuronal structure and function is also affected by environmental stimulation, learning, and ageing processes. These factors may induce changes in neuro-biochemical processes, neuronal connectivity, and neurogenesis, so that there is overwhelming evidence that that genetic, biological, psychological and social factors may all manifest in observable changes in brain structure or function (Fuchs and Flügge, 2014). Neuroimaging methods have played, and continue to play, an important role in measuring brain structure and function and are central to the drive to understand biological and neurocognitive processes in typically developing humans, and in those with medical and psychiatric conditions. Neuroimaging techniques also have a particular advantage over other available means of biological investigation as they are non-invasive and provide direct access to neural structure and processes.

The search for biomarkers of psychiatric illness is considered to be an important objective by most researchers in this field, given that currently, psychiatric diagnosis is made primarily on the basis of clinical assessment and opinion, rather than on the results of biological investigations, in contrast with the
diagnostic process relating to many medical illnesses. A biomarker is defined as “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic responses, or pharmacologic responses to a therapeutic intervention” (Colburn et al., 2001). An ideal biomarker would have both high sensitivity and specificity for diagnosis and be a good predictor of clinical outcome and prognosis. If developed, biomarkers can be utilised to diagnose, classify or predict the development and stage of a particular condition. Over recent decades, significant advances in the formulation of neurobiological models for some psychiatric illnesses have been made through such research, which have helped improve diagnostic approaches, risk identification, treatment approaches and overall assessment (Figure 2.8) (Phillips, 2012). However, in the main, these insights have been achieved through comparison of groups with and without the conditions. Currently, it is not possible for clinicians to make a psychiatric diagnosis on an individual basis with confidence using just etiological models or clinically significant biomarkers, as such tests have either not been either identified at all, or, if tentatively identified, not proved to be reliable for routine application (Linden, 2012). Nevertheless, such research is helping to refine our understanding of neurobiological correlates of psychiatric disorder, and may also influence revisions of diagnostic criteria for specific disorders over time.

2.7.2 Neuroimaging modalities used in this study

Neuroimaging techniques allow visualisation of anatomy, function, electrophysiology, connectivity and pharmacology of the brain. The division between structural and functional neuroimaging is rather difficult to define as structure and function co-exist in a dynamic framework. However, structural neuroimaging refers to the method of measuring static anatomical structure, while functional neuroimaging measures dynamic physiological processes in the brain (Symms et al., 2004). For the purposes of this thesis, I will focus on the three types of neuroimaging that I used in my experiments, namely, structural magnetic resonance imaging, diffusion tensor imaging and functional magnetic resonance imaging. I will describe each type, the concepts behind their use and how data sourced from these techniques is analysed.
2.7.2.1 Structural magnetic resonance imaging (sMRI)

2.7.2.1.1 Introduction to data acquisition using sMRI

Structural magnetic resonance imaging (sMRI), also known as nuclear magnetic resonance imaging, is a technique that was originally developed in the 1970s and subsequently refined over the years so that it produces high-quality and detailed 3D images of the various tissues in the human body.

For imaging purposes, the hydrogen nucleus (a single proton) is useful because it is found abundantly in water and fat and has the highest susceptibility to magnetic influence and magnetic resonance of any naturally-occurring element (Goldstein, 2004).

A hydrogen atom's nucleus comprises a single proton that rotates on its axis and produces a positive charge that generates a small magnetic field. Under normal circumstances, these hydrogen protons spin within the body with their axes randomly aligned. However, when exposed to a large external magnetic field ($B_o$) of sufficient strength, the alignment of the protons in the body changes so that they tend to align themselves in either a parallel or anti-parallel direction to that field. The parallel-orientated protons greatly outnumber those that align in an anti-parallel direction, and this process creates a net magnetisation force (M), the magnitude of which is directly proportional to the strength of the external magnetic field (Figure 2.9).

On initial exposure to $B_o$, the M vector of the protons may not align in parallel, but the $B_o$ field will induce a process called precession, whereby the spinning protons are quickly re-orientated via a spiral wobbling motion that occurs when subjected to this external force. These protons quickly become uniformly-aligned into equilibrium, and this process creates a magnetic vector that is orientated-along the axis of the MRI scanner.

sMRI uses a very powerful magnetic field (usually between 0.2 to 3 Tesla) to align the proton “spins” inside the body, and a strong longitudinal magnetic field ($B_o$) causes the atoms to resonate, a phenomenon called nuclear magnetic
Figure 2.9 The influence of an external magnetic field on proton alignment.

An external magnetic field \( (B_0) \) causes protons to align themselves in either a parallel or anti-parallel direction with it. This results in a small excess of protons in parallel alignment (highlighted in blue) which produces a net magnetisation vector \( M \) in the same direction as \( B_0 \).

resonance (NMR). Through this process, the hydrogen nuclei generate rotating magnetic fields that the scanner detects to form an image.

The scanner produces a radio-wave frequency (RF) current that, through the production of RF pulses, can add energy to the magnetic field in three planes \( (X, Y, \text{ and } Z) \). This process deflects the magnetic vector, which is dependent on the element sought (hydrogen) and the strength of the magnetic field. RF pulses alter the acquired longitudinal magnetisation by 90 degrees into the transverse plane, and the hydrogen protons absorb the energy from the radio-waves in the variable field and flip their spins. The protons can absorb the energy of radio-waves of characteristic frequencies, the exact measure being referred to as the Larmor frequency. The Larmor frequency depends on the type of nucleus, the strength of the magnetic field, and the physical environment of the nucleus, and is represented in the Larmor equation (Jones et al., 1993).

The strength of the magnetic field during the scan can be varied by the user, through the utilisation of a series of gradient electrical coils which alter the local magnetic field, and this will lead to resonance of different slices of anatomical areas as different frequencies are applied.
When the field is turned off, the protons gradually return to their normal spin, and the magnetic vector thereby returns to its resting state, a process called relaxation. During this time, two independent relaxation processes influence the protons as they return to their baseline state of equilibrium (parallel to $B_0$): magnetic vector spin-lattice interactions ($T_1$ relaxation) and spin-spin interactions ($T_2$ relaxation). The receiver coil of a magnet detects the energy emitted by the protons, and this signal is used to create the images. Receiver coils positioned around the specified body part act as aerials to improve the detection of the emitted signal. The time taken for this “relaxation” process to occur is measured by timing the $T_1$ relaxation process (the time taken for the magnetic vector to return to its resting state) and the $T_2$ relaxation process (the time taken for the axial spin to revert to resting state).

There are acquisition protocols designed to measure $T_1$ and $T_2$ for individual voxels, consisting of a series of $90^0$ and $180^0$ RF pulses that excite the protons and allow monitoring of the magnetisation loss ($T_1$) or axial dephasing ($T_2$) while returning to their respective resting states. $T_1$ can be measured with partial saturation-saturation recovery and inversion recovery sequences, and $T_2$ can be obtained using the spin-echo pulse sequence (, 1993). Since protons in body tissues return to their normal spins at different rates depending on the nature of the tissue involved, the scanner can distinguish among tissues and morphology can be visualised. These relaxation processes allow image-contrasting in MRI and can be selected by choice of timing parameters within the particular RF pulse-sequence employed. The multiple transmitted RF pulses can be used in sequence to emphasise or contrast specific structures, regions or abnormalities, and this emphasis takes place as the tissues return to pre-MR resting-states at different rates, after the RF pulse is turned off. Subsequently, the intensity of the received signal is plotted on a grey scale, and cross-sectional images are constructed. Other settings that influence the image of a particular tissue include echo times ($TE_c$), repetition times ($TR$) and flip angles. $TE$ corresponds to the time between RF pulse and measurement; $TR$ corresponds to times between sequential RF pulses; flip angles refer to the angle(s) to which the net magnetisation rotates, relative to the main magnetic field direction, through the application of an RF excitation-pulse.
\[ T_1 \]-weighted images are the standard scans used to assess brain anatomy. It provides good contrast between grey matter (GM) and white matter (WM), and can produce very high resolution (~1mm) making it useful in identifying various brain structures. On these images, fluid such as cerebral spinal fluid (CSF) appears hypointense (i.e., dark), adipose tissue appears hyperintense (i.e. bright) and grey matter (GM) demonstrates less intensity than white matter (WM), so that it appears darker. \[ T_1 \]-weighted measures allow for specific evaluation of GM atrophy related to loss of neurons, synapses, and dendrite dearborisation, and increased CSF-containing spaces. In contrast, on \[ T_2 \]-weighted scans compartments filled with water appear (e.g., CSF) appear hyperintense, those with high adipose tissue content (e.g., WM) demonstrate little signal and GM looks brighter than WM. In this contrast scan it can be difficult to discriminate a lesion from normal CSF, especially if the lesion is small. Therefore, often in practice, a fluid-attenuated inversion recovery (FLAIR) pulse sequence (i.e., an inversion recovery technique) is used to null fluids in \[ T_2 \]-weighted images, so that the CSF signal becomes almost entirely suppressed and appears dark on the final image, whereas lesion tissue will appear hyperintense (Hajnal et al., 2001). This type of scan with FLAIR is particularly useful when imaging structures close to the ventricles and relatively good for demonstrating pathology since most lesions and inflammatory responses are associated with an increase in water content (Fernandez-Andujar, 2014).

In contrast to other neuroimaging techniques, sMRI is widely used in both clinical and research settings and is particularly sensitive at detecting soft-tissue morphology, including that of the central nervous system (Park and Gonzales, 2004).

### 2.7.2.1.2 Approaches to preparation, processing and analysis of sMRI data

Manual tracing of examined brain structures was long-considered to be the gold-standard method of choice for MRI volumetry. However, it is very time-consuming and requires highly skilled experts in neuroanatomy to delineate brain structures accurately, and so is prone to intra-rater and inter-rater
reliability error. Also, there are no well-established, generally accepted protocols for the manual segmentation procedure (Geuze et al., 2005). Therefore, in recent years, voxel-based morphometry has become the method of choice for many neuroimagers, mainly because it is an automated, validated and reliable technique using modern software tools, but also because the chances of intra-rater and inter-rater reliability error occurring are very significantly reduced in comparison to methods involving manual-tracing.

The voxel-based morphometry (VBM) method of analysing sMRI data

Voxel-based morphometry (VBM) is an automated technique that enables whole-brain voxelwise group comparison of brain morphology. This technique involves examining the local composition of brain volumes so that GM and WM voxels are identified using image segmentation, before morphometric methods are employed to study the spatial distribution of the tissue types.

Morphometric methods aim to localise significant differences in brain structure in a study group, to characterise essential differences, and to demonstrate relationships between an effect of interest and overall brain structure. It produces statistical parametric maps (SPMs) of volumetric differences between groups.

Since its original introduction (Ashburner and Friston, 2000), several methodological improvements have been made and a number of different VBM approaches have been implemented. The optimized VBM protocol described here is implemented from the freely-available FMRIB Software Library (FSL, www.fmrib.ox.ac.uk/fsl) (Good et al., 2001). Carrying out a FSL-VBM analysis comprises the following steps:

(i) Brain extraction: Brain extraction is carried out on all high-resolution T1-weighted input images from the dataset, using FSL's Brain Extraction Tool (BET) (Smith, 2002).

(ii) Tissue-type segmentation: The brain-extracted MRI data undergo segmentation into GM, WM and CSF tissue classes using the Automated Segmentation Tool (FAST) by FMRIB (Zhang et al., 2001). The resulting output
of GM, WM and CSF partial-volume images contain voxel values ranging from 0 to 1, which represent the proportion of GM, WM and CSF, respectively, in all voxels.

(iii) **Template creation: there are two steps in this procedure.** Firstly, the GM partial-volume images of all subjects are affine-registered (involving 12 degrees-of-freedom) to the GM standard space template using FMRIB’s Linear Image Registration Tool (FLIRT) (Jenkinson et al., 2002). The registered images of those subjects selected for creation of the image template are then averaged together with their respective mirror-images and an initial symmetric, study-specific GM template is created.

Secondly, the original GM partial volume images of all subjects are non-linearly registered to the initial study specific GM template using FMRIB’s Nonlinear Image Registration Tool (FNIRT) (Andersson et al., 2007a). The non-linearly registered images of the subjects chosen for template creation are subsequently averaged together with their respective mirror images to create the final symmetric, study-specific GM template.

(iv) **Non-linear alignment of GM images to the template space:** In this step, the original GM partial-volume images are non-linearly registered to the final study-specific template.

(v) **Modulation:** Here, the non-linearly aligned GM images are modulated. Modulation is a processing step that compensates for either contraction or enlargement changes in the local volume which occur during the spatial alignment to the template. This comprises multiplying the image intensity values of each registered GM partial-volume image by the amount of local contraction applied during the non-linear registration (i.e., the Jacobian of the warp field). For example, if a particular brain area of one participant is double that in the study-specific template, then its volume will be halved during the registration step. In this case the modulation will double the voxel intensities of this region, which ensures that the total amount of GM remains the same as it was in the original image (i.e., before registration) (Whitwell, 2009). This adjustment allows measurement of potential regional differences in the GM volume, rather than in GM concentration. The FSL-VBM protocol compensates only for the non-linear component of the spatial alignment (**nl_modulation**).
(vi) **Smoothing:** In this step, the registered, modulated data are smoothed with a range of Gaussian kernels. This process aims to improve the signal-to-noise ratio (SNR), to reduce inter-subject variability (due to registration inaccuracies), and helps to satisfy the distributional requirements for applying parametric statistical tests (Ashburner and Friston, 2000). However, excessive smoothing can decrease the chances of detecting regional differences on a small spatial scale, so that a rule of thumb often applied is that the extent of smoothing should be comparable to the expected size of the effect of interest (Ashburner and Friston, 2000).

(vii) **Statistical analysis:** Finally, statistical analysis is performed to localise brain regions and determine if GM volume is significantly related to the variable(s) of interest. A non-parametric permutation test is recommended by the FSL-VBM protocol, as the assumptions of a parametric approach (e.g. $t$-statistic) are often inappropriate for data generated by VBM. In addition, because of the large number of voxels being tested (approximately 200,000), it is necessary to correct for multiple comparisons in order to decrease the probability of obtaining false-positive results. A typical approach that addresses this issue is based on Gaussian random field (GRF) theory (Worsley et al., 1992). However, the correction for multiple comparisons via non-parametric permutation testing is recommended, because VBM data may not be incompatible with the assumptions underlying GRF.

Thresholding of both voxels and clusters are available as part of the FSL's permutation testing ([http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Randomise/UserGuide](http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Randomise/UserGuide)). The voxel-based option adjusts the data for multiple comparisons by using the null distribution of the maximal voxelwise statistic, while the cluster-based option corrects for multiple comparisons by using the null distribution of the maximal cluster size/mass (Nichols and Holmes, 2002). The cluster-based thresholding is often a more sensitive technique compared to the voxel-based approach. However, the choice of the initial cluster-forming threshold can have a significant impact on the final results. Therefore, a method referred to as “threshold-free cluster enhancement” (TFCE) has been implemented in FSL to preserve the sensitivity of cluster-based correction without the need for an arbitrary cluster-forming threshold (Smith and Nichols, 2009).
Sometimes, researchers may want to examine a particular region of interest (ROI) of the brain, based on an *a priori* hypothesis that the specific disorder, disease or condition involves the specific structure(s) in this area. VBM methodology can also be used to perform a ROI analysis and has been found to be equivalent to manual tracing methods (Bergouignan et al, 2009).

The principal advantage of a VBM-style analysis is that it is fully automated and only requires structural T₁ data to be provided for analysis. However there are some important limitations to be aware of. Firstly, it is not possible to be absolutely sure that alignment of scans is completely accurate, and that any given voxel in the space on which voxel-wise statistics will be carried out, represents corresponding data from all subjects in a given anatomical region (Simon et al., 2005). In addition, the arbitrary choice of smoothing designated for the analysis may significantly affect final results (Jones et al., 2005), and smoothing may also increase partial-voluming, making it difficult to determine if estimated structural changes are caused by *de facto* changes in volume and structure, rather than those associated with changes in the volume of tissue types (Smith et al., 2006). These potential confounders of results can be addressed by good quality control checks during preprocessing, processing and statistical analysis of VBM data, including visual cross-checking of alignment issues ((Sommer, Koch et al. 2002)), manual editing of volumes, and careful post-statistical analysis.

Apart from sMRI methods, additional magnetic fields are used to localise body structures in 3D. There are many forms of MRI, but diffusion MRI and functional MRI (fMRI) are two of the most common.

### 2.7.2.2 Diffusion Tensor imaging (DTI)

#### 2.7.2.2.1 Introduction to data acquisition using DTI

Diffusion Tensor Imaging (DTI) is a non-invasive form of MR imaging based on an exceptionally high sensitivity to water diffusion rate within the tissue architecture (Soares et al., 2013). It rests on the observations that water
molecules diffuse according to Brownian (random) motion and are affected by ambient temperature. This process is influenced by the structure and integrity of the respective tissue and whether there are barriers to diffusion (Chenevert et al., 1990; Beaulieu, 2002). Barriers to diffusion include cell-membranes and myelin sheaths.

The diffusion term, \( D \), represents the translational movement of \( \text{H}_2\text{O} \) molecules which occurs in both live and postmortem brains (mori and Zhang, 2006). DTI detects and utilizes this water motion as a probe to assess tissue morphology, particularly static anatomy. Moreover, different tissue types tend to produce rather characteristic diffusion signals. For example, the term "isotropic diffusion" refers to a pattern of free, unrestricted movement of water molecules in any direction, whereas a pattern involving restrictions to water motion in particular directions (e.g., when boundaries exist in the tissue) is called "anisotropic diffusion" (White et al., 2008). In the WM of the brain, diffusion anisotropy is mainly caused by cellular membranes, with a contribution also from myelination and axonal packing ((Beaulieu 2002)), and tends to be elongated along the one axis due to the cylindrical morphology of the axons. In contrast, diffusion in GM is typically less anisotropic than in WM, as it is reduced by the presence of macromolecules and lipid membranes. Moreover, that of CSF is spatially unrestricted in all directions (isotropic), because it is effectively a fluid-filled cavity (Pierpaoli et al., 1996; Song et al., 2002; Hagmann et al., 2006).

DTI applies powerful magnetic field gradients in at least six non-collinear directions to detect the diffusion properties of water. A spin-echo sequence involves sequential applications of powerful bipolar diffusion-gradients along the respective number of multiple directions, and protons that diffuse will exhibit a change in their cumulative magnetic field exposure that is mathematically related to the distance spread, and so can be measured. In the first instance, DTI works by introducing extra gradient pulses whose effect is zero for stationary water molecules but causes a random phase-shift for those that move and diffuse (O'Donnell and Westin, 2011). When in a random phase, diffusing particles lose their signal, creating darker volumetric pixels, so that
WM tracts parallel to the gradient direction appear dark in the image for that direction.

Secondly, the diffusion tensor (D) is calculated by solving the Stejskal-Tanner equation, in which decreased signal \( S_k \) is compared to the original signal \( S_0 \) (Basser, 1995).

There is a system of equations solved for D, the diffusion tensor. For example, at least seven images are needed to calculate the six independent numbers in the \( 3 \times 3 \) symmetric matrix D, comprising six diffusion-weighted images from six gradient directions (giving six values for \( S_k \)) in addition to one baseline \( S_0 \) image. This system of equations can be solved using the least squares method at each voxel (which will be referred-to later in this section).

The apparent diffusion coefficient (ADC), represents a measure of the actual water diffusion within different tissue compartments. An ADC map of the brain can be created after sequential applications of this process has generated at least two images of different bipolar diffusion gradient-strengths. This process allows for the visualisation of regions that demonstrate high anisotropy, especially white matter tracts in the brain, and is lower in GM than in CSF due to the presence of proteins and other macromolecules within GM (White et al., 2008).

In DTI, fibre orientations are estimated from three independent diffusion measurements along the X, Y, and Z axes. However, fibre-orientation is almost always oblique to these axes and are not accurately represented according to these vectors, so that in theory, an accurate representation of the actual direction of a particular fibre could involve measuring thousands of axes. Basser and colleagues addressed this problem through formulating the diffusion process mathematically as a \( 3 \times 3 \) symmetrical matrix. This matrix is represented visually as a 3D diffusion ellipsoid and is computed from the length of the longest, middle and shortest axes (i.e., eigenvalues \( \lambda_1, \lambda_2, \lambda_3 \)) and their directional orientations (i.e., eigenvectors \( v_1, v_2, v_3 \)). Therefore, ADC measurements along six axes are sufficient to calculate this ellipsoid (see A, Figure 2.10). This matrix is also referred-to as a tensor (Basser et al., 1994).
practice, once a diffusion ellipsoid is determined, the value of the vector of the longest axis (eigenvector $v_1$) is assumed to indicate the fibre orientation.

After the diffusion tensor is estimated, other diffusion parameters can be produced, the most commonly used being mean diffusivity (MD) and fractional anisotropy (FA). MD represents the overall diffusion within a volume (voxel), regardless of its directionality and can be calculated by the following equation:

$$\text{MD} = \frac{\lambda_1 + \lambda_2 + \lambda_3}{3}$$

**Figure 2.10 The principle of DTI and contrast generation (Mori and Zhang, 2006).** The shape of a diffusion ellipsoid (B) is estimated from diffusion measurements along multiple axes (A). An anisotropy map can be then created from the shape, in which dark regions are isotropic and bright regions are anisotropic. The orientation of the longest axis can be determined (C) from B. This orientation data is converted into a colour (F) at each pixel. Subsequently, a colour-coded orientation map (E) can be created by combining the intensity of the anisotropy map (D) and F.
FA provides a measure of the degree to which diffusion anisotropy exists within a voxel and can be represented using the following equation:

$$FA = \sqrt{1.5 \sum_{i=1}^{3} \left( \frac{(\lambda_i - MD)^2}{\sum_{i=1}^{3} \lambda_i^2} \right)}$$

The information from the eigenvectors can be converted into a colour-coded orientation map (Makris et al., 1997) (see stage E in Figure 2.10). Also, the diffusion tensor can be viewed using glyphs, which are small 3D representations of the major eigenvector or whole tensor. The colour-scheme most commonly used to represent the orientation of the major eigenvector is as follows: blue corresponds to a superior-inferior direction, red means left-right direction, and green refers to an anterior-posterior fibre-orientation (Pajevic and Pierpaoli, 2000). To enhance visualisation of the WM and to suppress external information, the brightness of the colour is usually controlled by FA.

Tractography has become a regularly used method of viewing data in DTI. It refers to any method that estimates the trajectories of the fibre tracts in the white matter and visually reconstructs streamlined three dimensional (3D) information from the tensor field.

Considerations in DTI data acquisition

Data acquisition techniques can help reduce the potential for artefacts in diffusion-weighted imaging datasets. Artefacts can be described as features that appear in an image but that are not present in the originally-imaged object. Artefacts can obscure, and be mistaken for, pathology, and therefore can result in false negative and false positive results. When they occur, they are mainly associated with issues relating to the gradient system hardware, the pulse sequencing, data acquisition strategy, and motion. Diffusion-weighted imaging, of which DTI is a subtype, has low signal-to-noise ratio (SNR) and resolution so that it is very susceptible to motion (Polders et al., 2011). There are some
practical steps that can be taken to decrease the influence of motion artefacts. Firstly, and most importantly, prevention of motion is preferable to trying to correct it after the scan has occurred. Therefore, offering the participant the opportunity to prepare for scanning in a dummy-scanner made for orientation purposes, and allocating sufficient time to introduce them adequately and comfortably to the real scanner can help reduce unwelcome movement. Moreover, reduction of motion artefact can also be facilitated by using comfortable padding around the participant’s head and by asking them to remain still throughout the scan. Secondly, progressive developments in gradient and digital-data acquisition technology have reduced the time required to obtain individual MR slices, to between 50-100 msec, which minimises the effects of patient motion. This acquisition mode is known as single-shot echoplanar imaging (EPI) (Nana et al., 2008). Although EPI is very sensitive to other artefacts arising from fMRI, shorter readout times can decrease the echo-train length (ETL) and increase SNR, resulting in reduced motion-sensitivity and decreased susceptibility to artefacts related to geometric factors and blurring (Mukherjee et al., 2008). Alternative sequences such as fast-spin echo (FSE) (Pipe et al., 2002), line-scan diffusion imaging (LSDI) (Gudbjartsson et al., 1996), and stimulated echo acquisition mode (STEAM) (Nolte et al., 2000), can also decrease the sensitivity to motion. Also, the utilisation of automated artefact-correction software such as the Artefact Correction in Diffusion MRI (ACID) toolbox can help to compensate for motion artefact. Finally, when it is not possible to correct significant artefacts (such as severe motion or signal dropout) without significantly compromising image-quality, options include removing the affected scan slices, limiting the analysis to unaffected regions of the individual scan, or removing the subject completely from the analysis (Liu et al., 2010).

2.7.2.2.3 Approaches to preparation, processing and analysis of DTI data
There are some crucial steps required to prepare and process DTI information for analysis and interpretation. These include quality-control checks, pre-processing, processing and visualisation, and finally, quantitative analysis of the data (See Figure 2.11).
Quality-control of DTI data

There are some important quality-control steps that should be completed before the analysis of DTI images commences (Figure 2.11). Firstly, when importing the data, it is important to check if all images have been received and organised correctly and to ensure that the same scanning parameters have been used.
with every subject in the same study. This process can be facilitated through the use of image-viewing software, such as Mricron, Osiris and ImageJ (Liao et al., 2008; Soares et al., 2013).

Secondly, visual inspection of images is necessary to detect potential artefacts, the main ones being head-motion and eddy-current distortions, but scans should also be checked for missing slices, geometric distortions, signal dropouts and subtle system drifts (Mohammadi et al., 2012). Automated software can also identify corrupted images, and include tools such as RESTORE, which estimates tensors, and Monte Carlo simulated data, can examine effects of noise on DTI information (Basu et al., 2006).

Pre-processing of DTI data
In addition to quality-control assessment of DTI data, there are a number of pre-processing steps required, which depend on the MRI scanner, acquisition parameters, image quality, software package employed and the focus of the study. Firstly, it is necessary to convert the raw data into an image format, and software tools such as the Neuroimaging Informatics Technology Initiative (NIfTI) and Analyse are typically employed for this purpose. Also, the data can be converted from original DICOM format to file format using software converters such as Mricron and MRCIConvert, or software package converters such as AFNI, Freesurfer and SPM (Smith et al., 2004; Friston et al., 2007; Fischl, 2012).

Next, the raw images should be inspected for distortions, including eddy currents and head motion. These artefacts can be corrected for together in one single step as by using software such as FMRIB’s Diffusion Toolbox (FDT), Automated Image Registration (AIR), DT_Recon, DTIC, DTIPrep and ExploreDTI (Soares et al., 2013). Non-brain areas should also be removed from the analysis in a process called skull-stripping, and accomplished by utilising software tools such as Freesurfer, BET (from FSL), and Bioimage Suite. Subsequently, it is important to ensure that gradient information is retrieved from the MRI console or calculated precisely using tools such as DTI gradient creator, as this information forms the basis of tensor gradient tables, which are normalised for accurate tensor estimation and tractography analysis. After
tensor estimation, tensor orientation errors should be out-ruled through visual inspection of specific brain regions (such as the corpus callosum and cingulate cortex), using tools such as FSL View, DTISstudio, ExploreDTI and Bioimage Suite. However, if found, tensor orientation errors should be corrected by modifying the gradient table and repeating the reconstruction of the tensor. Software tools such as DTI-TK are available for this purpose.

Finally, it is important to assess the DTI dataset for the presence of bias, which can occur from sources such as experimental parameters, field inhomogeneities and noise. This can be assessed through the use of the SIMulation and Extrapolation (SIMEX) statistical approach software tool (Lauzon et al., 2011).

**Processing and visualisation of DTI data**

Once data preprocessing is completed, the next step of DTI analysis is a voxel-wise tensor estimation. A second-rank tensor analysis requires a minimum of six diffusion-weighted image acquisitions from non-collinear directions, where tensor ranks describe biophysical properties examined with tensor equations (Filler, 2009). An example of a rank 0 tensor is temperature, as it is measured on a scale but has no directionality; while a rank 1 tensor is a vector having both directionality and scalar magnitude. A second rank tensor describes the relationship between two vectors (e.g., between the random motion of water molecules and their displacement). In DTI analysis, there is usually an exploration of a construct called a dyad. A dyad usually involves two vectors with directionality and quantity or comprises a scalar qualitative measurement and two directions. There are three commonly-used methods of carrying out tensor estimation in the processing of DTI data: Ordinary least Squares (OLS), Nonlinear Least Squares (NNLS) and Weighted Linear Least Squares (WLS). However, it is important to use the same method consistently throughout analysis of the same dataset as each method can produce different results.

The diffusion tensor, as a symmetric 3 X 3 matrix, can be expressed in ellipsoid form by its eigenvalues ($\lambda_1$, $\lambda_2$, $\lambda_3$) and eigenvectors ($v_1$, $v_2$, $v_3$), which are subsequently used to process scalar indices and tractography as appropriate to the study.
In practice, viewing and presenting the tensor information in a way that is easy to visualise and understand is one of the most challenging aspects of DTI analysis. Typical approaches include using scalar indices and tensor glyphs. Scalar indices represent dimensionality reduction of the tensor. In contrast, glyphs are small 3D objects that can be used to describe a diffusion tensor through its size, shape, colour and location, and therefore displays information from each tensor eigensystem. Glyphs are used for quality control and visualisation but not in analysis and are often represented as 3D ellipsoid shapes elongated through the fastest axis of diffusion and limited along directions with restricted diffusion. Table 2.5 refers to the most common software tools used for DTI processing and presentation (Soares et al., 2013).

**Quantitative analysis of DTI data**

Once parametric maps are computed (including such values as FA and MD), summary measures are extracted from the whole brain and particular anatomical regions of interest (if relevant), using methods such as voxel-based analysis, histogram, tract-based spatial statistics (TBSS) and ROI analysis.

Voxel-based analyses (VBA) are commonly employed as sMRI data-analysis tools as they are automated, time-efficient, and require minimum user intervention. The VBA technique includes a process called normalisation, which is the registration of acquired diffusion maps onto a standard space. The basis for carrying out this step is that brains differ in size and shape between people so that spatial normalisation artificially deforms all scans in the analysis to ensure that the location of each brain structure in an individual scan corresponds to the same location in all the scans.

Normalisation enables between-group comparisons of diffusion parameters and correlations with other variables of interest (e.g., clinical indices). There are multiple software tools to assist neuroimagers in these types of analyses (Table 2.5). SPM is the most commonly used software tool for this kind of analysis, although BrainVoyagerQX is also gaining popularity. The VBA approach does not require previous ROI definition and allows analysis that is spatially-specific (e.g., ROI analysis) and unbiased (e.g., histogram analysis). An important
distinction between DTI and other imaging modalities (such as $T_1$-anatomicals or fMRI scans), is that DTI allows for a more sophisticated normalisation, so that whereas $T_1$ and fMRI scans are normalised according to intensity scales, diffusion tensor images offer the ability to register tensors that have both length and direction. This property allows an improved capability to register WM structures that have highly-anisotropic tensors.

Histogram analysis involves the use of frequencies of distributions to screen the voxels within specified parameters of interest (usually involving FA or MD) so that the histogram of each diffusion parameter exhibits the mean, location and peak height of the respective values. These histograms allow analysis of the brain using automated methods, using tools such as TrackVis or MedINRIA.

Table 2.5 Common software tools available for DTI processing.

<table>
<thead>
<tr>
<th>DTI software/tools</th>
<th>URL</th>
<th>Main purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>3D Slicer [Peper et al., 2006]</td>
<td><a href="http://www.slicer.org/">http://www.slicer.org/</a></td>
<td>Tensor estimation, ROI analysis, and tractography</td>
</tr>
<tr>
<td>AFNI (Cox, 2012)</td>
<td><a href="http://afni.nimh.nih.gov/afni">http://afni.nimh.nih.gov/afni</a></td>
<td>Preprocessing and tensor estimation</td>
</tr>
<tr>
<td>DoDTI [Park et al., 2004]</td>
<td><a href="http://neuroimage.yonsei.ac.kr/ddd/t/">http://neuroimage.yonsei.ac.kr/ddd/t/</a></td>
<td>Preprocessing, tensor estimation, and tractography</td>
</tr>
<tr>
<td>DTIStudio [Liang et al., 2006]</td>
<td><a href="https://www.mristudio.org/wiki/DTIStudioV2">https://www.mristudio.org/wiki/DTIStudioV2</a></td>
<td>Tensor estimation, ROI analysis, and tractography</td>
</tr>
<tr>
<td>ExploreDTI [Leemans et al., 2009]</td>
<td><a href="http://www.exploredti.com/">http://www.exploredti.com/</a></td>
<td>Preprocessing, tensor estimation, and tractography</td>
</tr>
<tr>
<td>FSL-FDT [Smith et al., 2004]</td>
<td><a href="http://www.fmrib.ox.ac.uk/fs/fdt/index.html">http://www.fmrib.ox.ac.uk/fs/fdt/index.html</a></td>
<td>Preprocessing, tensor estimation, and tractography</td>
</tr>
<tr>
<td>FSL-TBSS [Smith et al., 2006]</td>
<td><a href="http://www.fmrib.ox.ac.uk/fs/tbss/index.html">http://www.fmrib.ox.ac.uk/fs/tbss/index.html</a></td>
<td>TBSS analysis</td>
</tr>
<tr>
<td>MRDiffusion</td>
<td><a href="http://white.stanford.edu/mrdiff">http://white.stanford.edu/mrdiff</a></td>
<td>Tensor estimation and tractography</td>
</tr>
<tr>
<td>SPM and toolboxes</td>
<td><a href="http://www.fil.ion.ucl.ac.uk/spm/ext/">http://www.fil.ion.ucl.ac.uk/spm/ext/</a></td>
<td>Preprocessing and tensor estimation</td>
</tr>
<tr>
<td>(e.g., Diffusion II, DTI Toolboxes)</td>
<td><a href="http://trackvis.org/">http://trackvis.org/</a></td>
<td>Tensor estimation, tractography, and ROI analysis</td>
</tr>
<tr>
<td>TrackVis [Wang et al., 2007]</td>
<td><a href="https://science.nichd.nih.gov/confluence/display/nihpd/TORTOISE">https://science.nichd.nih.gov/confluence/display/nihpd/TORTOISE</a></td>
<td>Tensor estimation, tractography, and ROI analysis</td>
</tr>
<tr>
<td>TORTOISE [Pierpaoli et al., 2010]</td>
<td><a href="https://www.mristudio.org/wiki/TrackVisV2">https://www.mristudio.org/wiki/TrackVisV2</a></td>
<td>Tensor estimation, tractography, and ROI analysis</td>
</tr>
</tbody>
</table>

170
1. Non-linear registration into standard space

2. Creation and skeletonisation of mean FA image (where the skeleton represents the centres of all the tracts common to the group

3. The aligned FA data is projected onto the mean FA skeleton

4. Voxel-wise statistics are carried out. Areas of between-group differences are highlighted (e.g., in red).

**Figure 2.12 Steps involved in the tract-based spatial statistics (TBSS) DTI processing method.** *

* FA and MD images from patient and control groups are non-linearly registered for image alignment to a standard space, and are subsequently projected onto a mean FA skeleton. Voxel-wise statistical comparisons of WM change can be made between groups, where significant WM differences can be highlighted in the FA skeleton by brain region.

Results can then be compared between groups through statistical analysis. Disadvantages of this method of analysis include that it does not specify the location of any abnormalities found and that it is sensitive to tissues of no
interest (e.g., CSF, which has to be removed) and partial volume effect from atrophy (Jones and Cercignani, 2010; Zhou et al., 2011).

**Tract-based spatial statistics (TBSS)**

TBSS is a fully automated method of quantitative DTI analysis which can be used to detect group voxel-wise differences in diffusivity measures (e.g., FA and MD) over the whole brain. It only requires pre-processed diffusion data for analysis. It involves skeletonisation of group-registered FA maps (Figure 2.12). Advantages include that there is no need to perform spatial smoothing and that it increases the statistical power by reducing the number of total voxels tested in the analysis. Potential disadvantages include that it can be difficult to identify registration errors in the skeletonisation process and that large anatomical lesions may also affect its accuracy.

**Regions of interest analysis**

A ROI is defined as a specific area of a brain image from which individual or average pixel values are extracted for particular analysis (Froeling et al., 2016). The ROI analysis method is based on delineation of predefined (a priori) specific areas of the brain image. The ROI can be manually delineated or through (semi-) automated definitions of the specified area. In the voxel-wise analysis, each DTI scan is registered onto a standard space before voxel-wise statistical analysis compares regional differences in the mean outcome measures-of-interest between-groups (Abe et al., 2003). The main advantage of an ROI analysis is that it is highly sensitive to small changes in the parameters of interest, usually MD and FA (Cercignani, 2010). However, the investigator should possess an excellent knowledge of anatomy; the technique requires high-quality imaging data and it is best performed when there is a clear *a priori* hypothesis about differences in white matter in a well-defined neuroanatomical area. The ROI should not be too large for statistical reasons.

When the hypothesis regarding pathology is relatively weak, and multiple ROIs are investigated, a correction for multiple comparisons should be carried out to
reduce the chances of false positive findings (type 1 error), with the most commonly used method being the Bonferroni correction (Froeling et al., 2016).

The Bonferroni correction treats each comparison as an independent experiment and stipulates that the $p$-value at which the null hypothesis is rejected has to be divided by the number of comparisons. According to this method, the $p$-value becomes even lower when multiple parameters are compared to the same ROI (e.g., FA and MD). Other disadvantages include that the method is susceptible to inter-user and intra-user variability and can be associated with difficulties in co-registering diffusion with typical anatomical images (T1 or T2 weighted). It is also an unsuitable method for the investigation of structures with complex boundaries or where there are poorly differentiated alterations in the microstructure of white matter (Froeling et al., 2016). ROI analysis can be performed with the main tensor estimation and visualisation software, including as Slicer, MedINRIA, and ExploreDTI.

**Interpretation of DTI data**

DTI analysis allows inference of properties of tissues, through quantitative scalar measures. For example, eigenvalues provide a measure of the magnitude of diffusion along a particular direction. The sum of the eigenvalues is called the trace of the tensor. Another measure of the magnitude of diffusion and possibly the most useful scalar is the molecular diffusion rate [mean diffusivity (MD)], which represents the average eigenvalue for the three orthogonal tensors and so, provides an average measure of the directional preference of the diffusion process, within a voxel. This scalar is often also referred-to as the apparent diffusion coefficient (ADC) map. A limitation of the MD is that it cannot provide an estimate of each direction to the total diffusion magnitude. Therefore, along with MD, the other most common quantitative scalar measure used in DTI is fractional anisotropy (FA), a measure of the fraction of the diffusion tensors that contribute to anisotropic diffusion within a voxel. The interpretation of FA is made on the basis that an FA of zero represents a situation where the diffusion tensors are equal in all directions, whereas an FA of one indicates that the magnitude of the tensor is in only one direction (White et al., 2008). Therefore, the FA index can be used to indicate
the degree of anisotropy, as it is scaled from 0 (perfectly isotropic) to 1 (perfectly anisotropic). FA measures indicate orientation and integrity of white matter tracts but can also help to detect subtle changes on conventional T2-weighted sMRI and characterise changes in brain development.

In contrast, the trace and MD relate to the total amount of diffusion in a voxel, which corresponds to the amount of water in the extracellular space. The trace is relatively constant in normal brain WM and GM and is useful in detecting cellular swelling, such as that which occurs early after a cerebrovascular accident (O'Donnell and Westin, 2011). Other quantitative scalar measures used in DTI include the axial diffusivity and the radial diffusivity. The axial diffusivity (AD) is the diffusion rate occurring parallel to the main axis of diffusion and therefore is equal to the largest eigenvalue. In contrast, the radial diffusivity (RD) (also known as the perpendicular diffusivity), is the rate of diffusion occurring in the transverse (perpendicular) direction, and so is equal to the average of the two smaller eigenvalues.

Increased MD is often interpreted as representing a loss of anatomical barriers, such as myelin sheaths, cell membranes or axons. On the other hand, FA is considered to reflect integrity of white matter tracts and may also reflect the alignment of neuronal fibres (Johansen-Berg and Behrens, 2009). Both MD and FA provide sensitive measures for detecting microstructural changes, but
cannot be definitively associated with a specific microstructural component (e.g., myelin) (Figure 2.13) (Sen and Basser, 2005; Johansen-Berg and Behrens, 2009).

2.7.2.3 Functional Neuroimaging (fMRI)

2.7.2.3.1 Introduction to data acquisition using fMRI
At present, the electrical activity relating to neuronal activations or their associated magnetic tracers remain directly undetectable by modern neuroimaging methods. However, functional MRI (fMRI) is a non-invasive brain imaging method that can assess brain activity indirectly. It is most commonly performed using blood oxygenation level-dependent (BOLD) contrast to measure changes in the local concentration of the paramagnetic molecule deoxyhaemoglobin, so that it can detect dynamic changes in brain activation over time. Therefore, although the ideal would be that this technique would specifically capture neuronal activity, it actually measures signal changes due to haemodynamic effects, that occur in response to neuronal activity.

Deoxyhaemoglobin is the form of haemoglobin without oxygen, and is the predominant protein in red blood cells. When deoxyhaemoglobin is in this form (i.e., oxygen not bonded with Fe$^{2+}$), it is referred to as a paramagnetic molecule, as it produces a small magnetic gradient that increases the local magnetic field (Lindquist et al., 2008). In contrast, oxyhemoglobin is only very weakly attracted by the poles of a magnet and does not retain any permanent magnetism, so that it is referred to as being weakly diamagnetic in nature. Both paramagnetic and diamagnetic substances react to an externally applied magnetic field and distort its homogeneity. However, while paramagnetic materials increase both the local magnetic field and the MR signal, diamagnetic materials have an effect going in the opposite direction (i.e., reduce the local magnetic field and suppress the MR signal slightly).

The fMRI method of neuroimaging is based on the detection of local changes in oxygenated and deoxygenated haemoglobin in the blood supply to an activated brain region. It has been estimated that approximately 75% of the brain’s
energy is consumed by neuronal-signaling, particularly that involving excitatory inputs (rather than output signalling) of cells (Zhang and Raichle, 2010). When neurons are activated (depolarised), they subsequently return to their polarised state via the pumping of ions across their cell membranes, a process that requires glucose for energy. A higher rate of blood flow ensues locally (to within 2 or 3 mm of where the neural activity is occurring) to facilitate the transport of more glucose to the area, bringing oxygen in the form of oxygenated haemoglobin molecules (O’Hanlon, 2007). Therefore, through this process, when a particular structure or region of the brain is active at a certain time, the neuronal metabolism of oxygen leads to an increase in deoxyhaemoglobin concentrations. This change, in turn, results in a slight dilation of the arterial vessels and an increase in the supply of oxyhemoglobin to the area. Ongoing activity requires a dynamic supply of blood with oxygenated haemoglobin to the activated brain area, which leads to a relative increase in the ratio of oxygenated to deoxygenated haemoglobin locally, and generally results in a washout of paramagnetic deoxyhaemoglobin. The local reduction in the relative level of the deoxyhemoglobin to oxygenated haemoglobin causes decreased magnetic susceptibility; this then leads to slower $T_2^*$-relaxation, which in turn causes an elevated signal in $T_2^*$-weighted images. This increase in local signal intensity can be detected using an MRI scanner. Therefore, fMRI techniques are deliberately sensitised to differences in $T_2^*$, so that the magnetic properties of deoxyhaemoglobin manifest as image contrast. The ratio of oxygenated to deoxygenated blood in a particular part of the brain can be measured, and is called the blood oxygenation level dependent (BOLD) signal because the recorded local signal intensity depends on the local level of $O_2$. Most studies using fMRI measure the change in the BOLD signal during performance of a task compared with the signal at baseline (Bandettini et al., 1992; Kwong et al., 1992). The evoked haemodynamic response to a neural event is traditionally called the haemodynamic response function (HRF). Figure 2.14 shows the standard shape used to model the HRF, sometimes called the canonical HRF.

The BOLD fMRI method measures and compares field inhomogeneity-related changes in signal intensity between resting and stimulated brain states. However, these changes are so small (in the order of 1-5%) that a single image is not enough to compare conditions, so that a large number of serially acquired
images are necessary to be able to compare signal differences using statistical analysis.

A typical fMRI experiment consists of at least two different conditions (e.g., including one experimental and one baseline condition) whose BOLD signals are interpreted relative to each other. Therefore, the baseline condition (task) in particular has to be selected carefully.

During fMRI scanning, the participant is placed in the field of a large electromagnet, with a strong magnetic field (typically of between 1.5 to 7.0 Tesla) causing alignment of hydrogen protons in the brain. Within a scanning sequence of a slice (image) of brain, a RF pulse is applied to tip over the aligned hydrogen nuclei. This step is then followed by removal of the pulse which allows the nuclei to attempt to returned to their original resting state. The current that is thereby induced in the receiver coil forms the basic magnetic resonance (MR) signal.
In MR imaging the user has control in many ways over how the data are acquired and how they can be manipulated to influence the reconstructed image. The technician can modify parameters affecting the spatial and temporal resolution (SR and TRes, respectively), the field of view (FOV), the contrast, the speed of the acquisition and the influence of various types of artefacts. This is possible due to what is known as k-space, the data matrix obtained directly from the MR scanner before any kind of processing and application of the Fourier transformation, which will provide the final reconstructed image (Figure 2.15).

Raw data in MRI are the perpendicular components of the magnetisation in the imaging object after excitation, sampled from the receiver coil signal and stored as a function of time during the data acquisition of an MR imaging sequence. In a transverse slice, the horizontal axis is usually set as the frequency encoding direction, while the vertical axis is the phase encoding direction of excited protons. This is also known as k-space data (Moratal et al., 2008).

The k-space represents the matrix where the MR data will be stored prior to a Fourier transformation to obtain the desired image (Figure 2.15). The k-space represents the information on spatial frequency in a two or three-dimensional
form, and is defined by the space comprising the data from phase and frequency encoding. Every point in the raw data matrix includes a portion of the information required for the complete image, but a particular point in the raw data matrix does not directly correspond to a point in the image matrix.

However, k-space can be then translated into image space through an inverse Fourier transformation, so that data analysis can be performed (Lindquist et al., 2008).

Considerations in fMRI data acquisition: experimental designs

There are several types of experimental design employed in fMRI studies, categorised as block, event-related, and mixed-models designs. The first two categories are the most frequently-used, while the latter includes aspects of

---

**Figure 2.16 Illustration of block designs and event-related designs.**

In a block design, experimental conditions are separated into extended time-intervals (blocks) of the same type. In an event-related design, the stimulus consists of short discrete events whose timing and order can be randomised (Lindquist, 2008).
both block and event-related designs (Mechelli et al., 2003; Wenger et al., 2004). Figure 2.16 illustrates block and event-related designs.

In a block design the different experimental conditions are divided into intervals of time, and in general, increasing the time-intervals of each block will result in a larger evoked response during the task and improve the detection-power of the study (Lindquist, 2008).

However, it is also important to firstly, include multiple transitions between conditions in a block design experiment, because differences in signal due to low-frequency drift may be interpreted wrongly as differences resulting from the particular task conditions, and secondly, to ensure block lengths are not so long so as to cause subject fatigue or boredom.

The main advantages of employing a block design technique are that they possess high statistical power to detect activation and are resistant to heterogeneicities in shape of the HRF. Potential disadvantages are that they cannot be used directly to calculate features of the HRF such as onset or width, and that they only can infer the specific processes that caused localised brain activation.

An event-related design involves a stimulus that comprises brief circumscribed events and whose timing and order during the experiment can be randomised (Lindquist, 2008). This type of design enables discrimination of the effects of different conditions if either the inter-stimulus interval or the experimental event-types are varied. These manipulations also mean that the chances of subject fatigue or boredom can also be reduced. Potential disadvantages are that that the power of event related designs can be less than that of block related designs.

Block and event-related designs involve the presentation of an external stimulus to the subject, which produces a brain activation response. Block designs involve similar stimuli presented in a block-format and which are interspersed with "rest" periods which can be a brief break from the stimulus or take the form of a control condition. In contrast, event-related designs present individual trials relating to response to an external stimulus.
Typically, an fMRI session acquires a low resolution functional volume (i.e., image) every few seconds, and each image comprises approximately 100,000 voxels. Moreover, usually one hundred volumes are recorded over the course of one scanning session with one individual, although up to 2000 volumes may be gathered. Some of these scans will occur with the participant at rest, where they’re not exposed to a stimulus, and the objective of fMRI is to sensitively and validly detect those brain structures and networks that exhibit increased intensity after a particular stimulation is applied.

The fMRI data consists of a set of MR images, each consisting of uniformly-spaced voxels that parcel the brain into equally-sized cuboids. The intensity of the image from each voxel is representative of the spatial distribution of the nuclear-spin density in that region, and changes in the haemodynamic signal (responding to neuronal activity) affect the local intensity of the MR signal, so that alterations in voxel intensity over a period of time can indicate location and timing of this activity. However, a significant proportion of the voxels will consist of background noise only and will need to be removed from the analysis. An fMRI data-set from a particular experiment can be considered or represented as either \( t \) volumes (with one volume being taken every few seconds during a session) or \( v \) voxels (with each voxel having a corresponding series of \( t \) time points) (Wager and Lindquist, 2015).
2.7.2.3.2 Approaches to preparation, processing and analysis of fMRI data

There are several common objectives in fMRI data analysis which can be achieved through the application of appropriate statistical methods. These include delineation of brain areas activated by a stimulus experiment, finding neural networks that correlate with brain functioning, and being able to use the data to formulate biological models of psychological, psychiatric or medical disorders (Figure 2.17). Analysis of fMRI data is challenging as it comprises a very large dataset.

It is important to prepare and process fMRI data for analysis and interpretation and this can be carried out by taking a number of crucial steps. These steps are carried out with the objective of improving both the validity and sensitivity of subsequent statistical analysis, by removing artefacts and ensuring the assumptions of the statistical model are met. These include quality-control checks, pre-processing, processing and visualisation, and finally, quantitative analysis of the data (Smith et al., 2004; Wager and Lindquist, 2015).

**Preprocessing of fMRI data**

Quality control of fMRI data is essential and involves checking for artefacts and verification of the spatial coverage of the functional data, which is particularly relevant when carrying out group general linear model (GLM) analyses. Correction for artefacts including motion correction and signal dropout is essential and can be done through use of specialised fMRI analytical software.

The purpose of preprocessing is to condition the data, remove artefacts, validate model assumptions and maximise sensitivity of the dataset to later statistical analysis. This process includes an essential step of standardising the locations of brain regions across participants in order to increase both the validity and sensitivity of group analysis.
The major steps in fMRI preprocessing comprise slice-timing correction, realignment, co-registration of structural and functional images, normalisation and smoothing (Smith et al., 2004).

Preprocessing of fMRI data usually starts by reconstructing the raw acquired data (the “k-space” data) into images resembling brains (Smith et al., 2004). Then, slice-timing correction is applied, which is necessary as each brain image is acquired sequentially at slightly different times during the fMRI measurement. In this step, each voxel’s time course is shifted so that it appears that all voxels in each volume have been acquired at precisely the same time. This correction facilitates subsequent processing of the data.

Head motion during the course of an fMRI experiment can cause the signal from a specific voxel to be contaminated by the signal from adjacent voxels. This type of artefact can make the acquired scan useless unless it is managed appropriately so motion correction is performed. Therefore, motion correction is used to correct misalignment between fMRI scans due to subject head motion, and ensures that the images of brain within each scan are aligned with all the others in the dataset (Smith et al., 2004; Wager and Lindquist, 2015). It does this through matching each individual brain scan with a target image (which can be a mean of the total images). It is usually performed using a rigid-body model (6 degrees-of-freedom) registration of each image in the series to a chosen reference scan.

Typically, fMRI data is of low spatial resolution meaning that anatomical details are not well-delineated on the image. Therefore, in a step called co-registration, the functional images are mapped onto a high-resolution sMR image for presentation purposes. This is followed by normalisation, in which each participant’s brain scan is registered onto a standard stereotaxic space defined by a template brain (e.g., the Talairach brain). This includes a process called mapping between input and target images, followed by warping of the input scan onto the target scan, resulting in a normalised image that can be compared with the other subject scans (Lindquist et al., 2008).

Subsequently, spatial filtering (also known as smoothing or blurring) reduces the high spatial frequencies in the fMRI data, and consists of applying a small blurring kernel across each image, to average part of the intensities from
neighbouring voxels together (typically using a Gaussian filter). Each volume is blurred spatially in an effort to reduce noise. This filtering process may increase the SNR of the data and decrease individual anatomical differences, but can result in lower spatial resolution and higher partial volume effects. Therefore, care is taken not to significantly change the activation signal to avoid these unwanted effects.

The overall intensity level is adjusted to ensure that all scans have the same mean intensity, a process called "intensity-normalisation". Also, to reduce low and high frequency noise, each voxel’s time-series can be adjusted through utilisation of linear or non-linear tools (Lindquist et al., 2008; Wager and Lindquist, 2015).

**Processing and quantitative analysis of fMRI data**

Once the preprocessing steps are taken there are a number of statistical approaches available that can help determine which brain regions demonstrate signal-related BOLD signal changes, and statistical analysis usually involves modelling of the anticipated haemodynamic response to the stimulation, although correlation analysis may also be used instead. It is possible to apply statistical corrections to the data during this process, including for example, making a correction for smoothness of the measured time-series at each voxel. The most commonly used methods of analyses are based on the GLM. Voxels where the GLM analysis indicates a good fit between the predicted BOLD response (derived from the convolution of the stimulation timing with the HRF), and the actual time-series measurements are typically activated by the stimulus experiment. A brief outline of the concepts involved in fMRI data analysis is presented below, but more information can be found in the handbook by Poldrack, Mumford and Nichols (Poldrack et al., 2011).

**Modelling the fMRI signal**

The model assumes that the data consists of a brain scan with $N$ voxels, repeatedly measured at separate time-points $T$, and including a number of
subjects $M$. A model for activation in a single voxel for an individual participant can be expressed mathematically as:

$$
\gamma_{ij}(t) = \sum_{g=1}^{G} z_{ijg}(t) \gamma_{ijg} + \sum_{k=1}^{K} x_{ijk}(t) \beta_{ijk} + \epsilon_{ij}(t)
$$

, where $Z_{ijg}(t)$ equates to the contribution of nuisance covariates at time $t$ (comprising scanner drift, noise from heart rate and respiration, and head movement). $X_{ijk}(t)$ equates to the task-related BOLD response relating to the $k^{th}$ condition at time $t$. The model can be combined across voxels and expressed by the following equation:

$$
Y_j = X_j B_j + Z_j G_j + E_j
$$

, where $Y_j$ is a $T \times N$ matrix, in which each column is a time-series of data corresponding to a single voxel and each row is the sum of voxels that comprise a volume at a particular point in time of the series; the matrices $X_j$ and $Z_j$ are the design matrices employed for each voxel; and $B_j = (\beta_{1j}, \ldots, \beta_{Nj})$, $G_j = (\gamma_{1j}, \ldots, \gamma_{Nj})$ and $E_j = (\epsilon_{1j}, \ldots, \epsilon_{Nj})$ (Lindquist et al., 2008).

**Localising brain activity**

There are a number of underlying assumptions in most controlled experiments relating to using the GLM approach for localising brain activity in fMRI. These comprise, firstly, that the stimulus function $v_k(t)$ is both already known and equates to the experimental paradigm (e.g., which is a vector comprising zeros and ones, where 1 is a time-point when the stimulus is active, whereas 0 represents a time it is inactive); secondly, that the HRF is known *a priori*; and thirdly, that it reverts to a multiple regression model with known signal components, but not amplitudes (Friston, 2002). In practice, the assumption regarding HRF is not strictly applied.
In considering statistical analysis of fMRI data, the (unadjusted) standard statistical method of comparing group means and variability around those means is not the ideal approach, as it is unable to capture the gradual profile of fMRI responses. This problem is addressed in fMRI analyses by using correlation analyses, which allows the incorporation of the gradual increase and decrease of the predicted BOLD signal.

In a correlation analysis, a predicted gradual time course is used as the reference function. In this process, the time course of the reference function at each voxel is compared with the time course of the measured data, by calculating a correlation coefficient r, which indicates the strength of covariation as follows:

$$ r = \frac{\sum_{i=1}^{N} (X_i - \bar{X})(Y_i - \bar{Y})}{\sqrt{\sum_{i=1}^{N} (X_i - \bar{X})^2 \sum_{i=1}^{N} (Y_i - \bar{Y})^2}} $$

, where t refers to the time points at which pairs of temporally corresponding values occur from the reference \((X_i)\) and data \((Y_i)\) time-courses. In the numerator, the mean of the reference and data time course is subtracted from the corresponding value of each data pair and the two differences are multiplied. In the denominator, the equation normalises the covariation, so that the correlation co-efficient will lie in a range of -1 and +1. Values can be interpreted accordingly, with -1 indicating that the two time courses run in opposite directions, +1 indicating the converse, and a value close to 0 indicating no significant covariance of the two values (Lindquist et al., 2008; Wager and Lindquist, 2015).

A significant correlation coefficient indicates that the two conditions result in different average activation levels in the respective voxel. The statistical assessment can be carried out also by transforming an observed \(r\) value into a corresponding \(t\) value as follows:

$$ t = r\sqrt{N-2} / \sqrt{1-r^2} $$

186
These analytical methods are limited to comparisons of two conditions but the GLM extends these methods to multiple conditions.

Adjusting for multiple comparisons

The fMRI analysis produces a SPM which demonstrates the appropriate brain activations from the study (Figure 2.18). SPMs show brain activation using colour-coding of voxels to delineate those which demonstrate a statistically significance response to the experimental stimulus. The investigators have to consider what threshold they will use to decide that a voxel is activated. Also, since every voxel in every brain is tested simultaneously (representing tens of thousands of hypothesis tests), it is essential to correct the analysis for multiple testings (comparisons) to reduce the likelihood of reporting false positive results.

There are a number of ways in which this correction can be made. The false discovery rate (FDR) is an approach that controls for the expected proportion of false positives (type 1 errors) in the total number of rejected tests (Genovese et al., 2002). The FDR algorithm estimates a single-voxel threshold beyond which there are no more than the specified proportion of false positives. A threshold value of 0.05 means that the null hypothesis has been rejected correctly in 95% of the supra-threshold voxels. The controlling technique lowers the threshold applied as the signal increases in magnitude, and works only on the p-values. The Benjamini-Hochberg procedure (Benjamini and Hochberg, 1995) is the most commonly applied FDR procedure in fMRI analysis. It is particularly used in experiments where a certain number of false positive results can be tolerated. This method effectively applies a very strict threshold for multiple comparisons if there is not much activity in the data, but is associated with comparatively more relaxed thresholds if larger regions of the brain show task-related effects in the experimental condition. The FDR method for correction of multiple comparisons
Figure 2.18 Statistical parametric maps (SPM) of fMRI data.*
* These are used to exhibit the results of the statistical analysis. Voxels whose p-values are less than a specified threshold are colour-coded to indicate that they contain significant task-related signals. The results are superimposed onto a high-resolution anatomical image for presentation purposes.

is the default method used in the neuroimaging processing software BrainVoyager QX. The other method used to adjust for multiple-comparisons is the family-wise error rate (FWER), which controls the probability of making at least one false-discovery (type I error) among all the hypotheses when performing multiple hypotheses tests. In contrast with the FDR method, it is an appropriate test to use when the experimenter wants to ensure there are no false positives at all in the data, and so is a more stringent correction. The random field theory (RFT) (Worsley et al., 2004) technique is the most commonly applied approach for controlling this in fMRI analysis.

Monte-Carlo simulations is a correction method that incorporates the observation that adjacent voxels often activate in clusters. It aims to control the FWER and calculates the likelihood of obtaining different cluster sizes (Foman et al., 1995). In this adjustment method, calculated cluster-extent thresholds are
incorporated into the statistical map ensuring that a global error probability is \( p < 0.05 \). This technique does not involve spatial smoothing and would seem highly appropriate for analysis of fMRI data, the sole disadvantage being that the method is quite computer intensive. This multiple comparisons correction approach is available in BrainVoyager QX through the "Cluster Threshold Estimator" plugin.

The Bonferroni correction is another approach that aims to control the FWER and is a single step approach in which equivalent adjustments are made to each \( p \)-value. It adjusts the single-voxel threshold in such a way that an error probability of 0.05 is retained overall in the experiment. With an \( N \) number of independent tests, this is achieved by using a statistical significance level that is \( N \) times smaller than usual. However, this method is considered to have a number of important flaws in relation to fMRI analysis. Firstly, it could be applied to correct the alpha error if the data in adjacent voxels were truly independent from each other. However, this premise does not hold in fMRI analysis, as adjacent voxels exhibit similar response patterns within functionally defined brain regions. In addition, interpretation of findings depends on the number of other tests performed, which is counter-intuitive, so that Perneger commentated: “Bonferroni adjustments are, at best, unnecessary and, at worst, deleterious to sound statistical inference” (Perneger, 1998). In the presence of such spatial correlations, the Bonferroni correction method is too conservative and corrects more strictly than necessary. As a result of a too strict control of the alpha error, the sensitivity (power) to detect truly active voxels is reduced (so that there is a high probability of type 2 errors), which is undesirable.

Finally, a simple solution to the multiple tests issue is to decrease the number of comparisons by using anatomical data, and most correction techniques can be combined with this approach. Firstly, an intensity threshold for the level of the basic signal can assist in removing voxels based outside the head. In addition masking the brain, by performing a brain segmentation, can further decrease the number of voxels so that these two steps can halve the number of voxels involved to 50,000. Another approach involves restricting statistical analysis to grey matter voxels only, thus removing voxels containing WM and ventricles.
Such anatomically-guided techniques do not require spatial smoothing and make the overall process of detecting true negative results more efficient.

The general linear model (GLM) of analysis
The GLM is mathematically identical to a multiple regression analysis but is particularly suitable for both multiple qualitative and multiple quantitative variables. The GLM can flexibly incorporate multiple quantitative and qualitative independent variables, so that it has become the core tool for fMRI data analysis since its introduction (Friston et al., 1995). Its use assumes that errors are normal, independent and identically distributed (abbreviated as "normal i.i.d."). Under these conditions, the least squares method is preferred as it provides the most efficient unbiased estimation of the beta values.

Considerations and limitations in the application of fMRI methods
There are some issues to consider if fMRI is to work effectively. Firstly, the fluctuations in the MR signal are very short in duration and therefore require a very fast imaging sequence such as an EPI sequence to capture them. Typically, it takes EPI sequences between 1 and 2 seconds to capture fluctuations in the MR signal over the whole brain, through monitoring dynamic changes of several blood parameters including oxygen level, blood volume and blood flow (Ogawa et al., 1990). Moreover, although the change is small in magnitude at smaller field strengths (1.5 Tesla), the ability to detect subtle changes in the BOLD signal is significantly improved at higher field strengths (3 Tesla and higher).

Secondly, the SR of an fMRI study refers to how well it discriminates between nearby brain structures and indicates the smallest feature you can see based on your detector. It is measured according to voxel-size, as in sMRI. A voxel is defined as a 3D cuboid whose dimensions comprise the slice thickness, the slice area, and the grid imposed on the slice by the scanning process. Notably, the spatial resolution of fMRI is excellent, so that it can detect changes in the ratio of oxygenated to deoxygenated blood within a range of just a few millimetres.
Thirdly, temporal resolution can be defined as the smallest increment of time over which a change in an imaged dynamic process can be observed by fMRI. It is indicated by the time gap between consecutive images in MRI. The relevant figure is produced by the formula VPS multiplied by TR, where VPS represents views per segment (a user-defined variable) and TR represents time to repetition. For example, if the TR is 11 milliseconds (ms) and there are 5 views per segment, the temporal resolution would be 55 ms. It is important to note that the BOLD signal response to neuronal activation operates between one and several hundred milliseconds (ms) and is dampened by the haemodynamic response, but that neuronal activation can nevertheless be detected for stimulus periods as short as 0.5 seconds. Therefore, the development of ultra high-speed imaging, especially EPI and its variants, over recent years, have allowed the acquisition of single-image planes in 50 to 100 milliseconds. In addition, EPI has enabled fMRI studies to have unique spatiotemporal features, so that the temporal resolution of fMRI has improved and there is better capture of the neuronal response (better spatial and temporal resolution) for use in investigation of brain activation (Sava and Yurgelun-Todd, 2008).

Nevertheless, there are some limitations to fMRI. For example, the dynamics of the actual biological response to neuronal activation may not accurately reflect neuronal activity in response to a stimulus per se, depending on the stage of response to a neuronal activity stimulus. The biological response to neuronal activation is illustrated in Figure 2.14, which demonstrates the three stages involved. In the first stage, there is typically a lag period of between 1 and 2 seconds between neuronal activation and increased blood flow; in the second stage, there is a 4-6 second delay before peak blood flow is reached; and finally, the third stage involves a return to pre-excitation or baseline blood flow level, via a post-undershoot signal drop below the baseline (Lindquist et al., 2009).

The haemodynamic response typically takes between 6 to 10 seconds to peak (see Figure 2.14). Therefore, according to this biological process activated by neuronal activity, process sequences that detect the BOLD signal at a temporal resolution of 1-2 seconds capture the onset of the haemodynamic response (See Figure 2.14). This method, therefore, has both advantages and
disadvantages. An obvious advantage is that BOLD signals from voxels in proximity to the specified neuronal activity can be compared to those in a state of rest, which can help identify brain structures and regions associated with the particular stimulus task. On the other hand, local alterations in cerebral blood flow can occur without being caused by changes in metabolism of oxygen or glucose (Harris et al., 2011), and further, these changes may be incorrectly interpreted as being directly related to the fMRI task (Logothetis, 2008). In addition, the estimated 25% energy utilisation of the brain not directly related to neuronal activity may be associated with other biological processes including glutamatergic activity, interneuronal activity involving effects of GABA-ergic inhibition on glutaminergic neurons, and activity of locally-acting neuromodulators that can change blood-flow (e.g., nitric oxide, vasoactive intestinal peptide, somatostatin, and neuro-peptide Y) (Bartels et al., 2008; Harris et al., 2011). Therefore, changes in a BOLD signal ROI (i.e., B activation) should not be considered to directly reflect neuronal activation processes only. Nevertheless, this technique is a powerful measure of dynamic processes involving the brain’s large neuronal network and by its ability to do so, is an important investigative tool to assess brain functioning (Sava and Yurgelun-Todd, 2008).

Another limitation of fMRI techniques is that there is significant inter- and intra-subject variability in the haemodynamic response functions that are used for event-related fMRI analysis, and it is necessary to address this variability when performing voxel-wise analysis to examine structure-function relationships (Murphy and Garavan, 2004; Murphy et al., 2006; Miller and Van Horn, 2007).

2.7.3 Methodology used relating to the sMRI and DTI studies of patients with PNES in this thesis

2.7.3.1 MRI and DTI Scanning protocols

MRI anatomical scanning protocol
All scanning was conducted on a Philips Achieva 3.0 T equipped with a mirror that reflected the display projected on a 640 x 480 panel placed behind the subjects' head, outside the magnet. The mirror was mounted on the head coil in the subjects' line of vision. 180 axial high-resolution T1-weighted anatomic SPGR images (TE = 3.8 ms, TR = 8.4 ms, FOV 230 mm, 0.898 x 0.898 mm² in-plane resolution, slice thickness 0.9 mm, flip angle $\alpha = 8^\circ$) were acquired before the first functional imaging, to allow subsequent activation localisation and spatial normalisation.

**DTI scanning protocol**

Diffusion weighted images were obtained using spin-echo echo-planar imaging (SE EPI) pulse sequence (TE = 52 ms, TR = 11,260 ms, flip angle $\alpha = 90^\circ$, FOV 224 mm, 60 axial slices 1.75 x 1.75 mm² in-plane resolution, slice thickness 2.5 mm, no gap, $b$-value = 800 s mm⁻² in 15 non-collinear directions. The start of each series of directions was preceded by acquisition of a non-diffusion-weighted volume ($b = 0$) for the purpose of image registration and motion correction.

### 2.7.3.2 Pre-processing of sMRI and DTI data

The MR images were collected in Philips PAR and REC format and NIFTI file format for DTI and VBM analyses respectively. Structural analysis was performed using FSL, Oxford, UK, http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSL. A voxel based morphometry analysis was carried out using the FSL-VBM toolbox (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLVBM).

### 2.7.3.3 VBM data processing and analysis

To investigate possible structural brain differences between subjects with PNES and matched healthy controls, an ‘optimised’ VBM analysis was performed using FMRIB FSL VBM tools (Smith et al., 2004). Voxel-based morphometry is a voxel-wise automated analysis technique performed on high resolution structural images to investigate differences in local concentrations or volumes (with the inclusion of a modulation step) of grey and white matter [see...
Ashburner and Friston, 2000) and (Good et al., 2001) for detailed descriptions of the standard and optimised VBM methods. In summary, the FSL-VBM protocol created study-specific template images for normalisation of grey, white and CSF tissue classification maps from a constrained sample of 40 subjects (n= 20 people with PNES and n=20 healthy controls) to avoid group bias, utilising brain-extracted structural images using BET (Smith, 2002). The native grey and white matter images were non-linearly registered to the study specific templates and modulated (to correct for local expansion or contraction) by dividing by the Jacobian of the warp field. These modulated segmented images were then smoothed with an isotropic Gaussian Kernel with a sigma of 3 (~8mm FWHM).

2.7.3.3.1 MRICro

MRICro is a comprehensive software program that allows efficient visualisation of images from many different modalities including MRI, Computerised Axial Tomography (CAT, CT), Positron Emission Tomography (PET), Single Photon, Emission Computed Tomography (SPECT), Scanning Electron Microscopes (SEM) and 3D ultrasounds. It can be employed to view the NIfTI format of medical DICOM images popular with scientists and export medical images, including brain images, to other platforms (Rorden and Brett, 2000). During use, an image can be viewed simultaneously in horizontal, sagittal and coronal sections, so that a synchronised crossbar placed on a particular position of the brain surface on any of the three orientations of the MR image shows the same position simultaneously on the other sections. It has user-friendly tools that can be used to complement SPM software, a well-known package that is often used by neuro-imagers to analyse MRI, fMRI and PET images. Also, it can be used to identify and delineate ROIs. This is useful for illustrating regions of the brain that have sustained damage. In addition, the volume of the ROI is computed. Moreover, ROIs from different individuals can be overlapped (on brain images that have been normalised to the same template) allowing neuropsychologists to assess common areas of damage. The 'Overlay' menu allows you to select an image which is superimposed on top of another image. This is useful for displaying functional statistical maps (generated by SPM from PET, fMRI or
SPECT data). Overlays can also be used to check the co-registration of two images.

The statistical toolbox of MRICron was used to carry out voxel-wise non-parametric FDR statistical tests, featuring Brunner Munzel t-tests, for the purpose of group comparisons and the identification of global grey and white matter volume differences. Significant voxels passed a voxel-wise statistical threshold ($p \leq 0.05$ FDR corrected for multiple comparisons). To define findings more clearly, a second minimum cluster size criterion of 5µl (0.005mL) was applied, so that single and very-small clusters were removed, and larger and more extensive statistically-significant clusters were retained.

Data analysis and pre-processing was performed using ExploreDTI software (http://www.exploredti.com/). ExploreDTI is a graphical toolbox that has been designed for processing, analysing, and visualising diffusion MR data as well as to perform exploratory diffusion (tensor) MRI and fibre tractography (Leemans et al., 2009a). In this study, ExploreDTI was used to perform motion/distortion correction, B-matrix rotation, and robust estimation of tensors by outlier rejection (RESTORE) (Chang et al., 2005; Leemans and Jones, 2009b). FA images per subject were obtained from the motion and distortion corrected diffusion data for each subject for the purpose of white matter FA analysis.

### 2.7.3.3.2 DTI white matter statistical analysis using FSL

Initially, voxel-wise statistical analysis of the FA data was carried out using TBSS (Smith et al., 2006) as part of FSL (Smith et al., 2004). First, FA images were brain-extracted using the BET (Smith 2002). FA data were then aligned into a common space using the nonlinear registration tool FNIRT (Andersson et al., 2007a; Andersson et al., 2007b), which uses a b-spline representation of the registration warp field (Rueckert et al., 1999). Next, the mean FA image was created and thinned to create a mean FA skeleton, which represents the centres of all tracts common to the group. Each subject's aligned FA data were then projected onto this skeleton and the resulting data subjected to voxel-wise between-group statistics.
2.7.3.3 Regions of interest (ROI) analysis

We hypothesised that specific brain structures would demonstrate more subtle patterns of change localised to specific neurological systems reported in the literature. Therefore, specific standard-space template masks for the temporal region, frontal region, thalamus and amygdala, were constructed in FSL, using the MNI Structural Atlas and Harvard-Oxford Cortical and Sub-cortical Structural Atlases respectively. These brain regions are known to play an important role in normal emotional processing, executive functioning and regulation of movement and we deemed them important focal areas for further secondary analyses to investigate potential differences in neural regions subserving these functions in PNES. The binarised masks were applied to the VBM and DTI analyses independently. These grey and white matter masks are standard MNI space structural atlases found in FSL and cover grey and white matter tissue compartments of the brain. The resolution of these standard space masks was selected at 2mm for the VBM data and 1mm for the DTI data. Voxel-wise nonparametric FDR statistical Brunner Munzel t-tests were then conducted within each mask ROI. Significant voxels passed a voxel-wise statistical threshold \((p \leq 0.05\) and \(p \leq 0.01\) corrected for multiple comparisons for VBM and DTI analyses respectively) with an additional minimum cluster size criterion of 5\(\mu\)l.

2.7.4 Methodology used relating to the fMRI studies of PNES in this thesis

2.7.4.1 fMRI Scanning protocol

2.7.4.1.1 fMRI Imaging parameters

All scanning was conducted on a Philips Intera Achieva 3.0 Tesla MR system (Best, The Netherlands) at TCIN. The scanner was equipped with a mirror that
reflected a 640 x 480 pixel display projected on a panel placed behind the subject's head, outside the magnet. The mirror was mounted on the head coil in the participants' line of vision.

Imaging started with 31.5 seconds of standard scout images to adjust head positioning, followed by a reference scan to resolve sensitivity variations. Imaging used a parallel SENSitivity Encoding (SENSE) approach (Pruessman et al., 1999) with reduction factor 2. 180 high-resolution T1-weighted anatomic magnetisation-prepared rapid gradient echo (MPRAGE) axial images (FOV 230 mm, thickness 0.9 mm, voxel size 0.9 x 0.9 x 0.9) were then acquired (total duration 6 minutes), to allow subsequent activation-localisation and spatial normalisation. Thirty-two non-contiguous (10% gap) 3.5 mm axial slices covering the entire brain were collected using a T2* weighted echo-planar imaging sequence (TE = 35 ms, TR = 2000 ms, FOV 224 mm, 64 x 64 mm matrix size in Fourier space).

2.7.4.1.2 Stimuli and behavioural protocol

Emotional processing (face discrimination) task
Implicit processing in humans has been specifically associated with activation of the amygdala in particular, but also involves some activation of other structures including the fusiform gyri, temporal lobe and thalamus (Critchley et al., 2000). In this experiment, a face-discrimination task that involves the participant simply making a decision about the gender of presented-faces, was employed. This gender-decision task has been demonstrated to assess implicit neural mechanisms for processing emotional information and found to be reliably associated with activation of subcortical (e.g., amygdala), prefrontal and extra-striate regions in healthy humans (Morris et al., 1996; Phillips et al., 1997) (Figure 2.19).

Subjects participated in three 6-minute fMRI experiments for presentation of emotional and neutral facial stimuli, with each experiment displaying stimuli for one specific emotion. In each experiment, subjects were presented with circumscribed facial expressions exhibiting one of three primary emotions (fear,
Implicit Processing Experiment

Figure 2.19 Implicit processing fMRI experiment using facial expressions of fear, disgust & sadness (respectively) at neutral, 50% & 100% intensity.

disgust, sadness), interspersed with neutral expressions, from a standardised series of prototypical facial expressions posed by 10 different volunteers (four male and six females) (Young et al., 2002) (Ekman & Friesen, 1976). The emotional stimuli (showing fear, disgust and sadness) were presented at two levels of intensity (50% and 100%). For this study, facial stimuli from this set expressing fear, disgust and sadness were termed 100% disgust, 100% fear, and 100% sadness, respectively. These faces were computer-transformed to create the 50% level of intensity for all three emotions. The creation of the 50% intensity image involved the image being positioned with its features 50% along the continuum from neutral to the sadness, fear and disgust prototypes. Figure 2.20 illustrates an example of faces and the emotions displayed for each of the three experiments.

In each experiment, faces depicting 50% emotion, 100% emotion and neutral expression were projected in pseudo-randomized order, one at a time, for 2000 ms each (with randomised inter-stimulus intervals during which a fixation cross appeared on screen for a period varying between 3 to 8 seconds).

60 faces were presented in each block – 20 neutral facial stimuli, 20 50% emotional stimuli and 20 100% emotional stimuli. The experiment involved presenting faces showing both neutral expressions and emotional stimuli. Implicit processing would be assessed by the participant attending to and judging the gender of faces presented. Therefore, the subjects were asked to
Figure 2.20 Examples of the morphed stimuli utilised in the fMRI experiment. The stimulus range was from 100% neutral to (A) 100% fear, (B) 100% disgust and (C) 100% sadness, in 50% increments.

perform a simple gender recognition task where they simply had to indicate whether each face presented was male or female. Subjects were trained to use the in-scanner signalling device to register their decisions through pressing one of two buttons ("X" or "Y") on a stimulus box with their right thumb, so that if they thought the face presented was male they pressed ‘X’, and if female, ‘Y’. The task was programmed using E-Prime version 1.1 (Psychology Software Tools, Pittsburgh, USA). Subjects were explicitly not informed about the aim of this
particular experiment. During scanning, behavioural response data, including task accuracy, commission errors, omission errors and response time, were acquired on a PC for off-line behavioural analysis.

### 2.7.4.2 fMRI data processing and analysis

The fMRI data were processed and analysed using the analysis of functional neuroimages (AFNI) software package (Cox, 1996). Following image reconstruction, time-series data were time-shifted using Fourier interpolation to remove differences in slice acquisition times. Images were then motion-corrected using 3-D volume registration, involving a least-squares alignment of three translational and three rotational parameters. Activation outside the brain was removed using edge detection techniques. Event-related designs were analysed using time-series deconvolution techniques to estimate HRFs where the best fitting haemodynamic shape (using a gamma variate function) was determined for each voxel for face presentation periods using a nonlinear regression algorithm (Ward et al., 1998).

Activation measures are the area-under-the-curve of the haemodynamic response expressed as a percentage of the area under the baseline. Activation measures are derived from the percentage change in signal between task active and control condition periods. Activation maps were warped into a standard stereotaxic space (Talairach et al., 1988) and spatially blurred with a 4.2-mm full-width at half-maximum isotropic Gaussian kernel after performing a second edge detection on the skull stripped brain.
Chapter 3:

Study 1

The prevalence of PNES in the epilepsy monitoring unit of an Irish tertiary referral centre for epilepsy

This chapter retrospectively investigates the clinical database of patients that have been evaluated by Beaumont Hospital’s epilepsy monitoring unit to have their seizure-like events classified, over a period of three years. The aim was to specifically investigate the proportion of patients diagnosed with PNES in this specific population.

3.1 Setting for Study

Beaumont Hospital is the National Irish referral centre for Neurosurgery and has the most comprehensive Neurology service in the country, catering for over 2,000 neurosurgical and 800 neurology patient admissions per year. Its facilities include a specialised epilepsy monitoring unit (EMU).

3.2 Referral process to the epilepsy monitoring unit (EMU)

Patients are referred to Beaumont Hospital’s consultant neurologist and specialist epileptologist (Professor Norman Delanty) from consultant general/
internal physicians throughout the country, for an expert opinion on
classification and management of patient's seizure-like conditions. Typically,
patients are referred from other secondary-care settings based in the Republic
of Ireland (comprising a total population of over 4.7 million people) by specialist
physicians to the EMU for assistance with i) classifying seizure types; ii)
determining the frequency, type and nature of patient's episodes; iii)
distinguishing epileptic from non-epileptic disorders (e.g., syncope, cardiac
arrhythmias, transient ischaemic attacks, movement disorders, PNES and sleep
disturbances), iv) obtaining better control of seizures using medication, iv)
evaluating patients for their suitability for epilepsy-surgery.

On receipt of an external referral, the consultant epileptologist reviews the
information provided and may arrange that his team assess the patient
concerned either as an outpatient or inpatient. Following this preliminary
assessment at BH, he may decide that further admission to the EMU is
appropriate. Patients who may benefit from admission to the EMU include
patients who have treatment-resistant or intractable epilepsy, epileptic attacks
which are unclassified or are suspected of having a non-epileptic aetiology, and
patients for whom epilepsy surgery is being considered. The epileptologist then
refers the patient to a waiting list for EMU assessment. Cases are prioritised
according to the severity of their clinical presentation and the epileptologist
closely monitors and manages the waiting list (at least once weekly) according
to medical-priority of referred cases. It may take up to two years for a patient on
the waiting list to be admitted to the EMU, during which time they continue to be
managed by the treating secondary-care physician.

3.3 Role of the EMU

With a full complement of staff in the clinical neurophysiology department and
dedicated EMU staff nurses, the unit can monitor four patients at a time. The
principal function of the EMU is to accurately classify the types of seizure-event
each patient presents with, and to delineate epileptic disorders from those that
are non-epileptic in nature. Examples of non-epileptic conditions that may
resemble epileptic seizures include syncope, cardiac arrhythmias, transient ischaemic attacks, movement disorders, psychogenic seizures and sleep disturbances. Once patients are admitted to the unit, they are video-taped and have their EEG recorded continuously. EEG and video-recorded clinical features are correlated to confirm diagnoses and to localise a seizure focus. Also, the EMU team gathers as much information as possible in conjunction with the patient and their family or care-givers, to determine the frequency, type and nature of the patient’s episodes that they usually experience.

During their stay in the EMU, patients may have their anti-convulsant medication carefully reduced or withdrawn to increase the possibility of recording seizure activity. The EEG technologists and nurses are specially trained in recognising and responding to seizures.

There is no standard period of admission to the EMU. Rather, patients remain monitored until at least one example of a typical event or events are captured by vEEG and video-recorded. For example, if the patient has a history of different clinical presentations of seizure-like events, they remain in the EMU until all typical seizure-like events are captured. In this way, seizure-events which represent epileptic and non-epileptic etiology may be identified.

The EMU at BH is a vital component of the epilepsy service, including the national surgical programme. In cases where a diagnosis of epilepsy is confirmed, the specialist EMU assessment assists the team in deciding if patients are potentially suitable for epilepsy surgery. Surgery may be indicated, for example, if there is a clear and discrete epileptogenic focus found that is amenable to surgical correction or excision. The assessment will also help the treating team decide what treatments may offer better control of epilepsy, including, for example, options for combined anticonvulsant therapy.

On admission to the EMU, all patients are referred for neuropsychological and neuropsychiatric assessment as part of the multidisciplinary team approach to assessment and management of care. Typically, patients are assessed by the neuropsychiatry registrar on the same day of admission. Assessment is made according to clinical criteria, unless patients are enrolled in a prospective research study. In this study, which was both retrospective and ongoing in
nature over the specified period, diagnoses were made according to clinical
criteria and opinion. Consent for access to previous psychiatric and medical
case-notes is typically received and the relevant clinical centres are phoned and
faxed that day to ask them to forward summaries of relevant diagnostic and
care-planning records. In addition, each EMU patient assessed by the
neuropsychiatry registrar receives a consultant psychiatrist review within 3
working days of that preliminary assessment. This assessment and any
management recommendations (for an identified mental disorder) is recorded in
the patient’s medical case-notes.

EMU patients whose seizure-like events are classified as being of “functional”
etiology receive feedback from the neurological team about their assessment
results and are referred for a second time to the neuropsychiatry team for a
follow-up assessment, before they are discharged. The neuropsychiatric team
review the patient to determine the psychiatric diagnosis, which in practice is
most often one of conversion disorder (psychogenic non-epileptic seizures), if
malingering or factitious disorder is out-ruled. This assessment may include
review of collateral information from previous medical and psychiatric
assessments and collateral information from next of kin. Once the diagnosis is
made, feedback is given to the patient and their next of kin (as appropriate) and
a preferred management and follow-up plan is explicitly outlined and liaison
made with the appropriate health facility to communicate these
recommendations and to formalise these follow-up arrangements.

3.4 Objectives of the Study

The objectives of the study were first, to determine the prevalence of
psychogenic non-epileptic seizures in patients attending BH’s EMU and
secondly, to determine how patients diagnosed with PNES were subsequently
managed by the clinical teams, to determine if this process could be improved.
The study hypotheses have been outlined previously in Section 2.3.
Figure 3.1 Flowchart showing overall results of initial neuropsychiatric assessment of all patients attending EMU (before diagnosis of PNES).
3.5 Methodology of the Study

The methodology of this study, including that relating to the sourcing, extraction and analysis of data has been previously outlined in Section 2.5.1.

3.6 Results relating to general neuropsychiatric assessment of patients attending the Epilepsy Monitoring Unit (EMU)

Two-hundred and twenty-five patients were admitted to the EMU for assessment over the three year period of study, and of these, 98% (n=220) were assessed by the neuropsychiatry team. The remaining 2% (n=5) who had not been psychiatrically assessed comprised a small number of patients who had either refused psychiatric assessment (n=2), who had self-discharged before neuropsychiatric assessment could occur (n=2), or who had been diagnosed with non-epileptic seizures caused by medical reasons other than epilepsy (n=1), and not presenting with obvious psychiatric symptoms.

3.7 Diagnostic information and demographic data relating to the patients who underwent EMU assessment

Of the total patients referred for neuropsychiatric assessment before classification of their seizure-type, one hundred and fifty-one (67%) patients were female, seventy-four (33%) were male. Of the patients diagnosed with PNES (n=44), thirty-six (82%) of those with PNES were female and the average
age [standard deviation (SD)] of people presenting with PNES was 36 (+/-11) years. Age did not differ significantly between genders ($p = 0.47$). Of the group of patients that had been assessed by neuropsychiatry (n=220), ninety-seven (44%) were found to have a current or past history of mental disorder and had an average age (standard deviation) of 34.8 (+/-11.4) years. The flowchart shown in Figure 3.1 outlines clinical assessment of the patients in this study.

**Table 3.1 Results of video electroencephalography (vEEG) and neurological assessment of patients in the EMU**

<table>
<thead>
<tr>
<th>Diagnosis after vEEG</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epilepsy</td>
<td>180</td>
<td>80</td>
</tr>
<tr>
<td>NES of medical cause (syncope)</td>
<td>1</td>
<td>0.4</td>
</tr>
<tr>
<td>PNES &amp; Epilepsy</td>
<td>14</td>
<td>6.2</td>
</tr>
<tr>
<td>PNES alone</td>
<td>30</td>
<td>13.3</td>
</tr>
<tr>
<td><strong>Total number of patients assessed in EMU</strong></td>
<td>225</td>
<td>100.0</td>
</tr>
</tbody>
</table>

NES, non-epileptic seizures of medical origin; n, number; %, percentage; PNES, psychogenic non-epileptic seizures; EMU, epilepsy monitoring unit.

The overall prevalence rate of PNES in all patients who completed neurological assessment in the EMU was 19.5% (Table 3.1), and PNES was the most frequent psychiatric diagnosis (42%) in those found to have an acute psychiatric disorder in this sample-population (Figure 3.2). PNES and epilepsy were found to be present co-morbidly in just over 6.2% of patients attending the EMU (Table 3.1).

Of the group diagnosed with PNES, thirty-six (82%) were female and the average age (standard deviation) of people presenting with PNES was 36 (+/-11) years.
Figure 3.2 Psychiatric Diagnosis in EMU Patients (after neuropsychiatric assessment).

PNES, psychogenic non-epileptic seizures; Depression, depressive disorder; Anxiety, anxiety disorder; L. Disability, intellectual disability; Personality, personality disorder; Psychosis, psychotic disorder (schizophreniform); Other, other mental disorder not specified.

*Explanatory note: 97 patients had a current or past history of mental disorder, and there were 105 diagnoses made in this group. The figures provided above relate to proportion of each disorder in relation to overall number of diagnoses. (For example, n=44 had PNES, and 44/105=42%).

Fifteen people (34%) diagnosed with PNES also had a documented history (in their clinical case-notes) of previously diagnosed psychiatric illness, with depressive disorder (20%) being the most common mental health condition reported within that subgroup (Figure 3.3).

None of the patients with newly-diagnosed PNES were found to have an acute mental disorder (apart from dissociative-conversion disorder) that wasn’t already being treated.
3.8 Management of patients after diagnosis with PNES

Management involves presenting the diagnosis in a sensitive and positive manner, answering any queries the patient and their families may have and arranging appropriate follow-up treatment. Each of these steps are discussed in turn.
3.9 Presentation of the diagnosis of PNES & immediate follow-up as an EMU inpatient: the prevailing modus operandi and pathway to care

All patients diagnosed with PNES were initially reviewed by the neurology team to explain the medical diagnosis of functional neurological disorder and to plan tapered reduction and stopping of their anticonvulsant drugs if appropriate (i.e., if no co-existing epilepsy). The *modus operandi* of the consultant-led team involved presenting the diagnosis of PNES as a (relatively) positive finding, in that fortunately the patient did not have epilepsy or other discernible major neurological illness causing their symptoms and so did not need to be taking anticonvulsant medications. Within that framework, the diagnosis of PNES was presented as being of unknown cause but that stress was believed to be a triggering factor. The prevailing recommendations (at that time) were that once a patient was diagnosed with PNES, they were referred for neuropsychiatric and neuropsychological assessment in Beaumont Hospital, to take place before they were discharged from the EMU. If a patient was diagnosed as having co-morbid PNES and epilepsy, the neurological team presented them with information on both conditions, with PNES being explained as a co-morbid condition with different treatment and follow-up recommendations compared with those of epilepsy. These patients with co-morbid PNES and epilepsy were advised relating both to the particular medical treatment relevant to their epilepsy-type, and referred for neuropsychiatric and neuropsychological follow-up in the same way as for those diagnosed as having just PNES.

After the neurological team presented the diagnosis of PNES to the patient, they were referred to both of the neuropsychiatry and neuropsychology teams. However, there was no written policy in place at the time to guide which mental health professionals would follow-up with a particular patient after this process. Patients were reviewed by the neuropsychiatry team to formally diagnose PNES as a conversion disorder as appropriate, and to formulate a treatment plan with the patient, unless they refused to see a psychiatrist or discharged themselves against medical advice before this assessment could occur. The aim of the neuropsychiatric assessment was to identify co-morbid psychiatric pathology.
and to carry out a needs’ assessment of the level of psychiatric input the patient would require on follow-up.

For those patients found to have no other discernible psychiatric disorder apart from PNES (conversion disorder) (66%), they were offered or advised to seek further psychological assessment to explore their personal psycho-social circumstances, to help them identify any coping difficulties, and to manage their symptoms with psychological treatment. This psychological assessment was provided by the Beaumont Hospital neuropsychological team if the patient lived locally. If however, the patient lived outside of Beaumont Hospital’s catchment area or were already attending a local community-mental health service, they were usually referred onwards for follow-up to the relevant community mental-health team. For those patients found to have concurrent active psychiatric illness or disorder (34%), they were either commenced on the appropriate pharmacological treatment for their mental illness and referred to the neuropsychiatric outpatient clinic at Beaumont Hospital for follow-up (if living locally), or referred to their local community psychiatric service. Patients who were already receiving treatment for a mental disorder were referred back to their local community mental-health team.

Patients were reviewed by the neuropsychology team to make an assessment of their psychosocial circumstances, potential triggering factors for PNES events and coping style. They were also assessed regarding their motivation and suitability for cognitive behavioural therapy (CBT) at that time. The psychology services in Beaumont hospital used a specific paradigm for approach to treatment of PNES, developed by a psychologist who had worked there (unpublished). However, there was no information available regarding the nature of psychological treatment available for PNES in community-based teams. There was no written policy in place to guide neuropsychological assessment and follow-up procedures.
3.10 Results of follow-up of patients diagnosed with PNES in the EMU

There was no data available in the medical records indicating the factors and process of decision-making about follow-up arrangements for a particular patient. I present the findings relating to actual follow-up decisions documented in the clinical case-notes.

Eleven people (73%) diagnosed with PNES and with a previous history of psychiatric disorder were followed up by their local community mental health team and the remainder (27%) by the specialist neuro-psychiatry service in Beaumont Hospital (Table 3.2).

Eleven people (38%) diagnosed with PNES and with no previous history of mental illness were formally followed-up by psychiatry services: seven (24%) by a specialist neuropsychiatry service and four (14%) by local psychiatry services.

Overall, thirty-four people (77%) diagnosed with PNES were referred to psychology services for follow-up treatment: twenty-six (59%) to the specialist neuropsychology service in Beaumont Hospital and eight (18%) to local community-based psychology services. There were no records relating to neuropsychology follow-up in the medical case-notes for the remaining ten (23%) patients diagnosed with PNES so that it appeared they had not been reviewed by neuropsychology after diagnosis of PNES and prior to medical discharge from the EMU.

Of the twenty-six patients diagnosed with PNES that were referred to Beaumont Hospital’s specialist neuropsychology outpatient clinic for follow-up, none had co-morbid active psychiatric illness. Of these patients referred for neuropsychological follow-up, 79% of these patients (n=23) had no reported previous history of mental illness, while 20% (n=3) had, but appeared in remission at the time of referral. Two of the patients diagnosed with PNES (4%) refused all specialist treatment recommendations after being presented with the diagnosis of PNES by the neurology team (Table 3.2).
Table 3.2 Referrals of patients diagnosed with PNES for follow-up after discharge from EMU

<table>
<thead>
<tr>
<th>Referral for specialist treatment upon diagnosis of PNES</th>
<th>Those with no psychiatric diagnosis other than PNES / conversion disorder (n=29)</th>
<th>Those with a co-morbid psychiatric diagnosis with PNES / conversion disorder (n=15)</th>
<th>Overall (n=44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct referrals for psychological follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beaumont neuropsychology service</td>
<td>23 (79%)</td>
<td>3 (20%)</td>
<td>26 (59%)</td>
</tr>
<tr>
<td>Local community psychology service</td>
<td>0 (0%)</td>
<td>8 (53%)</td>
<td>8 (18%)</td>
</tr>
<tr>
<td>Direct referrals to psychology services overall</td>
<td>23 (79%)</td>
<td>11 (73%)</td>
<td>34 (77%)</td>
</tr>
<tr>
<td>Direct referrals for psychiatric follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beaumont neuropsychiatry service</td>
<td>7 (24%)</td>
<td>4 (27%)</td>
<td>11 (25%)</td>
</tr>
<tr>
<td>Local psychiatry service</td>
<td>4 (14%)</td>
<td>11 (73%)</td>
<td>15 (34%)</td>
</tr>
<tr>
<td>Overall direct referrals for psychiatric follow-up</td>
<td>11 (38%)</td>
<td>15 (100%)</td>
<td>26 (59%)</td>
</tr>
<tr>
<td>Refused Specialist Treatment</td>
<td>2 (7%)</td>
<td>0 (0%)</td>
<td>2 (4%)</td>
</tr>
</tbody>
</table>

PNES, psychogenic non-epileptic seizures.
Note: According to medical case-notes, 23% of all patients diagnosed with PNES were not referred for psychological assessment; 57% were not referred for any psychiatric follow-up.

3.11 Discussion

We found that almost 20% of patients who attended an Irish specialist neurology inpatient unit for evaluation of seizures had PNES. This prevalence rate is consistent with that (20-50%) reported in the few previous studies carried out in specialist neurology centres in other countries (Gates, 2000; Benbadis et al., 2001). Also, our finding that 6% of patients attending the EMU had co-existing PNES and epileptic seizures is within the range reported (5-50%) from other similar studies (Benbadis et al., 2001; Martin et al., 2003; Sigurdardottir et al., 1998; Howell et al., 1989). However, these rates are likely to underestimate the true prevalence of PNES in patients attending the general epilepsy service as only those who were referred for video EEG monitoring were included in this study. Also, it is difficult to reliably extrapolate the prevalence rates we report to those present in other specialist epilepsy services as admission criteria to
VEEG facilities may differ according to local resources and other pressures (for example, assessment of suitability for neuro-surgery). We found that only four out of the forty-five patients (4%) diagnosed with PNES refused specialist follow-up treatment with mental health services. This is a significantly lower rate of follow-up with specialist treatment than that (23%) reported in the one previous study examining reactions of patients with PNES to diagnosis and referral for treatment (Carton et al., 2003). However, although the reason for our low finding is unknown, recent studies suggest that patients with PNES are more likely to have a positive outcome with a multidisciplinary approach to treatment including specialised neuropsychiatry and neuropsychology input Reuber, 2005b; Mellers, 2005). The management model of PNES outlined in this study is consistent with this multi-disciplinary approach so that all patients receive standard assessments by neurology, neuropsychiatry and neuropsychology teams, both pre- and post-characterisation of seizures. Also, these assessments are reviewed routinely and discussed at regular ward rounds and inter-disciplinary meetings to help formulate appropriate plans, so that management of people with PNES is consistent and co-ordinated. Therefore, this approach may serve to improve therapeutic alliance and patient compliance with treatment recommendations (Aboukasm et al., 1998). Nevertheless, further studies examining modes of management and long-term outcome in these patients are necessary.

Our finding that one-third of people with PNES had other co-morbid psychiatric disorder is less than other reports suggesting prevalence rates of 43-100% (Bowman and Markand, 1996; Bowman, 2001). The reason for this finding is unknown. However, our study was retrospective and data were obtained from psychiatric assessments based on clinical interview and available collateral information. In contrast, those studies which reported higher prevalence rates were prospective in nature and employed structured clinical interview schedules and standard rating scales to evaluate psychopathology using, for example, the Structured Clinical Interview Schedule (SCID) and Minnesota Multiphasic Personality Inventory (MMPI) (Bowman and Markand, 1996; Bowman, 2001). Thus, the discrepancy in prevalence rates may be explained by heterogeneity in study methodology. For example, evaluation of psycho-symptomatology using standardised semi-structured interviews is likely to increase sensitivity to...
detection of co-morbid psychiatric disorder. Also, duration of admission to the EMU was quite short in some cases (3-5 days) so that it is possible that a more detailed history of, for example, abnormal illness behaviour and previous psychiatric contact may have been under-reported or unavailable for some patients interviewed during their period of admission. Nevertheless, our study adds to current evidence of high rates of psychiatric co-morbidity in people with PNES.

We found that many (58%) newly diagnosed patients with PNES were followed-up by Beaumont Hospital’s psychology service alone and not formally referred to the Neuropsychiatry services for later review. Further, only 23% (n = 7) of those newly diagnosed with PNES with no previous psychiatric history and 27% (n = 4) of patients with PNES and a previous history of psychiatric disorder were followed up by the specialist Neuropsychiatry service. However, while most patients were offered specialist treatment within the our epilepsy service framework, many were referred to their local community mental health teams (CMHT) for follow-up on the basis of patient preference (many were living outside Dublin and could not easily access the Beaumont Hospital service) and whether they were already engaged with their local CMHT for treatment of previously existing mental health problems.

In our study, 75% (n=34) of all people diagnosed with PNES were referred for psychological therapy. However, a recent Cochrane Review of behavioural treatments for PNES concluded that there is no reliable evidence to support the use of any behavioural treatment of PNES and recommended that randomised studies of all behavioural interventions are required Brooks et al., 2007).

Stone and colleagues reported that patients with PNES were less likely than those with epilepsy to see psychological factors as relevant to their symptoms, more likely to deny that they have suffered from life stress and also to have a more external locus of control (Stone et al., 2004b). They suggested that psychological treatment specifically designed to modify denial and locus of control may be useful although randomised controlled trials are required to test this hypothesis.

In this current study, the specialist neuropsychiatry service were more likely to follow-up those people with PNES who had a co-morbid psychiatric disorder
The **neurology team** meet with the patient and their next of kin (if consented to by adult patient) to explain:

1. That the assessment findings demonstrate that the patient’s seizure-events are PNES. This information is delivered clearly, positively, and sympathetically.
2. That anti-epileptic medication will be tapered and stopped completely (if the patient does not have co-presenting epilepsy).
3. That treatment for PNES will be delivered through neuropsychiatry and neuropsychology teams.

The **neuropsychiatry team** meets with the patient to:

1. Review the patient and formally make a psychiatric diagnosis of dissociative-conversion disorder (where no other psychiatric diagnosis applies).
2. Confirm that no-other co-morbid psychiatric disorder is present (e.g., post-traumatic stress disorder).
3. Explain the diagnosis and recommended treatment.
4. Decide if psychopharmacological intervention is appropriate.
5. Decide what psycho-social interventions and supports, apart from psychological therapy, are appropriate.
6. Arrange follow-up with neuropsychiatry and other psychiatric services as appropriate.

The **neuropsychologist team** meets with the patient to:

1. Explain the role of psychological therapy in treating PNES.
2. Explore possible etiological issues relating to trauma, coping style, etc.
3. Assess for appropriate motivation and suitability to undergo psychological therapy.
4. Decide which type of psychological intervention is appropriate to the patient’s needs (e.g., cognitive behavioural therapy).
5. Make follow-up arrangements.

Thereafter the neuropsychologist liaises regularly with the neuropsychiatry team regarding the patients progress and to arrange neuropsychiatry review as appropriate and after psychological treatment is completed.

There are regular multidisciplinary meetings (neurology, neuropsychiatry and neuropsychology) to:

- Discuss management and follow-up of patients with PNES.
- Arrange discharge and liaison with other health services as appropriate.

**Figure 3.4 Recommendations for multidisciplinary follow-up after vEEG diagnosis of psychogenic non-epileptic seizures.**
requiring change in psychotropic medication and ongoing psychiatric monitoring (40% of those with co-morbid disorder). In contrast, only two (12%) of those followed up by their general practitioner had co-morbid psychiatric disorder (all depressive disorder) and neither had a previous psychiatric history. Nevertheless, available evidence suggests that over 44% of these patients continue to have seizures and be dependant on healthcare services 10 years after diagnosis (if untreated) (Reuber et al., 2003c). Also, people with PNES have an increased risk of developing further psychiatric co-morbidity if psychological and psychiatric treatment is not available or unsuccessful (Reuber and Elger, 2003b). Therefore, it is necessary to formulate a clear multidisciplinary framework and international best practice guidelines for acute management and follow-up for patients with PNES.

In common with people with other neuropsychiatric disorders, people with PNES benefit most from treatment within the context of a multidisciplinary team that includes psychiatrists, neurologists and psychologists (NICE, 2004). In our experience, such a model facilitates a comprehensive and co-ordinated approach to diagnosis and treatment.

We suggest that the approach outlined in Figure 3.4 may be useful in guiding management and follow-up of people with PNES and we have now adopted this model in our Centre. However, more research, particularly involving randomised controlled trials of treatment interventions, is urgently required for this vulnerable patient group.
Chapter 4:

Study 2

Psychiatric and neuropsychological profiles of patients with psychogenic non-epileptic seizures

This chapter investigates and compares the psychiatric, neuropsychological and neurocognitive profiles of a group of patients with PNES with those of a healthy control group, matched for age and gender. The aim of this study was to specifically investigate the hypotheses that patients with PNES firstly, have significant levels of emotional dysregulation and dissociative conversion symptoms, and also share co-morbidity with psychiatric disorders that involve affective dysfunction, and secondly, that they have significant impairments on performance of executive functioning tasks, especially those relating to attention and working memory.

4.1 Summary of chapter

It has been proposed that patients with PNES have abnormal emotional and neurocognitive processing. However, results from previous studies have been inconsistent and evidence suggests that performance on neuropsychological assessment is affected by potential confounding variables such as the presence of neuropathology and psychopathology, and further, that the results of these
tests can be modulated by the degree of effort applied to the experimental tasks. Therefore, this study investigated and compared the results of comprehensive psychiatric and neuropsychological assessment in a group of 20 adult patients with PNES and 20 age and gender-matched healthy-controls, while known potential confounders of performance were taken into account in the study design. Only those participants who passed a validated test of effort had their data included in the analysis.

One patient failed the effort test so that they and their matched control were excluded from the final data analysis, which consisted of 19 people in each group. In addition, although the full-scale intelligence quotient (FSIQ) of all participants was at least in the normal range of ability, there was a significant difference in the average measures between patient and control groups, so that the control group had a significantly higher score.

Compared with the healthy control group, patients with PNES demonstrated abnormal neurocognitive functioning after controlling for the effects of FSIQ, specifically involving spatial working-memory. They also had significantly higher scores relating to chronic emotional dysregulation, emotional and dissociative-conversion symptoms, and tended to focus more on health problems. Nine of the patients (47%) with PNES had no other axis 1 or 2 psychiatric disorder apart from dissociative-conversion disorder. This study showed that patients with PNES have abnormal neurocognitive functioning after controlling for the effects of effort and FSIQ.

4.2 Aims and hypotheses

This study aims to examine psychiatric, neuropsychological and neurocognitive performance in patients with PNES compared to a healthy-control group matched for effort, age, gender, and FSIQ. Hypotheses 2 and 3 that were investigated by this study are re-stated below.

Hypothesis 2: People with PNES will have significant levels of emotional dysregulation and dissociative conversion symptoms and share co-
morbidity with other psychiatric conditions, particularly those which involve affective dysfunction, such as anxiety and depression.

3. Hypothesis 3: People with PNES will be significantly impaired relative to healthy controls on performance of executive functioning tasks, particularly those relating to attention and working memory.

4.3 Methods

The extensive methodology relating to this study is described in Section 2.6.

4.4 Data preparation and statistical analysis

Data preparation

All data for this study was entered into a database and analysed using SPSS version 20 (IBM-Corporation, 2011). All variables were subjected to “Explore” procedures in SPSS v.20, which gives both numerical and graphical interpretations of the data regarding its dispersion and its adherence to a normal distribution. This procedure was carried out to assess the distribution of the data and to check for outliers in the dataset. Kolmogorov-Smirnov and Shapiro-Wilks tests were calculated for each variable, and the Shapiro-Wilks statistic was used due to the relatively modest sample size. Non-normally distributed variables were initially analysed using non-parametric statistics (Pallant, 2007).

Of the 20 people with PNES who participated in this study, 1 female failed the MSVT. Therefore, the final study sample comprised 19 patients and 19 controls, matched for age, handedness and gender.
This study had 80% statistical power for a sample size of 38 to detect a difference between groups approximately equaling the standard deviation of the responses (in either depression, anxiety or dissociation scales). For example, small variation in responses, with an SD of 5, would allow us to detect a difference of 5-points. If larger variation is observed in the groups, for example, SD=15 points, then the study would not have sufficient power to detect a difference less than 15 points on the respective scale of measurement.

**Statistical analysis**

It was noted that there was a significant difference between the patient group and the control group with respect to mean FSIQ scores. It was considered likely that FSIQ could have a confounding effect on neuropsychological performance. Therefore, the neuropsychological test results were analysed using binary logistical regression, co-varying for FSIQ, and therefore the demographic and psychometric data was analysed using logistical regression, using PNES status as the binary outcome variable, for consistency of approach. Logistical regression was the method chosen to analyse the data because this is a robust method of determining if the assessment outcome variables predicted group status; it would demonstrate how good the model was at classifying cases versus healthy controls; and the analysis would allow identification of the relative importance of each predictor variable. This method of data analysis would also allow results of neuropsychological performance to take account of effects of FSIQ. A $p$-value of < 0.05 was considered statistically significant.

### 4.5 Results

Results will be presented under headings relating to the analysis of clinical data, psychometric assessment and neuropsychological assessment.
4.5.1 Clinical data

One patient failed the effort task so that the data generated by this patient and their matched control participant were excluded from further analysis in this study. Data for 19 patients with PNES and their matched controls were included in the final data analyses. There were no significant between-groups differences in age and gender.

Demographic data are presented in Table 4.1.

Table 4.1 Selected demographic data for participants.\(^a\)

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Group with PNES (N=19)</th>
<th>Control group (N=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (in years)</td>
<td>30.0 (8.8)</td>
<td>29.7 (7.0)</td>
</tr>
<tr>
<td>Years of Education</td>
<td>13.6 (2.0)</td>
<td>17.0 (3.2)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>6 (32%)</td>
<td>6 (32%)</td>
</tr>
<tr>
<td>Female</td>
<td>13 (68%)</td>
<td>13 (68%)</td>
</tr>
</tbody>
</table>

\(^a\) Age and Years of Education data are presented as mean (standard deviation).

The WTAR-predicted IQ and actual FSIQ (WASI) were analysed to determine if there were significant intra-group and between-groups differences in the scores. Predicted FSIQ (WTAR) and current FSIQ scores significantly differed between groups. The correlation between WTAR standard score and FSIQ predicted score was very high (i.e., > 0.99). This indicated a very high agreement between the two scores overall. There was a statistically significant difference (in predicted standard-score) between the groups: the predicted score was 4.7 points less than the standard score by 4.3 points in the cases (p < 0.001). However, differences in the range of 4-7 IQ points between these IQ parameters are not considered to be clinically-significant.

No control participant included in the study analysis had a personality disorder.
All patients with PNES had a diagnosis of somatoform (conversion) disorder, with a mean (standard deviation) duration of PNES symptoms to diagnosis of 3.8 (2.9) years, and years since diagnosis of PNES to inclusion in the study of a further 2.6 (2.0) years. Sixteen out of the nineteen patients with PNES (84.2%) had experienced at least one seizure-like event within three months prior to testing; one had experienced such an event within the previous 9 months; and the remaining two patients had experienced their last event between one year and four years previously. The average frequency of PNES events experienced in the patient group as a whole was three per week at the time of participation in the study. Nine patients (47% of the group with PNES) had no other axis I or II psychiatric diagnosis apart from conversion disorder. Of the remaining ten patients, two (10.5% of the group with PNES) had another active axis I co-morbid psychiatric illness (PTSD), and eight (42% of the group with PNES) had one or more personality disorders. Of those patients meeting criteria for personality disorder, five had one personality disorder, and three had more than one. Emotionally unstable (borderline) personality disorder (BPD) was identified in five of these patients and obsessive–compulsive (anankastic) personality disorder (OCPD) was diagnosed in the other three. There was one diagnosis each of paranoid personality disorder (PPD), histrionic personality disorder (HPD), and avoidant personality disorder (AvPD), and these three personality disorders were each co-morbid with either BPD or OCPD in each case.

Seven (36.8%) of the group with PNES had received a full course of cognitive behaviour therapy for treatment of PNES after diagnosis but had continued to have events.

4.5.2 Results of psychometric assessment

There were no significant between-group differences in self-reported scores on the CISS, LEC, and GHQ. However, there were significant differences between
Table 4.2 Results showing variables that predicted group status.a

<table>
<thead>
<tr>
<th>Variable</th>
<th>PNES (N=19) mean ± SD</th>
<th>Controls (N=19) mean ± SD</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSIQ</td>
<td>103.1 ± 10.8*</td>
<td>122.1 ± 9.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WTAR Standard IQ</td>
<td>91.0 ± 14.0</td>
<td>115.4 ± 11.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Education (years)</td>
<td>13.6 ± 2.0</td>
<td>17.0 ± 3.2</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Psychometric Assessment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beck Depression Inventory</td>
<td>17.6 ± 16.3</td>
<td>4.3 ± 5.4</td>
<td>0.010</td>
</tr>
<tr>
<td>Beck Anxiety Inventory</td>
<td>18.2 ± 17.4</td>
<td>5.6 ± 5.3</td>
<td>0.032</td>
</tr>
<tr>
<td>TAS-20</td>
<td>54.7 ± 13.4</td>
<td>39.6 ± 11.2</td>
<td>0.004</td>
</tr>
<tr>
<td>Dissociation Events Scale II</td>
<td>18.5 ± 16.7</td>
<td>8.7 ± 6.2</td>
<td>0.048</td>
</tr>
<tr>
<td><strong>Personality Assessment Inventory</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOM</td>
<td>62.4 ± 11.6*</td>
<td>46.2 ± 5.5</td>
<td>0.002</td>
</tr>
<tr>
<td>SOM-C</td>
<td>63.4 ± 16.0*</td>
<td>47.0 ± 6.9</td>
<td>0.006</td>
</tr>
<tr>
<td>SOM-S</td>
<td>55.5 ± 9.9</td>
<td>46.0 ± 7.1</td>
<td>0.010</td>
</tr>
<tr>
<td>SOM-H</td>
<td>63.6 ± 12.5*</td>
<td>47.1 ± 6.8</td>
<td>0.003</td>
</tr>
<tr>
<td>DEP</td>
<td>58.5 ± 14.9</td>
<td>49.2 ± 11.2</td>
<td>0.049</td>
</tr>
<tr>
<td>DEP-P</td>
<td>57.7 ± 11.4</td>
<td>46.2 ± 10.5</td>
<td>0.008</td>
</tr>
<tr>
<td>ALC</td>
<td>45.5 ± 5.9</td>
<td>51.0 ± 7.2</td>
<td>0.022</td>
</tr>
<tr>
<td>ANT-A</td>
<td>44.6 ± 5.7</td>
<td>50.2 ± 9.1</td>
<td>0.046</td>
</tr>
<tr>
<td>ANT-S</td>
<td>45.5 ± 6.9</td>
<td>51.9 ± 9.1</td>
<td>0.035</td>
</tr>
<tr>
<td>SPI</td>
<td>58.9 ± 13.4</td>
<td>50.2 ± 11.2</td>
<td>0.046</td>
</tr>
</tbody>
</table>

a Logistic-regression analysis. Significant p-Values are p<0.05. Scores are presented in the following format: mean (standard deviation). The PAI scale scores reflect the degree of concern identified in functioning of the relevant domain, where T-scores less than 60 identify that there is little concern regarding functioning in the specific domain assessed; scores greater than 60 (marked with *) identify that there is at least some concern with functioning.

PNES, psychogenic non-epileptic seizures; SD, standard deviation; FSIQ, full-scale intelligence-quotient; WTAR, Weschler’s Test of Adult Reading; IQ, intelligence quotient; Education, years of education; TAS-20, Toronto Alexithymia Scale 20-item; SOM, concern with health matters and somatic complaints that may be associated with somatisation and somatisation disorders; SOM-C, symptoms of conversion disorder such as sensory or motor dysfunctions; SOM-S, physical symptoms and complaints of ill-health & fatigue; SOM-H, preoccupation with health-status and physical problems; DEP, symptoms of depression; DEP-P, levels of physiological functioning, activity & energy (somatic symptoms of depression); ALC, tendency to abuse alcohol; ANT-A, history of antisocial acts/activities; ANT-S, craving for excitement and sensation, a low tolerance for boredom, indicating impulsivity; SPI, suicidal potential index, a measure of increased risk of suicide.
the group with PNES and the healthy-control group on the presence of symptoms of anxiety, dissociation, and depression and on alexithymia, where on each measure, the group with PNES had higher scores indicating the presence of greater pathology (Table 4.2).

Patients with PNES scored significantly higher than matched healthy-controls on PAI indices reflecting concern about health and physical functioning (all the SOM scales) and clinical features common to the syndrome of depression (DEP scales) including vegetative signs (DEP-P) and suicidal risk (SPI). The group with PNES scored significantly lower compared with the control group on indices of alcohol use (ALC) and features relevant to personality constructs of antisocial and stimulus-seeking behaviour (ANT-A & ANT-S) (Table 4.2). The other PAI sub-scales were not found to differ significantly between groups or to have scores indicative of clinical significance, including on indices of profile distortion.

Table 4.3 Results of CANTAB neuropsychological assessment analysis covarying for FSIQ

<table>
<thead>
<tr>
<th>Variable</th>
<th>PNES (N=19) mean ± SD</th>
<th>Controls (N=19) mean ± SD</th>
<th>p-Value</th>
<th>p-Value (adjusted for FSIQ)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Spatial Working Memory (SWM)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SWM Between Errors</td>
<td>23.1 ± 16.9</td>
<td>18.8 ± 17.7</td>
<td>0.453</td>
<td>0.025</td>
</tr>
<tr>
<td>SWM Between Errors 6 Boxes</td>
<td>6.2 ± 6.0</td>
<td>4.9 ± 6.6</td>
<td>0.542</td>
<td>0.042</td>
</tr>
<tr>
<td>SWM Between Errors 8 Boxes</td>
<td>16.3 ± 12.3</td>
<td>13.5 ± 11.9</td>
<td>0.482</td>
<td>0.036</td>
</tr>
<tr>
<td>SWM Total Errors</td>
<td>23.6 ± 17.3</td>
<td>19.9 ± 17.3</td>
<td>0.510</td>
<td>0.025</td>
</tr>
<tr>
<td>SWM Total Errors 6 Boxes</td>
<td>6.3 ± 6.1</td>
<td>5.3 ± 6.6</td>
<td>0.632</td>
<td>0.041</td>
</tr>
<tr>
<td>SWM Total Errors 8 Boxes</td>
<td>16.7 ± 12.7</td>
<td>14.2 ± 11.6</td>
<td>0.525</td>
<td>0.035</td>
</tr>
<tr>
<td>SWM Strategy</td>
<td>30.2 ± 7.0</td>
<td>28.3 ± 7.1</td>
<td>0.423</td>
<td>0.048</td>
</tr>
<tr>
<td><strong>Stockings of Cambridge (SOC)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Initial Thinking Time (3 moves)</td>
<td>4854 ± 2651</td>
<td>6264 ± 4945</td>
<td>0.281</td>
<td>0.031</td>
</tr>
<tr>
<td><strong>Rapid Visual Information Processing (RVP)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RVP Mean Latency</td>
<td>405.1 ± 55.8</td>
<td>407.5 ± 70.9</td>
<td>0.911</td>
<td>0.040</td>
</tr>
</tbody>
</table>

a Logistic regression analysis. Significant p-Values are <0.05.

PNES, psychogenic non-epileptic seizures; SD, standard deviation; BE, between-errors; TE, total errors; MITT, mean initial thinking-time; 6 and 8 boxes refer to levels of increasing complexity (respectively) within the SWM task; 3 moves refers to solving a problem within 3 moves on the SOC task.

225
4.5.3 Results of CANTAB neuropsychological battery assessment

Neuropsychological battery data were firstly assessed using multiple logistic regression, adjusting for FSIQ. There were significant differences between-groups on sub-tests of spatial working memory (the SWM task), planning and organisation (the SOC task), and attention (the RVP task) (Table 4.3). There were no significant differences between the patient group and the control group for the Big Circle/Little Circle Task and Intra extra-Dimensional Set Shift Task. In addition, I carried out a bivariate Spearman’s rho nonparametric correlation analysis within the group with PNES that included those variables found to predict group status, to test the hypotheses that, firstly, emotional dysregulation is associated with performance on neuro-psychological testing and that, secondly, indicators of emotional dysregulation are associated with severity of PNES. The main results of this analysis are reported in Table 4.4.

Alexithymia scores were found to positively correlate with SWM between-errors, but otherwise there was little evidence to support the first hypothesis. I found positive correlations between frequency of PNES events and those variables relating to dissociative experiences and preoccupation with health and physical functioning (in particular).

4.6 Discussion

To our knowledge, this is the first study to report that, compared with healthy controls, people with PNES have significant differences in personality, in emotional health, and in neuropsychological functioning after controlling for effects of effort and FSIQ. Specifically, we found that patients performed comparatively poorly on tests of spatial working memory and attention and had high levels of anxiety, depressive, and dissociative symptoms. In addition, they appeared to particularly focus on health problems and showed evidence of
Table 4.4 Results of nonparametric correlation analysis between demographic, psychometric and neuropsychological variables found to differ between-groups, within the group with PNES.

<table>
<thead>
<tr>
<th>Variable</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency of PNES events</td>
<td></td>
<td>-0.31</td>
<td>-0.43</td>
<td>-0.07</td>
<td>-0.53*</td>
<td>-0.70**</td>
<td>-0.04</td>
<td>-0.08</td>
<td>-0.02</td>
<td>0.12</td>
</tr>
<tr>
<td>BDI</td>
<td>-0.31</td>
<td></td>
<td>0.84**</td>
<td>0.75**</td>
<td>0.76**</td>
<td>0.46*</td>
<td>0.34</td>
<td>0.32</td>
<td>0.16</td>
<td>0.10</td>
</tr>
<tr>
<td>BAI</td>
<td>-0.43</td>
<td>0.84**</td>
<td></td>
<td>0.66**</td>
<td>0.75**</td>
<td>0.53*</td>
<td>0.45</td>
<td>0.45</td>
<td>0.44</td>
<td>0.04</td>
</tr>
<tr>
<td>TAS-20</td>
<td>-0.07</td>
<td>0.76**</td>
<td>0.66*</td>
<td></td>
<td>0.72**</td>
<td>0.14</td>
<td>0.49*</td>
<td>0.45</td>
<td>0.36</td>
<td>0.01</td>
</tr>
<tr>
<td>DES II</td>
<td>-0.53*</td>
<td>0.86**</td>
<td>0.75*</td>
<td>0.72**</td>
<td></td>
<td>0.61**</td>
<td>0.41</td>
<td>0.38</td>
<td>0.15</td>
<td>0.37</td>
</tr>
<tr>
<td>SOM</td>
<td>-0.70**</td>
<td>0.46*</td>
<td>0.53*</td>
<td>0.14</td>
<td>0.61**</td>
<td></td>
<td>0.26</td>
<td>0.29</td>
<td>0.08</td>
<td>0.25</td>
</tr>
<tr>
<td>SWM Between Errors</td>
<td>-0.04</td>
<td>0.34</td>
<td>0.45</td>
<td>0.49*</td>
<td>0.41</td>
<td>0.26</td>
<td></td>
<td>0.99**</td>
<td>0.76**</td>
<td>0.44</td>
</tr>
<tr>
<td>SWM Total Errors</td>
<td>-0.08</td>
<td>0.32</td>
<td>0.45</td>
<td>0.45</td>
<td>0.38</td>
<td>0.29</td>
<td>0.99**</td>
<td></td>
<td>0.79**</td>
<td>0.44</td>
</tr>
<tr>
<td>SWM Strategy</td>
<td>-0.02</td>
<td>0.16</td>
<td>0.44</td>
<td>0.36</td>
<td>0.15</td>
<td>0.08</td>
<td>0.76**</td>
<td>0.79**</td>
<td></td>
<td>0.15</td>
</tr>
<tr>
<td>RVP Mean Latency</td>
<td>-0.01</td>
<td>0.10</td>
<td>0.04</td>
<td>0.01</td>
<td>0.37</td>
<td>0.25</td>
<td>0.44</td>
<td>0.44</td>
<td>0.15</td>
<td></td>
</tr>
</tbody>
</table>

*Note: This was an exploratory analysis, controlling for the effects of FSIQ. No correction of the p-value to take account of multiple comparisons was performed. Correlations marked with an asterix * or ** were significant at p<0.05 and p<0.01, respectively.

PNES, psychogenic non-epileptic seizures; BDI, Beck’s Depression Inventory; BAI, Beck’s Anxiety Inventory; TAS-20, Toronto Alexithymia Scale, 20 item; DES II, Dissociation Experiences Scale version 2; SOM, concern with health matters and somatic complaints that may be associated with somatisation and somatisation disorders; SWM, spatial working memory task; RVP, rapid visual processing task.

chronic emotional dysregulation. No participant had taken psychotropic medication for at least two months prior to testing.

In our sample, we found that 42% of people with PNES had no other axis 1 or II mental disorders apart from conversion disorder, and the remaining 53% had either a co-morbid axis I or II psychiatric disorder. Our finding that just two people with PNES had an active co-morbid axis I disorder, apart from conversion disorder, is rather surprising, given that several studies have reported a high frequency of co-morbid anxiety and affective disorders with PNES (Bodde et al., 2009). These findings should be interpreted with caution, given that there is a risk of false negative findings from evaluation of a relatively small sample size. Nevertheless, there was significant evidence of ongoing
clinical dysfunction in the group with PNES, indicated by the average frequency of PNES events experienced of three per week, significantly greater average depression and anxiety scores compared with healthy controls, and that approximately 36% were continuing to experience PNES events despite having received cognitive behaviour therapy. Furthermore, eight (42%) of the total group with PNES had at least one personality disorder, with the emotionally unstable (borderline) type being the most frequent followed by the obsessive–compulsive (anankastic) type. These findings are consistent with findings of a high incidence of cluster B personality disorders and especially borderline personality disorder in people with PNES (Reuber et al., 2004; Reuber and Mayor, 2012; Turner et al., 2011).

Our PAI assessment findings included significant elevations in the group with PNES on indices of concern about health and physical functioning (SOM scales) and clinical features common to the syndrome of depression including vegetative signs (DEP and DEP-P scales) and suicidal risk (SPI) when compared with healthy controls. The SOM scale scores were clinically significant and reflected the experience of dramatic physiological symptoms typical of conversion disorders and a preoccupation with physical functioning, and signs of physical ill-health in particular, in the group with PNES (Morey, 2007). Our findings were internally consistent with results of our semi-structured psychiatric assessment, and there was no evidence of profile distortion, such as malingering or exaggeration of symptoms, so that our findings are highly consistent with those of previous studies examining personality construct in PNES (Cragar et al., 2005; Testa et al., 2011) and broadly similar to the personality subtype of “somatic defenders” reported by Cragar and colleagues as one of three subtypes of PNES, and which referred to patients presenting with the classic “conversion V” pattern on the Minnesota Multiphase Personality Inventory second version (MMPI-2) and having generally average cognition (Cragar et al., 2005).

Our finding of significantly elevated alexithymia scores in the group with PNES is consistent with previous research (Dineen et al., 2001; Baslet et al., 2011). There is strong and consistent evidence from longitudinal investigations that alexithymia is a stable trait that is largely independent of psychopathology or medical illness (Saarijarvi et al., 2006). Therefore, our findings support
evidence that people with PNES have personality traits consistent with chronically abnormal emotional regulation.

We found no between-groups difference in reported coping style, the numbers of traumatic life events reported, or self-reported quality-of-life indices. These findings are inconsistent with some studies of PNES (Strutt et al., 2011; Stone et al., 2004a). However, people with medically unexplained symptoms, including those with PNES, have been found to be less likely to perceive psychological factors as relevant to their symptoms and to be more likely to deny that they have suffered from life stress and to have automatic avoidance tendencies (Stone et al., 2004b; Bakvis et al., 2011). In addition, it has been proposed that alexithymia functions within the individual as a mechanism for avoiding distressing affect (Van Middendorp et al., 2008), and we found elevated alexithymia scores in our group with PNES, so we can speculate that both these factors may at least partially explain these non-significant findings.

We found levels of dissociative symptoms (DES-II) to be significantly higher in the group with PNES. Furthermore, interpretation of the mean DES-II score indicates that it falls within a range of values in which mental disorders such as anxiety disorder, affective disorder, and emotionally unstable personality disorder would be usual but not so high so as to be consistent with levels usually found in post-traumatic stress disorder or dissociative disorder (Bernstein et al., 1993). Therefore, these scores are consistent with our findings from structured psychiatric assessment and also highly consistent with previous studies that reported significantly high dissociative symptoms in people with PNES when compared with those found in the healthy control group (Proenca et al., 2011) and in groups with epilepsy (Proenca et al., 2011; Myers et al., 2013. In addition, we found a positive correlation between dissociation scores and frequency of PNES events so that, overall, our findings relating to dissociation support the hypothesis that dissociative mechanisms are involved in expression of these events (Baslet et al., 2011).

In our study, neuropsychological assessment occurred directly after participants passed a test of effort and our analysis of neuropsychological performance data controlled for the effects of FSIQ. Our results showed, firstly, that people with PNES performed abnormally on tests of spatial working memory (SWM) and
that those deficits were more consistently apparent on tests of higher task complexity; secondly, that the group with PNES also executed poorer strategy on SWM tasks, a finding also suggestive of cognitive dysfunction; and, thirdly, that the group with PNES took less time to initiate action on some, but not all, tasks involving planning and attention.

Spatial working memory is a memory system of limited capacity that allows the temporary storage and processing of information, and research indicates that it is impaired by concurrent performance on tasks that utilise executive resources (Ang and Lee, 2008). The CANTAB battery tasks we employed in this study particularly examine components of cognition known to be associated with frontal and medial temporal brain regions (Robbins et al., 1994) and have previously demonstrated a high degree of sensitivity in detecting brain dysfunction in regions including the amygdalo-hippocampal complex (Owen et al., 1996), thereby permitting inferences to be made about the underlying neural circuitry associated with performance of these tasks. Therefore, our neuropsychological results would appear to indicate that people with PNES have abnormal cognitive functioning that includes neural networks involved in attention and memory. These results appear inconsistent with those of a recent study that found no neuropsychological abnormality in PNES once effort only was controlled for (Strutt et al., 2011). However, that study only included females, participants did not have structured psychiatric and personality evaluations, and data relating to psychotherapeutic intervention or response were not included in their analyses. In contrast, our sample was age-, handedness- and gender-matched; participants received comprehensive psychiatric and neuropsychological evaluations; and our sample included patients who continued to experience PNES despite psychotherapeutic intervention. In addition, although the study by Strutt and colleagues did not find a statistically significant difference on neuropsychological performance between those with epilepsy and those with PNES, they did report a consistent relative weakness in attention and memory in the group with PNES. Therefore, it is likely that differences in sample characteristics and data analyses explain the disparate findings.

In this study, we compared and contrasted estimates of premorbid intelligence with current intelligence quotients to examine whether there was evidence of
intellectual decline over time, which is known to occur in conditions involving neurological insult or disease. We found significant statistical changes within groups. However, we considered the observed changes of between 4 IQ points and 5 IQ points to be negligible in terms of actual clinical significance (Kaufman, 2009). Therefore, our findings suggest that people with PNES do not suffer cognitive declines that are otherwise associated with neurological illness or brain injury, including epilepsy (Donnell et al., 2007).

Finally, we would like to comment on our use of the MSVT. Symptom-validity tests, such as the MSVT, are commonly utilised in medico-legal clinical examinations where a potential incentive to perform poorly exists. Recent studies have found associations between symptom validity performance and disability status in conditions classified as somatoform disorders (Johnson-Greene et al., 2013). Another study reported the extent to which patients presenting with medically unexplained symptoms fail effort tests to be 11%, although the authors also found that there was no clear evidence of deliberate failure (Kemp et al., 2008). Effort testing has also been carried out with people with PNES. One previous study carried out by Drane and colleagues had reported findings of suboptimal effort on neuropsychological evaluation of people with PNES (Drane et al., 2006). However, this finding was not replicated in a subsequent study of PNES utilising the same test and carried out by a different research group (Dodrill, 2008). The authors of the latter study suggested that the high rates of suboptimal effort found by Drane et al. were likely related to sample bias, which they attributed to the inclusion of people with PNES who had severe psychiatric difficulties, including people with “hysteroid” personality disorder. Moreover, a recent study examined performance of people with PNES on a symptom validity test while investigating potential confounders and reported that failure on the Word Memory Test (WMT) was strongly associated with reported abuse but not with variables such as the presence of financial incentives or severity of reported psychopathology (Williamson et al., 2012). These results indicate that for people with PNES, factors underlying WMT failure cannot be assumed to be similar to those found in other medical populations, such as exaggeration of distress or financial or disability incentives and may be more related to clinical variables such as traumatic experience. In our study, we included only those people with PNES who passed a well-
validated test of effort in an attempt to rule out the possibility of response bias in our study. However, on the one hand our clinical sample was found to have significant levels of psychopathology and cluster B type personality disorder and included people who continued to experience PNES despite treatment; on the other hand, there was no significant between-groups difference of reported traumatic experiences compared with controls. Therefore, further research studies are likely to be required to identify clinical and psychosocial variables that can help predict with confidence those people with PNES likely to perform sub-optimally on clinical tests. In general, however, these studies highlight the importance of effort testing in medical populations including those with PNES.

In summary, we studied a relatively homogeneous group of people with PNES and found significant differences from healthy controls on psychopathological indices of depression, anxiety, and dissociation. We also found significant differences between groups on personality construct, indicating an increased prevalence of alexithymia, preoccupation with physical health, and disordered personality in people with PNES, consistent with results from previous studies. Nevertheless, this is, to our knowledge, the first study that reports abnormal neuropsychological functioning in PNES after controlling for effort. In addition, our correlation analysis results found dissociation to be positively associated with frequency of PNES events. However, we found no evidence that our finding of abnormal neuropsychological functioning is associated with a cognitive decline often found in people who have suffered neurological illness or neural injury. Therefore, although the cause of our findings is unknown, we suggest that, overall, our findings support the hypothesis that PNES manifest through an interaction effect involving attention deficits (Strutt et al., 2011) and disrupted integration of emotional processing and perception (Baslet, 2011). Moreover, our results also support evidence that there are abnormally functioning neural circuits in PNES that subserve the relevant cognitive functions (Van der Velde et al., 2013).

The main limitations of our study are the small sample size and an associated increased risk of type II error in interpretation of our findings. However, on the other hand, our study was adequately powered, and we employed a rigorous structured approach to assessment and analysis of data. We also did not include people with epilepsy in our study. Hence, we do not know if our findings
will generalise when compared with other groups within the epilepsy spectrum. Therefore, we suggest that further carefully planned studies involving multimodal assessment techniques such as neuropsychological, neurophysiological, and neuroimaging modalities will be required to replicate our results and further delineate the neurobiological underpinnings of PNES.
Chapter 5:

Study 3

Investigation of brain structure and integrity using voxel-based morphometry and diffusion tensor imaging in patients with PNES

This chapter investigates and compares the psychiatric, neuropsychological and neurocognitive profiles of a group of patients with PNES with those of a healthy control group, matched for age, gender, and handedness. The aim of this study was to specifically investigate the hypotheses that patients with PNES firstly, have significant levels of emotional dysregulation and dissociative conversion symptoms, and also share co-morbidity with psychiatric disorders that involve affective dysfunction, and secondly, that they have significant impairments on performance of executive functioning tasks, especially those relating to attention and working memory.

5.1 Summary of chapter

There have been only a small number of neuroimaging studies that have investigated the neural correlates of PNES. Preliminary results have suggested that there is altered structure and function of some brain structures in patients with PNES. However, findings have been inconsistent, possibly reflecting
differences in sample characteristics and methodology, given that investigators did not gather data sufficient to provide a comprehensive psychiatric and neuropsychological profile of all participants (patients and controls). Therefore, this study employed two complementary neuroimaging modalities to investigate brain structure in PNES, using structural MRI (sMRI) and diffusion tensor imaging (DTI), and employing whole brain and region of interest (ROI) analyses, in a sample of participants which underwent comprehensive psychiatric and neuropsychological assessment. The final sample comprised 20 patients and 20 healthy-controls of at least average intelligence, matched for age, gender, and handedness.

Structural MRI analysis using voxel-based morphometry found that, compared with the healthy control group, patients with PNES had reduced gray matter in the posterior part of left middle temporal gyrus, including Superior Longitudinal Fasciculus (SLF), in the respective temporal lobe ROI. DTI ROI analyses showed that people with PNES had increased white matter fractional anisotropy (FA) in the left SLF, left forceps major and left thalamus. In addition, dissociative-conversion symptoms were negatively correlated with FA in the SLF. Also, negative correlations were found between SLF and neuropsychological performance relating to working memory and planning efficiency tasks. This study showed that patients with PNES have abnormalities of brain structure particularly affecting the left hemisphere and region involving the SLF white matter pathway, in particular.

5.2 Aims and hypotheses

This study aimed to investigate brain structure of patients with PNES using two complementary neuroimaging techniques (sMRI and DTI), and examine correlations of any such findings with clinical indices of dissociative-conversion symptoms. Hypotheses 4, investigated by this study, is re-stated below.
Hypothesis 4: People with PNES will show abnormalities of brain structure, particularly affecting regions associated with cortico-subcortical motor loops.

5.3 Methods

This sample of patients with PNES was a subgroup of the subjects from Study 2. All participants in this study were subjected to exactly the same inclusion and exclusion criteria for participation, and clinical, psychometric and neuropsychological assessment protocols as outlined in section 2.2. In addition they underwent structural and diffusion tensor imaging.

Details of the investigative methodology relating to this study is described in Sections 2.6 and 2.7 of this thesis. Section 2.6 describes the selection processes relating to the sample and the overall assessment process, including the psychiatric and neuropsychological testing. While section 2.7 broadly outlines the concepts behind neuroimaging data acquisition and analysis, section 2.7.1 describes the sMRI and DTI neuroimaging protocols and neuroimaging data processing and analyses that applied in this study.

5.4 Data preparation and statistical analysis

Data in this study were analysed using the Statistical Package for the Social Sciences version 20 (IBM-Corporation, 2011). The demographic and psychometric data were analysed using logistical regression tests, with PNES status being the binary outcome variable, according to the methods presented in section 2 (O’Brien et al., 2015).

VBM and DTI measures were compared using two-sample t-tests. Multiple regression analyses (ANCOVA) including FSIQ as a covariate were performed,
giving adjusted p-values for group differences. The nominal 5% level of
significance was adjusted for the multiple comparisons of VMB global plus the
DTI analysis of 5 brain regions with a Bonferroni-corrected significance level of
0.8% (p-value <0.008). Pairwise and partial correlations (adjusting for FSIQ)
were calculated for the clinical and neurological measures to investigate further
the predictive value of the neurological measures.

Assuming a Bonferroni-adjusted level of significance of 0.8%, statistical power
of 80%, a coefficient of variation of 0.01 and a group sample size ratio of 20:20,
this study has a minimal detectable difference of 0.01 in either the global VBM
or DTI brain sub-regions. This study is underpowered to determine statistically
significant differences in brain sub-regions with more variable DTI measures, for
the same detectable difference. However, ROI analyses increase the power of
the study.

As FSIQ (intelligence) was significantly different between groups (O'Brien et al.,
2015), all results were incorporated into an SPSS database and analysed using
logistical regression (forward conditional model) with group as the dependent
variable and FSIQ included as a covariate in every analysis. Each
neuroimaging variable was added separately to FSIQ in this analysis. Results
were read from the SPSS output under Block 1: “Variables in the equation”
where a significant difference between-groups occurred if p was less than 0.05
for the respective variable tested.

Secondly, in order to investigate potential neural correlates of clinical data,
relationships were examined between only those clinical variables of interest
and those neuroimaging variables that had been found to predict group status
significantly, and this analysis was carried out within the PNES group only.
Relationships between the selected variables were examined using a two-tailed
partial correlation analysis, controlling for FSIQ, within SPSS. This examined if
there was any significant associations between relevant predictor
neuropsychological variables and neuroimaging variables that had predicted
group status.
Table 5.1  Demographic data.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PNES (n=20)</th>
<th>Healthy Control (n=20)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>30.97 (9.70)</td>
<td>30.65 (7.91)</td>
<td>0.908</td>
</tr>
<tr>
<td>Full-scale IQ</td>
<td>103.05 (10.54)</td>
<td>121.60 (9.78)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Years of Education</td>
<td>13.63 (1.98)</td>
<td>16.70 (3.47)</td>
<td>0.002</td>
</tr>
<tr>
<td>Time living with PNES</td>
<td>6.11 (3.72)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average frequency of PNES (per month)</td>
<td>7.07 (8.85)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td>0.909</td>
</tr>
<tr>
<td>Male</td>
<td>6</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>14</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Hand Preference</td>
<td></td>
<td></td>
<td>0.585</td>
</tr>
<tr>
<td>Right</td>
<td>17</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

IQ, intelligence quotient; PNES, psychogenic non-epileptic seizures; Data is presented where relevant as mean (standard deviation); significant p-Values are highlighted in bold type.

5.5 Results

The results of the demographic and neuroimaging data will be presented in this section.

5.5.1 Demographic Data

The experimental data set for this study consisted of forty participants with PNES comprising 20 patients (14 female; 6 male, Mean age =30.97 years; standard deviation (SD) 9.7, SE = ±2.17) and 20 controls (14 female, 6 male, Mean age = 30.65 years, SD = 7.91, SE = ±1.77) matched for age, gender and handedness. This sample of patients with PNES was a subgroup of the subjects from Study 2 (Chapter 4). Participants with PNES had been experiencing seizure-like events for an average of approximately 6.11 ± 3.72 years at an average frequency of 7.07 ± 8.85 events per month.
Study group demographics were compared between groups (Table 5.1). FSIQ was found to be significantly lower in the PNES group (where difference between group means = -18, p< 0.001), although FSIQ for both groups was at least within the normal range of ability. Also, patients with PNES had spent relatively fewer years in education (where difference between group means = -3 years, p=0.002). There were no statistically significant differences in age, gender, or hand preference between PNES cases and controls.
5.5.2 Neuroimaging Results

No group differences were observed in whole-brain volumes, or on grey-matter, white-matter and total intra-cranial sub-volumes with both whole-brain VBM and DTI analysis. The VBM and DTI ROI analyses found statistically significant differences between-groups, after adjustment for multiple comparisons, in the frontal lobe, temporal lobe and thalamus (Figures 5.1 & 5.2; Table 5.2). However, after adjusting the analyses to account for the confounding factor of FSIQ with PNES status, these differences did not remain statistically significant.

A partial correlation analysis was used to explore the relationship between the ROI clusters that significantly differed between groups and demographic, clinical and neuropsychological variables that significantly predicted group status from our previous neuropsychological study of the same sample (O’Brien et al., 2015), while controlling for FSIQ scores. Pearson’s $r$ values and level of significance are presented for results that were found to be significant (Tables 5.3 and 5.4).

Left SLF white matter in the frontal lobe was significantly negatively correlated with duration of PNES, anxiety symptoms, depressive symptoms and rating of symptoms associated with conversion disorder (SOM-C sub scale of the personality assessment inventory) (Morey LC, 1992).

Left middle temporal gyrus [including inferior temporal gyrus (ITG)] grey-matter (GM) was also significantly negatively correlated with rating of symptoms associated with conversion disorder (SOM-C). Left thalamus white-matter (WM) was significantly positively correlated with rating of preoccupation with health status and physical problems (SOM-H).

A partial correlation analysis was used to explore the relationship between the ROI clusters that significantly differed between groups and clinical variables that
Table 5.2 All ROI analysis FDR results.

<table>
<thead>
<tr>
<th>Variable</th>
<th>PNES (n=20) mean ± SD</th>
<th>Healthy Controls (n=20) mean ± SD</th>
<th>Direction of volume difference</th>
<th>Adjusted p-value†</th>
<th>Adjusted p-value††</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Voxel Based Morphometry (VBM)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temporal Lobe Mask ROI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left Middle Temporal Gyrus (posterior part, including ITG)</td>
<td>1368.248 ± 202.507</td>
<td>1572.480 ± 255.423</td>
<td>HC&gt;PNES</td>
<td>0.008***</td>
<td>0.118</td>
</tr>
<tr>
<td><strong>Diffusion Tensor Imaging (DTI)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frontal Mask ROI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right Cerebral White Matter</td>
<td>0.131 ± 0.010</td>
<td>0.125 ± 0.009</td>
<td>PNES&gt;HC</td>
<td>0.039</td>
<td>0.107</td>
</tr>
<tr>
<td>Right SLF</td>
<td>0.094 ± 0.006</td>
<td>0.090 ± 0.005</td>
<td>PNES&gt;HC</td>
<td>0.018</td>
<td>0.088</td>
</tr>
<tr>
<td>Left Forceps Minor/Uncinate/IFO</td>
<td>0.084 ± 0.005</td>
<td>0.079 ± 0.008</td>
<td>PNES&gt;HC</td>
<td>0.040</td>
<td>0.096</td>
</tr>
<tr>
<td>Left Forceps Major</td>
<td>0.066 ± 0.005</td>
<td>0.061 ± 0.005</td>
<td>PNES&gt;HC</td>
<td>0.005***</td>
<td>0.098</td>
</tr>
<tr>
<td>Left SLF (temporal part)</td>
<td>0.121 ± 0.009</td>
<td>0.131 ± 0.008</td>
<td>HC&gt;PNES</td>
<td>0.000***</td>
<td>0.017</td>
</tr>
<tr>
<td>Left Uncinate</td>
<td>0.048 ± 0.006</td>
<td>0.052 ± 0.005</td>
<td>HC&gt;PNES</td>
<td>0.039</td>
<td>0.108</td>
</tr>
<tr>
<td>Right Cerebral White Matter</td>
<td>0.116 ± 0.006</td>
<td>0.119 ± 0.005</td>
<td>HC&gt;PNES</td>
<td>0.045</td>
<td>0.235</td>
</tr>
<tr>
<td>Temporal Lobe Mask ROI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left SLF (temporal part)/ SLF</td>
<td>0.150 ± 0.009</td>
<td>0.141 ± 0.009</td>
<td>PNES&gt;HC</td>
<td>0.003***</td>
<td>0.021</td>
</tr>
<tr>
<td>Left Cingulum (Hippocampus)</td>
<td>0.076 ± 0.007</td>
<td>0.072 ± 0.004</td>
<td>PNES&gt;HC</td>
<td>0.031</td>
<td>0.031</td>
</tr>
<tr>
<td>Left Sagittal striatum (incl. ILF &amp; IFO)</td>
<td>0.100 ± 0.006</td>
<td>0.096 ± 0.006</td>
<td>PNES&gt;HC</td>
<td>0.041</td>
<td>0.076</td>
</tr>
<tr>
<td>Left SLF (temporal part)/SLF</td>
<td>0.142 ± 0.010</td>
<td>0.150 ± 0.009</td>
<td>HC&gt;PNES</td>
<td>0.011</td>
<td>0.034</td>
</tr>
<tr>
<td>Left Cerebral White Matter (ILF)</td>
<td>0.111 ± 0.008</td>
<td>0.117 ± 0.009</td>
<td>HC&gt;PNES</td>
<td>0.023</td>
<td>0.024</td>
</tr>
<tr>
<td>Right SLF (temporal part)</td>
<td>0.113 ± 0.007</td>
<td>0.118 ± 0.006</td>
<td>HC&gt;PNES</td>
<td>0.016</td>
<td>0.159</td>
</tr>
<tr>
<td>Thalamus Mask ROI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left Cerebral White Matter/ Thalamus</td>
<td>0.080 ± 0.006</td>
<td>0.076 ± 0.004</td>
<td>PNES&gt;HC</td>
<td>0.011</td>
<td>0.049</td>
</tr>
<tr>
<td>Left Cerebral White Matter/ Thalamus</td>
<td>0.021 ± 0.002</td>
<td>0.019 ± 0.001</td>
<td>PNES&gt;HC</td>
<td>0.001***</td>
<td>0.022</td>
</tr>
<tr>
<td>Left Forceps Minor/Uncinate/IFO</td>
<td>0.103 ± 0.007</td>
<td>0.109 ± 0.007</td>
<td>HC&gt;PNES</td>
<td>0.010</td>
<td>0.104</td>
</tr>
<tr>
<td>Cerebellum Mask ROI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left Cerebellar VI/Crus I</td>
<td>0.065 ± 0.005</td>
<td>0.061 ± 0.007</td>
<td>PNES&gt;HC</td>
<td>0.031</td>
<td>0.179</td>
</tr>
<tr>
<td>Left Cerebellar I-IV/VVI</td>
<td>0.023 ± 0.002</td>
<td>0.022 ± 0.002</td>
<td>PNES&gt;HC</td>
<td>0.020</td>
<td>0.044</td>
</tr>
<tr>
<td>Right Crus II/I</td>
<td>0.073 ± 0.005</td>
<td>0.078 ± 0.008</td>
<td>HC&gt;PNES</td>
<td>0.046</td>
<td>0.161</td>
</tr>
<tr>
<td>Left Cerebellar VI-IV</td>
<td>0.059 ± 0.003</td>
<td>0.062 ± 0.003</td>
<td>HC&gt;PNES</td>
<td>0.014</td>
<td>0.057</td>
</tr>
</tbody>
</table>

ROI, region of interest; FDR, false discovery rate; PNES, psychogenic non-epileptic seizures; HC, healthy-controls; ITG, inferior temporal gyrus; IFO, inferior fronto-occipital tract; ILF, inferior longitudinal fasciculus; FA, fractional anisotrophy; †Bonferroni-corrected p-value= 0.05/6=0.008; ††Bonferroni-corrected p-value, adjusted for full-scale intelligence quotient (FSIQ);
*** Statistically significant after adjustment for multiple comparisons (p-value < 0.008).

Note: This table presents results as follows: uncorrected for multiple-comparisons or FSIQ (under the heading "p-value"); then adjusted for multiple-comparisons (under the heading "p-value†"); then adjusted additionally for FSIQ (under the heading "Adjusted p-value††").
Figure 5.2 Significant diffusion tensor imaging (DTI) findings from the ROI Mask Analysis.
significantly predicted group status from our previous neuropsychological study of the same sample (O’Brien et al., 2015), while controlling for FSIQ scores. Pearson’s $r$ values and level of significance are presented for results that were found to be significant (Table 5.3).

Table 5.3 Results of partial correlation analysis between neuroimaging findings and relevant demographic & psychometric variables.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Duration of PNES</th>
<th>BDI</th>
<th>BAI</th>
<th>DESII</th>
<th>SOM-C</th>
<th>SOM-S</th>
<th>SOM-H</th>
<th>ANT-A</th>
<th>ANT-S</th>
<th>L MTG</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Voxel-Based Morphometry</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Temporal Lobe ROI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left Middle Temporal Gyrus</td>
<td>-.323*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(including ITG)</td>
<td>-.255</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Diffusion Tensor Imaging</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Frontal Lobe ROI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left SLF (temporal part)</td>
<td>-.502*</td>
<td>-.500**</td>
<td>-580**</td>
<td>-.374*</td>
<td>-.508**</td>
<td>-.365*</td>
<td>.362*</td>
<td>.362*</td>
<td>.315*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-.530*</td>
<td>-.426**</td>
<td>-.510**</td>
<td>-.298</td>
<td>-.415*</td>
<td>-.273</td>
<td>.224</td>
<td>.270</td>
<td>.244</td>
<td></td>
</tr>
<tr>
<td>Left Forceps Major</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>.329*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-.274</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Thalamus ROI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left Thalamus</td>
<td>.505**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>.394*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ROI, region of interest; ITG, inferior temporal gyrus; SLF, superior longitudinal fasciculus; PNES, psychogenic non-epileptic seizures; BDI, Beck’s Depression Inventory; BAI, Beck’s Anxiety Inventory; DES II, Dissociation Experiences Scale version 2; SOM-C, symptoms of conversion disorder such as sensory or motor dysfunctions; SOM-S, physical symptoms and complaints of ill-health & fatigue; SOM-H, preoccupation with health-status and physical problems; ANT-A, history of antisocial acts/activities; ANT-S, craving for excitement and sensation, a low tolerance for boredom, indicating impulsivity; L MTG, left middle temporal gyrus found on VBM to be significantly different between groups.

Results in the first rows are the zero-order Pearson’s $r$ correlation value (uncontrolled for FSIQ) and those in the second rows are the correlation co-efficient value after controlling for FSIQ. Note: Pearson $r$ correlations marked with an asterisk, * or ** were significant at $p<0.05$ and $p<0.01$, respectively. Left SLF in temporal lobe had no significant correlations with clinical or psychometric data.
Table 5.4 Results of partial correlation analysis between neuroimaging findings and relevant neuropsychological data.

<table>
<thead>
<tr>
<th>Voxel-based Morphometry</th>
<th>SWM BE</th>
<th>SWMBE (6 Boxes)</th>
<th>SWMBE (8 Boxes)</th>
<th>SWM TE</th>
<th>SWM TE (8 Boxes)</th>
<th>SWM Strategy</th>
<th>SOC MITT (3 Boxes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temporal Lobe ROI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left Middle Temporal Gyrus (including SLF)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.341*</td>
<td>0.383*</td>
</tr>
<tr>
<td>Diffusion Tensor Imaging</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frontal Lobe ROI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left SLF (temporal part)</td>
<td>-0.425**</td>
<td>-0.352*</td>
<td>-0.433**</td>
<td>-0.386*</td>
<td>-0.407*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ROI, region of interest; SLF, superior longitudinal fasciculus; SWM, spatial working memory task; BE, between-errors; TE, total errors; SOC, Stockings of Cambridge task; MITT, mean initial thinking-time; 6 and 8 boxes refer to levels of increasing complexity (respectively) within the SWM task; 3 moves refers to solving a problem within 3 moves on the SOC task.

Results are presented as Pearson’s $r$ correlation value (controlled for FSIQ). Note: Pearson $r$ correlations marked with an asterix * or ** were significant at $p<0.05$ and $p<0.01$, respectively. Left SLF in temporal lobe ROI had no significant correlations with neuropsychological data.

An inspection of the relevant zero-order correlations suggested that controlling for FSIQ had a moderate effect on the strength of the relationship between these neuroimaging and clinical variables. Left SLF white-matter in the frontal lobe was significantly negatively correlated with duration of PNES, anxiety symptoms, depressive symptoms and rating of symptoms associated with conversion disorder (SOM-C sub scale of the personality assessment inventory) (Morey, 2007). Left middle temporal gyrus (including ITG) grey-matter was also significantly negatively correlated with rating of symptoms associated with conversion disorder (SOM-C). Left thalamus white-matter was significantly positively correlated with rating of preoccupation with health status and physical problems (SOM-H).

Left middle temporal gyrus (including ITG) volume was positively correlated with both SWM strategy and mean initial thinking time (latency) on the SOC neuropsychological task. Left SLF volume (temporal part) in the frontal lobe ROI was negatively correlated with four measures of SWM, namely, between-
errors (overall and for 4 and 6 box trials) and total errors (overall and for 8-box trials).

5.6 Discussion

To our knowledge, this is the first neuroimaging study to investigate the neurobiology of PNES using both VBM and DTI in the same sample. No participant had taken psychotropic medication for at least two months prior to testing. We carried out a whole brain and ROI analysis involving frontal lobe, temporal lobe, amygdala, thalamus and cerebellum in a sample of 20 people with PNES and a sample of healthy controls matched for age, gender and handedness. We did not find any between-group differences in whole brain and total intracranial volume. Specifically, we found that people with PNES had reduced grey-matter volume in the left middle temporal gyrus (MTG) and inferior temporal gyrus (ITG) region in this ROI analysis. In addition, people with PNES had increased FA values in white-matter of the left superior longitudinal fasciculus (SLF), left frontal lobe forceps major and the left thalamus. Our correlation analysis findings included, in particular, that scores on the SOM-C sub-scale of the Personality Assessment Inventory (PAI), a measure of symptoms associated with conversion disorder, were significantly negatively correlated with both grey-matter (in the left MTG and ITG of the temporal lobe) and white matter in the left SLF of the frontal lobe (Morey LC, 2007), after correction for FSIQ. In addition, we also found significantly negative correlations between left SLF and left MTG and ITG and neuropsychological measures affecting working memory and planning efficiency, respectively.

Our VBM finding of differences in grey-matter volume of the left middle temporal gyrus, including ITG, has not been reported previously and is inconsistent with findings from the one previous VBM study of PNES, which reported predominantly right-sided abnormalities affecting the frontal lobe and bilateral cerebellum (Labate et al., 2012; McSweeney et al., 2017). However, in that study, the authors included a control sample that was not matched for handedness and did not undergo neuropsychological assessment. Moreover,
the control sample was recruited from medical and university staff, so that in particular, FSIQ differences between PNES and control groups could have affected results, similar to our experience. In addition, the authors did not adjust their significance threshold using the Bonferroni correction to account fully for the effects of multiple comparisons in their ROI analyses when reporting results. In contrast, our study design involved investigation of neuropsychological, psychiatric and psychometric functioning in both PNES and control groups and we adjusted our analysis accordingly to take account of relevant potential confounding variables and multiple comparisons. Therefore, it is likely that differences in sample characteristics and methodology between these studies may partially explain differences in findings.

In our study, the reduced grey-matter volume of the left temporal lobe MTG-ITG in patients with PNES was positively correlated with executive function tasks relating to planning efficiency and memory, and SOM-C, a measure of a tendency to enhanced focus on symptoms of ill-health (relating to sensory and/or motor dysfunction in dissociative-conversion disorder). However, findings from previous studies of this specific region indicate that reduced grey matter could also relate to abnormal functioning not explicitly measured in this study, such as face-processing, cognitive-language processing and multi-modal integration (Cabeza and Nyberg, 2000; Martin and Chao, 2001; Kiehl et al., 2004; Garrido et al., 2009; Hu et al., 2011; Hu et al., 2013). For example, the left MTG-ITG region has been previously associated with various functions including language and semantic memory processing, face processing and multi-modal integration (Cabeza and Nyberg, 2000; Martin and Chao, 2001; Kiehl et al., 2004). Also, reduced grey matter volume in the left MTG-ITG region has been previously reported in patients with schizophrenia (Hu et al., 2011; Hu et al., 2013) and in patients with developmental prosopagnosia (Garrido et al., 2009); these volumetric abnormalities were reported to be associated with reduced internal verbal dialogue, language and cognitive processing in the patients with schizophrenia (Hu et al., 2011; Hu et al., 2013) and face-recognition performance in the developmental prosopagnosia study (Garrido et al., 2009). Therefore, it is possible that our findings could relate to other processes found to be associated with abnormal structure of these regions such
as cognitive processing, face-processing, and multimodal integration, and future studies are required to specifically investigate such operations in PNES.

Our DTI ROI findings differed from previous studies in PNES (McSweeney et al., 2017). For example, in contrast to Hernando et al.’s study (Hernando et al., 2015), we did not find that UF was abnormal, after adjusting our results for multiple comparisons and correcting for FSIQ, nor did we find significant between-group differences in the areas reported as abnormal in the study by Lee and colleagues (Lee et al., 2015). However, neither of those studies carried out psychiatric and neuropsychological assessment of their PNES and control samples, so that it is likely that clinical differences in the populations we studied, and differences in methodologies utilised, partially account for the differences in our findings. Nevertheless, it is interesting that in our study we also found significant between-group differences in left UF in both the frontal lobe and thalamus, before we applied a Bonferroni adjusted p-value of <0.008 to adjust for multiple comparisons, and also before adjustment for effects of FSIQ (Table 5.2). In addition, before we applied the Bonferroni correction, we also found group differences, at a p<0.05 threshold, in left frontal lobe inferior fronto-occipital tract (IFO), right frontal lobe SLF, left temporal lobe cingulum-hippocampus, left sagittal striatum including inferior longitudinal fasciculus (ILF) & IFO, left and right SLF. These findings include structures known to be involved in transmission, integration and processing of sensory and motor information between brain lobes and in memory (Ashtari et al., 2012; Peterson & Seger, 2013; Krause-Utz et al., 2014). Nevertheless, these findings did not survive Bonferroni correction of the p-value. Therefore, although the reasons for differences in findings are unknown, it is likely that (similar to our VBM anatomical results) clinical differences in the samples we studied and research methodology at least partially account for the differences in our findings.

In this study, we found that compared with healthy-controls, the SLF of people with PNES had increased white matter FA. SLF white-matter in the (temporal part of the) left frontal lobe was negatively correlated with multiple spatial working memory tasks and scores on the SOM-C sub-scale of the Personality Assessment Inventory, a measure of the tendency to focus on symptoms associated with ill-health relating to conversion disorder. These correlations
indicate that changes in integrity of this tract in this area were associated with poorer working memory performance and a specific personality trait relating to dissociative-conversion symptoms.

White matter differences in left SLF of the frontal lobe of patients were negatively correlated with length of time with PNES, a tendency of the patient to focus on conversion symptoms affecting sensory or motor function, and anxiety and depressive symptoms, which together indicated a significant relationship between structural integrity of SLF in this region, PNES symptoms, duration of PNES, and emotional disturbance. Lastly, differences in white matter integrity of thalamus was associated with a tendency of the patient to be preoccupied with health status and physical problems, a feature of conversion disorder.

Our finding that patients with PNES had abnormalities in SLF is, to our knowledge, the first time this has been reported. The SLF is a long white-matter tract which runs from anterior to posterior cerebrum connecting the frontal, occipital, parietal and temporal lobes and, in particular, the lateral frontal and lateral parietal areas (Hecht et al., 2015). The role of the SLF has not been extensively researched in humans but has been reported to be involved in spatial attention (Vallar et al., 2014) and neglect (Rousseaux et al., 2015) cognitive control (Chaddock-Heyman et al., 2013), working memory performance (Winston et al., 2013), language (Kamali et al., 2014) and motor movement (Budisavljevic et al., 2016), as well as integrating networks that involve executive functioning with areas responsible for motor, sensory and visual functioning (Makris et al., 2005).

In addition to our SLF findings, we also found that patients with PNES had increased FA in left frontal lobe forceps major and left thalamus. Forceps major (FM) is a fibre bundle that crosses the midline through the corpus callosum and connects occipital lobes (Jones et al., 2013). FM has not been previously reported to show abnormality in the few previous neuroimaging studies of PNES or conversion disorder. However, previous neuroimaging studies have reported reduced FA in this region in neurodegenerative conditions (Hulst et al., 2013) and mental illnesses such as chronic post-traumatic stress disorder (PTSD) (Schuff et al., 2011). On the other hand, increased FA in FM has been reported in a study of the effects of numerical skills practice (Jones et al., 2013) and also recently in a DTI study of brain changes after a recent traumatic event in people.
diagnosed with PTSD, suggesting that direction of FA changes in white matter of this region may relate to factors such as changes in connectivity or duration of those conditions (Li et al., 2016).

The thalamus has multiple functions that include regulation of consciousness, transmission of sensory and motor output to the cerebral cortex and modulation of those signals (Gandevia, 1987; Graybiel et al., 1994). Moreover, it is also proposed to be integrally involved in generation of effort, volition and intentional movement through activity of striato-thalamo-cortical circuits (Gandevia, 1987; Graybiel et al., 1994) and more recently, it has been reported to be involved in executive functioning & learning (Mitchell et al., 2015; Rabinovici et al., 2015).

In addition to finding abnormally increased FA in left thalamus of the PNES group, we found a relatively strong correlation between this region and the SOM-H sub-scale of the Personality Assessment Inventory, which measures subjective concern with health status and physical problems. The thalamus has not been previously reported to show abnormalities in the few previous structural neuroimaging studies of PNES specifically. However, our findings of abnormal left thalamic structure are consistent with reports of relatively smaller left thalamic volume in two previous volumetric studies (Atmaca et al., 2006; Nicholson et al., 2014) and one single photon emission computerised tomography (SPECT) study (Vuilleumier et al., 2001) of motor conversion disorder. Therefore, while our findings of reflecting abnormal thalamic structure in PNES have to be verified and replicated in future studies, it is possible that deficits in this anatomical region may be associated with dysregulation of some of its functions such as consciousness and intentional movement, which are components of the PNES experience.

We found increased FA in left SLF, FM and thalamus of people with PNES. It is noteworthy that increased FA was also reported in the other previous DTI study of PNES, although the exact brain structures in which this was observed differed between their study and ours. Nevertheless, although the cellular mechanisms underlying our findings are unknown, complex micro-structural processes such as increased myelination, axonal deficits and reduction in axonal packing density have been proposed to contribute to increased FA findings in other studies (Beaulieu, 2002). Moreover, increased FA in other brain disorders has been found to be variously associated with increased
severity of symptoms (Alba-Ferrara et al., 2013), response to acute/recurring emotional trauma (Li et al., 2016), cognitive dysfunction (Tuch et al., 2005) and adaptive or compensatory mechanisms (Holzapfel et al., 2006) to underlying neuro-biological processes. In addition, increased FA has also been proposed to indicate decreased efficiency in information transmission in psychiatric disorders such as schizophrenia (Alba-Ferrara et al., 2013) so that overall, we suggest that our findings are consistent with fMRI findings of poor connectivity between brain regions in PNES (Ding et al., 2013; Li et al., 2015a,b; Van der Krujs et al., 2014) and indicate that there is abnormal structural integrity and organisation in these regions in people with PNES correlating with clinical and neuropsychological findings. Nevertheless, the exact neurobiological underpinnings of these changes are unknown and it has yet to be elucidated whether these changes are primary or secondary effects of ongoing PNES events.

We previously reported that people with PNES demonstrate abnormal neuropsychological performance on tasks relating to spatial working memory and attention and this study included the same sample (O'Brien et al., 2015). Therefore, the results of our neuropsychological and structural neuroimaging studies imply that people with PNES have abnormal structural integrity of grey-matter regions of left temporal lobe including MTG-ITG, and of white matter tracts involving left SLF in particular, that is significantly associated with both conversion symptoms and poor neuropsychological performance on attention and memory tasks. This is consistent with our hypothesis that in PNES, there is abnormal structure and functioning of networks normally responsible for integration of higher and lower order executive functioning with areas responsible for motor, sensory and visual functioning.

In this study, we found that compared with healthy-controls, the SLF of people with PNES had increased white matter FA and that there was reduced grey-matter in the left MTG and ITG, in a region we found to be located just 2 mm from the SLF. This pattern of grey and white-matter changes has been previously reported in studies of the normal maturing process of adolescent brain (Giorgio et al., 2010), but also in disorders such as fibromyalgia (Lutz et al., 2008). Therefore, these abnormal changes in PNES may reflect abnormal
development of these regions and/or a pathological effect on SLF or MTG-ITG in those particular regions. Our findings are also consistent with the results of a recent fMRI study that reported abnormalities within some resting-state networks associated with fronto-parietal activation in PNES (Van Der Kruijs, 2014).

Our correlation analysis findings included, in particular, that scores on the SOM-C sub-scale of the Personality Assessment Inventory, a measure of symptoms associated with conversion disorder, were significantly negatively correlated with both grey-matter in the left MTG-ITG of the temporal lobe and SLF white matter in the left frontal lobe, both before and after correction for FSIQ.

Therefore, overall, our findings indicate that there are differences in structure and development of white and grey matter of left temporal lobe in people with PNES, which we found to be associated with clinical indices of dissociation-conversion symptoms, duration of PNES, emotional disturbance and poor neuropsychological performance on tasks relating to working memory and planning efficiency. Our correlation analysis findings included, in particular, that scores on the SOM-C sub-scale of the Personality Assessment Inventory, a measure of symptoms associated with conversion disorder, were significantly negatively correlated with both grey-matter in the left MTG-ITG of the temporal lobe and SLF white matter in the left frontal lobe.

We would like to comment on the impact of FSIQ on our study findings. FSIQ has been previously correlated with measures of grey and white-matter in neuroimaging studies (Luders et al., 2009). Furthermore, such correlations appear to have a greater effect in areas such as the dorsolateral prefrontal cortex, anterior cingulate and inferior parietal cortex so that the “Parieto-Frontal Integration Theory of Intelligence” has been developed, suggesting that frontal and parietal lobe function and connectivity are the main regions that underpin intellectual ability in humans (Jung & Haier, 2007). In our study, FSIQ of our healthy control (HC) sample significantly differed from our PNES sample, reflecting that our recruitment of HCs mainly derived from a university population. Therefore, it seemed important to co-vary for FSIQ in our analysis and we reported our main results after controlling for this variable. Nevertheless, we do not know if the between-group differences we found before
adjusting for FSIQ were partly due to lower FSIQ in our PNES sample or due to the PNES condition itself. Our study does not address this question. However, a previous fMRI study of PNES has indicated that intelligence is not a key factor underlying connectivity abnormalities in PNES (Van der Kruijs et al., 2011). Therefore, we suggest that future neuroimaging studies of PNES recruit HC and PNES of similar intelligence to help clarify this issue.

Our study findings are limited by our small sample size. Moreover, our findings became non-significant after a process of controlling for the effects of FSIQ and applying a Bonferroni-corrected threshold level of significance to results. Nevertheless, we included a relatively homogeneous sample of people with PNES who were continuing to experience regular PNES events but did not have co-morbid epilepsy, were otherwise physically healthy, had grossly normal MRI scans and were not taking anticonvulsant medication. We also employed two complementary neuroimaging techniques - sMRI and DTI - to help investigate brain structure and both white and grey matter integrity in the same study population. Moreover, we utilised FDR statistics and adjusted our significance level to account for multiple comparisons. In contrast to previous neuroimaging studies of PNES, we also employed comprehensive multimodal assessment of all participants (those with PNES and healthy controls) which included psychometric and psychiatric assessment and neuropsychological testing of only those who passed a validated test of effort. Our analysis also “controlled” for the effects of FSIQ on neuropsychological and neuroimaging data. Hence our finding of differences in structural integrity cannot be explained by potential confounding factors such as epilepsy, grossly detectable differences in brain anatomy or differences in intelligence. However, we do not know if our findings would extend to people who experience co-morbid epilepsy and PNES. While the reasons for our findings are unknown, we suggest that our study significantly extends the scientific literature in approaching discovery of the neurobiological underpinnings of PNES. Therefore, we suggest that further neuroimaging studies, involving sMRI and DTI are required to determine if our findings, relating to the left MTG-ITG grey-matter region and the SLF white-matter tract, in particular, can be replicated, and whether structural differences in white and grey-matter also occur in other brain regions not investigated in this study (e.g., parietal lobe ROI). We propose that future studies should consider
utilising functional neuroimaging to evaluate neural networks related to specific task-related activities and combination neuroimaging modalities in order to further characterise and delineate abnormalities of brain structure and function in people with PNES.
Chapter 6:

Study 4

An fMRI study of implicit (unconscious) emotional processing in patients with PNES

This chapter examines and compares implicit emotional processing in a group of patients with PNES with that of a healthy control group, matched for age, gender, and handedness. The aim of this study was to specifically investigate the hypothesis that patients with PNES unconsciously process emotional information in an abnormal way.

6.1 Summary of chapter

Implicit emotional processing refers to hypothetical psychological attributes that are evoked and occur automatically, outside of conscious awareness. Efficient implicit processes are critical to help a person meet the emotional demands of their daily life experiences and preserve positive mental health. PNES are currently classified as being features of a dissociative-conversion disorder, and traditional etiological theories for conversion disorder have proposed that disturbed unconscious emotional processing somehow “converts” psychic stress into physical symptoms through an unknown mechanism. Patients with PNES have evidence of disturbed emotional regulation and processing. However, no previous fMRI study had investigated implicit emotional processing in patients with PNES, and the mechanism by which PNES manifest remains
unknown. Therefore, this study employed fMRI to investigate concomitant blood oxygen level dependent (BOLD) responses to a face-processing task that had been previously demonstrated to activate implicit processing networks in the human brain. The sample comprised nineteen people diagnosed with PNES, and nineteen healthy-controls matched for age, handedness and gender. All participants underwent comprehensive psychiatric and psychometric assessment and all had passed a validated test of effort before they underwent neuropsychological assessment and fMRI. During fMRI, participants were presented with pictures of faces demonstrating fear, disgust, or sadness at either neutral, 50%, or 100% intensity and their task during scanning was to indicate the gender of the face presented in each case. Data was analysed using logistic regression techniques, controlling for full-scale IQ (FSIQ) and correlation analyses were performed.

The main findings were that patients with PNES demonstrated increased errors and longer reaction time while carrying out the gender-discrimination task-probe of implicit processing, indicating that there is abnormal processing of, and attention to, human faces in PNES. Patients were found to demonstrate significant hypo-activity in areas of the brain known to be involved in emotional face perception, emotional awareness, the sensory integration of experience, and the planning of movement action-responses in patients with PNES. Further, the hypo-active BOLD response observed in patients with PNES during the implicit task suggested that the implicated structures are abnormally recruited during emotional face processing. Moreover, clinical and psychometric indices that have been previously implicated in etiological models of PNES were not found to drive the observed hypo-activation to the task. Therefore, it is likely that other processes that were not discernible or measured during this experiment were contributing to this functional disturbance. This relatively hypoactive BOLD response was observed in the PNES group for all faces, regardless of the emotion type or intensity exhibited. It is possible that the abnormal functional responses observed in patients to this implicit face-processing task may extend to other functions of those brain regions found to be abnormally activated, and their associated cortical-subcortical circuits. These functions include the planning, executing and control of movements, including inhibitory and activation responses to internally-generated and
unconsciously processed stimuli, that may be perceived as emotionally threatening to the patient with PNES. This is the first study to show that patients with PNES have abnormal neural responses while processing faces and these findings raise important questions for the mechanism of PNES.

6.2 Aims and hypotheses

This study would investigate unconscious emotional processing in adult patients with PNES, by asking participants to engage in an implicit face-processing task while undergoing fMRI. Hypothesis 5, investigated by this study, is re-stated below.

Hypothesis 5: People with PNES will have abnormalities in unconscious (implicit) processing of emotion.

6.3 Methods

This sample of patients with PNES was a subgroup of the subjects from Study 2. All participants in this study were subjected to exactly the same inclusion and exclusion criteria for participation, and clinical, psychometric and neuropsychological assessment protocols as outlined in Section 2.2. In addition they underwent functional neuroimaging. In particular, for a subject to be included in this study, they had to pass a test of effort (MSVT) immediately prior to neuropsychological testing and fMRI. Only those who passed this test of effort would have their results included in the subsequent analysis. Participants were not told if they had passed or not passed the MSVT test of effort as it was felt that this could upset the participants.
Details of the investigative methodology relating to this study is described in Sections 2.6 and 2.7 of this thesis. Section 2.6 describes the selection processes relating to the sample and the overall assessment process, including the psychiatric and neuropsychological testing. While section 2.7 broadly outlines the concepts behind neuroimaging data acquisition and analysis, section 2.7.2 describes the fMRI scanning, stimuli, behavioural protocols and the functional neuroimaging data processing and analytic methodology that applied in this study.

6.4 Data preparation and statistical analysis

All demographic and psychometric data were analysed using binary logistical regression.

FSIQ (intelligence) was found to be significantly different between groups on initial analysis of demographic and psychometric data (O’Brien et al., 2015), so all performance-related data (neuropsychological, fMRI behavioural and fMRI neuroimaging data) were analysed using binary logistical regression (forward conditional model) with group as the dependent variable and FSIQ included as a covariate with the relevant variable separately, in each analysis. Each neuroimaging variable was added separately to FSIQ in this analysis. A significant difference between-groups occurred if \( p \) was less than 0.05 for the respective variable tested.

6.4.1 Methods of analysis of CISS coping style

To assess for abnormal coping style, we firstly carried out an analysis to determine the number of patients with PNES and healthy control subjects that endorsed using the CISS sub-scales (Task-Orientated), Emotion-Focused and Avoidance) to an extent that deviated significantly from normal adult means. The cut-off used in clinical practice is a T-score \( \geq 1.5 \) standard deviations from the mean, so this translates in the CISS sub scales as follows: Task-Oriented
scale: a T-score of <35; Emotion-Focused and Avoidance-Focused scales: a T-score > 65). Chi-squared tests of dependence were used to compare the frequency of significant T-score elevations between PNES and healthy-control groups in relation to their endorsement of each coping style. Then, to determine psychological factors associated with predominant coping strategies, we carried out a bivariate Pearson’s correlation analysis between t-scores from the CISS Task-Orientated, Emotion-Focused and Avoidance-Focused coping strategies and selected summary variables that had been found both to predict group status and to be different in the PNES group, relating to psychometric assessment [depression symptoms (BDI-II), anxiety symptoms (BAI), alexithymia symptoms (TAS-20), dissociative experiences (DES-II)], and personality assessment as per the PAI [SOM-C, SOM-S, SOM-H]. A Bonferroni adjustment was made for each of the CISS task’s correlations to account for experiment-wise error, so that $p (0.05)$ was divided by the number of correlation variables (n=10), to give a Bonferroni-adjusted threshold $p$ value of 0.005. Stepwise linear regression was then employed to determine predictors of the CISS scores separately for each of the three CISS scales, using the predictors mentioned above (i.e., BDI-II, BAI, TAS-20, DES-II, SOM-C, SOM-S, SOM-H), where significance occurred at a $p$ value of <0.05.

6.4.2 Methods of analysis of alexithymia (TAS-20) scores

Alexithymia scores were interpreted according to the authors’ guide, where scores equal to or less than 51 = non-alexithymia; and equal to or greater than 61 = alexithymia. Scores of 52 to 60 = possible alexithymia (Bagby et al., 1994). Bivariate Pearson’s correlation analysis was carried out between TAS-20 score and the following variables: FSIQ, years of education, and scores on DES-II, SOM-C, SOM-S and SOM-H.
6.4.3 fMRI behavioural data analysis

Behavioural data from the fMRI task were examined and compared between-groups for each emotion-condition. The following data was obtained: (1) correct gender discrimination for facial expressions (CGD): the participant correctly identified the face as male or female, calculated as a percentage of their total number of responses; (2) mean reaction time (MRT): the average reaction time of the participant to presented stimuli, computed on the basis of the number of actual responses they made during the experiment (i.e., the calculation is not averaged over the total number of stimuli presented, rather only those stimuli that the participant responded-to); (3) total errors (TE): the total number of errors made by the participant during the respective task, computed by computing the sum of incorrect gender discrimination (identification) errors and nonresponse errors (the number of participant non-responses to stimuli presented during the experiment, that they should have reacted to).

Group effects in performance accuracy (CGD), latency of response (MRT) and TE for all conditions during the fMRI task were separately analysed using independent t-tests.

To examine relationships between behavioural, psychometric and neuropsychological variables that were found to predict PNES group status, a partial Pearson’s correlation analysis was carried out. A Bonferroni adjustment was made for the number of correlations included in this analysis to account for experiment-wise error, so that \( p \) (0.05) was divided by the number of correlation variables, to give a Bonferroni-adjusted \( p \) value. In addition, to examine relationships between behavioural data with dichotomous variables and variables that were found to predict PNES group status, a binary logistical regression was employed, and significance occurred at a \( p \) value of <0.05.

6.4.4 fMRI activation data analysis
The fMRI activation data from the experiment would be analysed to answer the following questions:

1. Are there differences between PNES and healthy-control groups in response to the fMRI task (implicit EFE processing)?

2. Does the fMRI task activate similar brain regions in each group during the processing of neutral faces?

3. Are there between-group differences in brain activations to emotional expression and intensity in those regions (from question no. 2) found to be activated by neutral face-processing in both patient and control groups?

4. Are there significant relationships between fMRI activation data and relevant clinical and demographical variables?

6.4.4.1 Methods of analysis used to determine if there are differences between PNES and healthy-control groups in response to the fMRI task (implicit EFE processing)

Three independent repeated measures voxelwise 2 x 3 ANOVA's with group (people with PNES & healthy controls) x emotional intensity (neutral, 50%, & 100%) were performed for each emotion (Fear, Sadness and Disgust) block. Significant voxels passed a voxelwise statistical threshold (t = 8.94, t=8.88, t=8.88, p ≤ 0.005) and were required to be part of a larger cluster of contiguous significant voxels, as calculated by Monte Carlo simulations (282 µl for the Fear, 285 µl for the Sadness, and 285 µl for the Disgust conditions respectively), resulting in a final statistical threshold of p<0.05 corrected for multiple comparisons. In addition, group x condition interactions were assessed. Mean activation levels were extracted for each ROI within the cluster maps for each condition. Secondary post–hoc analyses were performed at an ROI independent level using independent UNIVARIATE analyses (controlling for FSIQ) within SPSS.

To assess the mechanisms of emotional face processing, the significant clusters derived from the between-group voxelwise ANOVA were examined at each level of activation (neutral, 50% and 100% emotional content) in SPSS and controlled
for the effects of FSIQ. To isolate the emotional activation from the experimental stimulus, those failing to show a significant between-group difference in the neutral condition were specifically examined via secondary post-hoc independent ANCOVA's at each cluster. The mean difference in activation levels (100%-0% and 50%-0%) were calculated and extracted for the purpose of individual ANCOVA analyses (correcting for FSIQ).

6.4.4.2 Methods of analysis used to determine if the fMRI task activates similar brain regions in each group during the processing of neutral faces

Having investigated where brain activation to implicit face-processing was different between-groups, it was important to verify that faces showing neutral expression across the three emotional conditions and in both groups were activating similar brain regions during the task. Therefore, one-sample t-tests against the null hypothesis were performed for each group and each emotion separately for the neutral face condition only, of the fMRI task. Significant voxels passed a voxel-wise statistical threshold ($t = 8.94, t=8.88, t=8.88, p \leq 0.005$), resulting in a final statistical threshold of $p<0.05$ corrected for multiple comparisons. These thresholded statistical maps were then combined using a “Boolean AND” operation resulting in a single composite map showing all significant group and condition areas that were consistently activated in response to the neutral face condition of the task. Hence this process produced common brain clusters that were activated to neutral face-processing in both groups over all conditions (i.e., neutral, fear, disgust, sadness). Mean activation levels for each cluster for the 50% and 100% task levels were extracted using this composite mask and compared statistically to assess emotional activation levels for potential between-group differences.
6.4.4.3 Methods of analysis used to determine if there are between-group differences in brain activations to emotional expression and intensity in those regions (from question no. 2) found to be activated by neutral face-processing in both patient and control groups

The initial voxelwise ANOVA analyses produced between-group differences in BOLD activation for each emotional condition. However, the areas of difference between the emotional conditions at neutral intensity were inconsistent (see Section 6.5.3.2.1). In considering what these results could mean, because there were findings of group differences for processing of faces demonstrating neutral intensity, this raised the possibility that patients were demonstrating general deficits in face-processing. However, it was possible that these inconsistencies also represented factors such as “noisiness” in the data [e.g., fMRI scanner-related noise and that related to physiological noise (e.g., from heart beat and respiration or endogenous neural activity unrelated to the task)] and/or an effect of preceding emotional faces on BOLD response to the next face during the fMRI task. Therefore it was decided to investigate the underlying processes and group differences (if any) using two further methods. Firstly, group-independent activation maps would be extracted detailing common “overlapping regions” of BOLD activation to neutral faces, and a ROI cluster-level ANOVA would be carried out using mean activation levels within each cluster and for each level of emotional intensity, to examine if there were any specific group differences. Therefore, that method would investigate areas that were activated by the fMRI face-processing of neutral faces in each group across all emotional conditions, and then compare these masks to determine if there were between-group differences in those areas that were activated in both patients and healthy-controls.

Secondly, a principal components analysis (PCA) would be carried out on the fMRI dataset to investigate the internal structure of the data in such as way to help explain the variance and answer specific questions about the underlying processes associated with this data. These analyses were co-varied for the effects of FSIQ.
6.4.4.4 Analysis of relationships between fMRI activation data and clinical and demographical variables

A second approach to analysis was used to corroborate the findings above and examine for relationships between the fMRI data and relevant clinical and psychometric measures. Data were analysed with Stata Release 14.2. A principal components analysis (PCA) was used to examine the fMRI measures at each stimulus intensity, and at all intensities combined, for each emotion (Fear, Disgust, Sadness). PCA is a statistical procedure that converts a set of observations of possibly correlated variables into a set of values of linearly uncorrelated variables called principal components in which the first principal component accounts for as much of the variance as possible in that data-set. Therefore, this method helps to reveal the internal structure of the data that best explains the variance in that data, and has the potential to exclude “noise” in the dataset. The eigenvalues associated with the first two principal components were examined as potential dimensions of response. Linear regression with robust standard errors, adjusted, where necessary, for clustering of observations within participants, was used to examine the effects of PNES and stimulus intensity and their interaction on principal component scores.

In order to investigate potential neural correlates of clinical data, relationships were examined between fMRI activation measurements for each emotion and relevant psychometric variables that had been found to predict group status. To do this, a PCA was carried out and the first principal component (FPC) for each emotion was extracted. Relationships between the relevant FPC and psychometric variables that had been found to predict membership of the PNES group was carried out using regression analysis, co-varying for effects of FSIQ and gender.

6.5 Results
The results of this study will be presented in this section, starting with those relating to demographic and clinical data (including psychometric data), followed by neuropsychological and fMRI data.

### 6.5.1 Results of analyses of demographic and clinical measures

People with PNES and healthy control participants were comparable on age, gender and hand-preference (Table 6.1), but the PNES group had significantly lower scores on FSIQ (difference = -19.06, \( p < 0.01 \)) and years of education (difference = -3.37 years, \( p < 0.01 \)).

There were no significant between-group differences on self-reported numbers of life events (as measured by the Life Events Checklist), general health (as measured but the General Health Questionnaire) and coping style (as measured by the CISS). However, patients with PNES had significantly higher scores on measures of depression (BDI-II, difference = +13, \( p = 0.002 \)), anxiety (BAI, difference = +12, \( p = 0.006 \)), alexithymia (TAS-20, difference = +15, \( p = 0.002 \)), and dissociative experiences (DES-II, difference = +9, \( p = 0.022 \)) (Table 6.1).

There were between-group differences on some PAI-measured personality indices. The PNES group scored significantly higher than the healthy control group for measures relating to the conversion disorder assessment sub-scales relating to indices of symptoms of conversion disorder (SOM-C, difference = +16.37, \( p = 0.001 \)), physical symptoms and complaints of ill-health and fatigue (SOM-S, difference = +9.53, \( p = 0.002 \)), and preoccupation with health-status and physical problems (SOM-H, difference = +16.47, \( p = 0.0001 \)). In addition, the patient group reported significantly higher symptoms of depression (DEP, difference = +9.32, \( p = 0.036 \)), physiological symptoms normally associated with depression (DEP-P, difference = +11.53, \( p = 0.004 \)), and suicide potential (SPI, difference = +8.73, \( p = 0.034 \)). The group with PNES scored significantly lower compared with the control group on indices of alcohol use (ALC) and features relevant to personality constructs of antisocial and stimulus-seeking behaviour.
Table 6.1  Demographic and clinical characteristics of PNES and healthy control groups.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PNES</th>
<th>Healthy Control</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td>0.909</td>
</tr>
<tr>
<td>Male</td>
<td>6</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>14</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Hand Preference</td>
<td></td>
<td></td>
<td>0.585</td>
</tr>
<tr>
<td>Right</td>
<td>17</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>29.97 (8.84)</td>
<td>29.71 (6.98)</td>
<td>0.906</td>
</tr>
<tr>
<td>Years of Education</td>
<td>13.63 (1.98)</td>
<td>17.00 (3.18)</td>
<td>0.001**</td>
</tr>
<tr>
<td>Full-scale IQ</td>
<td>103.05 (10.83)</td>
<td>122.11 (9.88)</td>
<td>0.0001**</td>
</tr>
<tr>
<td>Clinical Symptom Scales</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BDI Score</td>
<td>17.58 (16.26)</td>
<td>4.26 (5.43)</td>
<td>0.002**</td>
</tr>
<tr>
<td>BAI Score</td>
<td>18.16 (17.35)</td>
<td>5.63 (5.33)</td>
<td>0.006**</td>
</tr>
<tr>
<td>TAS-20 Score</td>
<td>54.68 (13.42)</td>
<td>39.63 (11.16)</td>
<td>0.002**</td>
</tr>
<tr>
<td>DES II Score</td>
<td>18.54 (16.68)</td>
<td>8.68 (6.18)</td>
<td>0.022*</td>
</tr>
<tr>
<td>Personality Inventory Scales</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DEP</td>
<td>58.53 (14.94)</td>
<td>49.21 (11.16)</td>
<td>0.036*</td>
</tr>
<tr>
<td>DEP-P</td>
<td>57.74 (11.36)</td>
<td>46.21 (10.54)</td>
<td>0.004**</td>
</tr>
<tr>
<td>SOM-C</td>
<td>63.37 (15.99)</td>
<td>47.00 (6.85)</td>
<td>0.001**</td>
</tr>
<tr>
<td>SOM-S</td>
<td>55.53 (9.92)</td>
<td>46.00 (7.08)</td>
<td>0.002**</td>
</tr>
<tr>
<td>SOM-H</td>
<td>63.58 (12.45)</td>
<td>47.11 (6.75)</td>
<td>0.0001**</td>
</tr>
<tr>
<td>ALC</td>
<td>45.53 (5.87)</td>
<td>51.00 (7.20)</td>
<td>0.02*</td>
</tr>
<tr>
<td>ANT-A</td>
<td>44.63 (5.67)</td>
<td>50.21 (9.11)</td>
<td>0.036*</td>
</tr>
<tr>
<td>ANT-S</td>
<td>45.53 (6.86)</td>
<td>51.89 (9.08)</td>
<td>0.032*</td>
</tr>
<tr>
<td>SPI</td>
<td>58.89 (13.83)</td>
<td>50.16 (11.24)</td>
<td>0.034*</td>
</tr>
</tbody>
</table>

a Results of binary logistical regression analysis, comparing groups. The p-Values of variables significantly different between groups at p<0.05 and p<0.01 are marked with an asterix (*) and (**), respectively. PNES, psychogenic nonepileptic seizures; SD, standard deviation; IQ, intelligence-quotient; BDI, Beck’s Depression Inventory; BAI, Beck’s Anxiety Inventory; TAS-20, Toronto Alexithymia Scale 20-item; DES II, Dissociation Experiences Scale version 2; DEP, symptoms of depression; DEP-P, levels of physiological functioning, activity & energy (somatic symptoms of depression); SOM-C, symptoms of conversion disorder such as sensory or motor dysfunctions; SOM-S, physical symptoms and complaints of ill-health & fatigue; SOM-H, preoccupation with health-status and physical problems; ALC, tendency to abuse alcohol; ANT-A, history of antisocial acts/activities; ANT-S, craving for excitement and sensation, a low tolerance for boredom, indicating impulsivity; SPI, suicidal potential index, a measure of increased risk of suicide.
Table 6.2 Length of time suffering with PNES and average frequency seizure-like events in patients with PNES.

<table>
<thead>
<tr>
<th></th>
<th>Mean (standard deviation)</th>
<th>Range (minimum, maximum)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Length of time with PNES (years)</td>
<td>5.87 (3.76)</td>
<td>14.50 (1.50, 16.00)</td>
</tr>
<tr>
<td>Average frequency of PNES seizures (monthly)</td>
<td>6.75 (8.71)</td>
<td>28.70 (0.30, 29.00)</td>
</tr>
</tbody>
</table>

PNES, psychogenic non-epileptic seizures.

(ANT-A & ANT-S) (Table 6.1).

The other PAI sub-scales were not found to differ significantly between groups or to have scores indicative of clinical significance, including indices of profile distortion.

Patients with PNES had been experiencing seizure-like events for an average of approximately 5.87 ± 3.76 years at an average frequency of 6.75 ± 8.71 events per month (Table 6.2).

Results of analysis of coping style (CISS)

Thirteen patients (68.4%) endorsed using at least one coping strategy that was 1.5 standard deviations or more away from the normal adult mean. Six patients (31.6%) utilised elevated Avoidance-Focused strategies (T-score mean=55.7 ± 13.4), and four patients (21.0%) had elevated Emotion-Focused coping strategies (T-score mean=52.0 ± 13.3). No healthy-controls endorsed elevated Emotion-Focused (T-score mean=47.3 ± 7.4) or Avoidance-Focused (T-score mean=50.9 ± 7.7) strategies. Low Task-Orientated coping strategies were found in four (21.0%) patients (T-score mean=48.5 ± 14.6) and one (5.3%) healthy-control subject (T-score mean=51.6 ± 10.0). One patient (5.3%) endorsed a combination of significantly low Task-Orientated and elevated Emotion-Focused coping strategies.
Table 6.3 Correlations between endorsement of an abnormal coping style and relevant psychometric variables in PNES and healthy-control groups.

<table>
<thead>
<tr>
<th>Variable</th>
<th>BDI</th>
<th>BAI</th>
<th>DESII</th>
<th>TAS-20</th>
<th>SOM-C</th>
<th>SOM-S</th>
</tr>
</thead>
<tbody>
<tr>
<td>CISS Task T-score</td>
<td>-.569**</td>
<td>-.465**</td>
<td>-.509**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CISS Emotion T-score</td>
<td>.683**</td>
<td>.762**</td>
<td>.588**</td>
<td>.565**</td>
<td>.556**</td>
<td></td>
</tr>
</tbody>
</table>

*a Results of bivariate correlation analysis. The Pearsons r-values of variables significantly different between groups at \( p<0.05 \) and \( p<0.005 \) (the latter being the cut-off \( p \) value, adjusted for multiple comparisons), are marked with an asterix (*) and (**), respectively. PNES, psychogenic non-epileptic seizures; CISS, Coping Inventory for Stressful Situations; Yrs of Educ, Years of Education; BDI, Beck’s Depression Inventory; BAI, Beck’s Anxiety Inventory; DES II, Dissociation Experiences Scale version 2; TAS-20, Toronto Alexithymia Scale 20-item; DEP, symptoms of depression (as per Personality Assessment Inventory scale); DEP-P, levels of physiological functioning, activity & energy (somatic symptoms of depression, as per Personality Assessment Inventory scale); SOM-C, symptoms of conversion disorder such as sensory or motor dysfunctions; SOM-S, physical symptoms and complaints of ill-health & fatigue.

Chi-squared tests of dependence compared PNES and healthy-control groups for their utilisation of each coping style and indicated that groups differed on utilising an Emotion-Focused [\( \chi^2(1, n=38) = 6.017; p=0.014 \)] and Avoidance-Focused coping strategy [\( \chi^2(1, n=38) = 9.449; p=0.002 \)], where the PNES group had significantly higher utilisation of these strategies. The effect size for each result was moderately high (\( \Phi =-0.343, p=0.034 \) for Emotion-Focused, and \( \Phi =-0.433, p=0.008 \) for Avoidance-Focused strategies). There was no statistically significant group difference on use of low Task-Focused coping strategies [\( \chi^2(1, n=38) = 2.201; p=0.138 \)].

Relationship between coping-strategies and clinical and psychometric variables of interest

The results of this analysis are illustrated in Table 6.3. Task-Orientated coping strategy t-scores were significantly negatively correlated with symptoms of depression (Pearson’s \( r = -0.569, p=0.0001 \)), anxiety (Pearson’s \( r = -0.465, p=0.003 \)) and alexithymia (Pearson’s \( r = -0.509, p=0.001 \)). Stepwise multivariate regression on the Task-Orientated scale from the CISS showed that BDI-II and BAI were co-linearly related so BDI was excluded from the model.
Regression was significant (F= 5.594; R² = 0.26, p = 0.031). One predictor was retained as significant, namely TAS-20 (t = -2.36; p=0.030).

Emotion-Focused coping strategy t-scores were significantly positively correlated with symptoms of depression (Pearson’s r = -0.683, p=0.0001), anxiety (Pearson’s r = -0.762, p=0.0001), dissociative experiences (Pearson’s r = -0.588, p=0.0001), and the somatic complaints sub-scales relating to focusing on symptoms relating to conversion disorder (Pearson’s r = -0.565, p=0.0001) and physical symptoms and complaints of ill-health and fatigue (Pearson’s r = -0.556, p=0.0001). Stepwise multivariate regression on the Emotion-Focused scale from the CISS showed that BDI-II and BAI were co-linearly related so BDI-II was excluded from the model. Regression was significant (F= 22.118, R²= 0.58, p=0.0001). One predictor was retained as significant, namely BAI (t = 4.703, p=0.0001).

There were no significant correlations observed between mean Avoidance-Focused coping strategy t-scores and the selected variables. No significant relationship was observed between Avoidance-Focused coping strategies and any other variables using stepwise multivariate regression.

**Results of alexithymia (TAS-20) analysis**

Of the patients with PNES, six (31.6%) scored as having alexithymia, a further six (31.6%) scored in the range for possible alexithymia, and seven (36.8%) did not have alexithymia. In contrast, one healthy-control (5.3%) had alexithymia, a further one (5.3%) scored in the range for possible alexithymia, and seventeen (89.5%) did not have alexithymia. TAS-20 score was negatively correlated with FSIQ (Pearson’s r = -0.419, p=0.009) and positively correlated with scores from the DES II (Pearson’s r = 0.576, p=0.0001), SOM-C (Pearson’s r = 0.356, p=0.028), SOM-S (Pearson’s r = 0.422, p=0.008) and SOM-H (Pearson’s r = 0.355, p=0.029). There was no significant relationship observed between TAS-20 and years of education (Pearson’s r = -0.210, p=0.205).
6.5.2 Results of analyses of neuropsychological data

There were significant between-group differences on some neuropsychological performance measures of the CANTAB battery, namely the spatial working memory (SWM) test, the Stockings of Cambridge (SOC) test, and the Rapid Visual Processing (RVP) test (Table 6.4). Patients with PNES performed significantly less well than healthy-controls on the SWM test, but better on specific elements of the SOC and RVP measures.

Table 6.4 Results of binary logistical regression analysis comparing patient and healthy control groups on CANTAB test performance (controlling for effects of FSIQ).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PNES</th>
<th>Healthy Control</th>
<th>Group Difference p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td></td>
</tr>
<tr>
<td><strong>Spatial Working Memory (SWM)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SWM BE</td>
<td>23.05 (16.92)</td>
<td>18.79 (17.70)</td>
<td><strong>0.025</strong></td>
</tr>
<tr>
<td>SWM BE 6 Boxes</td>
<td>6.16 (6.02)</td>
<td>4.89 (6.56)</td>
<td><strong>0.042</strong></td>
</tr>
<tr>
<td>SWM BE 8 Boxes</td>
<td>16.26 (12.31)</td>
<td>13.47 (11.88)</td>
<td><strong>0.036</strong></td>
</tr>
<tr>
<td>SWM TE</td>
<td>23.63 (17.32)</td>
<td>19.89 (17.31)</td>
<td><strong>0.025</strong></td>
</tr>
<tr>
<td>SWM TE 6 Boxes</td>
<td>6.26 (6.11)</td>
<td>5.26 (6.64)</td>
<td><strong>0.041</strong></td>
</tr>
<tr>
<td>SWM TE 8 Boxes</td>
<td>16.68 (12.71)</td>
<td>14.16 (11.55)</td>
<td><strong>0.035</strong></td>
</tr>
<tr>
<td>SWM Strategy</td>
<td>30.16 (6.98)</td>
<td>28.32 (7.05)</td>
<td><strong>0.048</strong></td>
</tr>
<tr>
<td><strong>Stockings of Cambridge (SOC)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOC MITT 3 moves</td>
<td>4853.82 (2650.87)</td>
<td>6263.47 (4944.80)</td>
<td>0.031</td>
</tr>
<tr>
<td><strong>Rapid Visual Processing (RVP)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RVP Mean Latency</td>
<td>405.14 (55.75)</td>
<td>407.50 (70.92)</td>
<td><strong>0.040</strong></td>
</tr>
</tbody>
</table>

The p-Values of variables significantly different between groups are highlighted in bold type and with an asterix, * indicating p<0.05. PNES, psychogenic non-epileptic seizures; SD, standard deviation; BE, between-errors; TE, total errors; MITT, mean initial thinking-time; 6 and 8 boxes refer to levels of increasing complexity (respectively) within the SWM task; 3 moves refers to solving a problem within 3 moves on the SOC task.

Spatial working memory

The Spatial Working Memory (SWM) test assesses working memory and
executive functioning. BE refers to the total frequency participants touched a box found to previously contain a token during that test, and BE 6 and BE 8 boxes refer to the frequency participants touched a box previously found to contain a token, on 6- and 8-box trials of the task. TE is a measure of all errors made over all trials of the test, and TE 6 and TE 8 boxes refer to the frequency of all errors on 6- and 8-box trials, respectively.

Patients with PNES performed significantly less well than the healthy control group on this neuropsychological test, committing on average a greater number of between errors (BE) and total errors (TE), as well as executing a poorer strategy to solve the problems (Table 6.4).

Stockings of Cambridge
The Stockings of Cambridge (SOC) test measures planning ability and executive functioning. Mean initial thinking time (MITT) refers to the time taken by the participant to think about the problem facing them before they start to try to solve it. “MITT 3 moves” refers to the complexity of the problem, which in this case is that the participant is expected to solve the problem within 3 moves. Patients with PNES responded significantly quicker than the healthy control group on the MITT aspect of this test, so that they spent an average of 1409.65 milliseconds less time thinking about solving the 3-move problems than the healthy-control group ($p<0.05$) (Table 6.4).

Rapid Visual Processing
The Rapid Visual Processing (RVP) test measures sustained attention to complex visual stimuli. The RVP mean latency index of this test refers to the time taken to respond to correct stimuli (in this task, to respond when a target sequence appears requiring a response from the participant). Patients with PNES had a shorter reaction time to respond to target sequences than the healthy-control group ($p<0.05$) (Table 6.4).

6.5.3 Results of analyses of fMRI data
This section will present the results of the fMRI data analyses, relating to the behavioural and implicit face-processing results.

### 6.5.3.1 Behavioural data results:

Given that the fMRI activation results showed between-groups differences for neutral face processing and that these differences were found to drive between-group differences at low and high intensity, behavioural data was analysed for all EFE conditions together, rather than for each separately.

Patient and healthy control groups both showed a high degree of accuracy for carrying out the implicit task, involving gender discrimination (GDT) across all conditions (Table 6.5).

#### Table 6.5 Results of general linear model analysis comparing and healthy control groups on fMRI task-related behavioural performance

<table>
<thead>
<tr>
<th>Behavioural Data (fMRI task)</th>
<th>PNES</th>
<th>Healthy Control</th>
<th>Group Difference p-value (Wilcoxon Mann-Whitney t-test)</th>
<th>Group Difference p-value after controlling analysis for FSIQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Correct Gender-Discrimination (CGD), (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average CGD over all EFE conditions</td>
<td>96.66 (5.37)</td>
<td>99.15 (0.94)</td>
<td>0.112</td>
<td>0.283</td>
</tr>
<tr>
<td>Mean Reaction Time (MRT)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average MRT over all EFE conditions</td>
<td>907.03 (171.13)</td>
<td>770.92 (109.58)</td>
<td>0.009*</td>
<td>0.007*</td>
</tr>
<tr>
<td>Total Errors (TE)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average TE over all EFE conditions</td>
<td>15.29 (21.95)</td>
<td>3.23 (2.63)</td>
<td>0.035*</td>
<td>0.062</td>
</tr>
</tbody>
</table>

PNES, psychogenic non-epileptic seizures; SD, standard deviation; CGD, correct gender discrimination; EFE, emotional face expression; MRT, mean reaction time to stimulus; TE, total errors during task, comprising errors of incorrect identification of gender & errors of omission (i.e., non-response to a stimulus); Significant between-group differences are marked with an asterix, *, where $p<0.05$. 

271
There was no significant group difference for accuracy on the GDT over all conditions (Z = -1.59, p>0.05). However, there were significant between-group differences for mean response time to EFE stimuli during the task (Z = -2.57, p<0.05) (Figure 6.1), and on total errors committed over the EFE task (Z = -2.09, p<0.05) (Figure 6.2), where in each case, the PNES group demonstrated more errors and greater latency of response to facial stimuli (Table 6.5).

A Pearson’s correlation analysis was carried out between behavioural data variables that predicted PNES group status [i.e., overall mean response time (MRT) scores, and total error (TE scores)] and the following psychometric predictor variables: scores for BDI-II, BAI, TAS-20, DES-II, SOM-C, SOM-S, SOM-H, SWM BE, SWM TE, SWM strategy. A Bonferroni adjustment was made for each of the behavioural task’s correlations to account for experiment-wise error, so that p (0.05) was divided by the number of correlation variables

Figure 6.1 Mean response times to all EFE stimuli during the fMRI face-processing task in PNES and healthy-control groups.
PNES, psychogenic non-epileptic seizures; OLS, ordinary least squares regression method of comparing means.
Response time is displayed in milliseconds.

272
PNES, psychogenic non-epileptic seizures. (n=12), to give a Bonferroni-adjusted $p$ value of 0.004. The significant results are presented in Table 6.6. MRT scores overall for face-stimuli were found to positively correlate with scores for depression (BDI-II), anxiety (BAI), dissociation (DES-II), and for a sub-scale of the personality assessment inventory (PAI) associated with dissociative (conversion disorders), namely physical symptoms and complaints of ill-health & fatigue (SOM-S).

TE committed during the fMRI task over all face stimuli were found to positively correlate with scores for depression (BDI-II), anxiety (BAI), dissociation (DES-II), and for a sub-scale of the personality assessment inventory (PAI) associated with dissociative (conversion disorders), namely sensory or motor dysfunctions (SOM-C).

Also, a binary logistical regression analysis was employed to examine relationships between abnormal coping style status and both MRT and TEs. However, endorsement of an abnormal coping style was not found to have any significant relationship with MRT or TEs on the behavioural task.
Table 6.6  Correlations between behavioural and psychometric variables that predicted PNES group status a.

<table>
<thead>
<tr>
<th>Variable</th>
<th>BDI</th>
<th>BAI</th>
<th>DESII</th>
<th>SOM-C</th>
<th>SOM-S</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRT over all EFE conditions</td>
<td>0.520*</td>
<td>0.542*</td>
<td>0.618*</td>
<td>0.681*</td>
<td></td>
</tr>
<tr>
<td>TE over all EFE conditions</td>
<td>0.500*</td>
<td>0.560*</td>
<td>0.633*</td>
<td>0.513*</td>
<td></td>
</tr>
</tbody>
</table>

a Results of correlation analysis.  PNES, psychogenic non-epileptic seizures; MRT, mean response (reaction) time to face stimulus; EFE, emotional face expression; BDI, Beck’s Depression Inventory; BAI, Beck’s Anxiety Inventory; DES II, Dissociation Experiences Scale version 2; SOM-C, symptoms of conversion disorder such as sensory or motor dysfunctions; SOM-S, physical symptoms and complaints of ill-health & fatigue.

Results are presented as Pearson’s $r$ correlation values.  Note: Pearson $r$ correlations marked with an asterix, * were significant at $p<0.004$.  There were no significant correlations between MRT or TE on the behavioural task and TAS-20, SOM-H, and the neuropsychological variables SMW BE, SWM TE or SWM strategy.

6.5.3.2 Implicit EFE processing results:

This section will outline the results of the between-group fMRI responses to each EFE (fear, disgust, sadness) at 0% (neutral), low (50%) and high (100%) intensity will be presented first, followed by relevant post-hoc analysis.

6.5.3.2.1 Between-group differences for each emotional condition showing neutral, low and high intensity of emotional intensity

A summary of brain regions where there were significant between-group differences in BOLD responses to the implicit face-processing task involving faces showing the 3 emotions (Fear, Disgust and Sadness), respectively, at neutral, 50% and 100% intensities are shown in Table 6.7, Table 6.8, and Table 6.9, respectively.  There were 20 activations that survived cluster-size thresholding for the Fear condition, 6 for the Disgust condition and 17 for the Sadness condition.  The results show the respective $p$-values after analyses of the data controlled for the effects of FSIQ.  Compared to the healthy-control group, the PNES group had reduced brain-activation to this face-processing task, for all anatomical regions of difference and across emotion conditions and...
Table 6.7 Brain regions showing uniformly lower task-related BOLD signal changes to the set of faces showing fear in the patients with PNES compared with healthy controls*.

<table>
<thead>
<tr>
<th>Brain Region</th>
<th>BA</th>
<th>Side</th>
<th>Tal (x)</th>
<th>Tal (y)</th>
<th>Tal (z)</th>
<th>Size (mm$^3$)</th>
<th>P value Neutral</th>
<th>P value 50%</th>
<th>P value 100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-Central Gyrus / Superior Temporal Gyrus</td>
<td>40/</td>
<td>L</td>
<td>-63</td>
<td>-24</td>
<td>16</td>
<td>1002</td>
<td>0.0003</td>
<td>0.001</td>
<td>0.007</td>
</tr>
<tr>
<td>Inferior Frontal Gyrus</td>
<td>47</td>
<td>R</td>
<td>24</td>
<td>20</td>
<td>-18</td>
<td>770</td>
<td>0.002</td>
<td>0.019</td>
<td>0.010</td>
</tr>
<tr>
<td>Lateral Occipital Gyrus / Lingual Gyrus</td>
<td>18</td>
<td>L</td>
<td>-35</td>
<td>-88</td>
<td>-3</td>
<td>330</td>
<td>0.001</td>
<td>0.002</td>
<td>0.0003</td>
</tr>
<tr>
<td>Middle Temporal Gyrus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Middle Temporal Gyrus</td>
<td>21</td>
<td>L</td>
<td>-60</td>
<td>-23</td>
<td>-12</td>
<td>735</td>
<td>0.003</td>
<td>0.065</td>
<td>0.066</td>
</tr>
<tr>
<td>Inferior / Middle Frontal Gyrus</td>
<td>9</td>
<td>L</td>
<td>-45</td>
<td>9</td>
<td>29</td>
<td>598</td>
<td>0.004</td>
<td>0.001</td>
<td>0.003</td>
</tr>
<tr>
<td>Middle Frontal Gyrus</td>
<td>10</td>
<td>L</td>
<td>-30</td>
<td>49</td>
<td>7</td>
<td>292</td>
<td>0.007</td>
<td>0.008</td>
<td>0.009</td>
</tr>
<tr>
<td>Inferior / Superior Parietal Lobule</td>
<td>7</td>
<td>R</td>
<td>33</td>
<td>-58</td>
<td>43</td>
<td>999</td>
<td>0.011</td>
<td>0.062</td>
<td>0.007</td>
</tr>
<tr>
<td>Middle Temporal Gyrus</td>
<td>37</td>
<td>L</td>
<td>-52</td>
<td>-54</td>
<td>1</td>
<td>565</td>
<td>0.011</td>
<td>0.002</td>
<td>0.068</td>
</tr>
<tr>
<td>Inferior Parietal Lobule</td>
<td>40</td>
<td>R</td>
<td>46</td>
<td>-40</td>
<td>55</td>
<td>480</td>
<td>0.011</td>
<td>0.084</td>
<td>0.014</td>
</tr>
<tr>
<td>Culmen (Cerebellum)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medial Frontal Gyrus</td>
<td>6</td>
<td>R</td>
<td>2</td>
<td>-14</td>
<td>54</td>
<td>481</td>
<td>0.015</td>
<td>0.001</td>
<td>0.054</td>
</tr>
<tr>
<td>Para-Hippocampal Gyrus / Uncus</td>
<td>28</td>
<td>L</td>
<td>-19</td>
<td>-14</td>
<td>-28</td>
<td>407</td>
<td>0.020</td>
<td>0.366</td>
<td>0.014</td>
</tr>
<tr>
<td>Inferior Temporal Gyrus</td>
<td>20</td>
<td>R</td>
<td>46</td>
<td>-13</td>
<td>-14</td>
<td>456</td>
<td>0.030</td>
<td>0.266</td>
<td>0.056</td>
</tr>
<tr>
<td>Pre-central Gyrus</td>
<td>4</td>
<td>L</td>
<td>-28</td>
<td>-26</td>
<td>50</td>
<td>386</td>
<td>0.034</td>
<td>0.003</td>
<td>0.183</td>
</tr>
<tr>
<td>Superior Temporal Gyrus</td>
<td>13</td>
<td>R</td>
<td>44</td>
<td>0</td>
<td>-12</td>
<td>302</td>
<td>0.049</td>
<td>0.036</td>
<td>0.009</td>
</tr>
<tr>
<td>Inferior Frontal Gyrus</td>
<td>47</td>
<td>L</td>
<td>-30</td>
<td>31</td>
<td>-6</td>
<td>1177</td>
<td>0.075</td>
<td>0.068</td>
<td>0.065</td>
</tr>
<tr>
<td>Pre-Central Gyrus</td>
<td>4/6</td>
<td>L</td>
<td>-35</td>
<td>-17</td>
<td>61</td>
<td>1669</td>
<td>0.078</td>
<td>0.0003</td>
<td>0.004</td>
</tr>
<tr>
<td>Medial Frontal Gyrus</td>
<td>10</td>
<td>R</td>
<td>8</td>
<td>52</td>
<td>6</td>
<td>581</td>
<td>0.083</td>
<td>0.138</td>
<td>0.009</td>
</tr>
<tr>
<td>Superior Temporal Gyrus</td>
<td></td>
<td>R</td>
<td>61</td>
<td>-47</td>
<td>13</td>
<td>667</td>
<td>0.085</td>
<td>0.005</td>
<td>0.139</td>
</tr>
</tbody>
</table>

*Names of brain regions, Brodmann’s areas (where appropriate), Talairach co-ordinates, size of voxel cluster, and significance levels are provided. BA, Brodmann’s area; Tal, Talairach co-ordinate; SD, standard deviation; Areas showing significant between-groups response to the implicit processing task, on a repeated measures ANOVA, controlling for FSIQ, are highlighted in bold type. All BOLD activations are greater for the healthy control group compared with PNES group.
Table 6.8 Brain regions showing uniformly lower task-related BOLD signal changes to the set of faces showing disgust in the patients with PNES compared with healthy controls*.

<table>
<thead>
<tr>
<th>Brain Region</th>
<th>BA</th>
<th>Side</th>
<th>Tal (x)</th>
<th>Tal (y)</th>
<th>Tal (z)</th>
<th>Size (mm³)</th>
<th>P value Neutral</th>
<th>P value 50%</th>
<th>P value 100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inferior Frontal Gyrus</td>
<td></td>
<td>R</td>
<td>35</td>
<td>35</td>
<td>3</td>
<td>288</td>
<td><strong>0.010</strong></td>
<td><strong>0.011</strong></td>
<td>0.177</td>
</tr>
<tr>
<td>Post-Central Gyrus</td>
<td>2</td>
<td>L</td>
<td>-49</td>
<td>-23</td>
<td>34</td>
<td>585</td>
<td><strong>0.014</strong></td>
<td>0.091</td>
<td>0.588</td>
</tr>
<tr>
<td>Insula / Pre-Central Gyrus</td>
<td>13/41</td>
<td>L</td>
<td>-48</td>
<td>-16</td>
<td>12</td>
<td>299</td>
<td><strong>0.014</strong></td>
<td>0.293</td>
<td>0.269</td>
</tr>
<tr>
<td>Fusiform Gyrus</td>
<td>20</td>
<td>R</td>
<td>52</td>
<td>-6</td>
<td>-25</td>
<td>323</td>
<td>0.154</td>
<td><strong>0.014</strong></td>
<td>0.759</td>
</tr>
<tr>
<td>Inferior Frontal Gyrus</td>
<td>47</td>
<td>L</td>
<td>25</td>
<td>14</td>
<td>-21</td>
<td>344</td>
<td>0.339</td>
<td>0.136</td>
<td>0.920</td>
</tr>
<tr>
<td>Insula</td>
<td>13</td>
<td>R</td>
<td>47</td>
<td>17</td>
<td>16</td>
<td>290</td>
<td>0.409</td>
<td>0.335</td>
<td>0.162</td>
</tr>
</tbody>
</table>

*Names of brain regions, Brodmann’s areas (where appropriate), Talairach co-ordinates, size of voxel cluster, and significance levels are provided. BA, Brodmann’s area; Tal, Talairach co-ordinate; SD, standard deviation; Areas showing significant between-groups response to the implicit processing task, on a repeated measures ANOVA, controlling for FSIQ, are highlighted in bold type. All BOLD activations are greater for the healthy control group compared with PNES group.

intensities.

The results of the implicit processing task for all three emotions showed that patients with PNES demonstrated abnormal processing of faces, as can be seen in the results showing significant between-group differences for neutral face-processing. The main areas that showed between-group differences for activations to the faces showing fear involved the middle and inferior frontal gyri, the superior, middle and inferior temporal gyri, superior and inferior parietal lobule, occipital gyrus, pre and post central gyri, and cerebellum (Figure C1 in Appendix) (Table 6.7).

The main areas that showed between-group differences for activations to the faces showing disgust involved the inferior frontal gyrus, pre and post central gyri and the insula (Figure C2 in Appendix) (Table 6.8). The main areas that showed between-group differences for activations to the faces showing sadness
involved the superior, middle and inferior frontal gyri, the superior and middle temporal gyri, superior parietal lobule, cingulate cortex, caudate nucleus (basal ganglia) and cerebellum (Figure C3 in Appendix) (Table 6.9).

Table 6.9 Brain regions showing uniformly lower task-related BOLD signal changes to the set of faces showing sadness in the patients with PNES compared with healthy controls*.

<table>
<thead>
<tr>
<th>Brain Region</th>
<th>BA</th>
<th>Side</th>
<th>Tal (x)</th>
<th>Tal (y)</th>
<th>Tal (z)</th>
<th>Size (mm³)</th>
<th>P value Neutral</th>
<th>p value 50%</th>
<th>p value 100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Posterior Cingulate</td>
<td>29</td>
<td>L</td>
<td>-6</td>
<td>-46</td>
<td>17</td>
<td>1348</td>
<td>0.001</td>
<td>0.002</td>
<td>0.005</td>
</tr>
<tr>
<td>Pre-Cuneus (Superior Parietal Lobule)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebellum</td>
<td></td>
<td></td>
<td>-3</td>
<td>-35</td>
<td>-39</td>
<td>480</td>
<td>0.005</td>
<td>0.004</td>
<td>0.007</td>
</tr>
<tr>
<td>Fusiform Gyrus / Middle Temporal Gyrus</td>
<td>20/21</td>
<td>L</td>
<td>-39</td>
<td>-8</td>
<td>-21</td>
<td>495</td>
<td>0.006</td>
<td>0.112</td>
<td>0.016</td>
</tr>
<tr>
<td>Superior Frontal Gyrus</td>
<td>9</td>
<td>R</td>
<td>24</td>
<td>54</td>
<td>28</td>
<td>679</td>
<td>0.008</td>
<td>0.011</td>
<td>0.0003</td>
</tr>
<tr>
<td>Middle Temporal Gyrus</td>
<td>21</td>
<td>R</td>
<td>60</td>
<td>-10</td>
<td>-11</td>
<td>545</td>
<td>0.008</td>
<td>0.062</td>
<td>0.010</td>
</tr>
<tr>
<td>Fusiform Gyrus / Middle Temporal Gyrus</td>
<td>37</td>
<td>L</td>
<td>-44</td>
<td>-52</td>
<td>-11</td>
<td>514</td>
<td>0.011</td>
<td>0.016</td>
<td>0.002</td>
</tr>
<tr>
<td>Superior Temporal Gyrus</td>
<td>41</td>
<td>R</td>
<td>39</td>
<td>-39</td>
<td>14</td>
<td>316</td>
<td>0.014</td>
<td>0.079</td>
<td>0.013</td>
</tr>
<tr>
<td>Inferior / Middle Frontal Gyrus</td>
<td>9</td>
<td>L</td>
<td>-48</td>
<td>9</td>
<td>30</td>
<td>521</td>
<td>0.016</td>
<td>0.002</td>
<td>0.011</td>
</tr>
<tr>
<td>Caudate Nucleus / Anterior Cingulate Cortex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Middle Temporal Gyrus / Middle Occipital Gyrus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medial Frontal Gyrus</td>
<td>6</td>
<td>L</td>
<td>-2</td>
<td>-19</td>
<td>53</td>
<td>745</td>
<td>0.038</td>
<td>0.171</td>
<td>0.002</td>
</tr>
<tr>
<td>Caudate Nucleus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-central Gyrus</td>
<td>6</td>
<td>L</td>
<td>-36</td>
<td>-13</td>
<td>60</td>
<td>1265</td>
<td>0.058</td>
<td>0.208</td>
<td>0.029</td>
</tr>
<tr>
<td>Middle Frontal Gyrus</td>
<td>11</td>
<td>L</td>
<td>-27</td>
<td>32</td>
<td>0</td>
<td>746</td>
<td>0.099</td>
<td>0.103</td>
<td>0.026</td>
</tr>
<tr>
<td>Superior / Middle Temporal Gyrus</td>
<td>21/22</td>
<td>R</td>
<td>-19</td>
<td>-14</td>
<td>-28</td>
<td>351</td>
<td>0.224</td>
<td>0.071</td>
<td>0.026</td>
</tr>
<tr>
<td>Post-Central Gyrus / Para-Central Lobule</td>
<td>3/4</td>
<td>R</td>
<td>8</td>
<td>-34</td>
<td>66</td>
<td>458</td>
<td>0.300</td>
<td>0.005</td>
<td>0.009</td>
</tr>
</tbody>
</table>

*Names of brain regions, Brodmann’s areas (where appropriate), Talairach co-ordinates, size of voxel cluster, and significance levels are provided. BA, Brodmann’s area; Tal, Talairach co-ordinate; Areas showing significant between-groups response to the implicit processing task, on a repeated measures ANOVA, controlling for FSIQ, are highlighted in bold type. All BOLD activations are greater for the healthy control group compared with PNES group.

The results from the post-hoc independent ANCOVAs carried out at each
cluster that did not show significant between-group differences for neutral face processing are displayed in Table 6.10. This analysis was carried out to examine if there were BOLD response differences to low and high emotional intensity of faces in those clusters.

Table 6.10 Results of post-hoc analysis of those brain-activation clusters that failed to show a significant between-group difference to the neutral face condition*.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Brain Region</th>
<th>BA</th>
<th>Side</th>
<th>Tal (x)</th>
<th>Tal (y)</th>
<th>Tal (z)</th>
<th>Size (mm³)</th>
<th>P-Value Neutral (%)</th>
<th>P-Value 50-0%</th>
<th>P-Value 100-0%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fear</td>
<td>Inferior Frontal Gyrus</td>
<td>47</td>
<td>L</td>
<td>-30</td>
<td>31</td>
<td>-6</td>
<td>1177</td>
<td>0.075</td>
<td>0.649</td>
<td>0.965</td>
</tr>
<tr>
<td></td>
<td>Pre-Central Gyrus</td>
<td>4/6</td>
<td>L</td>
<td>-35</td>
<td>-17</td>
<td>61</td>
<td>1669</td>
<td>0.078</td>
<td><strong>0.005</strong></td>
<td>0.492</td>
</tr>
<tr>
<td></td>
<td>Medial Frontal Gyrus</td>
<td>10</td>
<td>R</td>
<td>8</td>
<td>52</td>
<td>6</td>
<td>581</td>
<td>0.083</td>
<td>0.653</td>
<td>0.450</td>
</tr>
<tr>
<td></td>
<td>Superior Temporal Gyrus</td>
<td>R</td>
<td>61</td>
<td>-47</td>
<td>13</td>
<td></td>
<td>667</td>
<td>0.085</td>
<td><strong>0.034</strong></td>
<td>0.886</td>
</tr>
<tr>
<td>Disgust</td>
<td>Fusiform Gyrus</td>
<td>20</td>
<td>R</td>
<td>52</td>
<td>-6</td>
<td>-25</td>
<td>323</td>
<td>0.154</td>
<td>0.247</td>
<td>0.343</td>
</tr>
<tr>
<td></td>
<td>Inferior Frontal Gyrus</td>
<td>47</td>
<td>L</td>
<td>25</td>
<td>14</td>
<td>-21</td>
<td>344</td>
<td>0.339</td>
<td>0.433</td>
<td>0.467</td>
</tr>
<tr>
<td></td>
<td>Insula</td>
<td>13</td>
<td>R</td>
<td>47</td>
<td>17</td>
<td>16</td>
<td>290</td>
<td>0.409</td>
<td>0.795</td>
<td>0.733</td>
</tr>
<tr>
<td>Sadness</td>
<td>Pre-central Gyrus</td>
<td>6</td>
<td>L</td>
<td>-36</td>
<td>-13</td>
<td>60</td>
<td>1265</td>
<td>0.058</td>
<td>0.604</td>
<td>0.295</td>
</tr>
<tr>
<td></td>
<td>Middle Frontal Gyrus</td>
<td>11</td>
<td>L</td>
<td>-27</td>
<td>32</td>
<td>0</td>
<td>746</td>
<td>0.099</td>
<td>0.982</td>
<td>0.278</td>
</tr>
<tr>
<td></td>
<td>Superior / Middle</td>
<td>21/</td>
<td>R</td>
<td>-19</td>
<td>-14</td>
<td>-28</td>
<td>351</td>
<td>0.224</td>
<td>0.392</td>
<td>0.135</td>
</tr>
<tr>
<td></td>
<td>Temporal Gyrus</td>
<td>22</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Post-Central Gyrus /</td>
<td>3/4</td>
<td>R</td>
<td>8</td>
<td>-34</td>
<td>66</td>
<td>458</td>
<td>0.300</td>
<td><strong>0.015</strong></td>
<td>0.106</td>
</tr>
<tr>
<td></td>
<td>Para-Central Lobule</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Names of brain regions, Brodmann’s areas (where appropriate), Talairach co-ordinates, size of voxel cluster, and significance levels are provided. Results of individual ANCOVAs of the mean differences in activation levels (100%-0% and 50%-0%) controlling for FSIQ at each cluster are shown. BA, Brodmann’s area; Tal, Talairach co-ordinate; Areas showing significant between-groups response to the implicit processing task at a p<0.05 level are highlighted in bold type. Bonferroni-adjusted p-Values for fear, disgust and sadness are 0.0125, 0.016 and 0.0125, respectively. All BOLD activations are greater for the healthy control group compared with PNES group.

Table 6.11 shows specifically the brain activations means (standard deviations) for those areas found to be significant from these post-hoc ANCOVAs. There were two regions of brain activation for processing of fearful faces that were significant at a p<0.05 level. However, a Bonferroni adjustment was applied to control for multiple comparisons computed as dividing the normal threshold
level of significance (i.e., \( p < 0.05 \)) by the number of activations examined (i.e., 4 in the case of Fear), leading to an adjusted \( p \) value of less than or equal to 0.0125. After applying this adjusted threshold, no region of brain activation significantly differed between-groups. Also, there was no region of brain activation found to differ between-groups for processing faces showing Fear at a 100% level of intensity.

There was one region of brain activation that was significantly different between-groups at a \( p < 0.05 \) level during processing of sad faces. A Bonferroni adjustment was applied to control for multiple comparisons computed as dividing the normal threshold level of significance (i.e., \( p < 0.05 \)) by the number of activations examined (i.e., 4 in the case of Sadness), leading to an adjusted \( p \) value of less than or equal to 0.0125. After applying this adjusted threshold, one region of brain activation significantly differed between-groups at the 50% level of intensity of Sadness \( [F(1, 37)=6.556, p=0.015] \), located in the post-central gyrus/para-central lobule. No region of brain activation was found to differ between groups for processing faces showing Sadness at a 100% level of intensity.

There were no between-group differences in BOLD response to the processing of faces showing Disgust at either 50% or 100% level of intensity.

The most important findings from these analyses were that firstly there were significant group differences for viewing (neutral) facial expressions, and secondly, that examining between-group differences for each emotional condition there were no areas of difference common to all three sets of emotional faces. Because no common areas were found with all three emotional conditions, this raised the question of whether the between-group results could be influenced by factors such as physiological noise, or whether preceding emotional faces may have continued to have an effect on subsequent response to the next face during the task. Therefore, having found where groups produced significantly different responses to EFEs, it was decided to
Table 6.11  Brain-activation clusters that failed to show a significant between-group difference to the neutral face condition but showed between-group differences at 50% intensity after removing the effects of neutral activation*.

<table>
<thead>
<tr>
<th>Emotion</th>
<th>Brain Region</th>
<th>BA</th>
<th>Side</th>
<th>Tal (x)</th>
<th>Tal (y)</th>
<th>Tal (z)</th>
<th>Size (mm³)</th>
<th>PNES Mean Activation (SD)</th>
<th>Healthy Controls Mean Activation (SD)</th>
<th>P value 50-0%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fear</td>
<td>Pre-Central Gyrus</td>
<td>4/6</td>
<td>L</td>
<td>-35</td>
<td>-17</td>
<td>61</td>
<td>1669</td>
<td>-0.0013 (0.0283)</td>
<td>0.0263 (0.0425)</td>
<td><strong>0.005</strong></td>
</tr>
<tr>
<td></td>
<td>Superior Temporal Gyrus</td>
<td>R</td>
<td>61</td>
<td>-47</td>
<td>13</td>
<td>667</td>
<td>0.0056 (0.0316)</td>
<td>0.0291 (0.0338)</td>
<td><strong>0.034</strong></td>
<td></td>
</tr>
<tr>
<td>Sadness</td>
<td>Post-Central Gyrus / Para-Central Lobule</td>
<td>3/4</td>
<td>R</td>
<td>8</td>
<td>-34</td>
<td>66</td>
<td>458</td>
<td>-0.0103 (0.0354)</td>
<td>0.0101 (0.0341)</td>
<td><strong>0.015</strong></td>
</tr>
</tbody>
</table>

*Names of brain regions, Brodmann’s areas (where appropriate), Talairach co-ordinates, size of voxel cluster, and significance levels are provided. Results of individual ANCOVAs of the mean differences in activation levels (100%-0% and 50%-0%) controlling for FSIQ at each cluster are shown. BA, Brodmann’s area; Tal, Talairach co-ordinate; SD, standard deviation; Areas showing significant between-groups response to the implicit processing task at a p<0.05 level are highlighted in bold type. Bonferroni-adjusted p values for fear, disgust and sadness are 0.0125, 0.016 and 0.0125, respectively. All BOLD activations are greater for the healthy control group compared with PNES group.

investigate where the groups demonstrated overlaps in activation to (all) EFEs and then to examine between-group differences in those areas of overlap. In this way we could be more certain that the results would represent true between-group differences.

6.5.3.2.2 Results of analysis investigating if the fMRI task activates similar brain regions in each group during the processing of neutral faces:

The results from the group-specific combination maps for the “neutral versus null-hypothesis” test across all emotional conditions (Fear, Disgust, Sadness) for the PNES group and the healthy-control group are illustrated in Figures C4 and C5 (in the Appendix), respectively. We found that similar brain regions were activated graphically by thresholding within groups and then overlaying the activations. This process produced twenty-two common brain regions (clusters) that were activated by both groups when processing neutral faces. The overlap
clusters involved in these activation maps are shown separately for the healthy control and PNES groups, in Tables 6.12 and 6.13, respectively.

Table 6.12 Table showing the overlap clusters for all emotions for the HC group only.

<table>
<thead>
<tr>
<th>Brain Region</th>
<th>BA</th>
<th>Side</th>
<th>Tal (x)</th>
<th>Tal (y)</th>
<th>Tal (z)</th>
<th>Size (mm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lingual Gyrus</td>
<td>18</td>
<td>R</td>
<td>5.3</td>
<td>70.0</td>
<td>2.5</td>
<td>143467</td>
</tr>
<tr>
<td>Pre-central Gyrus</td>
<td>4</td>
<td>L</td>
<td>-26.6</td>
<td>22.6</td>
<td>51.7</td>
<td>35772</td>
</tr>
<tr>
<td>Inferior Frontal Gyrus</td>
<td>9</td>
<td>R</td>
<td>42.1</td>
<td>-5.4</td>
<td>28.0</td>
<td>4917</td>
</tr>
<tr>
<td>Thalamus / Medial Dorsal Nucleus</td>
<td></td>
<td></td>
<td>12.2</td>
<td>18.2</td>
<td>11.4</td>
<td>1604</td>
</tr>
<tr>
<td>Inferior Frontal Gyrus</td>
<td>9</td>
<td>L</td>
<td>-50.8</td>
<td>-5.5</td>
<td>31.9</td>
<td>965</td>
</tr>
<tr>
<td>Thalamus / Lateral Posterior Nucleus</td>
<td></td>
<td></td>
<td>-13.7</td>
<td>18.4</td>
<td>12.8</td>
<td>694</td>
</tr>
<tr>
<td>Insula</td>
<td></td>
<td>R</td>
<td>28.9</td>
<td>-18.7</td>
<td>8.6</td>
<td>552</td>
</tr>
<tr>
<td>Pre-central Gyrus / Insula</td>
<td></td>
<td>L</td>
<td>-46.8</td>
<td>-5.0</td>
<td>6.6</td>
<td>403</td>
</tr>
<tr>
<td>Superior Temporal Gyrus</td>
<td>22</td>
<td>R</td>
<td>50.1</td>
<td>44.9</td>
<td>12.7</td>
<td>403</td>
</tr>
<tr>
<td>Middle Frontal Gyrus</td>
<td>9</td>
<td>R</td>
<td>41.1</td>
<td>-28.8</td>
<td>26.7</td>
<td>284</td>
</tr>
<tr>
<td>Inferior Frontal Gyrus / Pre-central Gyrus</td>
<td>9</td>
<td>L</td>
<td>-33.3</td>
<td>-6.6</td>
<td>24.9</td>
<td>280</td>
</tr>
<tr>
<td>Precuneus</td>
<td>7</td>
<td>L</td>
<td>-15.5</td>
<td>71.7</td>
<td>40.3</td>
<td>259</td>
</tr>
<tr>
<td>Insula / Post-central Gyrus</td>
<td>13</td>
<td>R</td>
<td>48.4</td>
<td>19.0</td>
<td>19.9</td>
<td>160</td>
</tr>
<tr>
<td>Thalamus</td>
<td></td>
<td>L</td>
<td>-24.6</td>
<td>22.5</td>
<td>-2.2</td>
<td>108</td>
</tr>
<tr>
<td>Pre-central Gyrus / Medial Frontal Gyrus</td>
<td>6</td>
<td>R</td>
<td>10.1</td>
<td>26.8</td>
<td>68.4</td>
<td>38</td>
</tr>
<tr>
<td>Precuneus</td>
<td>7</td>
<td>L</td>
<td>-26.4</td>
<td>65.5</td>
<td>33.2</td>
<td>36</td>
</tr>
<tr>
<td>Inferior Frontal Gyrus</td>
<td></td>
<td>R</td>
<td>21.0</td>
<td>-23.9</td>
<td>-5.4</td>
<td>27</td>
</tr>
<tr>
<td>Post-central Gyrus / Putamen</td>
<td></td>
<td>L</td>
<td>-16.6</td>
<td>41.6</td>
<td>68.5</td>
<td>22</td>
</tr>
<tr>
<td>Thalamus</td>
<td></td>
<td>R</td>
<td>8.3</td>
<td>26.2</td>
<td>-7.2</td>
<td>12</td>
</tr>
<tr>
<td>Lentiform Nucleus / Putamen</td>
<td></td>
<td>R</td>
<td>18.2</td>
<td>2.5</td>
<td>13.3</td>
<td>11</td>
</tr>
<tr>
<td>Claustrum</td>
<td></td>
<td>R</td>
<td>22.9</td>
<td>-21.6</td>
<td>4.4</td>
<td>8</td>
</tr>
<tr>
<td>Precuneus</td>
<td>7</td>
<td>R</td>
<td>13.3</td>
<td>74.2</td>
<td>41.5</td>
<td>6</td>
</tr>
<tr>
<td>Thalamus / Anterior Nucleus</td>
<td></td>
<td>L</td>
<td>-16.6</td>
<td>3.2</td>
<td>13.0</td>
<td>5</td>
</tr>
<tr>
<td>Middle Frontal Gyrus</td>
<td>6</td>
<td>R</td>
<td>22.7</td>
<td>9.7</td>
<td>53.0</td>
<td>3</td>
</tr>
<tr>
<td>Superior Frontal Gyrus</td>
<td>6</td>
<td>R</td>
<td>6.0</td>
<td>-8.0</td>
<td>62.5</td>
<td>2</td>
</tr>
<tr>
<td>Cerebellum (Tuber)</td>
<td></td>
<td>R</td>
<td>48.0</td>
<td>64.0</td>
<td>-28.0</td>
<td>1</td>
</tr>
</tbody>
</table>

BA, Brodmann’s area; Tal, Talairach co-ordinate; *Names of brain regions & BA (where appropriate), Talairach co-ordinates, laterality (side), and size of voxel cluster are provided.

281
# Table 6.13 Table showing the overlap clusters for all emotions for the PNES group only.

<table>
<thead>
<tr>
<th>Brain Region</th>
<th>BA</th>
<th>Side</th>
<th>Tal (x)</th>
<th>Tal (y)</th>
<th>Tal (z)</th>
<th>Size (mm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lingual Gyrus</td>
<td>18</td>
<td>L</td>
<td>-2.6</td>
<td>72.3</td>
<td>1.2</td>
<td>96555</td>
</tr>
<tr>
<td>Medial Frontal Gyrus</td>
<td>6</td>
<td>L</td>
<td>-1.3</td>
<td>0.0</td>
<td>52.1</td>
<td>4095</td>
</tr>
<tr>
<td>Precuneus</td>
<td>7</td>
<td>R</td>
<td>25</td>
<td>56.1</td>
<td>48.8</td>
<td>2982</td>
</tr>
<tr>
<td>Pre-central Gyrus</td>
<td>6</td>
<td>R</td>
<td>30.1</td>
<td>17.0</td>
<td>59.0</td>
<td>767</td>
</tr>
<tr>
<td>Pre-central Gyrus / Middle Frontal Gyrus</td>
<td>6</td>
<td>R</td>
<td>41.9</td>
<td>-2.4</td>
<td>36.0</td>
<td>342</td>
</tr>
<tr>
<td>Inferior Frontal Gyrus</td>
<td>6</td>
<td>R</td>
<td>37.1</td>
<td>-8.3</td>
<td>23.7</td>
<td>279</td>
</tr>
<tr>
<td>Post-central Gyrus / Inferior Parietal Gyrus</td>
<td>R</td>
<td></td>
<td>39.4</td>
<td>32.7</td>
<td>45.7</td>
<td>206</td>
</tr>
<tr>
<td>Middle Temporal Gyrus</td>
<td>39</td>
<td>L</td>
<td>-48</td>
<td>69.6</td>
<td>19.4</td>
<td>181</td>
</tr>
<tr>
<td>Pre-central Gyrus</td>
<td>6</td>
<td>R</td>
<td>47.4</td>
<td>5.2</td>
<td>40.5</td>
<td>107</td>
</tr>
<tr>
<td>Inferior Frontal Gyrus</td>
<td>6</td>
<td>L</td>
<td>-39.5</td>
<td>-0.8</td>
<td>30.2</td>
<td>98</td>
</tr>
<tr>
<td>Thalamus</td>
<td></td>
<td></td>
<td>7.7</td>
<td>26.9</td>
<td>-4.2</td>
<td>66</td>
</tr>
<tr>
<td>Superior Frontal Gyrus</td>
<td>6</td>
<td>L</td>
<td>-9.5</td>
<td>13.3</td>
<td>65.5</td>
<td>55</td>
</tr>
<tr>
<td>Middle Frontal Gyrus</td>
<td>46</td>
<td>R</td>
<td>43.1</td>
<td>-39.2</td>
<td>15.6</td>
<td>50</td>
</tr>
<tr>
<td>Post-central Gyrus</td>
<td>5</td>
<td>R</td>
<td>35.3</td>
<td>41.2</td>
<td>58.6</td>
<td>38</td>
</tr>
<tr>
<td>Insula</td>
<td></td>
<td></td>
<td>29.1</td>
<td>-21.3</td>
<td>2.1</td>
<td>35</td>
</tr>
<tr>
<td>Middle Frontal Gyrus</td>
<td></td>
<td></td>
<td>40.7</td>
<td>-28.5</td>
<td>17.5</td>
<td>15</td>
</tr>
<tr>
<td>Cingulate Cortex (middle portion)</td>
<td>24</td>
<td>R</td>
<td>1.6</td>
<td>2.9</td>
<td>30.4</td>
<td>14</td>
</tr>
<tr>
<td>Superior Frontal Gyrus</td>
<td>6</td>
<td>R</td>
<td>16.8</td>
<td>11.7</td>
<td>65.8</td>
<td>6</td>
</tr>
<tr>
<td>Inferior Frontal Gyrus</td>
<td></td>
<td></td>
<td>25.2</td>
<td>-22.8</td>
<td>-5.0</td>
<td>4</td>
</tr>
<tr>
<td>Inferior Frontal Gyrus / Pre-central Gyrus</td>
<td>R</td>
<td></td>
<td>51.2</td>
<td>-2.5</td>
<td>29.8</td>
<td>4</td>
</tr>
<tr>
<td>Inferior Frontal Gyrus / Insula</td>
<td>47</td>
<td>R</td>
<td>29.3</td>
<td>-21.0</td>
<td>-3.7</td>
<td>3</td>
</tr>
<tr>
<td>Anterior Cingulate Cortex</td>
<td>24</td>
<td>L</td>
<td>-4.3</td>
<td>-33.0</td>
<td>7.3</td>
<td>3</td>
</tr>
<tr>
<td>Pre-central Gyrus</td>
<td>6</td>
<td>R</td>
<td>30.0</td>
<td>10.0</td>
<td>52.3</td>
<td>3</td>
</tr>
<tr>
<td>Fusiform Gyrus</td>
<td>37</td>
<td>R</td>
<td>49.0</td>
<td>58.5</td>
<td>-16.0</td>
<td>2</td>
</tr>
<tr>
<td>Inferior Frontal Gyrus / Insula</td>
<td>47</td>
<td>R</td>
<td>32.0</td>
<td>-19.0</td>
<td>-5.0</td>
<td>1</td>
</tr>
</tbody>
</table>

BA, Brodmann’s area; Tal, Talairach co-ordinate; *Names of brain regions & BA (where appropriate), Talairach co-ordinates, laterality (side), and size of voxel cluster are provided.

The areas activated by face-processing across all conditions and across both healthy-control and PNES groups are shown in Figure C6 (in the Appendix), and the details of the relevant overlap activation clusters are listed in Table.
Table 6.14 Table showing the overlap between face-processing for neutral vs the null hypothesis consistent across all three emotional stimuli and combined across both groups.

<table>
<thead>
<tr>
<th>Brain Region</th>
<th>BA</th>
<th>Side</th>
<th>Tal (x)</th>
<th>Tal (y)</th>
<th>Tal (z)</th>
<th>Size (mm$^3$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lingual Gyrus</td>
<td>18</td>
<td>R</td>
<td>0.5</td>
<td>78.6</td>
<td>-3.4</td>
<td>69381</td>
</tr>
<tr>
<td>Post-central Gyrus</td>
<td>3/40</td>
<td>L</td>
<td>-39.5</td>
<td>30.4</td>
<td>52.1</td>
<td>6753</td>
</tr>
<tr>
<td>Medial Frontal Gyrus</td>
<td>6</td>
<td>L</td>
<td>-1.4</td>
<td>0.8</td>
<td>52.3</td>
<td>3207</td>
</tr>
<tr>
<td>Precuneus / Superior Parietal Lobule</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-central Gyrus</td>
<td>6</td>
<td>R</td>
<td>32.6</td>
<td>15.7</td>
<td>56.3</td>
<td>472</td>
</tr>
<tr>
<td>Inferior Frontal Gyrus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inferior Frontal Gyrus / Pre-central Gyrus</td>
<td>6</td>
<td>R</td>
<td>39.9</td>
<td>-2.3</td>
<td>33.5</td>
<td>237</td>
</tr>
<tr>
<td>Inferior Parietal Lobule / Post-central Gyrus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Culmen (Cerebellum)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medial Frontal Gyrus / Superior Temporal Gyrus</td>
<td>6</td>
<td>L</td>
<td>-8.2</td>
<td>12.7</td>
<td>65.4</td>
<td>25</td>
</tr>
<tr>
<td>Lingual Gyrus / Parahippocampal Gyrus</td>
<td>19</td>
<td>L</td>
<td>-19.5</td>
<td>58.1</td>
<td>-3.7</td>
<td>24</td>
</tr>
<tr>
<td>Pre-central Gyrus</td>
<td>4/6</td>
<td>R</td>
<td>48.1</td>
<td>5.4</td>
<td>43.4</td>
<td>17</td>
</tr>
<tr>
<td>Inferior Parietal Lobule</td>
<td>40</td>
<td>L</td>
<td>-33.1</td>
<td>44.4</td>
<td>40.7</td>
<td>15</td>
</tr>
<tr>
<td>Insula</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dentate / Declive (Cerebellum)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inferior Frontal Gyrus / Pre-central Gyrus</td>
<td>6/9</td>
<td>R</td>
<td>51.2</td>
<td>-2.5</td>
<td>29.8</td>
<td>4</td>
</tr>
<tr>
<td>Thalamus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Culmen (Cerebellum)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fusiform Gyrus</td>
<td>37</td>
<td>R</td>
<td>49.0</td>
<td>58.5</td>
<td>-16.0</td>
<td>2</td>
</tr>
<tr>
<td>Precuneus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inferior Occipital Gyrus / Middle Occipital Gyrus</td>
<td>18</td>
<td>R</td>
<td>38.0</td>
<td>84.0</td>
<td>-11.0</td>
<td>1</td>
</tr>
<tr>
<td>Fusiform Gyrus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BA, Brodmann’s area; Tal, Talairach co-ordinate; *Names of brain regions & BA (where appropriate), Talairach co-ordinates, laterality (side), and size of voxel cluster are provided.
Table 6.15 Table showing brain regions in which there was a differential activation between patients with PNES and healthy controls and derived from the common regions of activation during the neutral, versus the baseline condition*

<table>
<thead>
<tr>
<th>Emotion</th>
<th>Brain Region</th>
<th>Emotional intensity of presented-faces</th>
<th>0%</th>
<th>50%</th>
<th>100%</th>
<th>BA</th>
<th>Side</th>
<th>Tal (x)</th>
<th>Tal (y)</th>
<th>Tal (z)</th>
<th>Size (mm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fear</td>
<td>Left Post-central Gyrus</td>
<td>0.012</td>
<td>0.001</td>
<td>0.012</td>
<td>3/40</td>
<td>L</td>
<td>-39.5</td>
<td>30.4</td>
<td>52.1</td>
<td>6753</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Left medial frontal gyrus</td>
<td>ns</td>
<td>0.008</td>
<td>ns</td>
<td>6</td>
<td>L</td>
<td>-1.4</td>
<td>0.8</td>
<td>52.3</td>
<td>3207</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Right Inferior Frontal Gyrus / Pre- central Gyrus</td>
<td>0.034</td>
<td>ns</td>
<td>0.034</td>
<td>6</td>
<td>R</td>
<td>39.9</td>
<td>-2.3</td>
<td>33.5</td>
<td>237</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Left Inferior parietal lobule</td>
<td>0.015</td>
<td>0.009</td>
<td>0.015</td>
<td>40</td>
<td>L</td>
<td>-33.1</td>
<td>44.4</td>
<td>40.7</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Disgust</td>
<td>Right Insula</td>
<td>ns</td>
<td>0.047</td>
<td>ns</td>
<td>R</td>
<td>-29.0</td>
<td>-20.6</td>
<td>2.8</td>
<td>13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sadness</td>
<td>Left Culmen (Cerebellum)</td>
<td>0.05</td>
<td>0.026</td>
<td>0.06</td>
<td>L</td>
<td>-43.5</td>
<td>43.0</td>
<td>-21.0</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Left Post-central Gyrus</td>
<td>0.039</td>
<td>0.02</td>
<td>0.021</td>
<td>3/40</td>
<td>L</td>
<td>-39.5</td>
<td>30.4</td>
<td>52.1</td>
<td>6753</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Left Culmen (Cerebellum)</td>
<td>0.04</td>
<td>ns</td>
<td>ns</td>
<td>L</td>
<td>-29.7</td>
<td>38.0</td>
<td>-24.2</td>
<td>106</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Names of brain regions, Brodmann’s areas (where appropriate), Talairach co-ordinates, size of voxel cluster, and significance levels are provided. BA, Brodmann’s area; Tal, Talairach co-ordinate; Areas showing significant between-groups response to the implicit processing task, on a repeated measures ANOVA, controlling for FSIQ, are highlighted in bold type. All BOLD activations are greater for the healthy control group compared with PNES group.

6.5.3.2.3 Between-group differences in brain activations to emotional expression and intensity in those regions (from question no. 2) found to be activated by neutral face-processing in both PNES and control groups:

Twenty-two brain (regions) clusters were found to consistently activate to neutral faces (relative to baseline) across both groups. Data from each of these twenty-two clusters was extracted relating to fMRI response to each emotion and emotional intensity and then compared between PNES and healthy-control groups. A summary of brain regions where there were significant between-group differences in BOLD responses to the implicit face-processing task involving faces showing the 3 emotions (Fear, Disgust and Sadness),
respectively, at neutral, 50% and 100% intensities are shown in Table 6.15.

The results show the respective \( p \)-values after analyses of the data controlled for the effects of age, gender, and FSIQ. Compared to the healthy-control group, the PNES group had significantly reduced implicit brain-activation to this face-processing task, to faces showing Fear and Sadness across all intensities of those faces in three regions: left post-central gyrus, left culmen (cerebellum) and left inferior parietal lobule. Right inferior frontal gyrus was significantly different between-groups at neutral and 100% intensity of expression.

6.5.3.2.4 Relationships between fMRI activation data, clinical and demographical variables:

These analyses were carried out to investigate relationships between BOLD activation responses in the brain areas that predicted group status, and relevant clinical and demographical variables that differed between groups.

fMRI neural response to EFEs exhibiting fear

The results of the principal components analysis (PCA) to examine the fMRI measures at each stimulus intensity, and at all intensities combined, for EFEs showing fear demonstrated that there was no gradient of fMRI values across the three intensities of the stimulus. The mean fMRI activation values for patients with PNES and healthy-controls were clearly different at each time-point, but the values were close, with no evidence of trend.

The PCA of each fMRI measure separately found just one principal component was retained, which in each case accounted for over 40% of the variance. Also, in each case there was no important second principal component, as the as the eigenvalues were relatively close to 1 and accounted for under 11% of the variance (Table 6.16a). The absence of a second principal component suggested that the measurements belonged to a process that was common across all participants, and that differences were quantitative rather than qualitative.
Table 6.16a Results of PCA of fMRI measures to EFEs showing fear.

<table>
<thead>
<tr>
<th>Emotional Intensity of faces showing fear</th>
<th>Eigenvalue for first principal component (FPC)</th>
<th>Variance explained by FPC (%)</th>
<th>Eigenvalue for second principal component (SPC)</th>
<th>Variance explained by SPC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0% (neutral)</td>
<td>9.20</td>
<td>46.03</td>
<td>1.60</td>
<td>7.99</td>
</tr>
<tr>
<td>50%</td>
<td>8.74</td>
<td>43.69</td>
<td>2.00</td>
<td>10.04</td>
</tr>
<tr>
<td>100%</td>
<td>9.12</td>
<td>45.61</td>
<td>1.59</td>
<td>7.98</td>
</tr>
</tbody>
</table>

Overall PCA

In order to test the effects of stimulus intensity and PNES, all the fMRI measures were combined and a principal component extracted for analysis. For emotional intensity stimulus there was only one principal component with an eigenvalue well above 1 (8.86), accounting for 44.28% of the variance. The second component had an eigenvalue of 1.49, explaining 7.47% of the variance. Therefore, grouped together the fMRI measures differed on an intensity component but there was no evidence of a second dimension. The intensity component accounted for over 40% of variance in the case of the fear stimulus, and there was no important second component, suggesting that the rest of the variance probably reflected fMRI “noise”.

Results of Regression Model Analysis of the first principal component for Fear

A regression analysis comparing the fMRI activation response between patients with PNES and healthy controls as the stimulus intensity increases showed no significant interaction effect (Table 6.16b).

Therefore, the interactions were removed and main effects were calculated (Table 6.16c). There was a significant difference observed between patients with PNES and HCs (p<0.001).
Table 6.16b Results of regression model of fear showing interaction effects*.

<table>
<thead>
<tr>
<th>PCA fMRI</th>
<th>Coefficient (β)</th>
<th>Robust SE</th>
<th>t</th>
<th>p Value</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensity#PNES</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50% Fear#PNES</td>
<td>-0.071</td>
<td>0.464</td>
<td>-0.15</td>
<td>0.879</td>
<td>-1.010</td>
<td>0.869</td>
</tr>
<tr>
<td>100% Fear#PNES</td>
<td>-0.208</td>
<td>0.518</td>
<td>-0.40</td>
<td>0.690</td>
<td>-1.257</td>
<td>0.841</td>
</tr>
</tbody>
</table>

*Coefficient=the mathematical weightings of the explanatory variables in the equation (the regression coefficient or β-weight); SE=estimated precision of the coefficients; 95% CI=95% confidence intervals for the coefficients. Number of observations=114; F(5, 37)=13.34; Prob >F=0.0000; R-squared= 0.5891; Root MSE=1.9513; Standard Error is adjusted for sample of n=38.

Table 6.16c Results of regression model of fear showing main effects*.

<table>
<thead>
<tr>
<th>PCA fMRI</th>
<th>Coefficient (β)</th>
<th>Robust SE</th>
<th>t</th>
<th>p Value</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Main Effects: intensity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50% Fear</td>
<td>0.079</td>
<td>0.230</td>
<td>0.34</td>
<td>0.734</td>
<td>-0.387</td>
<td>0.544</td>
</tr>
<tr>
<td>100% Fear</td>
<td>-0.239</td>
<td>0.257</td>
<td>-0.93</td>
<td>0.359</td>
<td>-0.760</td>
<td>0.282</td>
</tr>
<tr>
<td>PNES</td>
<td>-4.539</td>
<td>0.569</td>
<td>-7.97</td>
<td>0.000</td>
<td>-5.693</td>
<td>-3.386</td>
</tr>
<tr>
<td>Healthy-Controls</td>
<td>2.323</td>
<td>0.485</td>
<td>4.79</td>
<td>0.000</td>
<td>1.340</td>
<td>3.35</td>
</tr>
</tbody>
</table>

*Coefficient=the mathematical weightings of the explanatory variables in the equation (the regression coefficient or β-weight); SE=estimated precision of the coefficients; 95% CI=95% confidence intervals for the coefficients. Number of observations=114; F(3, 37)=22.32; Prob >F=0.0000; R-squared= 0.5889; Root MSE=1.934; Standard Error is adjusted for sample of n=38.

There was no difference observed between the levels of intensity (i.e., 50% stimulus intensity versus 0% and PNES provided t=0.34; p=0.734; 100% stimulus intensity versus 0% and PNES provided t=-0.93; p=0.359). Treating intensity as a continuous variable showed no evidence of a graded effect across the categories (p=0.936) (Table 3.4.16d). Figure C7 (in the Appendix) illustrates the data.
Table 6.16d Results of regression model of fear showing intensity*.

<table>
<thead>
<tr>
<th>PCA fMRI</th>
<th>Coefficient (β)</th>
<th>Robust SE</th>
<th>t</th>
<th>p Value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensity</td>
<td>-0.067</td>
<td>0.195</td>
<td>-0.35</td>
<td>0.732</td>
<td>-0.462</td>
</tr>
</tbody>
</table>

*Coefficient=the mathematical weightings of the explanatory variables in the equation (the regression coefficient or β-weight); SE=estimated precision of the coefficients; 95% CI=95% confidence intervals for the coefficients. Number of observations=114; F(3, 37)=22.52; Prob >F=0.000; R-squared= 0.5881; Root MSE=1.9359; Standard Error is adjusted for sample of n=38.

Summary of regression analyses of fMRI neural response to EFEs exhibiting Fear:

There were significant differences in response between the PNES and healthy-control (HC) groups (p<0.001). However, the intensity of the stimulus was not associated with any effect on fMRI parameters.

fMRI neural response to EFEs exhibiting disgust

The results of the principal components analysis (PCA) to examine the fMRI measures at each stimulus intensity, and at all intensities combined, for EFEs showing disgust demonstrated that the mean values for PNES and control were clearly different at each time point, but there was no apparent graded response to the emotional content of the stimulus.

The PCA of each fMRI measure separately found just one principal component was retained, which in each case accounted for at least 40% of the variance. Also, in each case there was no important second principal component, as the eigenvalues were quite close to 1 and accounted for under 20% at most, of the variance (Table 6.17a). The absence of a second principal component suggested that the measurements belonged to a process that was common across all participants, and that differences were quantitative rather than qualitative.
Table 6.17a  Results of PCA of fMRI measures to EFEs showing disgust.

<table>
<thead>
<tr>
<th>Emotional Intensity of faces showing disgust</th>
<th>Eigenvalue for first principal component (FPC)</th>
<th>Variance explained by FPC (%)</th>
<th>Eigenvalue for second principal component (SPC)</th>
<th>Variance explained by SPC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0% (neutral)</td>
<td>2.98</td>
<td>49.76</td>
<td>0.90</td>
<td>15.02</td>
</tr>
<tr>
<td>50%</td>
<td>2.99</td>
<td>49.92</td>
<td>0.98</td>
<td>16.36</td>
</tr>
<tr>
<td>100%</td>
<td>2.44</td>
<td>40.63</td>
<td>1.16</td>
<td>19.34</td>
</tr>
</tbody>
</table>

Overall PCA

In order to test the effects of stimulus intensity and PNES, all the fMRI measures were combined and a principal component extracted. Again, for emotional intensity stimulus there was only one principal component with an eigenvalue well above 1 (eigenvalue = 2.78). Therefore, grouped together the fMRI measures differed on an intensity component but there was no evidence of a second dimension. The intensity component accounted for over 46% (46.31%) of the variance in the case of the disgust stimulus, and there was no important second component (eigenvalue = 1.02, explaining 17.01% of the variance), suggesting that rest of the variance probably reflected fMRI “noise”.

Results of Regression Model Analysis of the first principal component for Disgust

A regression analysis comparing the fMRI activation response between patients with PNES and healthy controls as the stimulus intensity increases showed no significant interaction effect (Table 6.17b).
Table 6.17b Results of regression model of disgust showing interaction effects*.

<table>
<thead>
<tr>
<th>PCA fMRI</th>
<th>Coefficient (β)</th>
<th>Robust SE</th>
<th>t</th>
<th>p Value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensity#PNES</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50% Disgust#PNES</td>
<td>-0.023</td>
<td>0.418</td>
<td>-0.06</td>
<td>0.956</td>
<td>-0.871 - 0.824</td>
</tr>
<tr>
<td>100% Disgust#PNES</td>
<td>0.589</td>
<td>0.454</td>
<td>1.30</td>
<td>0.202</td>
<td>-0.331 - 1.510</td>
</tr>
</tbody>
</table>

*Coefficient=the mathematical weightings of the explanatory variables in the equation (the regression coefficient or β-weight); SE=estimated precision of the coefficients; 95% CI=95% confidence intervals for the coefficients. Number of observations=114; F(5, 37)=8.74; Prob >F=0.0000; R-squared= 0.4307; Root MSE=1.2865; Standard Error is adjusted for sample of n=38.

Therefore, the interactions were removed and main effects were calculated (Table 6.17c). There was a significant difference observed between patients with PNES and HCs (p<0.001). 50% intensity versus 0% and PNES provided t=0.84; p=0.404; 100% stimulus intensity versus 0% and PNES provided t=-0.84; p=0.405).

Table 6.17c Results of regression model of disgust showing main effects*.

<table>
<thead>
<tr>
<th>PCA fMRI</th>
<th>Coefficient (β)</th>
<th>Robust SE</th>
<th>t</th>
<th>p Value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Main Effects: intensity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50% Disgust</td>
<td>0.175</td>
<td>0.207</td>
<td>0.84</td>
<td>0.404</td>
<td>-0.245 - 0.595</td>
</tr>
<tr>
<td>100% Disgust</td>
<td>-0.194</td>
<td>0.230</td>
<td>-0.84</td>
<td>0.405</td>
<td>-0.661 - 0.273</td>
</tr>
<tr>
<td>PNES</td>
<td>-2.139</td>
<td>0.326</td>
<td>-6.55</td>
<td>0.000</td>
<td>-2.800 - -1.477</td>
</tr>
<tr>
<td>Healthy-Controls</td>
<td>1.076</td>
<td>0.280</td>
<td>3.84</td>
<td>0.000</td>
<td>0.508 - 1.643</td>
</tr>
</tbody>
</table>

*Coefficient=the mathematical weightings of the explanatory variables in the equation (the regression coefficient or β-weight); SE=estimated precision of the coefficients; 95% CI=95% confidence intervals for the coefficients. Number of observations=114; F(3, 37)=14.73; Prob >F=0.0000; R-squared= 0.4234; Root MSE=1.2829; Standard Error is adjusted for sample of n=38.

However, there was no difference observed between the levels of intensity (i.e., 50% stimulus. Treating intensity as a continuous variable showed no evidence
of a graded effect across the categories ($p=0.401$) (Table 6.17d) (Figure C8, in the Appendix).

**Table 6.17d  Results of regression model of disgust showing intensity**

<table>
<thead>
<tr>
<th>PCA fMRI</th>
<th>Coefficient ($\beta$)</th>
<th>Robust SE</th>
<th>t</th>
<th>p Value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensity</td>
<td>-0.097</td>
<td>0.114</td>
<td>-0.85</td>
<td>0.401</td>
<td>-0.328</td>
</tr>
</tbody>
</table>

*Coefficient=the mathematical weightings of the explanatory variables in the equation (the regression coefficient or $\beta$-weight); SE=estimated precision of the coefficients; 95% CI=95% confidence intervals for the coefficients. Number of observations=114; $F(1, 37)=0.72; \text{Prob } F=0.4011; \text{R-squared}=0.0023; \text{Root MSE}=1.6725; \text{Standard Error is adjusted for sample of } n=38.$

**Summary of regression analyses of fMRI neural response to EFEs exhibiting Disgust:**

There were significant differences in response between the PNES and healthy-control (HC) groups ($p<0.001$). However, the intensity of the stimulus was not associated with any effect on fMRI parameters.

**fMRI neural response to EFEs exhibiting sadness**

The results of the principal components analysis (PCA) to examine the fMRI measures at each stimulus intensity, and at all intensities combined, for EFEs showing sadness demonstrated that there was no gradient response of fMRI values to the emotional content of the stimulus. The PCA of each fMRI measure separately found just one principal component was retained, which in each case accounted for over 41% of the variance. Also, in each case there was no important second principal component, as the eigenvalues were quite close to 1 and accounted for under 11% of the variance (Table 6.18a). The absence of a second principal component suggested that the measurements
belonged to a process that was common across all participants, and that differences were quantitative rather than qualitative.

**Table 6.18a Results of PCA of fMRI measures to EFEs showing sadness.**

<table>
<thead>
<tr>
<th>Emotional Intensity of faces showing sadness</th>
<th>Eigenvalue for first principal component (FPC)</th>
<th>Variance explained by FPC (%)</th>
<th>Eigenvalue for second principal component (SPC)</th>
<th>Variance explained by SPC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0% (neutral)</td>
<td>6.67</td>
<td>44.45</td>
<td>1.32</td>
<td>8.84</td>
</tr>
<tr>
<td>50%</td>
<td>7.16</td>
<td>44.76</td>
<td>1.54</td>
<td>9.64</td>
</tr>
<tr>
<td>100%</td>
<td>6.66</td>
<td>41.62</td>
<td>1.66</td>
<td>10.37</td>
</tr>
</tbody>
</table>

**Overall PCA**

In order to test the effects of stimulus intensity and PNES, all the fMRI measures were combined and a principal component extracted. Again, for emotional intensity stimulus there was only one principal component with an eigenvalue well above 1 (eigenvalue = 6.84). Therefore, grouped together the fMRI measures differed on an intensity component but there was no evidence of a second dimension. Again, the intensity component accounted for over 40% (42.77%) of the variance in the case of the sadness stimulus, and there was no important second component (eigenvalue = 1.26, explaining 7.86% of the variance), suggesting that rest of the variance probably reflected fMRI “noise”.

**Results of Regression Model Analysis of the first principal component for Sadness**

A regression analysis comparing the fMRI activation response between patients with PNES and healthy controls as the stimulus intensity increases showed no significant interaction effect (Table 6.18b).
Table 6.18b  Results of regression model of sadness showing interaction effects*.

<table>
<thead>
<tr>
<th>PCA fMRI</th>
<th>Coefficient (β)</th>
<th>Robust SE</th>
<th>t</th>
<th>p Value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensity#PNES</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50% Sadness#PNES</td>
<td>-0.056</td>
<td>0.510</td>
<td>-0.11</td>
<td>0.913</td>
<td>-1.090 - 0.978</td>
</tr>
<tr>
<td>100% Sadness#PNES</td>
<td>0.128</td>
<td>0.527</td>
<td>0.24</td>
<td>0.810</td>
<td>-0.941 - 1.197</td>
</tr>
</tbody>
</table>

*Coefficient=the mathematical weightings of the explanatory variables in the equation (the regression coefficient or β-weight); SE=estimated precision of the coefficients; 95% CI=95% confidence intervals for the coefficients. Number of observations=114; F(5, 37)=14.93; Prob >F=0.0000; R-squared= 0.5796; Root MSE=1.735; Standard Error is adjusted for sample of n=38.

Table 6.18c  Results of regression model of sadness showing main effects*.

<table>
<thead>
<tr>
<th>PCA fMRI</th>
<th>Coefficient (β)</th>
<th>Robust SE</th>
<th>t</th>
<th>p Value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Main Effects: intensity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50% Sadness</td>
<td>-0.053</td>
<td>0.253</td>
<td>-0.21</td>
<td>0.836</td>
<td>-0.565 - 0.460</td>
</tr>
<tr>
<td>100% Sadness</td>
<td>0.021</td>
<td>0.261</td>
<td>0.08</td>
<td>0.937</td>
<td>-0.509 - 0.551</td>
</tr>
<tr>
<td>PNES</td>
<td>-3.964</td>
<td>0.471</td>
<td>-8.41</td>
<td>0.000</td>
<td>-4.919 - -3.010</td>
</tr>
<tr>
<td>Healthy-Controls</td>
<td>1.993</td>
<td>0.413</td>
<td>4.82</td>
<td>0.000</td>
<td>1.155 - 2.830</td>
</tr>
</tbody>
</table>

*Coefficient=the mathematical weightings of the explanatory variables in the equation (the regression coefficient or β-weight); SE=estimated precision of the coefficients; 95% CI=95% confidence intervals for the coefficients. Number of observations=114; F(3, 37)=24.64; Prob >F=0.0000; R-squared= 0.5794; Root MSE=1.7196; Standard Error is adjusted for sample of n=38.

Therefore, the interactions were removed and main effects were calculated (Table 6.18c). There was a significant difference observed between patients with PNES and healthy-controls ($p<0.001$). There was no difference observed between the levels of intensity (i.e., 50% stimulus intensity versus 0% and PNES provided $t=-0.21$; $p=0.836$; 100% stimulus intensity versus 0% and PNES provided $t=-0.08$; $p=0.937$).
Treating intensity as a continuous variable showed no evidence of a graded effect across the categories ($p=0.936$) (Table 6.18d). Figure C9 (in the Appendix) illustrates the data.

### Table 6.18d Results of regression model of sadness showing intensity*.

<table>
<thead>
<tr>
<th>PCA fMRI</th>
<th>Coefficient ($\beta$)</th>
<th>Robust SE</th>
<th>t</th>
<th>p Value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensity</td>
<td>0.010</td>
<td>0.129</td>
<td>0.08</td>
<td>0.936</td>
<td>-0.252</td>
</tr>
</tbody>
</table>

*Coefficient=the mathematical weightings of the explanatory variables in the equation (the regression coefficient or $\beta$-weight); SE=estimated precision of the coefficients; 95% CI=95% confidence intervals for the coefficients. Number of observations=114; $F(1, 37)=0.01$; Prob $>F=0.9362$; R-squared= 0.0000; Root MSE=2.6277; Standard Error is adjusted for sample of $n=38$.

**Summary of regression analyses of fMRI neural response to EFEs exhibiting Sadness:**

There were significant differences in response between the PNES and healthy-control (HC) groups ($p<0.001$). However, the intensity of the stimulus was not associated with any effect on fMRI parameters.

**Summary of the PCA analyses of all fMRI data**

The results of the PCA to examine the fMRI measures at each stimulus intensity, and at all intensities combined, for each emotion (Fear, Sadness, Disgust) confirmed our findings that there was no gradient response of fMRI values to the emotional content of each EFE stimulus, across the three emotions. For the PCA of fMRI response to each emotion condition (Fear, Sadness, Disgust), just one principal component was retained, which in each case accounted for over 40% of the variance. However, there was no important second component, as in each case the eigenvalues were close to 1 and accounted for under 11% of the variance. The absence of a second principal component suggested that the measurements belonged to a process that was
common across all participants, and that differences were quantitative rather than qualitative.

**Relationships between psychometric variables and fMRI activations**

I examined the relationship between PNES status and fMRI first principal component, adjusting for the psychometric variables. Each model had fMRI predicted by PNES status, adjusted for gender and FSIQ, and the respective psychometric variable(s) of interest. The results from investigation of relationships between psychometric variables and fMRI activations for fear found that, in all cases, fMRI FPC scores were significantly lower in patients with PNES and HCs (Table 6.19a).

**Table 6.19a  Fear PCA fMRI, adjusting for psychometric and clinical variables that predicted group status.**

<table>
<thead>
<tr>
<th>Fear fMRI PCA</th>
<th>Coefficient ($\beta$)</th>
<th>Robust SE</th>
<th>$t$</th>
<th>$p$ Value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDI</td>
<td>-0.015</td>
<td>0.013</td>
<td>-1.21</td>
<td>0.235</td>
<td>-0.041</td>
</tr>
<tr>
<td>BAI</td>
<td>-0.017</td>
<td>0.013</td>
<td>-1.31</td>
<td>0.200</td>
<td>-0.042</td>
</tr>
<tr>
<td>TAS-20</td>
<td>-0.028</td>
<td>-0.021</td>
<td>-1.34</td>
<td>0.189</td>
<td>-0.070</td>
</tr>
<tr>
<td>SOM-C</td>
<td>-0.042</td>
<td>0.014</td>
<td>-2.93</td>
<td>0.006</td>
<td>-0.071</td>
</tr>
<tr>
<td>SOM-S</td>
<td>-0.027</td>
<td>0.021</td>
<td>-1.26</td>
<td>0.217</td>
<td>-0.070</td>
</tr>
<tr>
<td>SOM-H</td>
<td>-0.012</td>
<td>0.017</td>
<td>-0.72</td>
<td>0.478</td>
<td>-0.046</td>
</tr>
</tbody>
</table>

*Coefficient=the mathematical weightings of the explanatory variables in the equation (the regression coefficient or $\beta$-weight); SE=estimated precision of the coefficients; 95% CI=95% confidence intervals for the coefficients. Standard Error is adjusted for sample of n=38.

The relationship between fMRI activation and case-control status was not explained by the psychometric variables relating to FSIQ, mood, alexithymia and scores on the SOM sub-scales of the PAI], except for SOM-C. In the latter case, there was a significant relationship observed with the fear fMRI first PCA
score (i.e., the difference in fMRI activation between groups remained significant after adjustment for gender, FSIQ, and each psychometric variable in turn; only SOM-C was associated with the level of fMRI activation after adjustment for gender, FSIQ and PNES status).

Table 6.19b  Disgust PCA fMRI, adjusting for psychometric and clinical variables that predicted group status.

<table>
<thead>
<tr>
<th>Disgust fMRI PCA</th>
<th>Coefficient (β)</th>
<th>Robust SE</th>
<th>t</th>
<th>p Value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDI</td>
<td>-0.002</td>
<td>0.013</td>
<td>-0.15</td>
<td>0.885</td>
<td>-0.029</td>
</tr>
<tr>
<td>BAI</td>
<td>0.008</td>
<td>0.013</td>
<td>0.061</td>
<td>0.545</td>
<td>-0.018</td>
</tr>
<tr>
<td>TAS-20</td>
<td>0.001</td>
<td>0.011</td>
<td>0.08</td>
<td>0.934</td>
<td>-0.021</td>
</tr>
<tr>
<td>SOM-C</td>
<td>0.002</td>
<td>0.011</td>
<td>0.15</td>
<td>0.885</td>
<td>-0.021</td>
</tr>
<tr>
<td>SOM-S</td>
<td>0.019</td>
<td>0.013</td>
<td>1.42</td>
<td>0.165</td>
<td>-0.008</td>
</tr>
<tr>
<td>SOM-H</td>
<td>0.009</td>
<td>0.015</td>
<td>0.56</td>
<td>0.578</td>
<td>-0.022</td>
</tr>
</tbody>
</table>

*Coefficient=the mathematical weightings of the explanatory variables in the equation (the regression coefficient or β-weight); SE=estimated precision of the coefficients; 95% CI=95% confidence intervals for the coefficients. Standard Error is adjusted for sample of n=38.

The results from investigation of relationships between psychometric variables and fMRI activations for both disgust and sadness found that, in all cases, fMRI first principal component (FPC) scores were significantly lower in patients with PNES and HCs (Table 6.19b and Table 6.19c, respectively).

In these cases, the relationship between fMRI scores and case-control status for each emotional condition was not explained by any of the psychometric variables [i.e., independent of differences in FSIQ, mood (anxiety, depression), alexithymia and scores on the SOM sub-scales of the PAI].
Analyses examining the effects of behavioural performance and spatial working memory performance on fMRI activations

Patients with PNES had been found to demonstrate relative hypo-activation in all brain areas that had been found to be different between-groups. Therefore, a regression model analysis was carried out to investigate if either performance during the fMRI task or spatial working memory performance were associated with the activation response observed.

a. Results of Regression Model Analysis of the first principal component for fMRI total errors committed during the face-processing task.

A regression analysis comparing the fMRI activation response between patients with PNES and healthy controls to total errors (TEs) during the face-processing task showed no significant interaction effect (regression co-efficient = -0.006, p=0.682) (Table 6.20). It does not account for differences between PNES and healthy-control (HC) groups. Adjusted for TEs, the difference in fMRI between the PNES and HCs is statistically significant (p<0.001).

Table 6.19c  Sadness PCA fMRI, adjusting for psychometric and clinical variables that predicted group status.

<table>
<thead>
<tr>
<th></th>
<th>Coefficient (β)</th>
<th>Robust SE</th>
<th>t</th>
<th>p Value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDI</td>
<td>-0.018</td>
<td>0.018</td>
<td>-1.00</td>
<td>0.325</td>
<td>-0.056, 0.019</td>
</tr>
<tr>
<td>BAI</td>
<td>-0.003</td>
<td>0.015</td>
<td>-0.24</td>
<td>0.815</td>
<td>-0.034, 0.027</td>
</tr>
<tr>
<td>TAS-20</td>
<td>-0.026</td>
<td>0.018</td>
<td>-1.43</td>
<td>0.162</td>
<td>-0.064, 0.011</td>
</tr>
<tr>
<td>SOM-C</td>
<td>-0.014</td>
<td>0.013</td>
<td>-1.08</td>
<td>0.288</td>
<td>-0.041, 0.012</td>
</tr>
<tr>
<td>SOM-S</td>
<td>-0.016</td>
<td>0.024</td>
<td>-0.68</td>
<td>0.503</td>
<td>-0.064, 0.032</td>
</tr>
<tr>
<td>SOM-H</td>
<td>0.040</td>
<td>0.024</td>
<td>1.68</td>
<td>0.101</td>
<td>-0.008, 0.089</td>
</tr>
</tbody>
</table>

*Coefficient=the mathematical weightings of the explanatory variables in the equation (the regression coefficient or β-weight); SE=estimated precision of the coefficients; 95% CI=95% confidence intervals for the coefficients. Standard Error is adjusted for sample of n=38.
Table 6.20  Results of regression model analysis investigating the relationship between mean response time to facial stimuli and fMRI activations.

<table>
<thead>
<tr>
<th>fMRI PCA over all face-processing conditions</th>
<th>Coefficient (β)</th>
<th>Robust SE</th>
<th>t</th>
<th>p Value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>PNES</td>
<td>-2.081</td>
<td>0.324</td>
<td>-6.42</td>
<td>0.000</td>
<td>-2.74</td>
</tr>
<tr>
<td>Mean response time over all tasks</td>
<td>1.971E-04</td>
<td>1.574E-03</td>
<td>0.13</td>
<td>0.901</td>
<td>-0.003</td>
</tr>
<tr>
<td>Healthy Controls</td>
<td>0.865</td>
<td>1.261</td>
<td>0.69</td>
<td>0.498</td>
<td>-1.701</td>
</tr>
</tbody>
</table>

*Coefficient=the mathematical weightings of the explanatory variables in the equation (the regression coefficient or β-weight); SE=estimated precision of the coefficients; 95% CI=95% confidence intervals for the coefficients. Number of observations=102; F(2, 33)=21.79; Prob >F=0.0000; R-squared= 0.3924; Root MSE=1.2978; Standard Error is adjusted for sample size of n=34 clusters.

b. Results of Regression Model Analysis of the first principal component for fMRI and mean response time to all facial stimuli, during the face-processing task.

A regression analysis comparing the fMRI activation response between patients with PNES and healthy controls to mean response time (MRT) over all tasks showed no significant interaction effect (regression co-efficient =0.0002, p=0.901) (Table 6.21) (Figure C10, in the Appendix). It does not account for differences between PNES and healthy-control (HC) groups. Adjusted for MRT, the difference in fMRI between the PNES and HCs is statistically significant (p<0.001).
Table 6.21  Results of regression model analysis investigating the relationship between total errors committed during the implicit face-processing task and fMRI activations.

<table>
<thead>
<tr>
<th>FMRI PCA over all face-processing conditions</th>
<th>Coefficient (β)</th>
<th>Robust SE</th>
<th>t</th>
<th>p Value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>PNES</td>
<td>-1.982</td>
<td>0.344</td>
<td>-5.75</td>
<td>0.0001</td>
<td>-2.68</td>
</tr>
<tr>
<td>Total errors over all tasks</td>
<td>5.991E-03</td>
<td>1.449E-02</td>
<td>-0.41</td>
<td>0.682</td>
<td>-0.035</td>
</tr>
<tr>
<td>Healthy Controls</td>
<td>1.036</td>
<td>0.250</td>
<td>4.14</td>
<td>0.0001</td>
<td>0.527</td>
</tr>
</tbody>
</table>

*Coefficient=the mathematical weightings of the explanatory variables in the equation (the regression coefficient or β-weight); SE=estimated precision of the coefficients; 95% CI=95% confidence intervals for the coefficients. Number of observations=102; F(2, 33)=18.83; Prob >F=0.0000; R-squared= 0.3952; Root MSE=1.2949; Standard Error is adjusted for sample size of n=34 clusters.

c. Results of Regression Model Analysis of the first principal component for fMRI and spatial working memory performance (total errors).

The variable, spatial working memory total errors (SWM TE) was chosen as a representative measure of SWM performance as it appeared to integrate more information on SWM than the other SWM variables (e.g., between errors, strategy). A regression analysis comparing the fMRI activation response between patients with PNES and healthy controls to spatial working memory total errors (TEs) showed an interaction effect trending towards statistical significance (regression co-efficient =-0.016, p=0.052) (Table 6.22). It does not account for differences between PNES and healthy-control (HC) groups. Adjusted for TEs, the difference in fMRI between the PNES and HCs is statistically significant (p<0.001).
Table 6.22 Results of regression model analysis investigating the relationship between spatial working memory performance (total errors) and fMRI activations.

<table>
<thead>
<tr>
<th>fMRI PCA over all face-processing conditions</th>
<th>Coefficient (β)</th>
<th>Robust SE</th>
<th>t</th>
<th>p Value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>PNES</td>
<td>-2.080</td>
<td>0.305</td>
<td>-6.81</td>
<td>0.0001</td>
<td>-2.70</td>
</tr>
<tr>
<td>SWM TE</td>
<td>0.016</td>
<td>0.008</td>
<td>-2.01</td>
<td>0.052</td>
<td>-0.031</td>
</tr>
<tr>
<td>Healthy Controls</td>
<td>1.381</td>
<td>0.313</td>
<td>4.41</td>
<td>0.0001</td>
<td>0.746</td>
</tr>
</tbody>
</table>

*Coefficient* = the mathematical weightings of the explanatory variables in the equation (the regression coefficient or β-weight); SE = estimated precision of the coefficients; 95% CI = 95% confidence intervals for the coefficients; SWM TE, total errors committed during the spatial working memory test on CANTAB. Number of observations = 114; F(2, 37) = 23.38; Prob > F = 0.0000; R-squared = 0.4405; Root MSE = 1.258; Standard Error is adjusted for sample size of n = 38 clusters.

c. Results of Regression Model Analysis of the first principal component for fMRI and behavioural data, controlling for full-scale intelligence quotient (FSIQ).

When we add FSIQ to the model for first principal component over all tasks, it's not significant \(p=0.065\), nor is total errors made during the fMRI task \(p=0.588\). PNES remains the only significant predictor of fMRI \(p=0.002\).

Likewise, when we run a model with mean response time, neither FSIQ nor response time are significant predictors, just PNES \(p=0.010\).

Overall comment:
None of the three variables examined explained the difference in fMRI levels between PNES and HC groups.

6.6 Discussion

This discussion will firstly outline the main findings of this study, followed by comment on notable aspects of the results.

To our knowledge this is the first fMRI study to investigate implicit emotional
processing in patients with PNES. We carried out a cross-sectional event-related fMRI study in adults with PNES and healthy controls, matched for age, gender and handedness. No participant had taken psychotropic medication for at least two months prior to testing. All participants underwent a comprehensive psychiatric, psychometric and neuropsychological assessment and carried out a gender-identification task during fMRI scanning that examined implicit (unconscious) neural responses to faces showing three primary emotions: fear, disgust and sadness, at neutral, low and high intensity. Our main findings were: a) psychometric assessment found that patients with PNES demonstrated significant differences from healthy-controls on measures of emotional regulation and coping style; b) brain networks that are known to be involved in face processing were engaged by the implicit fMRI task in both patients with PNES and healthy controls; c) but, compared to controls, patients with PNES made significantly more errors and exhibited relatively increased mean reaction times to face-stimuli during the face-processing task, and also showed significantly reduced neural activation in all areas that demonstrated a differential group response to faces; d) patients with PNES were found to have abnormal response to faces showing neutral expression; e) the emotional intensity of the face stimuli (showing fear, disgust and sadness) was not associated with any significant effect on fMRI parameters in both groups, so that both groups displayed a similar pattern of modulation for all emotional facial expressions (EFEs); f) there were no areas where patients with PNES showed greater activation to EFEs of any type or intensity compared with healthy controls; g) with the exception of SOM-C, a measure from the PAI assessment relating to the level of a person’s focus on symptoms relating to motor or sensory dysfunction, there were no significant relationships found between brain areas showing differential response to neutral faces and scores of spatial working memory, depression, anxiety, alexithymia, dissociation, and clinical features associated with conversion disorder; h) performance on the behavioural task and spatial working memory performance did not explain the difference in fMRI activations between patient and healthy-control groups. i) This psychometric measure relating to the patient’s focus on ill-health from PNES deserves further study as a potential neurobiological marker of PNES.
6.6.1 Comment on Psychometric and Neuropsychological findings

Our demographic, psychometric and neuropsychological findings were highly consistent with those obtained in Study 2 and relevant interpretation and commentary on those findings is provided in Section 4.6.

We found that alexithymia was definitely present in 31.6% of our sample of patients, which is consistent with results from two other studies that reported prevalence rates ranging from 30-40% in patients with PNES (Myers et al., 2013; Tojek et al., 2000), while being considerably lower than the rate of 90.5% found in another study (Bewley et al., 2005). However, the latter finding has not been generally replicated and is in contrast with alexithymia rates that have been observed in other psychopathological conditions including psychosomatic conditions (33.3%) and depressive disorders (26.9%) (Celikel et al., 2010), and a combination of outpatients with various mental disorders (21.4%) (Leweke et al., 2012).

In addition, we observed positive correlations between alexithymia score and indices of dissociative-conversion symptoms. This finding is consistent with our hypothesis that alexithymia, as a construct representing abnormal identification, recognition, regulation and expression of emotion is associated with PNES, and with models of PNES (Baslet et al., 2011).

In contrast, our finding that 5.3% of our healthy-control group met the threshold for having alexithymia is lower than the reported rate of approximately 10% found in other healthy-adult populations (Salminen et al., 1999; Mattila et al., 2006; Franz et al., 2008). However, some studies have proposed that the cut off TAS-20 score of >61 is too limited for experimental studies (Franz et al., 2008). In addition, there have been inconsistent reports on whether alexithymia is associated or not with socio-demographic variables such as age, gender, educational level, socioeconomic status, and intelligence, so that prevalence rates of alexithymia that are reported may vary accordingly (Parker et al., 1989; Franz et al., 2008). Therefore, it is likely that differences in rating of alexithymia
case-ness in the general population reflect sampling and methodological
differences.
Finally, our finding that alexithymia score was positively correlated with
measures of dissociation and personality sub-scale measures of symptoms
associated with conversion disorder (that include a focus on complaints of
physical symptoms and a preoccupation with physical problems), is highly
consistent with findings from previous studies of PNES (for a recent review, see
Brown and Reuber, 2016a).

We found that the use of Avoidance and Emotion-focused strategies in the
clinically impaired range was endorsed by over 31% and 21%, respectively, of
the group of patients with PNES. Avoidance-Focused coping styles refer to
activities and cognitive strategies that are aimed at avoiding stress by
employing distraction or social diversion techniques, while Emotion-Focused
strategies describe emotional reactions that are directed inwards, and include
self-blame, anger, tension, self-preoccupation and fantasising. Avoidance-
Focused strategies do not constitute constructive attempts to deal with the
problem causing the distress, while emotional self-oriented responses can lead
to increased tension and upset, and so are more likely to increase stress, rather
than reduce it. In addition, patients endorsed an abnormally low use of Task-
Orientated strategies in response to stress, which refer to purposeful task-
oriented efforts to react to a stressful situation by employing problem-solving
techniques. Overall, the finding that over 68% of our sample of patients
endorsed one or more Emotion, Avoidance and Task-Orientated coping styles in
the clinically impaired range is highly consistent with previous findings of
abnormal and decreased utilisation of effective problem-solving strategies in
people with PNES (Myers et al., 2013; Testa et al., 2012; Goldstein et al., 2000;
Frances et al., 1999). The abnormally increased utilisation of Avoidance- and
Emotion-Focused coping styles, in combination with abnormally low utilisation
of Task-Orientated strategies would likely be associated with greater ongoing
stress and exposure to unresolved problems in this population (Myers et al.,
2013).
It has been previously proposed that findings of significantly higher level of
avoidance behaviours in patients with PNES (Goldstein et al., 2006; Dimaro et
al., 2014) may represent a particular way that they process emotionally relevant
information (Baslet et al., 2011). Nevertheless, we did not find any significant association between use of an Avoidant coping strategy and any of our predictor variables, including those that related to features of emotional dysregulation. Therefore, our finding suggests that avoidance, as a stress-management mechanism, is not strongly associated with disturbances of emotional regulation, or frequency or duration of PNES per se. This idea is consistent with previous research that reported this scale on the CISS to be positively correlated with extraversion (Uehara et al, 1999), and is partially consistent with the findings of Myers and colleagues of no correlations with other clinical indices of psychopathology (including alexithymia), with the exception of low positive emotions scores on the Minnesota Multiphasic Personality Inventory (MMPI) (Myers et al., 2013). Therefore, differences in methods of measurement likely contributed to these partially inconsistent findings. Further studies are required to delineate the relationship between avoidance tendencies and psychopathology in PNES.

We found that endorsement of a Task-Orientated coping strategy was negatively-correlated with elevations of alexithymia in particular. This is unsurprising, given that people with alexithymia find it challenging to identify and describe their feelings, among other difficulties, and therefore are more likely not to identify and manage (indicators of) stress in a healthy or timely manner (Ricciardi et al., 2015b). Moreover, this negative correlation with alexithymia is highly consistent with observations reported in previous studies (Parker et al., 1998; Ricciardi et al., 2015b). We also found that this type of coping style was negatively associated with depression and anxiety symptoms, which is consistent with other reports that task-focused coping styles negatively correlate with depression (McWilliams et al., 2003) and anxiety (Oles et al., 2014) symptoms. Task-Orientated coping strategies that include proactive planning, problem-solving and social-support seeking techniques to deal with stressful experiences are widely considered to be the healthiest stress-management methods for most situations (Meyers et al., 2013), so that overall, our findings are highly consistent with evidence of abnormal coping in PNES (Brown and Reuber, 2016b).
Our finding that the elevated use of an Emotion-Focused coping-strategy correlated significantly with depression and anxiety symptoms in particular, is consistent with similar results from studies that have evaluated how coping style relates to stress and affective symptoms (Myers et al., 2013, Mc Elroy et al., 2014; Tomczak-Witych et al., 2006). We also observed positive correlations between use of an Emotion-Focused coping strategy and both experiences of dissociation and personality indices relating to conversion disorder. For example, our finding of a positive correlation between this type of coping style and indices of dissociation has been previously reported in one study that examined coping strategies in people with post-traumatic stress disorder (PTSD) and found that people who had dissociative experiences in the aftermath of a traumatic event employed emotion-centred strategies to a greater extent than those without dissociative symptoms (Brousse et al., 2011). It has been proposed that dissociation functions as a defensive “conversion” mechanism that can enable people to cope with overwhelming feelings (Brown and Reuber, 2016b; Bowman, 2006; Kuyk et al., 1996), so that our study results would suggest that this association occurs in relation to abnormal use of a coping strategy that includes self-directed, negative cognitive and affective responses to stress, rather than use of an avoidant or task-focused approach. Finally, our finding of a positive correlation between Emotion-Orientated coping and personality measures that focus on symptoms associated with conversion disorder and preoccupation with physical health problems, has not been reported previously in studies of mature adults using this coping assessment tool per se, but this association has been reported in young adults that were suffering with long-term psychosomatic problems after experiencing adversity (neglect) in childhood (Sesar et al., 2010). Further, this finding is also highly consistent with the idea that patients with PNES tend to focus on their experience of physical symptoms as a way of avoiding emotional difficulties (Brown and Reuber 2016b). Overall, therefore these findings have potential implications for the therapeutic approach to patients with PNES, in that psychological treatment may be best targeted at reducing Emotion-Focused strategies of coping in order to ameliorate dissociative-conversion symptoms.

Our findings add to evidence that, taken as a group, patients with PNES have no one personality type or abnormal coping style that could represent a unitary
mechanism for manifestation of PNES (Cragar et al., 2005; Myers et al., 2013; O’Brien et al., 2015). However, such findings help to identify subgroups within the population of patients with PNES that may each represent differences in underlying pathophysiology and mechanism of action for manifestation of PNES, despite theoretical models of PNES providing for an overall framework in which PNES occur (Baslet, 2011; Brown and Reuber, 2016).

We previously reported that there was no significant difference between our PNES and healthy-control groups in the number of stressful life-events reported (O’Brien et al., 2015). However, we suggest that caution should be exercised in taking these findings at face value, given that previous studies have reported that patients with PNES are more likely to not only deny life stresses (Testa et al., 2012), but also to attribute their problems to somatic rather than psychological causes (Stone et al., 2004b). Therefore, we suggest that our psychometric results, taken together, indicate that the number of self-reported stressors are not as meaningful in terms of association with PNES, as the psycho-somatic impact of a particular stressor on the individual patient, combined with abnormal emotional-information and stress-processing strategies.

6.6.2 Comment on behavioural data findings

We observed that there were significant between-group differences relating to errors made during the fMRI task and mean response (reaction) time to facial stimuli. This finding was consistent with our hypothesis that patients with PNES would likely demonstrate processing difficulties during behavioural performance of the implicit face-processing fMRI task, which was employed in this study as a probe of emotional processing circuitry.

Gender-identification tasks of upright faces utilised during fMRI scanning are considered to be relatively straightforward and have been demonstrated to be rather undemanding on attentional resources in healthy people (Reddy et al., 2004). In this study, total errors committed during the face-processing task comprised incorrect identification of gender, and omission errors of non-response to facial stimuli during the experiment. Total errors were higher in the PNES group and were significantly associated with symptoms of depression,
anxiety, dissociation and conversion disorder. We had previously found that patients with PNES demonstrated relatively intact sustained attention in general on neuropsychological assessment, using the CANTAB rapid visual processing test (O'Brien et al., 2015). Therefore, these findings indicate that under conditions of facial processing, patients with PNES demonstrate evidence of impaired attention, under conditions where satisfactory effort has been demonstrated.

We also found that patients with PNES had a relatively delayed reaction to face stimuli overall and that, similar to the findings for errors committed during this task, response latency was positively associated with measures of anxiety, depression and dissociation-conversion symptoms. There may be a number of reasons why a group of patients exhibit a relatively delayed response to EFE stimuli. For example, such an observation could potentially represent reduced effort during the task, automatic avoidance of the stimuli, or difficulties processing the stimuli. However, in our study, only those participants who passed a test of effort just before undergoing functional neuroimaging were included in the final analysis, so that reduced effort is unlikely to be a significant factor. Therefore, we suggest that our finding is more likely to reflect either avoidance tendencies or disturbed face-processing processes, or both, in PNES, which will be discussed further below.

There is growing evidence that patients with PNES use avoidance as a coping mechanism to deal with stressful situations, including in response to threatening stimuli under experimental conditions. On the one hand, in this study we found that patients with PNES endorsed abnormally high avoidance strategies in managing their stress. This observation is highly consistent with reports of increased avoidance tendencies in patients with PNES, not only in response to generally stressful situations (Frances et al., 1999; Goldstein et al., 2000, Goldstein et al., 2006), but also particularly to socially-threatening stimuli involving angry faces (Bakvis et al., 2009b, Bakvis et al., 2011). On initial inspection at least, our findings of non-significant relationships between coping style and latency of response on the behavioural task would appear to indicate that coping strategy (including that of avoidance-focused) is not particularly associated with the speed of response to EFE stimuli (involving fear, disgust, and sadness). Nevertheless, this does not mean that the patients did not employ avoidance or have associated interference in processing during the
fMRI task, and definitively addressing this question was beyond the scope of this study. However, faces exhibiting anger, fear and disgust, are classed as threat-related stimuli and have been associated with a behavioural activation response to social threat in healthy people (Le Doux, 1996; Jusyte et al., 2014). Furthermore, Bakvis and colleagues reported relative increases in both latency of response and attentional bias to angry (but not happy) EFEs in PNES (Bakvis et al., 2009b; Bakvis et al., 2011). Therefore, our findings of latency in response are potentially consistent with evidence that patients with PNES exhibit relatively increased avoidance tendencies to stressful situations involving the processing of socially-threatening stimuli, and that this may be largely an automatic response, processed outside of conscious awareness (Bakvis et al., 2009, 2011).

On the other hand, the latency of response to the fMRI task in our study could represent evidence of disturbed processing of facial stimuli in PNES. This is highly likely to be the case as we also found that the PNES group committed more errors during the task. Fear and disgust (like anger) are threat-related stimuli that, compared to other classes of facial expressions, represent types of signals that are particularly relevant for survival in human beings (Jusyte et al., 2014) in that human facial expressions communicate both emotional state and behavioural intentions or action demands to the viewer (Horstmann, 2003). Also, it has been hypothesised that processing of threat-related stimuli is prioritised automatically (Bar-Haim et al., 2009), which provides an evolutionary advantage (Elliot and Covington, 2001) in being able to rapidly respond to danger in the environment (Le Doux, 1996). Moreover, the ability to identify EFEs is crucial to normal interpersonal relationships (Bell et al., 2011) in that facial expressions both signal the emotional states of others and influence the production and regulation of affective states and behaviour in response to these signals (Phillips et al., 2003). Therefore, overall, our findings that the PNES group demonstrated firstly, relatively increased latency to facial stimuli, secondly, increased errors during processing of threat-related stimuli (EFEs) and thirdly, that these abnormalities were significantly associated with clinical indices of stress and dissociative-conversion symptoms, likely indicates that there is relatively less effective face processing in PNES, which is associated with abnormal integration of sensory and emotional experience.
6.6.3 Comment on fMRI findings

This study investigated the neural correlates of implicit emotional processing in PNES, and examined where the face-processing task produced similar and differential neural activation between-groups. We found that brain regions that are known to be involved in implicit processing of emotional facial expressions (EFEs) were engaged by our implicit fMRI task in both patients with PNES and healthy controls (Scheuerecker et al., 2007; Lane et al., 2008; Fusar-Poli et al., 2009), indicating that the task reliably performed in both groups. Our EFE task evoked activation responses in both groups in structures known to be implicated in both face and emotional processing, including the superior, middle and inferior frontal gyri, the pre-central gyri, the superior, middle and inferior temporal gyri, the parahippocampal gyrus, fusiform gyrus, occipital areas including the lingual gyrus, parietal areas including the post-central gyri and inferior parietal lobule and insula, thalamus, and cerebellum (Phillips et al., 2003; Snow et al., 2014; Fossati, 2012). Also, the regions that were activated were consistent with previous studies of implicit processing of facial emotions (Lichev et al., 2015; Fusar-Poli et al., 2009; Scheuerecker et al., 2007).

However, while our finding that the amygdala region was not discernibly activated by our face-processing task of neutral faces in both PNES and HC groups was notable, this is consistent with reports that amygdala enhancement during the processing of neutral faces is a less consistent finding than for fearful faces (Fusar-Poli et al., 2009).

A number of brain regions were found not only to be reliably activated by our task in both PNES and HC groups, but also to have equivalent activation, suggesting that the neural circuitry involved in face-processing is probably intact in these areas. These regions comprised some frontal regions [left middle frontal gyrus (MFG)], temporal regions [left para-hippocampal gyrus (PHG) and right fusiform gyrus (FFG)], occipital regions [bilateral lingual gyrus (LG), right middle occipital gyrus (MOG) and right inferior occipital gyrus (IOG)], parietal regions [bilateral superior parietal lobule (SPL), precuneus (PC)], right insula (Ins), thalamic regions (right-sided), and some cerebellar regions [left dentate (DEN)]. In contrast, there were five areas that were activated consistently in...
both groups for viewing of neutral faces, but which exhibited abnormal activation in patients with PNES. These comprised frontal regions [right inferior frontal gyrus (IFG), right pre-central gyrus (PrCG)], parietal regions [left post-central gyrus (PosCG), right inferior parietal lobule (IPL)], and some cerebellar regions [left culmen (CUL)]. These regions will be discussed individually further below.

Reduced brain activation in the PNES group was found in the right IFG [Brodmanns Area (BA) 9]. In general, the IFG forms part of the mirror-neuron system, which becomes activated during imitation of visual cues, observation of actions in others, and during the understanding of both intention and emotional states of others (Carr et al., 2003). It also comprises part of the frontostriatal brain system, which is involved in top-down modulation of cognitive control (Fan et al., 2005). Further, the IFG contributes to the dorsolateral prefrontal cortex (DLPFC) and the medial prefrontal cortex (MPFC), which, in the right hemisphere, are involved in socio-emotional responses and govern executive functions such as working memory, cognitive flexibility, abstract reasoning, inhibition and planning (Mars and Grol, 2007; Talpos and Shoaib, 2015). However, in terms of function-laterality, the right IFG is specifically recruited when important salient or task related cues are detected. In addition, it has been implicated in risk aversion, and in both response inhibition and exerting influence over the motor system via potentiating inputs to the pre-supplementary motor area (pre-SMA, in BA 6) (Hampshire et al., 2009). Therefore, relative hypo-activation of this structure during implicit processing of emotional faces may indicate that there is a disturbance of functions normally subserved by this brain region in implicit processing, including cognitive processing, and may relate to the failure to recognise and/or emotionally respond appropriately to faces, and failure to inhibit motor responses to emotionally relevant stimuli.

We found that an area, which included the PreCG and encompassed BAs 4 and 6, was abnormally hypoactive on the right side during implicit face processing. On the one hand, the PreCG is the location of the primary motor cortex (M1) and corresponds to BA 4, so that its functions include the integration of motor function signals from various regions of the brain, and the initiating and
controlling of contralateral voluntary movements of skeletal muscles (Siegel and Sapru, 2010). On the other hand, BA 6 encompasses the premotor area and supplementary motor area (SMA), which both plan and control movements in association with the basal ganglia (BG), and BA4 to execute movements. The SMA has been implicated in motor co-ordination (Sumner et al., 2007; Moore et al., 2010), including that of sequential actions, (Deecke et al., 1978; Dum et al., 1991; Luppino et al., 1994; Rowe et al., 2005; Passingham et al., 2010), and also in the initiation of internally (compared with stimulus-) generated movement (Deecke et al., 1978; Voon et al, 2010b; Lau et al., 2004). Therefore, our findings may indicate that patients with PNES have deficient neural processing in brain regions crucially involved in the planning, executing and control of movements, including those in response to internally-generated and unconsciously processed stimuli.

We found that patients with PNES exhibited an abnormal activation response to emotional face processing in parietal regions, including the left PosCG (including BAs 3 and 40), and right inferior parietal lobule (IPL). On the one hand, the PosCG (including BA 3) is the location of the primary somatosensory cortex, the primary receiving area for somesthetic information from skin and joints, and the structure that receives most of the thalamaco-cortical projections from contralateral sensory input regions. The primary somatosensory cortex has been shown to be critically involved in the processes of emotional mimicry (Adolphs et al., 2000), simulation of the body states that are associated with the viewed emotional condition (Heberlein and Adolphs, 2007), empathy (Preston and de Waal, 2002) and trait emotional awareness (Lichev et al., 2015). On the other hand, the IPL, which lies at a junction of the visual, auditory, and somatosensory cortices, has been implicated in the observation and imitation of emotional face expressions (Carr et al., 2003; Hennenlotter et al., 2005). BA 40 comprises the rostral portion of the IPL which relates to the supra-marginal gyrus, and shows strong connections with inferior frontal, motor, premotor, and somatosensory areas. It also forms part of the human mirror neuron system, and it’s functions include motor planning and action-related responses (Lacoboni 2005; Rizzolatti 2005; Keysers and Gazzola 2009; Caspers et al. 2010). Also, it has been implicated in the ability to maintain attention to current task goals and to encode appropriate responses to salient environmental stimuli.
Finally our findings of abnormal activation in left BA 40 also relates to the location of the temporoparietal junction (TPJ), a structure that has been implicated in integrating information from multiple domains such as internal goals, involved in abstraction of meaning from language or logic in relation to social reasoning tasks, and is closely associated with the default mode network (Samson et al., 2004; Braga et al., 2013). The DMN is involved in self-generated thoughts (Davey et al. 2016). Therefore, overall we suggest that abnormal activation in this region may reflect disturbed neural processes responsible for emotional awareness, emotional face perception, the sensory integration of experience, and the planning of movement action-responses in patients with PNES.

Evidence suggests that apart from its well-recognised roles in balance and proprioception, the cerebellum also controls and regulates movement. In addition, cerebellar areas are involved in distributed neural circuits that relate to emotional perception and social interaction (Schmahmann, et al., 2010). For example, cerebellar activation has been observed during affective processing tasks, including responses to EFEs (Reiman et al., 1997; Paradiso et al., 1999; Schutter and Honk, 2005; Fusar-Poli et al., 2009; Keren-Happuch et al., 2014), and although no consistent pattern for different emotions has been reported, it has been proposed that this region may contribute to processing of emotional states (Beauregard et al., 1998; Schmahmann, et al., 2007) and empathy (Singer et al., 2004; Jackson et al., 2005), and has been associated with social behavioural problems in autism spectrum disorders (Deeley et al., 2007). The culmen (CUL) in particular, has been associated with visuo-motor coordination in preparation for a future event (Bares et al., 2011). Further, the left CUL, in particular, has been found to have close connections with limbic system structures and proposed to be important for the integration of imagined limb configuration in dissociative states (Nicholson et al., 2015). In addition, the left CUL has also been implicated in positron emission tomography studies of emotional disorders (Su et al., 2014). Therefore, we suggest that our finding of abnormal left culmen activation in the patient group may reflect disturbed neural processing of movement, including anticipatory movement, in response to threat-related stimuli in PNES.
Our results indicated that the between-group differences in neural activations to emotional faces (fear, disgust, sadness) at low and high intensity was driven by the baseline response to neutral faces rather than being an effect of each emotion or the relevant emotional intensity. This was an entirely consistent finding across fMRI activation responses to the three emotions investigated in this study. Also, the fMRI protocol we used, in which we presented each face to participants for 2000ms, was consistent with recommendations that face-processing should be assessed within a threshold of 3000ms, as after that the relevant stimuli would include additional assessment of attentive viewing (Jehna et al., 2011). Therefore, we suggest that our results provide robust evidence that patients with PNES have abnormal processing of human faces, whether expressing neutral or negative emotional expression.

We found neural hypo-activation throughout the facial emotion processing network, including subcortical, fronto-parietal and cerebellar regions, in patients with PNES. It is likely that affective face processing relies on functional interconnections and feedback between the core structures involved in initial perceptual processing [which include the FFG (BA 37), superior temporal sulcus (BA 22), and TPJ (BA 40)], and the extended “emotional processing” network (Bruce and Young, 1986; Haxby et al., 2000), which comprises temporo-limbic and prefrontal areas implicated in the evaluation and modulation of emotion.

We found that there was overlap in both PNES and healthy-control groups in core face processing areas, and group-differences in BA 40 that corresponds to the TPJ. Therefore, the hypo-active responses we observed in areas relevant to both of these networks may explain face processing and general impairments of socio-emotional and cognitive regulation, found in patients with PNES (Chen et al., 2008).

Our finding of between-group differences in the neural activation response to implicit processing was consistent with our study hypothesis. However, that the differences in neural activation in the PNES group consisted of relative hypo-activation in all brain areas that demonstrated a differential group response, and that there were no areas of hyper-activation in this regard was unexpected, as some previous studies had indicated that firstly, greater attention to threatening facial stimuli has been associated with hyper-activation of neural networks.
involved in emotional processing (Guyer et al., 2008; Adolphs et al., 2010), and secondly, that patients with PNES exhibit heightened affective arousal (Baslet et al., 2011) and greater pre-conscious allocation of attention to fearful faces (Bakvis et al., 2009b), implying that neural activity in relevant face-processing areas on exposure to negative emotional faces would more likely increase in some areas compared to that in healthy controls.

Any observable change in regional brain activity can be potentially interpreted in three ways: whether the impairment relates to the neurobiological cause of PNES, whether it is a consequence of PNES, or whether it is a compensation for the disorder (Lewis et al., 1999). The reasons for the observed hypoactive response in our study are unknown and beyond the scope of this study. However, in considering these questions, our observation that patients with PNES demonstrated evidence of relatively increased latency of response to facial stimuli and that they committed more errors during the implicit face-processing task may initially indicate that these disparities in brain activation are reflective of impaired performance on the task (Callicott and Weinberger, 1999; Price and Friston, 1999; Murphy and Garavan, 2004; Price et al., 2006). However, neither mean response time nor total errors committed during the fMRI task explained the difference in fMRI activation levels between PNES and HC groups. In addition, with the exception of one measure (SOM-C), the observed functional hypo-activation was not found to be driven by other clinical indices that have been previously implicated in aetiology of PNES, including characteristics of the negative emotion illustrated in the facial stimuli (type and emotional intensity), clinical measurements of alexithymia, anxiety, depression, dissociative experience, and duration and frequency of PNES events. The only measure found to relate to level of fMRI activation was SOM-C, a measure from the PAI assessment relating to the level of a person’s focus on symptoms relating to motor or sensory dysfunction. None of the other personality-profile measurements related to fMRI activation level. This psychometric measure relating to the patient’s focus on ill-health from PNES deserves further study as a potential neurobiological marker of PNES. However, overall, I suggest that the abnormal neural activations found in our PNES group probably relate more to specific processes or abnormal circuitry involved in face and emotional-processing than with particular clinical abnormalities.
There are a number of potential causes for the hypoactive response observed during the implicit face-processing task in this study including abnormal processes or circuitry involved in face processing. Firstly, one potential reason for our finding of a relatively reduced neural response to the face processing task in patients with PNES is that it could represent disturbed functioning and/or functional connectivity between those regions. For example, a recent resting-state positron emission tomography (PET) study reported significant hypometabolism within the right IPL and central parietal regions, and within the bilateral anterior cingulate cortex (ACC) of patients with PNES (Arthuis et al., 2016), and we found relative neural hypo-activation in right IPL, but not ACC. In addition our findings are consistent with the findings of previous resting-state fMRI studies of PNES, that found convergent evidence of abnormal resting functional connectivity values between networks involved in emotional processing, executive control and movement, and involving several of the same regions that demonstrated between-group differences in our study, including IFG, PrCG, and PoCG (Van der Kruijs et al., 2011; Van der Kruijs et al., 2014; Ding et al., 2013; Ding et al., 2014; Li et al., 2015 a,b). Therefore, our findings support the preliminary evidence that these networks function abnormally in PNES, and extend them by demonstrating robust evidence of abnormally reduced neural processing in specific regions and functions associated with both unconscious emotional processing and evaluation of upright human faces.

There are other potential causes or influences on the hypoactive response. Firstly, it could relate to attention and demands of the specific task. For example, the magnitude of activation in face-processing areas, especially in the fusiform cortex, appears to depend on the degree of attention towards faces or to the exercise itself (Vuilleumier et al., 2001), and in addition, attention during emotional processing of EFEs has been reported to depend on task loads (Chen et al., 2016), so that reduced attention during face-processing could potentially explain neural hypo-activation. On the one hand, our findings that patients with PNES performed greater errors during the task and took longer to process facial stimuli study, is potentially consistent with abnormal attentional mechanisms to facial stimuli. However, on the other hand, neither mean response time nor total errors committed during the fMRI task explained the
difference in fMRI activation levels between PNES and HC groups. Therefore, our findings would appear to suggest that abnormal behavioural performance, as a proxy measure of attention, was not a significant driver of the observed hypoactive response. Nevertheless, this does not exclude this possibility as more specific measures of attention that are operating during implicit processing in PNES would be required to elucidate the role of attentional mechanisms further in this population.

Secondly, another potential cause of the observed hypo-activation to face processing is that reduced response to EFEs may form part of a dissociative response to potentially threatening or unpleasant social stimuli in some patients with PNES, or may reflect intentional cognitive avoidance of the pictures during the fMRI task (Pick et al., 2016). In evaluating if these factors may apply to the results of our study, it can be noted firstly, that all participants passed a general test of effort before undergoing fMRI (reflecting potential application to the task) and secondly, dissociative experience scores had no effect on the fMRI findings. On the other hand, dissociation experiences and cognitive avoidance during the study were not specifically investigated in our experimental design. Therefore, although the above results indicate that the observed hypo-activation was not driven by any of the behavioural or clinical parameters measured in this study and relate more to specific processes involved in face and emotional-processing than with particular clinical abnormalities (Bustamante et al., 2011), these findings do not exclude the possibility that dynamic changes in dissociative and cognitive processes occurred during the task.

Thirdly, it is likely that other relevant biological processes that could have affected neural processing were operating during this experiment but were not discernible or measured under our experimental conditions. One potential influence on the hypoactive neural response in PNES relates to patients having an abnormal biological response to stress. For example, hormones such as cortisol act via the hypothalamic-pituitary-adrenal (HPA) axis to modulate emotional and other associated responses to sensory information, and cortisol levels have been associated with enhanced limbic activation during fMRI studies of face-processing in normal humans (Weldon et al., 2015). In recent years, there has been emerging evidence that elevated baseline cortisol levels (Bakvis et al., 2009a, Bakvis et al., 2010, Bakvis et al., 2011) and abnormalities in stress circuitry are associated with the pathogenesis of PNES (Reuber, 2009;
Devinsky et al., 2011; Allendorfer et al., 2014). Moreover, abnormal cortisol exposure has been found to adversely affect cognitive and affective functioning, and development of brain structures in medial temporal, limbic, and frontal regions (Langenecker et al., 2012), and we found impairments in all these domains in our neuropsychological and neuroimaging studies of PNES (O’Brien et al., 2015; Studies 2, 3, 4 of this thesis). In addition, other biological conditions involving cortisol dysregulation have been previously studied using fMRI and found to be associated with both impaired accuracy of affective discrimination of EFEs, and altered activation of brain structures relevant to emotion processing and regulation (Langenecker et al., 2012). Also, several fMRI studies of other medical and psychiatric conditions have found elevated cortisol levels to be associated with hyper-activation of brain regions involved in affective processing (Peters et al., 2016). Overall, in considering the results of these previous studies together, we believe that our findings of neural hypo-activation could reflect decreased or abnormal stress reactivity in PNES. In addition, another research group has indicated that they have found (unpublished) evidence of reduced stress reactivity in PNES (Allendorfer et al., 2014). Therefore, further studies are required to investigate whether disturbances in the HPA axis are associated with hypo-activation of neural response to EFEs in PNES.

There has been no other fMRI study published that has investigated implicit emotional processing in PNES. However, two studies have investigated unconscious emotional processing in motor conversion disorder (Section 1.13.2.1). In the first study reported of its kind, Voon and colleagues conducted a block-design affective task using fearful, neutral and happy face stimuli in 16 patients with motor CD and the same number of matched healthy-controls. They found evidence of increased amygdala and SMA functional activity (Voon et al., 2010a). Also, in a recent study, Aybek and colleagues evaluated the neural correlates of implicit processing of negative emotions (fearful and sad faces) in 12 motor CD patients and 14 matched controls. They reported that in contrast to controls, patients showed increased activation to negative facial expressions in amygdala, PAG, cingulate cortex and SMA (Aybek et al., 2015). In contrast to our findings, both motor CD studies reported no group differences in either response (reaction) times to facial stimuli or errors in processing the
facial stimuli, and found both that patients with motor CD demonstrated increased amygdala activation when processing negative emotions and that their results provided evidence for the presence of a hyperarousal state in patients with motor CD during processing of emotional stimuli (Voon et al., 2010a; Aybek et al., 2015). Therefore, those studies, which involved patients with several types of motor CD but not PNES, shared quite consistent findings. Also, Voon and colleagues found no between group differences in processing of neutral faces (Voon et al., 2010a). Therefore, as the results of our study are very different from those studies of emotional face processing involving other types of motor CD, it is likely that the underlying neurobiology of PNES represent a distinct subgroup of CD.

6.6.4 Limitations

There are several limitations of our study. For example, our healthy-control group scored significantly higher on tests of intellectual ability, compared with the patient group with PNES, and it may have been better to include a FSIQ-matched control group if that had been possible. However, we accounted for known confounders in our design and analyses. Firstly, only those participants who passed a test of effort just before undergoing neuropsychological and neuroimaging assessment were included in the analysis; secondly, we controlled for effects of age, gender and FSIQ in our fMRI analysis. In addition, our results cannot be explained by the presence of depression or anxiety symptoms, as we found no significant relationship between fMRI activations and these variables, and also cannot be explained by gross detectable differences in brain structure as patients were included only if they had no detectable changes in brain anatomy. Another limitation was that the sample size was relatively small (n=19), so that it is possible that some of our results may be explained by type 1 error as we carried out multiple comparisons. However, our results were consistent and robust; we found that both groups exhibited activations in brain regions that have been specifically associated with face and emotional processing (Haxby et al., 2002; Surguladze et al., 2003), and further, that the same pattern of neural hypo-activity to faces on an implicit task was demonstrated in the patients with
PNES across three negative emotional conditions and in response to neutral, low and high emotional-intensities of each condition. Therefore, despite the relatively small sample size in this study, our results demonstrate we had sufficient statistical power to detect abnormal activations and further, we believe that our results are likely to reflect true positive activations as we utilised conservative methods in thresholding and analysis to reduce the risk of Type 1 errors (see our “Methods” section).

We did not include other stimuli, apart from faces, to localise regions that respond specifically to faces, which limits our ability to extend our findings of hyperactivity to regions that are selective for other objects. Another potential criticism of this study is that we did not assess both implicit and explicit emotional processing in the same experiment. Explicit emotional processing can be investigated by assessing participants’ (conscious) recognition of EFEs. However, although neural correlates for each type of processing have been found to be relatively distinct (Critchley et al., 2000), we were concerned that there could be potential overlap in neural activations during the same fMRI session, which would make results less clear and therefore make interpretation more difficult. However, we decided to specifically focus on implicit (unconscious) emotional processing, using a task involving gender recognition, because unconscious processes had been posed to be involved in etiological theories of dissociative (conversion) disorder since the time of Freud (Miller, 1985). In addition, we focused on examining unconscious responses to EFEs as appraisal of emotions and faces occurs during routine social interactions, often as an automatic process that occurs outside of the individual’s awareness (Lazarus, 1991). Therefore, we believe that our experimental paradigm was appropriate within this context.

We found widespread regional activations in our face versus fixation cross contrasts for fear, disgust and sad emotions across different levels of intensity. However, we did not find that the amygdala was activated either within-group during the implicit task, or in any of our between-group contrasts, which was surprising, as the amygdala has been demonstrated by fMRI to have an integral role in implicit face-processing of threatening stimuli, including fearful and sad faces (Vuilleumier et al., 2005; Surguladze et al., 2005; Fusar-Poli et al., 2009), as well as in assessment of salient (Sander et al., 2003) and new stimuli (Blackford et al., 2010). Nevertheless, not all previous studies assessing
implicit EFEs, including fearful faces, have demonstrated activation of the amygdala (Sprengelmeyer et al., 1998; van Amelsvoort et al., 2006), and also, a recent meta-analysis of face-processing studies reported that amygdala enhancement during the processing of neutral faces to be less consistent than for fearful faces (Fusar-Poli et al., 2009). Moreover, our findings do not necessarily mean that the amygdala was not activated per se during this experiment. For example, this finding may relate to relatively small sample size and limitations of MRI acquisition (Azuma et al., 2015). In addition, it could also be possible that, in our study, the amygdala of patients with PNES was consistently over-activated even before negative EFEs were presented, as this has been demonstrated in a previous neuropsychological study of preconscious response to EFEs (Bakvis et al., 2009b, 2011). Further studies are required to investigate these processes and replicate our results. Finally, we didn't include an epilepsy control group in this study, and this would have been useful for comparison purposes and particularly to help identify potentially discriminative biomarkers.

6.6.5 Conclusions

Both patients with PNES and healthy-controls demonstrated activation in brain regions implicated in face-processing. However, in contrast to healthy-controls, patients with PNES demonstrated abnormal task-performance to controls, relating to increased latency of response and errors made during the implicit face-processing task. In addition, patients with PNES demonstrated consistently lower brain activations in these regions in response to implicit face-processing of EFEs, including that of neutral face expressions. The observed functional hypo-activation was not driven by abnormal behavioural performance, characteristics of the negative emotion (type and emotional intensity), clinical symptoms of alexithymia, dissociation, anxiety, depression, clinical data relating to duration and frequency of PNES events, or spatial working memory performance. The only measure found to relate to level of fMRI activation was SOM-C, a measure of the person’s focus on symptoms of ill-health relating to motor or sensory dysfunction. I suggest that, taken together, these results indicate a core impairment of the functional brain circuitry involved in face and
emotional processing in PNES and that the abnormal neural activations
probably relate more to specific processes involved in face and emotional-
processing than with particular clinical abnormalities. Nevertheless, SOM-C
deserves further study as a potential neurobiological marker of PNES.
However, I suggest that the abnormal neural activations found in our PNES
group probably relate more to specific processes or abnormal circuitry involved
in face and emotional-processing than with particular clinical abnormalities.
The results of this study indicate that the initial perception of salient facial
information is abnormal and deficient in PNES, and more specifically that there
is a functional breakdown in low-order mechanisms involved in an early stage of
the execution of face and emotional processing, that is likely to adversely affect
normal contextual integration and appraisal of social cues further downstream in
this process. This initial perception, which is abnormal, may be related to a
state of abnormal focus on the symptoms of ill-health. This has important
implications for mechanistic models of social cognitive impairment in PNES and
in developing treatment strategies to improve functional outcome. We suggest
that abnormal face-emotion processing is a candidate endophenotype for
PNES. Further studies are necessary to replicate these findings and investigate
how these abnormalities arise.
Chapter 7:

General Discussion

This chapter will begin with a summary of the main findings from Studies 1, 2, 3 and 4, presented with respect to each of the core hypotheses that were outlined at the end of Chapter 1. Then, the implications of the findings with respect to a model of pathogenesis of PNES will be outlined and the chapter will conclude by briefly discussing potential future studies that may be helpful in understanding and treating PNES.

7.1 Summary of main findings from this project in relation to each hypothesis

This project consisted of a preliminary study examining prevalence of PNES in a tertiary referral centre, and three main studies that investigated neuropsychological functioning and neurobiological correlates of PNES in adults. The main results of the studies will be interpreted with respect to each of the core hypotheses outlined previously in Section 2.3 of this thesis.

7.1.1 Hypothesis 1: People with PNES will represent a significant proportion of those who attend Beaumont Hospital with treatment-resistant epilepsy and there will be challenges in providing follow-up treatment

This hypothesis was supported by the main findings from Study 1 that, over the three year period relating to this study, 19.5% of all patients that were evaluated
in the epilepsy monitoring unit (EMU) of Beaumont Hospital (BH) had PNES, with approximately 80% being female with an average age of 36 years. A number of findings indicated that there were treatment challenges for patients with PNES. Firstly, some patients (albeit a small number) of patients diagnosed with PNES self-discharged without engaging in making follow-up arrangements, once the diagnosis was explained. Therefore, these patients were lost to follow-up, at least in the immediate term. Secondly, for those diagnosed with having PNES, psychiatric and psychological follow-up was not provided by BH after inpatient discharge if the patient did not live locally. Given that the neurological, neuropsychiatric and neuropsychological teams in BH were the medical and mental health professionals that were the most experienced managing these patients, that no formal treatment strategy guidelines were in operation at the time of the study, and further, that there was no data available on what follow-up management actually occurred once the patient left BH, it would seem likely that these patients were facing uncertain management and treatment by health professionals in the community that had no expertise in PNES. Thirdly, the prevalence data from this study related to the proportion of patients attending a specialised inpatient admission unit for evaluation of seizure semiology, and did not extend to investigating the prevalence of PNES in general neurology inpatients or outpatients presenting with seizure-like events in BH. Therefore, the true proportion of patients that were attending BH with PNES, was opposed to epilepsy, was not and could not be addressed in this study, as only EMU assessment could definitively classify seizure type. Nevertheless, our results were consistent with reported prevalence rates of 20-50% from other similar studies (Howell et al., 1989; Sigurdardottir and Olafsson, 1998; Benbadis et al., 2001; Martin et al., 2003), which indicate a substantial proportion of patients in busy neurological centres have PNES. Fourthly, our finding that one-third of patients diagnosed with PNES in the EMU had co-morbid psychiatric disorder, (apart from PNES, which is classified as a dissociative-conversion disorder) consisting mainly of depressive disorders, indicates that these patients would require co-ordination of their mental healthcare at primary and secondary care levels to effectively address their needs, which could represent an ongoing challenge. Lastly, at the time this study was conducted, the findings indicated that there was no consistent pattern in how patients were referred for follow-up management of their PNES, and, in
addition, there were no formal guidelines on how patients with PNES should be followed-up. Given that research studies have since reported that patients with PNES benefit most from treatment within the context of a multidisciplinary team that includes psychiatrists, neurologists and psychologists (NICE, 2004), it was clear that these patients were facing systemic challenges in being provided with consistent and effective follow-up treatment. In drawing conclusions from the study findings, an evidence-based approach to follow-up of patients with PNES was recommended, which would hopefully improve the provision of care to this vulnerable patient group.

7.1.2 Hypothesis 2: People with PNES will have significant co-morbidity with other psychiatric conditions, particularly those which involve anxiety and depression, and will have significant levels of emotional dysregulation and dissociative conversion symptoms

This hypothesis was supported by main findings from Study 2 and Study 4. The finding in Study 2 that 53% of patients with PNES had co-morbidity with either an axis I or axis II disorder was consistent with the a priori expectations. Most of these patients had an axis II, rather than axis I disorder, with cluster B personality disorders (particularly that of emotionally-unstable type) being most prevalent in this group. However, that just two of the patients with PNES had an active axis I disorder was less than the prevalence of axis I disorders reported in other population samples of PNES (Bodde et al., 2009). Nevertheless, that the average frequency of PNES events reported by patients was three per week, and that 36% of the sample had treatment resistance to cognitive behavioural therapy, represented considerable evidence of severe and ongoing seizure-like events in this sample. In addition, patients with PNES were found to have significantly elevated scores of anxiety, depression, dissociation and alexithymia compared with our healthy-control group, indicating they had ongoing emotional dysregulation. Also, the personality profiles of the PNES
The group was highly consistent with what would be expected, with significantly elevated scores on indices associated with conversion disorder, reflecting the patient's experience of physiological symptoms typical of dissociative-conversion disorders, and a preoccupation with signs of physical ill-health. Finally, patients with PNES demonstrated significant evidence of endorsing clinically elevated scores relating to coping styles that were more emotion and avoidance focused than task focused. These findings indicated that when patients with PNES were confronted with stress or problems, they were more likely to internalise them and/or avoid positively addressing them, and therefore increase their distress, rather than to endorse positive coping styles that involved active and positive steps towards problem-solving. Notably, although the PNES group did not have significant differences in the number of stress or traumatic events they had reported experiencing in their lives, the study findings indicated that they continued to endorse personality traits and coping styles that represented an ongoing risk for stress-related emotional problems and difficulties processing stress.

7.1.3 Hypothesis 3: People with PNES will be significantly impaired relative to healthy controls on performance of executive functioning tasks, particularly those relating to attention and working memory

This hypothesis was partially supported by main findings from Studies 2 and 4, which were carried out on participants from the same samples of patients with PNES and healthy controls.

On the one hand, performance on some tests of executive functioning was relatively normal. Firstly, performance on the MOT was equivalent in patients and controls, indicating grossly intact visuomotor skills in patients with PNES. Secondly, in relation to cognitive tasks involving attention, the results from Study 2 indicated that patients with PNES responded relatively quicker to tests of sustained attention and thinking time for planning tasks, than healthy
controls, without significantly compromising overall performance on those neuropsychological tests. Thirdly, patients demonstrated relatively equivalent performance to healthy-controls on IED tests of attentional set formation, maintenance, shifting and flexibility of general attention; on RVP tests of sustained attention; and on SOC tests of executive functioning and planning abilities.

On the other hand, the results from Study 4 showed that patients with PNES committed more errors during the behavioural task and took longer to complete the task. These test results indicate that the PNES group have difficulties attending to and processing faces. As previously outlined, the gender discrimination task is considered to be relatively straightforward and not demanding of attentional resources in healthy people. Therefore, these findings likely represent abnormal interference in attentional mechanisms during the specific face-processing task in patients with PNES. In addition, patients performed abnormally on multiple tests of SWM, and moreover, where present, the deficits were consistently apparent on tests of higher task complexity. Patients also executed poorer strategy on tasks relating to SWM.

Therefore, overall, the evidence from this series of studies suggested that gross motor skills, visual planning and attention was generally normal in patients. However, on the other hand, patients with PNES demonstrated abnormal spatial working memory processes which related to increasing task complexity, and abnormal implicit socio-cognitive processing of faces during a gender-discrimination task. Taken together, the neuropsychological testing results indicated that patients with PNES exhibited generally intact fronto-striatal functioning (as tested by the IED test), and spatial planning (as tested by SOC), but had disturbed frontal lobe functioning in specific circuits relating to SWM (as tested by the SWM task) and abnormal reaction to and processing of human faces.
7.1.4 Hypothesis 4: People with PNES will show abnormalities of brain structure, particularly affecting regions associated with cortico-subcortical motor loops

This hypothesis was supported by the results from Study 3, in which the brain structure of patients with PNES was investigated using two complementary neuroimaging techniques (sMRI and DTI) and found to have specific abnormalities on ROI analyses. By time of writing, this was the first neuroimaging study to explore the neurobiology of PNES using both VBM and DTI in the same sample. No between-group differences were observed using the technique of whole-brain VBM and DTI analysis. However, there were significant differences between-groups in ROI analyses of frontal lobe, temporal lobe and thalamic regions affecting the left hemisphere, after adjusting for multiple comparisons. These effects became non-significant after controlling for the effects of FSIQ. Nevertheless, no previously published neuroimaging study of PNES had assessed or controlled for possible effects of FSIQ in reporting their findings so that our decision to report our results in this way is consistent with contemporary research studies of PNES by time of writing which allows general comparisons to be made between study findings.

Compared with healthy-controls, patients with PNES had reduced grey matter in the left middle and inferior temporal gyri regions on the VBM ROI analyses, and increased FA values in the left SLF on the DTI ROI analyses. The left middle and inferior temporal gyri have been previously found to subserve visual processing, language and semantic memory processing, and multimodal sensory integration (Onitsuka et al., 2004). The SLF is a long white matter tract connecting frontal, occipital, parietal and temporal lobes, and especially lateral fronto-parietal regions (Hecht et al., 2015). The SLF has been reported to subserve functions such as cognitive control (Chaddock-Heyman et al., 2013), working memory (Winston et al., 2013), language (Kamali et al., 2014) and motor movement (Budisavljevic et al., 2016), and also integrates networks involved in executive functioning with those responsible for sensorimotor functioning (Makris et al., 2005). In addition, relatively increased FA values
were found in white matter of the left frontal lobe FM and the left thalamus in patients. FM is a white matter fibre bundle that crosses the midline through the corpus callosum, and includes inter-hemispheric fibres that connect associative areas in occipital and parietal lobes of both hemispheres. The thalamus is an important structure for the relaying of sensory and motor signals to the cerebral cortex and is involved in production of intentional movement via striato-thalamo-cortical circuits (Gandevia, 1987; Graybiel et al, 1994), has a role in executive functioning & learning (Mitchell et al., 2015; Rabinovici et al., 2015), and helps to regulate alertness and consciousness (Metzger et al., 2013). On the one hand, DTI studies commonly interpret increases in FA as being representative of relatively greater density, organisation and myelination of fibres, and so, has been associated with maturation or compensatory responses (Mori and Zhang, 2006). However, on the other hand, this finding may also represent relative reductions of neuronal branching and reductions in white matter integrity (Silk et al., 2009). However, the correlation analysis findings of a negative correlation between dissociative-conversion disorder symptoms and poor neuropsychological performance in the patient group with SLF in each case, suggest abnormal development and maturation of SLF and is consistent with evidence of abnormal regional connectivity of cortico-subcortical circuits in people with PNES (Van der Kruijs et al., 2011; Van der Kruijs et al., 2014; Ding et al., 2013; Ding et al., 2014; Li et al., 2015 a,b).

7.1.5 Hypothesis 5: People with PNES will have abnormalities in unconscious (implicit) processing of emotion

This hypothesis was supported by results from Study 4, which showed that firstly, patients with PNES demonstrated increased errors and longer reaction time while carrying out a gender-discrimination task, indicating abnormal processing of and attention to human faces. In addition, patients were found to demonstrate significant hypo-activity in areas of the brain known to be involved in emotional face perception, emotional awareness, the sensory integration of
experience, and the planning of movement action-responses in patients with PNES.

The hypo-active BOLD response observed in patients with PNES during the implicit task suggest that these structures are abnormally recruited during emotional face processing. The study found that, with the exception of SOM-C, which measures a focus on symptoms of motor or sensory (conversion) dysfunction, clinical and psychometric indices that have been traditionally implicated in models of PNES did not drive the observed hypo-activation to the task and therefore could not explain this response. This psychometric measure (SOM-C) relating to the patient’s focus on ill-health from PNES deserves further study as a potential neurobiological marker of PNES. However, overall, I suggest that processes that were not discernible or measured during this experiment were contributing to this functional disturbance, including disturbed multi-sensory integration and impaired connectivity between fronto-parietal and cortical-subcortical regions. The abnormal functional responses to face-processing may extend to other functions of those brain regions found to be abnormally activated, and their associated cortical-subcortical circuits. These functions include the planning, executing and control of movements, including inhibitory and activation responses to internally-generated and unconsciously processed stimuli that may be perceived as emotionally threatening to the patient with PNES.

7.2 Contemporary models of the pathogenesis of PNES and implications of the findings of this thesis for improving our understanding of this condition

In this section, contemporary psychological and neurobiological models of psychogenic non-epileptic seizures (PNES) will be outlined. Then, the evidence from this thesis project will be interpreted to determine how this research has contributed to improved understanding of PNES.
7.2.1 Psychological models of psychomotor conversion disorders, including PNES

The contemporary understanding of consciousness is that it involves the individual generating a model of their environment via conscious and unconscious processing of multi-sensory data by information in memory, including semantic memory (Brown et al., 2011). Semantic memory comprises conceptual knowledge gathered through experience, of which only a small portion is required to guide processing of a particular task at a particular time. This working model is connected to behavioural-action systems. In this model, the processing of new action-responses involves both conscious and unconscious processing. Already established cognitive-action programs selected as a response to previously encountered environmental contexts are initially modified and controlled by conscious appraisal, will and intentional effort. In contrast, routine learned behaviours are controlled by established and maintained cognition and action programs that are unconsciously and automatically selected in response to processing of environmental stimuli. These cognitive-action programs, once established, are rapid and neurally efficient, requiring little conscious effort to direct them (Brown et al., 2011).

A recent psychological model of psychogenic motor disorders (PMDs) proposed that these disorders can be understood in terms of the individual holding “pathologically precise” beliefs which receive enhanced attention and are modulated by beliefs about physical symptoms and prior experiences (emotional and physical), and lead to the triggering of psychogenic motor responses (Edwards et al., 2012). In addition, that model suggests that processes relating to agency are disturbed, so that the patient interprets the movement as being involuntary.

Similarly, it has been proposed that in PNES, disturbed activity of memory can affect conscious processing of environmental cues and the associated action-responses of the individual. The experience stored in memory may pertain to
disordered representations of physical symptoms in the experience of the individual (e.g., witnessing seizures in family members, socio-cultural beliefs, including those relating to illness and behaviours) and other misperceptions of the individual that may be activated in the context of a triggering event and feed into activation of motor-action responses such as PNES (Brown et al., 2011). Suggested triggers include increased negative attention to physical symptoms and emotional distress, and attentional system disturbances possibly contributed to by disturbed stress processing are implicated in this model.

Four main psychological candidate mechanisms have been proposed for PNES and detailed in a recent review (Brown and Reuber, 2016b). These revolve around four central ideas, as follows: first, that PNES occur through activation of a dissociative mechanism, arising in response to the individual being reminded of a traumatic event; second, that PNES manifest as pre-wired intrinsic behavioural responses to threat similar to a protective reaction; third, that PNES are typically defensive responses which allow the individual to express distress or solve personal problems, without explicitly addressing the associated emotions; and fourth, that PNES are essentially learned behaviours maintained by operant conditioning (i.e., via positive and negative behaviour reinforcement) and/or because they are associated with some benefit to the individual (i.e., involving primary or secondary gain). The key strengths and limitations of these psychological models of PNES are outlined in Table 7.1, based on empirical evidence.
Table 7.1 The main psychological models of PNES: key strengths and limitations (Brown and Reuber, 2016).

<table>
<thead>
<tr>
<th>Model</th>
<th>Key strengths</th>
<th>Key Limitations</th>
</tr>
</thead>
</table>
| 1. PNES as the activation of dissociated material | • Explains increased rate of childhood trauma in patients with PNES and apparent clinical relevance of traumatic events.  
• Explains elevated scores on trait dissociation measures.  
• Predicts elevated suggestibility seen in some studies, as well as apparent utility of suggestion methods for eliciting PNES.  
• Explains perceived involuntariness of attacks, unusual motor activity and potentially loss of consciousness. | • Many patients with PNES do not report a history of potentially traumatising events.  
• Only a minority of patients with PNES meet criteria for PTSD.  
• Trait dissociation findings are mixed  
• Some patients with PNES don’t report significant dissociation or flashbacks.  
• Scores on trait dissociation measures may pertain to different aspects of dissociation.  
• Suggestibility findings are mixed and not all patients score in suggestible range. |
| 2. PNES as hard-wired responses, such as “panic without panic” | • Explains why PNES are relatively stereotyped and could potentially account for phenomenology and semiology.  
• Panic without panic is consistent with ictal unreality, disconnection and detachment in many patients with PNES.  
• Panic without panic explains why many patients with PNES report physical symptoms of arousal at the time of their attacks but not explicit anxiety.  
• Panic without panic predicts increased scores on trait dissociation measures. | • Stereotyping less marked than in epilepsy and significant variations are apparent between and within individuals.  
• Number of seizure categories inconsistent with a single hard-wired response.  
• Panic without panic does not explain perceived involuntariness, loss of consciousness, unresponsiveness and unusual motor activity.  
• Many PNES occur without apparent arousal, anxiogenic triggers or panic symptoms.  
• Scores on trait dissociation measures may pertain to different aspects of dissociation. |
| 3. PNES as physical manifestations of emotional distress | • Explains apparent disparity between increased physical symptom reports and low explicit anxiety.  
• Consistent with evidence for defensiveness, avoidance, alexithymia and emotional processing deficits in some studies. | • Does not explain key aspects of PNES semiology and phenomenology, which are unlikely to be simple symptoms of arousal.  
• Findings on defensiveness, avoidance, alexithymia and emotional processing deficits are inconsistent.  
• A significant proportion of patients deny emotional distress; claims that this is evidence of defence are circular. |
| 4. PNES as learned behaviours | • Explains motor features and unresponsiveness seen in some PNES.  
• Explains increased prevalence of PNES in patients with previous epilepsy.  
• Explains link between PNES and prior history of physical illness, injury, and loss of consciousness. | • Account of semiology and phenomenology seems to imply deliberate stimulation/deceit.  
• Unclear whether it can account for PNES that arise in the absence of obvious seizure models and that have changed little over time.  
• Cannot explain why very similar PNES-behaviours have been observed across different cultures.  
• It is often difficult to identify reinforcers/gains for PNES, making it difficult to explain symptom onset and resistance to extinction. |
Figure 7.1 Brown and Reuber’s hypothesised sequence of events in PNES, focusing on “how” rather than “why” PNES arise (Brown and Reuber, 2016).

Essential components of the outlined process are represented within the dashed-line area. In this hypothetical model, abnormal arousal is not an essential part of PNES generation (e.g., strong activation of the seizure scaffold in the presence of an inhibitory processing dysfunction could be sufficient to precipitate an attack even in the absence of heightened arousal).

Figure 7.1 illustrates the hypothetical sequence of events proposed by Brown leading to manifestation of PNES. These include firstly, an experience of elevated arousal, which may not be abnormal. Secondly, this increased arousal feeds into prediction and anticipation of a seizure event occurring in the context of abnormal processing of internal or external cues and a neurally-mediated vulnerability to PNES, described under the term “seizure scaffold”. The abnormal processing activates the seizure scaffold, while at the same time there is abnormal inhibitory processing, producing PNES.
7.2.2 Neurobiological models of psychomotor conversion disorders, including PNES

Only a relatively small number of studies have examined neurobiological correlates of PNES, and these studies were introduced (Chapter 1, Sections 1.12, 1.3 and 1.31), and then discussed (Sections 5.6 and 6.6) in light of the results of the research findings from this project of this thesis.

A recent hypothetical model relating to neural networks involved in psychogenic movement disorders was diagrammatically illustrated by Mehta and colleagues (Figure 7.2), based on neuroimaging research to that point (Mehta et al., 2013). In this model, it is hypothesised that firstly, there is an abnormally

---

Figure 7.2 Possible neural networks involved in psychogenic movement disorders (Mehta et al., 2013).

An interrupted line denotes a weakened network. PNES, psychogenic non-epileptic seizures; SMA, supplementary motor area; TPJ, temporo-parietal junction.
hypersensitive emotional network that connects via the striatum into the extended motor network.

Secondly, there is hypo-activity of the SMA, a structure that normally generates a “corollary discharge” signal which communicates with the TPJ “comparator” regarding what it should expect from sensory feedback as a result of internally generated, as opposed to externally generated, movements. It proposes that thirdly, the trigger mechanism involves abnormal self-directed attention. The abnormal self-directed attention is mediated by abnormal prefrontal cortical activation that is functionally disconnected from the core motor network. Lastly, it proposes that these changes drive the production of paroxysmal movements that are not tied to a normal sense of self-agency. According to this model, as a consequence of the abnormal network activity the patients interpret the generated movements as being involuntary.

7.2.3 Towards a revised model of PNES: how do the findings from this study enhance our understanding of the neurobiology of this condition?

Firstly, the sample characteristics of patients with PNES in this study will be outlined to determine consistency with proposed samples of interest from a recent review (Brown and Reuber, 2016b) and help place our findings in context. Secondly, the findings from this study will be compared with the hypothetical model of PNES proposed by a recent review of the neurobiological basis of PNES (Mehta et al., 2013). Thirdly, a revised hypothetical model of PNES will be introduced, using the results from this thesis.

7.2.3.1 Characteristics of patients in this study: a sample of interest in the research of PNES?

In this thesis, the sample of patients with PNES had the following characteristics:
The PNES group did not differ from the healthy-control group in relation to the number of life events they had experienced. Nevertheless, patients with PNES, compared with healthy-controls, had relatively higher scores on measures of anxiety, depression, alexithymia and dissociative experiences outside of PNES attacks, where people with PNES scored higher on these symptom indices. The mean BDI-II and BAI scores in the PNES group indicated symptomatology within a mild to moderate range, although no patient was found to meet criteria consistent with a diagnosis of major depressive or anxiety disorder. In addition, the mean TAS-20 scores for patients indicated they lay in a range of “possible alexithymia” (Bagby et al., 1994). The mean dissociation scores in the PNES group (as measured by DES-II) were relatively low in comparison with those that have been reported in groups of patients with dissociative identity disorder or post-traumatic stress disorder, but relatively high when compared to average scores previously reported in people with anxiety and depressive disorders, and similar to scores found in psychiatric conditions such as eating disorders, schizophrenia and emotionally-unstable personality disorder (Carlson and Putnam, 1993). In addition patients with PNES endorsed personality indices associated with dissociative-conversion disorders, specifically their experience of physiological symptoms typical of dissociative-conversion disorders, and a preoccupation with signs of physical ill-health. The PNES group also endorsed abnormal levels of coping, with a tendency to utilise greater emotion-focused and avoidance-focused coping strategies for stress-management, and to underutilise task-focus methods.

Taken together, these findings are consistent with interpretations that firstly, patients have difficulty identifying and appreciating emotional responses in themselves and others (i.e., have deficient perception relating to emotional awareness); secondly, that patients with PNES have a tendency to internalise and avoid their problems, and conversely, be less likely to problem-solve and positively address stressful situations as they arise; thirdly, they are more likely to report and focus on physical signs of ill-health and health-related disability (Brown and Reuber, 2016b); and fourthly, focus relatively more on the physical rather than the emotional components of distressing personal experiences (Brown and Reuber, 2016b). Therefore, it appears that the characteristics of this sample largely represented the PNES variant of dissociative conversion disorder that cannot be fully accounted for by any other psychiatric condition.
(e.g., post-traumatic stress disorder, panic disorder) and that has been proposed to be of fundamental interest to researchers in trying to explain how PNES arise (Brown and Reuber, 2016b).

7.2.3.2 Relating our findings to contemporary hypothetical models of psychogenic movement disorders, including PNES

The most recently published hypothetical model of the generation of PMDs is illustrated by Figure 7.2 (Mehta et al., 2013). In their conceptualisation, which was based on published data at that time, Mehta and colleagues proposed that firstly, patients with PMDs have a hypersensitive emotional processing network, that, through associations with stratal structures (such as the caudate, putamen and nucleus accumbens), is linked with the extended motor network; secondly, that patients have a self-directed attentional process that is mediated by abnormal prefrontal regional activation; thirdly, that there is abnormal functioning of the neural circuits responsible for providing sensory feedback that signals whether movements are internally-generated as opposed to externally-generated [involving hypo-activity of the SMA which normally communicates this information to TPJ and associated areas]; fourthly, the patient perceives the movements that are generated during this processing as being involuntary.

Baslet, in his 2011 review, speculated that PNES can occur from a number of different pathophysiological mechanisms including dissociation and re-PTSD-related experiencing phenomena, and interact with personality trait vulnerability factors such as alexithymia, avoidance as a coping strategy and deficient cognitive resources operating at the time of attacks (Baslet, 2011). Moreover, he proposed that dissociation could represent autonomous action of neural circuits involved in cognitive and sensorimotor functioning, as these processes do not reach prefrontal regions necessary for creation and interpretation of conscious experience (Baars, 2002). In his model of PNES, the interaction between areas responsible for action of inhibition of movement, emotional processing would likely relate to the underlying pathogenic mechanism. For example, triggers for PNES, including those of an emotional nature, could be processed unconsciously. In addition psychiatric conditions, if present, could
Figure 7.3 Baslet's hypothetical model for pathogenesis of psychogenic non-epileptic seizures

(taken from Baslet et al., 2011; Pessoa L. On the relationship between emotion and cognition. Nat Rev Neurosci. 2008 Feb;9(2):148-58. doi: 10.1038/nrn2317. Review. PubMed PMID: 18209732.). The figure shows two diagrams A and B. Diagram A illustrates circuitry for cognitive-emotional control, while diagram B shows hypothetical changes in this circuitry in PNES. In A, the relative thickness of the solid line connections represent the strength of circuit connections. Dashed lines represent the connections thought to connect between cognitive control areas, or limbic regions and somatosensory cortices. The thalamus and basal ganglia are added without illustrating connectivity. In B, solid circles with relatively increased thickness represent areas with greater connectivity in dissociative-conversion disorder. Dashed circles indicate brain areas with variably altered activity in PNES. Dashed circles with increased thickness represent brain regions that demonstrate variable function, but most likely greater activity in PNES-related conditions. ACC, anterior cingulate cortex; LPFC, lateral prefrontal cortex; OFC, orbitofrontal cortex; Thal/BG, thalamus/basal ganglia.

exacerbate an already unstable cognitive-emotional system for processing information. This unstable system would involve medial prefrontal region and anterior cingulate cortex dysfunction, and include lateral frontal regions contribution to the generation or modulation of the PNES events, and structures such as the TPJ could also be implicated in the patient’s sense that the movements are involuntary (Baslet, 2011). His model is illustrated in Figure 7.3.

Both Mehta’s and Baslet’s models share consistencies in how these disorders manifest. They share a model where firstly, there is abnormal functioning of emotional processing circuitry, and secondly, that the generation of psychogenic
motor phenomena involve abnormal prefrontal top down modulation of sensorimotor processes that allow movements to be generated that are perceived as involuntary. However, in contrast with Mehta and colleagues, Baslet does not speculate about the type of activity that might occur in fMRI studies of PNES.

In comparing our findings with these models we find some general consistencies. On the one hand, firstly, we found abnormal functioning of brain regions that subserve face and emotional processing in PNES. Secondly, we found that the structures in this network that were functionally abnormal during the implicit processing task included prefrontal, motor and premotor regions. Thirdly, we found that the region containing the SMA was hypoactive in patients with PNES during the implicit emotional face-processing task. In addition, we found that the specific regions implicated in the abnormal hypoactive response in patients with PNES included structures that are normally involved in providing sensory feedback in generating motor responses to internally-generated and unconsciously processed stimuli.

On the other hand, our findings, relating to neurobiological studies of PNES, have some differences in the type of expected activity observed in certain structures, in comparison with that hypothesised in Mehta’s model. Firstly, we found that the brain region containing the TPJ (BA 40) was hypoactive, which is consistent with Mehta’s model that implicates that this region is involved in manifestation of PMDs, but differs from the latter model in that our research demonstrated that the left TPJ specifically functions abnormally during emotional processing. Secondly, our findings were inconsistent with Mehta’s model and the relevant face processing studies relating to functional motor disorders, in that we found that the abnormal BOLD response that occurred during negative emotional face-processing was hypoactive in all the regions that were different between-groups, in contrast to increased activations being reported by the face processing studies of motor CD (Voon et al., 2010a; Aybek et al., 2015). In addition, our finding of relative hypo-activation was a robust and consistent finding to both neutral and negative emotional face stimuli in PNES, while in contrast, no abnormal activation has been reported to processing of neutral faces in patients with motor CD (Voon et al., 2010a).
7.2.3.3 Implications of these findings: towards an updated model of PNES

Our neuropsychological and structural neuroimaging studies help improve our conceptualisation of the neurobiology of PNES. We found that patients with PNES scored significantly higher than HCs on clinical indices of emotional dysregulation and dissociation-conversion symptoms, but that overall mean scores did not meet criteria for associated axis 1 mental disorders. The main findings of our neuropsychological assessments were that patients with PNES demonstrated relatively greater endorsement of abnormal coping styles involving low task-focused, and increased emotion and avoidance-focused stress-management. Patients with PNES performed significantly worse than HCs on assessment of executive functioning specifically on tests of SWM. We found structural abnormalities involving specific regions in the left hemisphere only, involving fronto-temporal regions of SLF, FM and thalamus. The structural abnormalities found in these areas were associated with dissociation-conversion indices of PNES. In addition the fronto-temporal WM changes in SLF were associated with abnormal spatial working memory performance. It is important to note that we carried out ROI analyses in the temporal, frontal, thalamic and amygdala regions only, in accordance with our hypothesis at the time. Thus we cannot say if there may have been abnormal structural changes involving the parietal, occipital and cerebellar regions.

Our functional neuroimaging study probed face and implicit emotional processing areas through use of a gender-discrimination task. We found abnormal (hypoactivation) recruitment of specific fronto-parietal and fronto-cerebellar motor regions, whose functions include processing of internally and externally stimuli and associated formulation, generation and modulation of action responses.

In considering the results and interpretation of all of our results together, I suggest a neurobiological model of PNES that is different from that previously proposed for other types of motor CD (Figure 7.2). In particular, the hypoactive response to implicit processing probably reflects something different is
happening neurobiologically with PNES than with other forms of PMDs and may reflect a specific marker for PNES. Nevertheless, in considering what may be happening neurobiologically with PNES, it is important to note that a recent review of psychogenic movement disorders (PMDs) overall (including PNES), concluded that duration of symptoms appeared to be the strongest prognostic factor, and that the majority of studies reported persistence or worsening of symptoms in approximately one-third of patients at follow-up, regardless of PMD subtype (Gelauff et al., 2014).

In this revised hypothetical neurobiological model of PNES (Figure 7.4), there is structural brain abnormality of white matter tracts regions involved in connecting frontal, parietal, occipital and thalamic regions in particular, in the left hemisphere (SLF, FM, Thal), and abnormal grey-matter changes in left middle temporal lobe (including MTG and ITG). The SLF (and its SLF II branch in particular) links inferior parietal cortex with premotor cortex and dorsolateral prefrontal cortex, including connecting via the TPJ. There is abnormal WM integrity of frontal and temporal regions of the SLF in particular. The abnormal WM and GM changes found in these regions are associated with dissociative-conversion features of PNES itself. Although we cannot infer without further research whether these changes are caused by the disorder, a consequence of the disorder, or are a compensatory response to the disorder, there is evidence that suggests that these structural changes could represent an abnormal maturation process, and may relate to an abnormal stress-reactivity response involving the hypothalamo-pituitary-adrenal (HPA) axis release of excessive cortisol, and the associated effects of cortisol over time on the development and functioning of associated middle temporal, limbic, and frontal regions. These changes may also contribute to the relatively hypoactive neural responses to salient stimuli as a consequence of decreased stress-reactivity. In addition, the functioning of these particular regions and their interconnectivity is abnormal. Notably, in contrast with models of motor CD, the neural structure and function of the amygdala appears intact in relation to emotional face processing in PNES. The abnormal functioning of the specific fronto-parietal and motor networks relates to a disturbed ability to unconsciously process upright human faces, is not related to usual indices of emotional and dissociative-conversion disorder, and extends to impaired implicit emotional processing.
Figure 7.4 Hypothetical neurobiological model of psychogenic non-epileptic seizures showing major connections of motor cortex and interactions between areas found to be abnormal in the neuroimaging studies of this condition in this thesis.

Areas shown in red showed structural abnormalities; areas in blue showed functional hypo activation; areas in green did not demonstrate abnormality but are implicated in major connections of motor cortex.
The disturbed neurobiology of the specific functional regions mentioned is directly implicated in possible mechanisms of production of PNES (Sections 6.6, 7.1 and 7.2 of this thesis). Firstly, there is an impaired core ability to unconsciously recognise and process human faces and emotionally relevant stimuli both from internal and external sources, so that somatic symptoms that may represent evolving emotional stress are not identified as such and are instead processed by the patient as relating primarily to physical health and physical problems. This occurs as an increased focus on the physical manifestations of stress, and because the patient utilises emotion and avoidance-focused strategies to manage their symptoms, the stress response continues to escalate. This may occur inside conscious awareness as a greater awareness of and focus on body symptoms (and the patient does not identify them as being emotional or stress-related), and outside of conscious awareness in a dynamic disturbance of implicit emotion processing.

Secondly, there is abnormal and deficient functioning of low-order mechanisms involved in an early stage of the execution of face and emotional processing, that is likely to adversely affect normal contextual integration and appraisal of social cues further downstream in this process. This may involve functions such as disturbed semantic memory retrieval that guides processing of the stimuli, that occurs as a consequence of abnormal structural integrity of the MTG and abnormal functional integrity of the left IFG in PNES, which work together to control this memory retrieval process (Davey et al., 2016). Normally, the pMTG links anterior temporal and prefrontal regions (especially the IFG) for representation and control of retrieval of relevant data for processing environmental contexts. Furthermore, both pMTG and IFG form a semantic control network distinct from executive control, so that it is considered to operate largely outside of conscious awareness (Davey et al., 2016). Additionally, fronto-parietal networks including IPL that have been proposed to support engagement with semantic retrieval in line with instructions relating to a particular task, and exert top-down modulation during the supporting of goal-driven aspects of cognition (Duncan and Owen, 2000, Duncan, 2010, Fedorenko et al., 2013; Noonan et al., 2013) also demonstrate disturbed functional connectivity in PNES.
Other cognitive functions involved in execution of face and emotional processing include those of attention, metacognition and self-monitoring and have been implicated in Mehta's model of PMDs (Mehta et al., 2013). In relating potential disturbance of these cognitive functions to PNES we can say that firstly, although our study design did not specifically assess attentional mechanisms that may be involved in triggering PNES, we observed that patients with PNES had a delayed response to processing emotional faces and that they made more errors on what is generally considered to be a relatively undemanding gender-identification task (in terms of attentional resources need to complete it). Therefore, abnormal attentional performance is probably involved when patients with PNES are processing emotional or threat related stimuli. Secondly, we found that specific regions involved in metacognitive activity were abnormally activated during unconscious face and emotional processing, including anterior prefrontal cortex, left TPJ, and left IPL. Normally, a network involving both anterior frontal cortex and default mode network (DMN) structures (that include the IPL and left TPJ) is associated with theory of mind and metacognitive processes including internal self-representations and interpretations of agency. It has been proposed that activation of these self-monitoring processes may trigger psychogenic deficits in PMDs. For example, it has been hypothesised that disturbance in these processes can allow suggestion to mediate motor activity in PMDs (Cojan et al., 2009b; Voon et al., 2014). Therefore, our findings of disturbed structure and functioning in these areas in patients with PNES may relate to abnormal processing of stimuli that trigger motor programs in PNES. This may not necessarily mean that the patient shows objective signs of being very stressed for the PNES to be triggered. Rather, the motor manifestations may occur reflexively to different stimuli that represent a particular meaning to the individual and are stored in semantic memory, particularly relating to semantic memory. Therefore, this model, drawing from the results of our neuropsychological and neuroimaging results, would appear to be consistent with psychological theories of manifestation of PNES (Edwards et al., 2012; Mehta et al., 2013). Alternatively a stimulus that is emotionally meaningful to the patient, and processed by an already compromised neural network (anterior prefrontal cortex) may fail to be acutely integrated and processed through the face and
emotional processing network, leading to triggering of a disinhibition of neural circuits involved in controlling and modulating physical movement. This leads to paroxysmal movements which serve as an expression of the neural overload, and is associated with an accompanying dissociative state that represents a failure of integration of multi-sensory and emotional input during that process. This aspect of the model is based on our neuroimaging findings of functional disturbance in prefrontal cortical and motor regions and is also consistent with evidence suggesting that decreased SMA and prefrontal area activity during action tasks in motor CD may represent impaired top-down regulation during generation and control of actions (Voon et al., 2011).

We suggest that rather significant differences from previous neuroimaging studies (and especially related studies of face processing) of motor CDs indicate that PNES represent a distinct neurobiological subgroup of dissociative-conversion disorders. Therefore, our finding may be a specific marker for PNES, and differentiate PNES from other dissociative-conversion motor disorders.

7.2.3.4 Stress reactivity in PNES: a unifying hypothesis?

Over the last decade, there has been growing interest in the concept of stress sensitivity and stress reactivity in psychiatric disorders, and these concepts have led to research and formulation of psycho-neuro-endocrinological, neuro-genetic, and cognitive-emotional models for the development of psychopathology in different medical and psychiatric disorders, including affective illness, schizophrenia and autism (Pezawas et al., 2005; Harkness et al., 2015). This increase in interest largely followed two findings: first, Post’s research produced his kindling hypothesis (Post et al., 1992), which states that major life stress has a greater role in the triggering of a first episode of affective disorder than subsequent relapses, and that over time more minor stressful events are required to cause recurrence of illness (Monroe and Harkness, 2005). Second, Robinson and Becker, through researching the effects of chronic amphetamine administration on human brain and behaviour, came up with the concept of stimulant sensitisation, where the brain becomes sensitised...
to the psychoactive stimulus and produces associated changes over time (Robinson and Becker, 1986). The terms stress sensitivity (StS) and stress reactivity (StR) are often used interchangeably but may relate to subtly different concepts and mechanisms relating to development and maintenance of psychopathology. On the one hand, StS refers to the individual’s tendency to manifest stress-related psychopathology at levels of stress that are considered to be relatively low, and is considered to develop through genetically-mediated interface between temperamental and environmental factors (Meaney, 2001). For example, evidence suggests that reactivity of limbic areas and hypothalamic-pituitary-adrenal (HPA) axis in children is mediated by genetic-endocrine inter-relationships, and relates to risk of development of psychopathology later in their lives (Hankin et al., 2015). On the other hand, StR refers to a person’s greater vulnerability to developing associated psychopathology following repeated exposure to exogenous and endogenous stressors over time (Hammen, 2005; Harkness et al., 2015). In this case, the evidence suggests that over time, minor stressors can maintain the disorder in comparison to what initially triggered it (Monroe and Harkness, 2005), and this phenomenon has been reported in relation to bipolar affective disorder (Weis et al, 2015) and emotional disorder (Ruscio et al., 2015).

The HPA axis represents the central mediating circuit of the neuroendocrine stress system, which is crucial in modulating many psychological functions, including emotional processing, cognitive functioning and emotion regulation (Figure 7.5) (Tsigos and Chrousos, 2002). While an acute stressor triggers the HPA axis temporarily, progressive or accumulated exposures to stress over time can lead to disruption of the feedback pathways of the HPA axis, the regulation of glucocorticoid receptors (GCR) and the relationship between GR and mineralocorticoid receptors (MCR), leading to potentially chronic changes in secretion of cortisol and how it effects target tissues (Parker et al., 2003). Such effects include reduced dendritic arborisation and cortical atrophy (Bao et al., 2008; Lupien et al., 2009), which typically affect structures in which there is a high concentration of GCR and MCR, including the amygdala-hippocampal region (AHR) and PFC (Peters et al., 2016). Therefore, there is overlap between neural networks involved in both the modulation of cortisol and both
Stress activates the HPA axis, which provokes the secretion of corticotropin releasing hormone (CRH) from the hypothalamus. CRH then stimulates the release of adrenocorticotropic hormone (ACTH) from the pituitary gland. ACTH, in turn, signals the release of cortisol from the adrenal cortex. Cortisol binds to glucocorticoid receptors throughout the brain, including limbic regions. There is a negative feedback loop mechanism (illustrated by the red arrows) involving the modulation of the HPA axis release of cortisol via glucocorticoid receptors in the hypothalamus, pituitary, hippocampus and medical prefrontal cortex. Positive feedback mechanism by the amygdala also modulates HPA activity (Image taken from Allendorfer et al., 2014).

face and emotional processing. Notably, a fronto-subcortical circuit called the cognitive control network (CCN), has been found to be involved in “top-down” regulation of cognitive and behavioural inhibitory processes, and been reported to be particularly sensitive to the effects of cortisol and stress reactivity (Chudasama and Robbins, 2006; Bonelli and Cummings, 2007; Seo et al., 2012; Peters et al., 2016). The CCN includes the IFG, IPL and Thal (in addition to ACC, caudate, globus pallidus and putamen) (Chudasama and Robbins, 2006; Bonelli and Cummings, 2007; Seo et al., 2012). Moreover, left and right activation of the CCN by cortisol has been associated with increased and decreased cortisol reactivity to psychosocial stress, respectively (Sullivan and Gratton, 2002; Wang et al., 2005; Kern et al., 2008; Taylor et al., 2008). These
associations have implied that the CCN may mediate the down-regulation of the stress response over time and facilitate reduction of cortisol levels (Phelps, 2004; Amodio and Frith, 2006; Urry et al., 2006; Veer et al., 2012).

Several studies have investigated the neural correlates of StR in healthy humans. On the one hand, multiple studies have shown that some limbic structures act as primary regulators of the HPA axis stress-response (Pruessner et al., 2010; Hart and Rubia, 2012), and higher cortisol output and endocrine stress responses have been reported to be related to hypo-activation of both fronto-limbic regions (Holsen et al., 2011), and fronto-parietal regions (including the IPL) (Keulers et al., 2015).

In addition, a recent functional MRI study found that acute cortisol reactivity attenuated engagement of fronto-parietal and striatal regions (including the CCN) during processing of EFEs in patients with depression and bipolar affective disorder and that anticipatory cortisol predicted attenuated activation in several regions of the fronto-subcortical circuit (Peters et al., 2016).

Finally, structural neural correlates of SR have been investigated in non-patient populations. For example, a diffusion tensor imaging (DTI) study investigated white matter architecture in young female children, having categorised their StR as low or high (Sheikh et al., 2014). They found significant associations between StR and fractional anisotropy (FA) measures in thalamo-limbic regions of the brain, including left Thal, right ACC and right SFG. These results showed that early cortisol reactivity to stress was associated with WM integrity of various regions of the brain.

In reviewing the above theory and findings in relation to stress reactivity and negative emotional disorders it is relevant to review if there is evidence for SR in psychogenic motor disorders, including PNES. Firstly, a recent study investigated relationships between functional somatic symptoms (FSS), StR, childhood trauma and resilience factors in a sample of students over a six month period using a structural equation modelling analytic method, and reported significant positive relationships between experiences of emotional neglect and abuse in childhood, and both elevated StR and reduced resilience, which in turn predicted occurrence of FSS mediated by chronic stress (Fischer et al, 2014). Although these findings occurred via a survey of students (and so may not be representative of the general population) and relied on self-report
assessments, the study results suggest that StR in FSS may be potentially reduced through measures taken to improve resilience. However, on the other hand, another study found no differences in circulating cortisol levels over the course of 24 hours in hospitalised patients with psychogenic motor disorders (Maurer et al., 2015). However, in this latter study, patients with PNES were not included and no other physiological markers of StR were taken (e.g., heart rate variability, respiratory sinus arrhythmia and self-perceived physiological stress). Another study examined determinants of physiological and perceived StR in children and adolescents and found that individual factors such as gender and temperament, developmental factors such as age and urbaniy, environmental factors such as experience of adversity and family environment, and substance abuse factors such as the use of tobacco and drugs, were all found to influence different aspects of StR and be different between children and adolescents (Evans et al., 2013). Therefore, inconsistencies between studies of SR may relate to differences in sample composition and methodologies of assessing pertinent StR factors. This is an evolving research area.

There has been no study of StR in PNES published to date. Nevertheless, a number of consistencies with the findings from this project and other studies of PNES. Firstly, the CCN includes the IFG, IPL and Thal, which we found to be abnormally activated in our implicit face processing study of PNES. Secondly, activation of CCN structures in the left hemisphere by cortisol has been associated with increased cortisol reactivity to psychosocial stress, which is consistent with both findings of abnormally increased baseline cortisol levels in PNES (Bakvis et al., 2009a) and with our findings of hypo-activity in this region. Thirdly, StR has been associated with changes in thalamo-limbic regions of the brain, including left thalamus, which is quite consistent with the findings from our DTI study of PNES. Therefore, we suggest that differences in structural integrity of thalamo-limbic brain regions and functional hypo-activation of fronto-parieto-subcortical circuits in PNES may reflect a core dysregulation in the HPA-axis feedback loop, and this hypothesis should be investigated in future studies of PNES.

While the specific mechanisms of how StS and StR can affect the development and time-course of psychiatric disorder are not fully elucidated, recent research
implicates limbic-HPA axis hyper-reactivity (Hankin et al., 2015) metacognitive processes such as negative attentional bias and rumination (Farb et al., 2015; Ruscio et al., 2015) and dopaminergic system processes (Hernaus et al., 2015; Morris and Rottenberg, 2015).

7.3 Future research studies that could potentially improve the understanding and treatment of PNES

This project was novel at the time it took place in that in terms of the assessment of participants, all underwent comprehensive (Axis 1 and 2) psychiatric, neuropsychological, psychometric and multimodal neuroimaging assessment. In addition to usual exclusion criteria associated with neuroimaging studies, no participants were taking psychotropic medication and none were included if their tests indicated they were malingering or applying unsatisfactory effort to neuropsychological tasks. Also the neuropsychological and neuroimaging studies were carried out with the same population of participants, which meant that results between studies could be compared with confidence.

It was notable in carrying out pertinent research reviews that, with just one or two exceptions, all previous neuroimaging studies of PNES did not carry out a comprehensive psychiatric assessment on all their participants (both patients and controls), screen for malingering, or control for known potential confounders of neuroimaging results. This point was also highlighted in a recent review of published neuroimaging studies of PNES (Perez et al., 2015). These limitations in methodology would explain at least some of the inconsistencies between study findings. Therefore, it is important that future studies carry out comprehensive psychiatric and neuropsychological assessment of both patients and controls, and design their analysis to account for potential confounders such as age, gender, IQ, and effort.

Secondly, studies should incorporate multimodal assessment including
complementary neuroimaging modalities and neurophysiological assessment particularly relating to indices of stress and functioning of the stress response in patients with PNES. Ideally, being able to identify neurophysiological and neural correlates of brain activity during a PNES event would be very helpful, as studies investigating the neurobiology of PNES have so far, done so when patients are in a relatively non-active phase in comparison to studies of motor CD, where patients were often actively exhibiting the deficit at the time of neuroimaging. However, this would present ethical and practical difficulties, especially with current neuroimaging techniques and methodologies, but future technological developments may make such investigation possible. Nevertheless, the investigation of stress reactivity in PNES would be a very interesting project and relatively straightforward to carry out, and would help to focus on potential stress mechanisms of PNES and how they develop. Thirdly, future fMRI research studies of PNES should further probe networks involved in facial and emotional processing to determine if our findings can be replicated and to examine neural correlates of explicit aspects of these functions that can help to delineate specific pathways to PNES. Also, it would be important that complementary structural neuroimaging methodology further examine gray and white matter of specific regions and circuits implicated in the psychopathology of PNES. Fourthly, study designs, particularly involving functional neuroimaging, should incorporate ways of specifically examining attentional and spatial working memory functioning to delineate if and how exactly these process are abnormal and how this relates to clinical manifestations. Finally, longitudinal studies would be important in examining how neurobiological correlates of PNES develop and change over time and how the condition relates to human experience and environmental factors in this regard.

7.4 Concluding comments

This project firstly highlighted that the prevalence of PNES was almost 20% in a specialist epilepsy monitoring unit in Ireland. Secondly, the neuropsychological and neuropsychiatric study of PNES found that patients with PNES had
abnormal executive functioning, specifically that relating to spatial working memory, that was not explainable by potential confounds such as FSIQ and effort. Thirdly, the voxel-based morphometry and diffusion tensor imaging studies of the same sample of patients and healthy-controls demonstrated that patients with PNES had relative differences brain structure affecting a region incorporating the left middle temporal and left inferior temporal gyri, and suggested the presence of an abnormal maturation process affecting white matter tracts connecting multiple regions of the brain, including SLF, whose functions involve working memory and movement. Finally, the fMRI study of unconscious face-processing found evidence that, firstly, patients with PNES demonstrated impaired face-processing abilities irrespective of whether the faces viewed were of neutral expression or exhibiting primary negative emotions (fear, disgust, sadness), and secondly that neural circuits implicated in socio-emotional processing and movement were functioning abnormally in patients with PNES. The impaired face-processing was not driven or explained by most of the clinical measures utilised in this study, with the exception of SOM-C, a measure from the PAI assessment relating to the level of a person’s focus on symptoms relating to motor or sensory dysfunction. This psychometric measure relating to the patient’s focus on ill-health from PNES deserves further study as a potential neurobiological marker of PNES. Overall this project has both confirmed existing knowledge of psychiatric and psychometric aspects of PNES and significantly extended knowledge of neural correlates of the clinical deficits using complementary neuroimaging modalities. Future studies should aim to determine if these findings are replicated and to carry out longitudinal neuroimaging studies of patients with PNES and in particular, to assess neurophysiological markers relating to stress and associated neural correlates in helping to further understand the process by which PNES occur and any potential modulating factors that can be used to design improved treatments for this vulnerable and often stigmatised group of patients.
REFERENCES


Binzer, M., Stone, J. and Sharpe, M., 2004. Recent onset pseudoseizures—

Black, L.C., Schefft, B.K., Howe, S.R., Szafirski, J.P., Yeh, H.S. and Privitera,
M.D., 2010. The effect of seizures on working memory and executive


definition, etiology, treatment and prognostic issues: a critical review. Seizure,
18(8), pp.543-553.

Bodde, N.M.G., Van der Kruijs, S.J.M., Ijff, D.M., Lazeron, R.H.C., Vonck,
patients with psychogenic non-epileptic seizures. Epilepsy & Behavior, 26(3),
pp.279-289.

Bonelli, R.M. and Cummings, J.L., 2007. Frontal-subcortical circuitry and

Bowman, E.S., 1993. Etiology and clinical course of pseudoseizures:
333-342.

Bowman, E.S. and Markand, O.N., 1996. Psychodynamics and psychiatric

Bowman, E.S., 2001. Psychopathology and outcome in pseudoseizures. In:
Ettinger AB, Kanner AM, editors. Psychiatric issues in epilepsy: a practical
guide to diagnosis and treatment. Philadelphia: Lippincott Williams & Wilkins,


Brown, R., 2006. Different types of “dissociation” have different psychological mechanisms. *Journal of Trauma and Dissociation*, 7, pp.7-28.


365


characteristics of patients with psychogenic nonepileptic seizures. *Epilepsia*, 40(9), pp.1292-1298.


Nana, R., Zhao, T. and Hu, X., 2008. Single-shot multiecho parallel echo-planar imaging (EPI) for diffusion tensor imaging (DTI) with improved signal-to-noise ratio (SNR) and reduced distortion. Magnetic resonance in medicine, 60(6), pp.1512-1517.


Pavlov, J., 1933. Essai d'une interpretation physiologique de l'hysterie.


Robinson, T.E. and Becker, J.B., 1986. Enduring changes in brain and behavior produced by chronic amphetamine administration: a review and evaluation of


Rowe, J.B., Stephan, K.E., Friston, K., Frackowiak, R.S. and Passingham, R.E., 2005. The prefrontal cortex shows context-specific changes in effective connectivity to motor or visual cortex during the selection of action or colour. *Cerebral Cortex, 15*(1), pp.85-95.


Siegel, A. and Sapru, H., 2010. Essential Neuroscience (Point (Lippincott Williams & Wilkins)).


APPENDIX A:
STUDY ETHICS DOCUMENTATION, INFORMATION SHEETS, CONSENT FORMS AND SCANNING SHEETS
Beaumont Hospital
Ethics (Medical Research) Committee

Chairperson: Professor Gerry McElvaney
Convenor: Professor Alice Stanton
Administrator: Gillian Vale

REC reference: 08/47

Dr. Finian O’Brien,
Senior Registrar in Liaison Psychiatry,
Cluain Mhuire Family Service,
Blackrock,
Co. Dublin.

Dear Dr. O’Brien

RE: 08/47 – Prof. K. Murphy – The Neurobiology of Psychogenic Non-Epileptic Seizures

Amendment #1, 19/5/09 – Change to Documentation Requested by TCD Research Ethics Committee

Please find enclosed updated approval documentation for this study. All documents which TCD Research Ethics Committee requested changes to are now listed in this approval.

Please note that the lack of version numbering in these documents will cause problems at a later stage should you wish to submit any further amendments to either TCD Research Ethics Committee or Beaumont Hospital Ethics (Medical Research) Ethics Committee and it advisable to put version numbers on your documents prior to beginning to use these to consent and recruit patients in order to avoid any potential for confusion in the future.

Yours sincerely

Ms. Gillian Vale
Administrator

c.c. Professor Kieran Murphy, Chairperson, Department of Psychiatry, RCSI, Smurfit Building,
Beaumont Hospital
# Ethics (Medical Research) Committee - Beaumont Hospital

**Notification of ERC/IRB Approval**

**Investigator:** Prof. K. Murphy  
**Protocol No.:** 08/47  
**Protocol Title:** The Neurobiology of Psychogenic Non-Epileptic Seizures

**Ethics Committee Meeting date:** 30\textsuperscript{th} May 2008  
**Final Approval Date:** 21\textsuperscript{st} August 2008

**From:** Ethics (Medical Research) Committee - Beaumont Hospital, Beaumont, Dublin 9

<table>
<thead>
<tr>
<th>Document and Date</th>
<th>Documents Reviewed Date Reviewed</th>
<th>Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Application, V2, 8/7/08</td>
<td>21/8/08</td>
<td>Yes</td>
</tr>
<tr>
<td>- signed K. Murphy</td>
<td>21/8/08</td>
<td>Yes</td>
</tr>
<tr>
<td>Patient Information Leaflet, &amp; Consent Form, V2, 8/7/08</td>
<td>21/8/08</td>
<td>Yes</td>
</tr>
<tr>
<td>TCD Requested Consent Form for Patients, No version number</td>
<td>29/5/09*</td>
<td>Yes</td>
</tr>
<tr>
<td>TCD Requested General MRI Data Consent Form, No version number</td>
<td>26/5/09*</td>
<td>Yes</td>
</tr>
<tr>
<td>Control Information Leaflet, &amp; Consent Form V2, 8/7/08</td>
<td>21/8/08</td>
<td>Yes</td>
</tr>
<tr>
<td>TCD Requested Consent Form for Controls No version number</td>
<td>29/5/09*</td>
<td>Yes</td>
</tr>
<tr>
<td>TCD Requested General MRI Data Consent Form For Controls, No version number</td>
<td>26/5/09*</td>
<td>Yes</td>
</tr>
<tr>
<td>Recruitment Poster for Controls: V2, 8/7/08</td>
<td>21/8/08</td>
<td>Yes</td>
</tr>
<tr>
<td>TCD Requested Recruitment Poster for Controls, No version number</td>
<td>26/5/09*</td>
<td>Yes</td>
</tr>
<tr>
<td>GP Letter V2, 8/7/08</td>
<td>21/8/08</td>
<td>Yes</td>
</tr>
<tr>
<td>Protocol Amendment: #1, 19/5/09 (changes to documentation requested by TCD Research Ethics Committee)</td>
<td>29/5/09*</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Proof of Indemnity:
H. Garavan (TCD)
- e-mail, F. O'Brien, 19/1/09 30/1/09 Yes
F. O'Brien (Cluain Mhuire) 7/08/08 Noted
CV, K. Murphy 21/8/08 Noted

Professor Alice Stanton
ERC/IRB – Convenor’s Signature
Approval # 3, dated 29th May 2009*
16th September 2009

Professor Kieran Murphy
Professor of Psychiatry
Education and Research Building
Beaumont Hospital
Dublin 9

Re: The Neurobiology of Psychogenic Non-Epileptic Seizures.

Dear Professor Murphy

Expeditied approval is granted to carry out the above study at the following site:

➢ Cork University Hospital.

The following documents were approved:

➢ Application Form
➢ Participant Information Sheet
➢ Consent Form
➢ GP Letter.

We note that the co-investigators involved in this study in Cork will be:

➢ Dr Eugene Cassidy, Dr Brian Sweeney, Dr Ashling Ryan and Dr Brian McNamara.

Yours sincerely

[Signature]
Dr Michael Hyland
Chairman
Clinical Research Ethics Committee
of the Cork Teaching Hospitals
Dear Hugh,

Following receipt of specified amendments, I am pleased to inform you that your application entitled “The neurobiology of psychogenic non-epileptic seizures” has been approved by the School of Psychology Research Ethics Committee.

Yours sincerely,

Kevin Thomas, PhD
Chair,
School of Psychology Research Ethics Committee
Information Leaflet

Protocol Title:

The Neurobiology of Psychogenic Non-Epileptic Seizures

Principal Investigator’s Name: Kieran Murphy

Principal Investigator’s Title: Professor

Telephone No. of Principal Investigator: 01-8093740

You are being invited to take part in a clinical research study carried out at Beaumont Hospital. Before you decide whether or not you wish to take part, you should read the information provided below carefully and if you wish discuss it with your family, friends or GP. Take time to ask questions – do not feel rushed or under any obligation to make a hasty judgement. You should clearly understand the risks and benefits of participating in this study so that you can make a decision that is right for you – this process is known as Informed Consent.

You are not obliged to take part in this study and failure to participate will have no effect on your future care.

You may change your mind at any time (before the start of the study or even after you have commenced the study) for whatever reason without having to justify your decision and without any negative impact on the care you will receive from the medical staff.

WHY IS THIS STUDY BEING DONE?
We are going to investigate what causes non-epileptic seizures. Non-epileptic seizures are episodes that briefly change a person's behaviour and often look like epileptic seizures. The difference in these two kinds of episodes is often hard to recognize by just watching the event, even by trained medical personnel. But there
is an important difference: epileptic seizures are caused by abnormal electrical changes in the brain and, in particular, in its outer layer, called the cortex. However, psychogenic non-epileptic seizures (PNES) are not caused by electrical disruptions in the brain. Doctors believe that people with PNES may cope with stress differently to those who don’t have this condition and although many patients with PNES report difficulty dealing with stressful experiences, no previous study has closely examined brain structure and functioning of people with this condition. Furthermore, little is known about how to help people with PNES and they often continue to suffer these seizures, with significant adverse effects on their ability to live their lives independently.

We are going to investigate whether people with PNES have differences in their brain structure and whether they show differences when doing tasks that require them to process emotions. If you participate in this study you will be helping to contribute to scientific knowledge of PNES and we hope to use the results to develop better treatments for people with this condition.

WHO IS ORGANISING AND FUNDING THIS STUDY?
Dr. Finian O’Brien and Professor Kieran Murphy are organising this study. All funding has been awarded by Molecular Medicine Ireland, an organisation which encourages clinicians-in-training (in this case, Dr. O’Brien) to undertake research which is likely to lead to future benefits for patients.

HOW WILL IT BE CARRIED OUT?
This study is commencing in July 2008 and will take three years to complete. There will be approximately 30 people with PNES and 30 healthy volunteers recruited to take part. People with PNES will be recruited from medical registers of people who have attended a specialist neurology service. Healthy volunteers will be recruited from orthopaedic outpatient clinics and by advertisement. The study will take place in Beaumont Hospital and at the brain-imaging unit in Trinity College Dublin.

WHAT WILL HAPPEN TO ME IF I AGREE TO TAKE PART?
Firstly, you will be asked to complete some questionnaires and pen and paper tests. Dr. O’Brien will meet with you and go through these tests with you in a relaxed atmosphere at the Smurfit building, Beaumont Hospital. This visit will take approximately 3 hours.
On another day, you will have a brain scan during which you will be asked to carry out simple tasks (like playing a video game). Dr. O’Brien will meet with you beforehand so that you can familiarise yourself with the scanner and the tasks before starting the scan. This will take place at Trinity College Dublin and will take approximately 1 hour.
BENEFITS:
If you agree to participate in this study, you will be helping doctors to understand PNES better. Also, at present there are no proven cures for PNES and we hope that this work will lead to development of effective treatments for PNES. Therefore, by your participation you will be helping doctors to better help people with PNES in the future. You will be reimbursed relevant expenses for travel to and from participation. Also, you will receive a colour picture of your brain scan for helping out. You can also let us know if you want to know the results of the study and we will contact you when these are available so that we can discuss them with you at your next scheduled outpatient appointment.

RISKS:
As this study involves having an MRI brain scan, people who have metal plates, metal pins, pacemakers or other metallic objects in their body cannot participate in this study. If you have any queries about this please ask Dr. O’Brien when you are considering participating in the study.

Having a brain scan involves lying on your back in a confined space and the scanner makes some noises as it takes pictures of your brain. Some people feel claustrophobic and unsettled by this experience, particularly if they are having a brain scan for the first time. Therefore, Dr. O’Brien will meet with you beforehand to show you the scanning room and allow time for you to become comfortable with the scanner and the tasks you will be doing during your brain scan, before the actual scanning starts. Also, you are in direct communication with Dr. O’Brien during the scanning and can stop the scan at any time, if you wish to. If you have a fear of narrow spaces you should discuss this with Dr. O’Brien when you are considering participating in the study.

WILL THERE BE ANY ADDITIONAL COSTS INVOLVED?
You will be reimbursed relevant expenses for travel to and from participation.

YOUR RESPONSIBILITIES AS A PARTICIPANT
You should inform Dr. O’Brien if you are on medications or think you may be pregnant. You have a responsibility to follow instructions to the best of your ability. However, you may withdraw at any time during the study without having to give a reason and should you withdraw this will not affect your future treatment in Beaumont Hospital.

OUR RESPONSIBILITIES TO YOU AS INVESTIGATORS
You have a right to new information as it becomes available during the course of the study which may affect your willingness to continue to participate. For example, if we plan to change the type of pen and paper tests we ask you to complete, we will inform you and you may decide to participate or not.
CONFIDENTIALITY ISSUES
We intend to contact your GP to let them know that you are participating in this study, but you can choose to refuse to have your GP contacted, if you wish. Your medical chart will be examined by Dr. O’Brien (hospital employee) to obtain information necessary to the study - for example, on your age, medical history - to ensure that you are eligible to participate. All information you provide for the study will be kept confidential to best practice recommendations and will be stored for the duration of the study. Paper records you provide for the study will be then shredded and destroyed. The information you provide will also be stored on a computer and this computer may be brought outside the hospital (for example, to the Trinity College Dublin scanning department). However, the information you provide will be encrypted, password-protected and stored without reference to your name or address to protect your identity. Only the researchers involved in this study will have access to this data. The data you provide may be used again in future studies not yet known but you have the option to consent to this or not. This study is approved by the Beaumont Hospital Ethics Committee.

IF YOU REQUIRE FURTHER INFORMATION
If you have any further questions about the study or if you wish to withdraw from the study, you may do so without justifying your decision and your future treatment will not be affected.

For additional information now or any future time please contact:
Dr. Finian O’Brien
Address: Department of Psychiatry, Smurfit Building Beaumont Hospital, Dublin 9.
Phone No: 01-8093740
# MAGNETIC RESONANCE IMAGING (TCIN)

<table>
<thead>
<tr>
<th>Name: ________________________________</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Phone: ______________________________</td>
<td></td>
</tr>
<tr>
<td>Sex: Male [ ] Female [ ]</td>
<td></td>
</tr>
<tr>
<td>Date of Birth: ______________________</td>
<td></td>
</tr>
<tr>
<td>Weight: _______kg</td>
<td></td>
</tr>
</tbody>
</table>

Please provide us with the details of another person (e.g., next-of-kin) should we need to contact you in the future.

<table>
<thead>
<tr>
<th>Name of contact person: ______________________________</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Phone: ______________________________</td>
<td></td>
</tr>
</tbody>
</table>

Please provide us with the details of your GP should we need to contact him/her in the future.

<table>
<thead>
<tr>
<th>Name of GP: ______________________________</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Phone: ______________________________</td>
<td></td>
</tr>
<tr>
<td>Address: ______________________________</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Study: ______________________________

| Time in: ___:___ | Time Out: ___:___ | Investigator: ______________________________ |

![TCIN Logo](https://example.com/logo.png)
Information:

Your MR study

As part of your study we will obtain a limited number of pictures of your brain. Our research studies are designed to improve our knowledge of the brain. They are not designed for diagnostic or clinical purposes.

Minor changes are sometimes found in completely healthy people. You should be aware that because our pictures are taken for a specific research purpose, not all abnormalities that might be detected by other MR scans are necessarily seen. On extremely rare occasions, we might find an abnormality that is significant and which should be investigated further. If we find such a significant abnormality in your brain, we will contact you directly and will likely recommend that you follow up these findings by contacting your own doctor.

Although a significant abnormality is extremely unlikely, you should be aware that if such an abnormality is detected and you are informed, then this knowledge may have consequences for you. Please take the time to consider carefully what it would mean to you if we told you of an abnormality in your brain which might, or might not, affect you later in life. Knowledge of an abnormality may affect your ability to work in certain professions, obtain life or health insurance and other facets of daily living. If you do not want to know, then it is better not to participate.

There are some items that may interfere with the Magnetic Resonance Imaging and some that may be potentially hazardous. To help us to determine your suitability for an MRI scan and to ensure your safety, please complete the following checklist carefully.

Not all people can have an MRI scan because the strong magnetic field may be hazardous to them.

- People with
  - permanent pacemakers
  - prosthetic heart valves
  - implanted cardiac defibrillators
  - certain types of vascular clips

  Cannot have an MRI

Instructions for Patient/Volunteers

1. You are urged to use the earplugs or headphones we supply during your MRI examination since some patients may find the noise levels unacceptable, and the noise levels may affect your hearing.
2. Remove all jewelry (eg, necklaces, pins, rings).
3. Remove all hairpins, bobby pins, barrettes, clips, etc.
4. Remove all dentures, false teeth, and partial dental plates.
5. Remove hearing aides.
6. Remove eyeglasses.
7. Remove your watch, pager, cell phone, credit cards, bankcards, and all other cards with a magnetic strip.
8. Remove body piercing objects.
9. Use gown, if provided, or remove all clothing with metal fasteners, zippers, etc.

**CHECK LIST FOR 3T MAGNETIC RESONANCE IMAGING**

<table>
<thead>
<tr>
<th>Do you have any of the following:</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac Pacemaker:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have you ever had any surgical procedures?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>If yes, what type and where</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The following items may be harmful to you during your MR scan or may interfere with the MR examination. You must provide a “yes” or “no” for every item. Please indicate if you have or have had any of the following:

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
<th>Item</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Any type of electronic, mechanical, or magnetic implant Type:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cardiac pacemaker</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aneurysm clip</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Implanted cardiac defibrillator</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neurostimulator</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Biostimulator Type:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Any type of internal electrodes or wires</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cochlear implant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hearing aid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Implanted drug pump (eg, insulin, Baclofen, chemotherapy, pain medicine)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Halo vest</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Spinal fixation device</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Spinal fusion procedure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Any type of coil, filter, or stent Type:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Any type of metal object (eg, shrapnel, bullet, BB)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Artificial heart valve</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Any type of ear implant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Penile implant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Artificial eye</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Eyelid spring</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Any type of implant held in place by a magnet Type:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Any type of surgical clip or staple</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Any IV access port (eg, Broviac, Port-a-Cath, Hickman, Picc line)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Medication patch (eg, nitroglycerine, nicotine)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Shunt</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Artificial limb or joint What and where:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tissue expander (eg, breast)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Removable dentures, false teeth, or partial plate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diaphragm, IUD, Pessary Type:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Surgical mesh Location:</td>
</tr>
</tbody>
</table>

445
Comments:
CONSENT FORM (PATIENTS)

Protocol Title:
The Neurobiology of Psychogenic Non-Epileptic Seizures

Please tick the appropriate answer.

I confirm that I have read and understood the Patient Information Leaflet dated attached, and that I have had ample opportunity to ask questions all of which have been satisfactorily answered.  Yes  No

I understand that my participation in this study is entirely voluntary and that I may withdraw at any time, without giving reason, and without this decision affecting my future treatment or medical care.  Yes  No

I understand that my records may be viewed by individuals with delegated authority from Beaumont Hospital  Yes  No

I understand that my identity will remain confidential at all times.  Yes  No

I am aware of the potential risks of this research study.  Yes  No

I have been given a copy of the Patient Information Leaflet and this Consent form for my records.  Yes  No

Pregnancy and MRI
There are no known risks of MRI during pregnancy. However as a precautionary safety measure pregnant individuals will not be included in this study.
It is essential that female participants tell us if there is any possibility that they are pregnant.
To participate in the current study women of child-bearing potential must be using one of the following acceptable methods of birth-control:
a. oral or trans-dermal contraceptives
b. barrier (diaphragm or condom) with spermicide
c. intrauterine progesterone contraceptive system
d. levonorgestrel implant
e. medroxyprogesterone acetate contraceptive injection
f. complete abstinence from sexual activity

I confirm that I am using one of the methods of birth control listed above and can confirm that I am not pregnant.

Name _______________________________
Signature ____________________________
Date ________________________________

Future Use of Anonymous Data:
I agree that I will not restrict the use to which the results of this study may be put. I give my approval that unidentifiable data concerning my person may be stored or electronically processed for the purpose of scientific research and may be used in related or other studies in the future. (This would be subject to approval by an independent body, which safeguards the welfare and rights of people in biomedical research studies - the Trinity College Dublin Research Ethics Committee.)

Yes ☐ No ☐

Patient ________________ ___________________
Signature and dated Name in block capitals

To be completed by the Principal Investigator or his nominee.
I, the undersigned, have taken the time to fully explain to the above patient the nature and purpose of this study in a manner that he/she could understand. I have explained the risks
involved, the experimental nature of the treatment, as well as the possible benefits and have invited him/her to ask questions on any aspect of the study that concerned them.

<table>
<thead>
<tr>
<th>Signature:</th>
<th>Name in Block Capitals:</th>
<th>Qualification:</th>
<th>Date:</th>
</tr>
</thead>
</table>

GENERAL MRI DATA CONSENT FORM

Trinity College Institute of Neuroscience, (TCIN) is performing research, utilising an MRI scanner at Trinity College, Dublin 2. These research scans, although not full clinical scans, will be read by a radiologist.

In the unlikely event of an irregularity being found, the radiologist, [Dr William Torreggiani of The Adelaide and Meath Hospital Incorporating the National Children's Hospital (AMNCH), Tallaght] will inform the participants GP, that a proper clinical scan may be required to determine whether or not an irregularity is of clinical significance.

To enable us to perform the research scans the participant agrees to give consent/permission for:
(i) TCIN to conduct the MRI scan and store MRI scan-data of participant;
(ii) TCIN or Principal Investigator, (PI) to contact participants GP;
(iii) TCIN radiographer to send MRI scan-data to radiologist acting for TCIN;
(iv) Radiologist to store data in a hospital system with same care as other patient data ensuring participants confidentiality;
(v) Radiologist/ Clinician (acting for TCIN) to contact participants GP;
(vi) TCIN to store data on the study for a period of at least 5 years or as specified in the specific consent form.

A dated standard letter signed by the appropriate Principal Investigator will be sent to all participants GP’s, it is the responsibility of the Principal Investigator to ensure that this is sent at
least two days before scanning to allow for postal delays. The principal investigator is responsible for their project at all times.

The TCIN designated radiologist will be sent data in a form that allows identification so that if a response is required he can act quickly (a copy of this is also held at TCIN). This will be stored in the hospital system with the same rigour and attention to confidentiality as all other medical data, as per the rules of that institution; a copy of this data will also be stored at TCIN. The raw scan data will be stored at TCIN in anonymous form for research purposes as agreed on the consent form of the specific research project.

I agree to the above points and understand that my data will be treated carefully at TCIN and in the hospital system.

Participant Name and Address___________________________________________
___________________________________________________________________
___________________________________________________________________
Signed by Participant:___________________________

Participants GP Name and Address
___________________________________________________________________
___________________________________________________________________

Date:___________________________

3 copies to be made: 1 for patient, 1 for PI and 1 for hospital records.
CONSENT FORM (CONTROLS)

Protocol Title:

The Neurobiology of Psychogenic Non-Epileptic Seizures

Please tick the appropriate answer.

I confirm that I have read and understood the Control Information Leaflet dated ____________ attached, and that I have had ample opportunity to ask questions all of which have been satisfactorily answered.

[ ] Yes  [ ] No

I understand that my participation in this study is entirely voluntary and that I may withdraw at any time, without giving reason, and without this decision affecting my future treatment or medical care.

[ ] Yes  [ ] No

I understand that my records may be viewed by individuals with delegated authority from Beaumont Hospital.

[ ] Yes  [ ] No

I understand that my identity will remain confidential at all times.

[ ] Yes  [ ] No

I am aware of the potential risks of this research study.

[ ] Yes  [ ] No

I have been given a copy of the Control Information Leaflet and this Consent form for my records.

[ ] Yes  [ ] No

Pregnancy and MRI

There are no known risks of MRI during pregnancy. However as a precautionary safety measure pregnant individuals will not be included in this study.

It is essential that female participants tell us if there is any possibility that they are pregnant.

To participate in the current study women of child-bearing potential must be using one of the following acceptable methods of birth-control:

a. oral or trans-dermal contraceptives
b. barrier (diaphragm or condom) with spermicide
c. intrauterine progesterone contraceptive system
d. levonorgestrel implant

e. medroxyprogesterone acetate contraceptive injection
f. complete abstinence from sexual activity

I confirm that I am using one of the methods of birth control listed above and can confirm that I am not pregnant.

Name _______________________________

Signature ____________________________

Date ________________________________

Future Use of Anonymous Data:
I agree that I will not restrict the use to which the results of this study may be put. I give my approval that unidentifiable data concerning my person may be stored or electronically processed for the purpose of scientific research and may be used in related or other studies in the future. (This would be subject to approval by an independent body, which safeguards the welfare and rights of people in biomedical research studies - the Trinity College Dublin Research Ethics Committee.)

Yes  No

Participant ___________________________

Signature and dated  Name in block capitals

To be completed by the Principal Investigator or his nominee.
I, the undersigned, have taken the time to fully explain to the above patient the nature and purpose of this study in a manner that he/she could understand. I have explained the risks-involved, the experimental nature of the treatment, as well as the possible benefits and have invited him/her to ask questions on any aspect of the study that concerned them.
GENERAL MRI DATA CONSENT FORM

Trinity College Institute of Neuroscience, (TCIN) is performing research, utilising an MRI scanner at Trinity College, Dublin 2. These research scans, although not full clinical scans, will be read by a radiologist.

In the unlikely event of an irregularity being found, the radiologist, [Dr William Torreggiani of The Adelaide and Meath Hospital Incorporating the National Children's Hospital (AMNCH), Tallaght] will inform the participants GP, that a proper clinical scan may be required to determine whether or not an irregularity is of clinical significance.

To enable us to perform the research scans the participant agrees to give consent/permission for:
(i) TCIN to conduct the MRI scan and store MRI scan-data of participant;
(ii) TCIN or Principal Investigator, (PI) to contact participants GP;
(iii) TCIN radiographer to send MRI scan-data to radiologist acting for TCIN;
(iv) Radiologist to store data in a hospital system with same care as other patient data ensuring participants confidentiality;
(v) Radiologist/ Clinician (acting for TCIN) to contact participants GP;
(vi) TCIN to store data on the study for a period of at least 5 years or as specified in the specific consent form.

A dated standard letter signed by the appropriate Principal Investigator will be sent to all participants GP’s, it is the responsibility of the Principal Investigator to ensure that this is sent at least two days before scanning to allow for postal delays. The principal investigator is responsible for their project at all times.
The TCIN designated radiologist will be sent data in a form that allows identification so that if a response is required he can act quickly (a copy of this is also held at TCIN). This will be stored in the hospital system with the same rigour and attention to confidentiality as all other medical data, as per the rules of that institution; a copy of this data will also be stored at TCIN. The raw scan data will be stored at TCIN in anonymous form for research purposes as agreed on the consent form of the specific research project.

I agree to the above points and understand that my data will be treated carefully at TCIN and in the hospital system.

Participant Name and Address

___________________________________________________________________

___________________________________________________________________

Signed by Participant: ______________________________

Participants GP Name and Address

___________________________________________________________________

___________________________________________________________________

Date: ______________________________
Study name: PNES
Scan ID: ______________________

Subject

Initials: ______________________
Age: ______________________
Gender: ______________________
Handedness: ______________________

Experiment:

Investigator(s): Dr. Finian O’Brien
Prof. Kieran Murphy
Prof. Hugh Garavan

Scan Operator: Sojo

This subject was run on version:
Run Comments:

Anatomical:

Type: MPRAGE FOV (mm): 230x230
Plane: Transverse Matrix: 256x256
No. Slices: 180 Thickness (mm): 0.9 Duration: 5min 44sec Voxel Size: 0.9X 0.9 X 0.9

Functional:

No. Slices: 39 Thickness (mm): 3.5 Duration:
No. Volumes: number of TRs gap (ms): 0.35 Plane: Transverse Matrix: 64x64
FOV (mm): 224x224 TR (ms): 2000 TE (ms): 30 Voxel Size: 3.5 X 3.5 X 3.5

DTI:

No. Slices: 65 No. Directions: 15 (medium) Duration: B Factor 800 Bzero
FOV (mm): 224 X 224 Voxel Size (mm): 2 X 2 X 2

<table>
<thead>
<tr>
<th>Series</th>
<th>Time</th>
<th>Seq. Name</th>
<th>Subject No.</th>
<th>Session No.</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>SmartBrain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ref_SHC_8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2W_TSE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2W_FLAIR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1W_SE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1W_IR1150</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>fMRI # FEAR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>fMRI # DISGUST</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>fMRI # SADNESS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>fMRI # XY RUN 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>fMRI # XY RUN 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DTSSh 1505E</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
PARTICIPANT CHECKLIST FOR PNES STUDY

Name: ________________________________

<table>
<thead>
<tr>
<th>Patient</th>
<th>Control</th>
</tr>
</thead>
</table>

**Questionnaires**
- Beck Depression Inventory
- Beck Anxiety Inventory
- Coping Inventory for Stressful Situations
- CISS: SSC
- Dissociation Experiences Scale II
- Toronto Assessment Scale for Alexithymia
- TAS-20
- Life Events Checklist
- General Health Questionnaire
- Edinburgh Handedness Inventory
- Personality: Personality Assessment Inventory (PAS)

**Assessments**
- Pre-morbid (estimated intellectual) functioning WTAR
- Level of Effort: Medical Symptom Validity Test (Green's MSVT)
  - Intelligence quotient (IQ): WASI
- Neuropsychological Testing: CANTAB Neuropsychological Battery
- SCID 1 & 2

**Scanning**
- Letter to GP re their involvement in the study sent in advance
- Consent Form for Participation/MRI scanning
- MRI Checklist
APPENDIX B:

SUPPLEMENTARY DATA FOR CHAPTER 3

RESULTS
Figure C1  Comparison of brain activations of patients with PNES and healthy controls during processing of faces showing fear.
Figure C2  Comparison of brain activations of patients with PNES and healthy controls during processing of faces showing disgust.
Figure C3  Comparison of brain activations of patients with PNES and healthy controls during processing of faces showing sadness.
Figure C4 The PNES group-specific combination maps for the “Neutral_v_Null-Hypothesis” test across all three emotions (Fear, Disgust, Sadness).

Legend: Orange = Fear; Cyan = Disgust; Green = Sadness; Blue = Overlap between Fear and Disgust; Violet = Overlap between Fear and Sadness; Red = Overlap between Disgust and Sadness; Yellow = Overlap between all emotions.
Figure C5  The healthy-control group-specific combination maps for the “Neutral_v_Null-Hypothesis” test across all three emotions (Fear, Disgust, Sadness).

Legend: Orange = Fear; Cyan = Disgust; Green = Sadness; Blue = Overlap between Fear and Disgust; Violet = Overlap between Fear and Sadness; Red = Overlap between Disgust and Sadness; Yellow = Overlap between all emotions.
Figure C6  Illustration of the overlap between face-processing for neutral vs the null hypothesis consistent across all three emotional stimuli and combined across PNES and healthy-control groups.
Figure C7  First principal component fMRI response to EFEs showing fear.
Figure C8  First principal component fMRI response to EFEs showing disgust.
Figure C9  First principal component fMRI response to EFEs showing sadness.
APPENDIX C:

PUBLICATIONS FROM THE THESIS TO-DATE
Psychiatric and neuropsychological profiles of people with psychogenic nonepileptic seizures

Finian M. O'Brien a,h,k,1, Gillian M. Fortune c,d,2, Patrick Dicker c, Erik O’Hanlon a, Eugene Cassidy e, f, Norman Delanty h,i, Hugh Garavan j,k, Kieran C. Murphy a,l

a Department of Psychiatry, Royal College of Surgeons in Ireland, Dublin 2, Ireland
b Department of Psychiatry, Cavan Monaghan Mental Health Service, Cavan General Hospital, Cavan, Ireland
c Department of Psychology, Beaumont Hospital, Dublin 9, Ireland
d Department of Psychology, Our Lady’s Children’s Hospital, Crumlin, Dublin 12, Ireland
e Department of Epidemiology & Public Health Medicine, Royal College of Surgeons in Ireland, Dublin 2, Ireland
f Cork University Hospital, Cork, Ireland
g Department of Psychiatry, College of Medicine and Health, University College Cork, Ireland
h Department of Molecular and Cellular Therapeutics, Royal College of Surgeons in Ireland, Dublin 2, Ireland
i Department of Neurology, Beaumont Hospital, Dublin 9, Ireland
j Trinity College Dublin, Dublin 2, Ireland
k University of Vermont, VT, USA
l Department of Psychiatry, Education and Research Centre, Beaumont Hospital, Dublin 9, Ireland

Abstract

Objective: This study examined the psychiatric and neuropsychological profiles of people with psychogenic nonepileptic seizures (PNES).

Methods: Twenty people who had been diagnosed with psychogenic nonepileptic seizures (PNES), but not epilepsy, were recruited into this study. A healthy control group was also recruited and was matched for age and gender. All participants underwent structured psychiatric assessment and psychometric assessment. Neuropsychological assessment was carried out using the Cambridge Neuropsychological Test Battery (CANTAB) after participants passed the Medical Symptom Validity Test (MSVT) of effort.

Results: One patient failed the MSVT and was excluded from the analysis. Therefore, data from 19 people with PNES and their matched healthy controls were analyzed. Compared with controls, people with PNES had significantly higher levels of depressive symptoms, anxiety symptoms, dissociative experiences, and alexithymic traits. In addition, people with PNES had impairments in spatial working memory and attention when compared with healthy controls.

Conclusion: To our knowledge, this is the first study to report that, compared with controls, people with PNES have abnormal cognitive functioning after controlling for effects of effort and FSIQ. People with PNES also have high levels of anxiety, depressive, and dissociative symptoms. In addition, they appear to particularly focus on health problems and show evidence of chronic emotional dysregulation. Further studies are required to replicate our results and to help clarify the pathogenic mechanisms underlying PNES.

© 2014 Elsevier Inc. All rights reserved.
intrapsychic distress is converted into physical neurological symptoms [2]. There is consistent evidence that, compared with people with epilepsy, those with PNES have higher levels of anxiety, depressive, somatisation, and conversion symptoms on personality assessment and a relatively high frequency of personality disorders [4]. In addition, we and others have reported high rates of alexithymia, a personality trait characterized by deficits in emotional recognition and processing, in people with PNES [5,6]. However, in the absence of any other clinical investigation to confirm the diagnosis of PNES, VEEG remains the gold standard to discriminate PNES from epilepsy.

It has been proposed that people manifest PNES as a result of an as-yet-unknown psychophysiological process that occurs in response to stress [6]. The manifestation of PNES has been associated with a range of interacting psychosocial stressors [1], and studies have found that, compared with healthy control subjects, people with PNES have poorer memory performance under conditions of social distraction [7], suggesting that they have an abnormally increased stress response.

People with PNES may also have differences in neurocognitive functioning [4]. Some of the earliest studies compared performance on neuropsychological testing between groups of people with PNES, epilepsy, and mixed PNES and epilepsy. However, results from those studies were inconsistent. For example, people with PNES were reported to perform better [8], worse, or no different [9,10] on a range of tests compared to people with epilepsy. Subsequent studies suggested that neuropsychological deficits reported in PNES were indicative of factors such as emotional disturbance, personality disturbance, and suboptimal motivation [11]. Since then, suboptimal effort during neuropsychological testing, in particular, has been highlighted as a frequent finding in people with PNES compared with patients with epilepsy and associated with poor neuropsychological performance [12]. Therefore, it is possible that in those early studies, variable levels of effort between participants contributed to inconsistent neuropsychological findings.

Several studies have evaluated indices of suboptimal performance of patients with PNES on neuropsychological testing. Bakvis and colleagues used the Amsterdam Short-Term Memory Test (ASTMT) to examine effort and compared patients with PNES and a healthy control group on performance of a specific working memory test under baseline and stressful conditions [7]. Although the authors used one index of symptomatology (SCL-90-R) and one neuropsychological test, the intelligence quotients of participants were not controlled for with formal assessment. Locke and colleagues examined the relationship of composite indicators of neuropsychopathy, psychopathology, and effort to neuropsychological results in patients with epilepsy and PNES and found that patients with PNES had relatively higher control stress responses and impaired cognitive integrative functioning [13]. They recorded participants’ scores on the Test of Memory Malingering (TOMM) but did not directly compare groups on this measure. The sample included patients with neurological abnormality, but patients were not formally psychiatrically assessed, and affective symptoms were not measured. A notable finding was a significant relationship between effort and scores on all cognitive domains apart from executive functioning. In addition, neuropathology was related to memory functioning in both groups. A further cognitive domain apart from executive functioning. In addition, neurological results in patients with epilepsy and PNES and found that patients with PNES were impaired. Therefore, it is possible that in those early studies, variable levels of effort between participants contributed to inconsistent neuropsychological findings.

In summary, these findings suggest that people with PNES have abnormalities of neurocognitive and emotional processing. However, there is convincing evidence that neuropsychological performance in PNES is affected by variables such as neuropsychopathy, psychopathology, stress, and performance effort. While Strutt and colleagues reported impaired neuropsychological functioning while controlling for effort in women with PNES only, the generalizability of these results is unclear [12]. Moreover, the results of prior studies have to be interpreted cautiously because of differences in sampling and methods of psychiatric, psychometric, and neuropsychological test assessments and analyses. Therefore, we used comprehensive medical, psychiatric, psychometric, and neuropsychological assessments of patients with PNES and employed a test of effort to, firstly, examine neuropsychological functioning and, secondly, to determine if findings could be used to help identify patients with PNES in the clinical setting. We hypothesized that, compared with age- and gender-matched controls, people with PNES (1) have elevated rates of psychopathology including increased rates of dissociation and emotional dysregulation and (2) have significant differences in attention and cognitive processing.

2. Methods

2.1. Settings for study

This multisite study was conducted at the Royal College of Surgeons in Ireland (RCSI) and Trinity College Dublin (TCD) academic centers and at Beaumont Hospital (BH) and Cork University Hospital (CUH) clinical centers.

2.2. Sample

Patients diagnosed with PNES without comorbid epilepsy in the three years prior to and during the period of this study were identified from case registers and invited by letter to participate in this research project. All participants had a comprehensive neurological examination comprising physical assessment, structural neuroimaging, and VEEG monitoring. Moreover, all participants met the gold standard for “diagnosis with high confidence” of PNES according to a recent consensus guideline, where the diagnosis is made on the basis of both patient history and a typical seizure-like event is observed, simultaneously co-registered with EEG [14]. The study was approved by each center’s research ethics committee, and all participants provided written informed consent for involvement in the study. Patients were included if all of the following criteria were met: if they had been diagnosed with psychogenic nonepileptic seizures after capture of a typical seizure-like event on VEEG monitoring; if they had experienced multiple seizure-like events; and if neurological and structural MRI examinations excluded demonstrable neurological abnormality.

Patients diagnosed with PNES while under the age of 18 years were excluded. Other exclusion criteria were a history of comorbid neurological or endocrine disorder, intellectual disability, difficulties in reading or writing, and major psychiatric illness including psychotic disorder or substance abuse. No subject had been taking anticonvulsant medication within three months of participation. Clinical data were gathered from participants’ self-report and from both hospital and primary physician medical records. Of forty patients identified from case registers as having PNES, twenty met the criteria for inclusion in the study and agreed to participate.

Control participants were recruited on-site and through webmail advertisement at BH, TCD, and RCSI and by inviting those who previously participated in research projects (research registers) at the relevant academic centers. Control participants were included if they were physically healthy and did not meet any exclusion criteria. They were also matched for gender and age with the group with PNES.

2.3. Clinical interview

All participants underwent a structured clinical interview for DSM-IV for both axis I and II disorders (SCID-I and SCID-II). We administered all six sections of the SCID-I and assessed for all ten of the 10 DSM-IV personality disorders using the SCID-II. Our assessment also gathered information on medical and psychiatric histories and basic demographic information including age, gender, race, and number of years spent in education. Additional clinical data in those with PNES, such as age at...
onset, age at diagnosis, frequency of seizures, prescribed psychotropic medication, and whether previously treated with cognitive behavioral therapy, were also gathered.

2.4. Self-report questionnaires

The following self-report questionnaires were completed by all participants.

2.4.1. Beck Depression Inventory (BDI-II)
This is a 21-item self-report scale. It measures the person’s experience of depressive symptoms within the previous two weeks and reliably discriminates patients with clinical depression from patients without clinical depression [15].

2.4.2. Beck Anxiety Inventory (BAI)
The BAI is a 21-item self-report scale. It measures the person’s experience of anxiety symptoms within the previous month and reliably discriminates people with anxiety disorders from people without anxiety disorders [16].

2.4.3. Dissociative Experiences Scale II (DES II)
The DES II comprises 28 questions and measures dissociative symptoms [17].

2.4.4. Toronto Alexithymia Scale (TAS-20)
This instrument measures deficiency in understanding, processing, or describing emotions [18].

2.4.5. The Coping Inventory for Stressful Situations (CISS)
The CISS is a 48-item self-report measure that is used to assess the preferred coping style of the individual and the relationship between their coping style and their personality [19].

2.4.6. Life Events Checklist
The LEC is a 17-item, self-report measure that screens for potentially traumatic events in a respondent’s lifetime [20].

2.4.7. Personality Assessment Inventory (PAI)
The PAI is an objective inventory of adult personality that assesses psychopathological syndromes and provides information relevant for clinical diagnosis and screening for psychopathology. It includes validity scales that measure the respondent’s approach to the test, including screening for exaggerated or false responses and defensiveness. Profiles can be compared with both healthy and clinical populations [21].

2.4.8. General Health Questionnaire (GHQ)
The GHQ is a 28-item instrument developed to detect those likely to have or be at risk of developing psychiatric disorders. It screens for problems such as depression, anxiety, somatic symptoms, and social withdrawal [22].

2.4.9. Edinburgh Handedness Inventory (EHI)
The EHI is a measurement scale used to assess the dominance of a person’s right or left hand in their everyday activities and can be completed as self-report or by observer assessment [23].

2.5. Neuropsychological evaluation

All participants completed the Wechsler Abbreviated Scale of Intelligence (WASI) to ascertain a full-scale intelligence quotient (FSIQ) and a Wechsler Test of Adult Reading (WTAR) to estimate an individual’s level of intellectual functioning before the onset of illness [24,25]. In addition, all participants completed the Medical Symptom Validity Test (MSVT) to examine effort applied to assessment tasks [26]. The MSVT has demonstrated high sensitivity and specificity in differentiating good effort from simulated memory impairment in previous studies of clinical populations, where a potential incentive to perform poorly exists [27]. Only participants who passed the MSVT had their data included in the analyses.

2.5.1. The Cambridge Neuropsychological Test Automated Battery (CANTAB)
The CANTAB is a computer-administered and visually presented (nonverbal) set of neuropsychological tests containing 22 neuropsychological tests in five cognitive domains: attention, visual memory, semantic/verbal memory, decision-making and response control, and executive function [28]. A more detailed technical description of the tests may be found on the Cambridge Cognition’s website: http://www.cantab.com.

Each participant completed a CANTAB battery of neuropsychological tests to examine attention and frontostriatal function (Intradimensional/Extradimensional Shift Task), sustained attention to compound stimuli (Rapid Visual Processing Task), planning efficiency and memory (Stockings of Cambridge Task), and executive functioning and memory (Spatial Working Memory Task).

Each participant made between one and three visits to the research center over the course of the study because of the length of time required to complete all assessments. The WTAR, WASI, and MSVT assessments always occurred on the same day and immediately before the participant underwent the CANTAB neuropsychological battery. Each participant spent a total of between 3 h and 4 h participating in the assessment process. One researcher (FOB) carried out all assessments. The researcher was trained by a senior clinical neuropsychologist (GF) in neuropsychological test administration and interpretation, and interrater reliability was >.9.

2.6. Statistical analysis

The demographic and psychometric data were analyzed using a logistical regression analysis, with PNES status as the binary outcome variable. Working memory items, SOC and RVP were included as individual predictors and also in combination (multiple logistic regression). It was noted that there was a significant difference between the patient group and the control group in full-scale intelligence quotient (FSIQ). Therefore, the neuropsychological test results were analyzed using binary logistical regression, covarying for FSIQ. A p-value of <.05 was considered statistically significant. Data in this study were analyzed using the Statistical Package for the Social Sciences version 20 (SPSS Inc., Chicago, IL).

3. Results

3.1. Clinical data

One patient failed the effort task so that the data generated by this patient and their matched control participant were excluded from further analysis in this study. Data for 19 patients with PNES and their matched controls were included in the final data analyses. There were no significant between-groups differences in age and gender.

This study had 80% statistical power for a sample size of 38 to detect a difference between groups, approximately equaling the standard deviation of the responses (in depression, anxiety, or dissociation scales). Demographic data are presented in Table 1. The WTAR-predicted IQ and actual FSIQ (WASI) were analyzed to determine if there were significant intragroup and between-groups differences in the scores. Predicted FSIQ (WTAR) and current FSIQ scores significantly differed between groups. The correlation between WTAR standard score and FSIQ predicted score was very high (>.09). This indicated very high agreement between the two scores overall. However, there was a statistically significant difference (predicted standard score) between the groups: the predicted score was 4.7 points less than the predicted score...
standard score for controls; in contrast, the predicted score exceeded the standard score by 4.3 points in the cases (p = 0.001).

No control participant included in the study analysis was found to have a personality disorder.

All persons with PNES had a diagnosis of somatotomaf (conversion) disorder, with a mean (standard deviation) duration of PNES symptoms to a diagnosis of 3.8 (2.9) years and years since the diagnosis to inclusion in the study of a further 2.6 (2.0) years. Sixteen out of the 19 (84.2%) patients had experienced at least one PNES event within the three months prior to testing, one had experienced an event within the previous 9 months, and the remaining two patients had experienced their last event between one year and four years previously. The average frequency of PNES events experienced in the patient group as a whole was three per week at the time of study.

Nine patients (42% of the group with PNES) had no other axis I or II psychiatric diagnosis apart from conversion disorder. Of the remaining 10 patients, two (10.5% of the group with PNES) had one or more personality disorders. Of those patients meeting criteria for personality disorder, five had one personality disorder, and three had more than one. Emotionally unstable (borderline) personality disorder (BPD) was identified in, and three had more than one. Emotionally unstable (borderline) personality disorder (BPD), which met criteria for personality disorder, and those three personality disorders were each comorbid with either BPD or OCPD.

Seven (36.8%) of the group with PNES had received a full course of cognitive behavior therapy for treatment of PNES after diagnosis but had continued to have events.

3.2. Results of psychometric assessment

There were no significant between-groups differences in self-reported scores on the CISS, LEC, and GHQ. However, there were significant differences between the group with PNES and the control group on measures of anxiety, dissociative, and depressive symptoms and alexithymia, where on each measure, the group with PNES had higher scores indicating greater pathology (Table 2).

The group with PNES scored significantly higher than the matched healthy controls on PAI indices reflecting concern about health and physical functioning (all the SOM scales) and clinical features common to the syndrome of depression (DEP scales) including vegetative signs (DEP-P) and suicidal risk (SPI). The group with PNES scored significantly lower compared with the control group on indices of alcohol use (ALC) and features relevant to personality constructs of antisocial and stimulus-seeking behavior (ANT-A and ANT-S) (Table 2). The other PAI subscales were not found to differ significantly between groups or to have scores indicative of clinical significance, including indices of profile distortion.

3.3. Results of CANTAB neuropsychological battery assessment

Neuropsychological battery data were firstly assessed using multiple logistic regression, adjusting for FSIQ. There were significant differences between groups on tests of spatial working memory (SWM task), planning and organization (SOP task), and attention (RVP task) (Table 3). There were no significant differences between the patient group and the control group for the Big Circle/Little Circle Task and Intraextra Dimensional Set Shift Task.

In addition, we carried out a bivariate Spearman's rho nonparametric correlation analysis within the group with PNES that included those variables found to predict group status to test the hypotheses that, firstly, emotional dysregulation is associated with performance on neuropsychological testing and that, secondly, indicators of emotional dysregulation are associated with severity of PNES. The main results of this analysis are reported in Table 4. Alexithymia scores were found to positively correlate with SWM between errors, but otherwise there was little evidence to support the first hypothesis. We found positive correlations between frequency of PNES events and those variables relating to dissociative experiences and preoccupation with health and physical functioning (in particular).

4. Discussion

To our knowledge, this is the first study to report that, compared with healthy controls, people with PNES have significant differences in personality, in emotional health, and in neuropsychological functioning after controlling for effects of effort and FSIQ. Specifically, we found that patients performed comparatively poorly on tests of spatial working memory and attention and had high levels of anxiety, depressive, and dissociative symptoms. In addition, they appeared to particularly focus on health problems and showed evidence of chronic emotional dysregulation.

In our sample, we found that 42% of people with PNES had no other axis I or II mental disorders apart from conversion disorder, and the remaining 53% had either a comorbid axis I or II psychiatric disorder. Our finding that just two people with PNES had an active comorbid axis I disorder, apart from conversion disorder, is rather surprising, given that several studies have reported a high frequency of comorbid anxiety and affective disorders with PNES [29]. These findings should be interpreted with caution, given that there is a risk of false negative findings from evaluation of a relatively small sample size. Nevertheless, there was significant evidence of ongoing clinical dysfunction in the
The results of nonparametric correlation analysis within the group with PNES are presented in Table 3. The table shows the comparison of PNES and control groups on various measures, including spatial working memory (SWM), rapid visual information processing (RVP), and several personality scales. The values provided are the mean ± SD, and the p-values indicate the statistical significance of the differences.

We found no between-groups difference in reported coping style, the numbers of traumatic life events reported, or self-reported quality-of-life indices. These findings are inconsistent with some studies of PNES [12,22]. However, people with medically unexplained symptoms, including those with PNES, have been found to be less likely to perceive psychological factors as relevant to their symptoms and to be more likely to deny that they have suffered from life stress and to have automatic avoidance tendencies [32,33]. In addition, it has been proposed that alexithymia functions within the individual as a mechanism for avoiding distressing affect [34], and we found elevated alexithymia scores in our group with PNES, so we can speculate that both these factors may at least partially explain these nonsignificant findings.

Our study, neuropsychological assessment occurred directly after participants passed a test of effort and our analysis of neuropsychological performance data controlled for the effects of FSIQ. Our results showed, firstly, that people with PNES performed abnormally on tests of spatial working memory (SWM) and that those deficits were more

---

Table 3: Results of analysis covarying for FSIQ (means).a

<table>
<thead>
<tr>
<th>Variable</th>
<th>PNES (N = 19) mean ± SD</th>
<th>Controls (N = 19) mean ± SD</th>
<th>p-Value</th>
<th>p-Value (adjusted for FSIQ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spatial working memory (SWM)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SWM between errors</td>
<td>23.1 ± 16.9</td>
<td>18.8 ± 17.7</td>
<td>0.453</td>
<td>0.025</td>
</tr>
<tr>
<td>SWM between errors (6 boxes)</td>
<td>6.2 ± 6.0</td>
<td>4.9 ± 6.6</td>
<td>0.542</td>
<td>0.042</td>
</tr>
<tr>
<td>SWM between errors (8 boxes)</td>
<td>16.3 ± 12.3</td>
<td>13.5 ± 11.9</td>
<td>0.482</td>
<td>0.036</td>
</tr>
<tr>
<td>SWM total errors</td>
<td>216 ± 173</td>
<td>19.9 ± 17.3</td>
<td>0.510</td>
<td>0.025</td>
</tr>
<tr>
<td>SWM total errors (6 boxes)</td>
<td>6.3 ± 6.1</td>
<td>5.3 ± 6.6</td>
<td>0.632</td>
<td>0.044</td>
</tr>
<tr>
<td>SWM total errors (8 boxes)</td>
<td>16.7 ± 12.7</td>
<td>14.2 ± 11.6</td>
<td>0.525</td>
<td>0.035</td>
</tr>
<tr>
<td>SWM strategy</td>
<td>30.2 ± 7.0</td>
<td>28.3 ± 7.1</td>
<td>0.423</td>
<td>0.048</td>
</tr>
<tr>
<td>Stockings of Cambridge (SOC)</td>
<td>4854 ± 2651</td>
<td>6264 ± 4945</td>
<td>0.281</td>
<td>0.031</td>
</tr>
<tr>
<td>Rapid visual information processing (RVP)</td>
<td>405.1 ± 55.8</td>
<td>407.5 ± 70.9</td>
<td>0.911</td>
<td>0.040</td>
</tr>
</tbody>
</table>

a Logistic regression analysis.
consistently apparent on tests of higher task complexity; secondly, that the group with PNES also executed poorer strategy on SWM tasks, a finding also suggestive of cognitive dysfunction; and, thirdly, that the group with PNES took less time to initiate action on some, but not all, tasks involving planning and attention.

Spatial working memory is a memory system of limited capacity that allows the temporary storage and processing of information, and research indicates that it is impaired by concurrent performance on tasks that utilize executive resources [38]. The CANTAB battery tasks we employed in this study particularly examine components of cognition known to be associated with frontal and medial temporal brain regions [39] and have previously demonstrated a high degree of sensitivity in detecting brain dysfunction in regions including the amygdalo-hippocampal complex [40], thereby permitting inferences to be made about the underlying neural circuitry associated with performance of these tasks. Therefore, our neuropsychological results would appear to indicate that people with PNES have abnormal cognitive functioning that includes neural networks involved in attention and memory. These results appear inconsistent with those of a recent study that found no neuropsychological abnormality in PNES once effort only was controlled for [12]. However, that study only included females, participants did not have structured psychiatric and personality evaluations, and data relating to psychotherapeutic intervention or response were not included in their analyses. In contrast, our sample was age-, handedness- and gender-matched; participants received comprehensive psychiatric and neuropsychological evaluations; and our sample included patients who continued to experience PNES despite psychotherapeutic intervention. In addition, although the study by Strutt et al. did not find a statistically significant difference on neuropsychological performance between those with epilepsy and those with PNES, they did report a consistent relative weakness in attention and memory in the group with PNES. Therefore, it is likely that differences in sample characteristics and data analyses explain the disparate findings.

In this study, we compared and contrasted estimates of premorbid intelligence with current intelligence quotients to examine whether there was evidence of intellectual decline over time, which is known to occur in conditions involving neurological insult or disease. We found significant statistical changes within groups. However, we considered the observed changes of between 4 IQ points and 5 IQ points to be negligible in terms of actual clinical significance [41]. Therefore, our findings suggest that people with PNES do not suffer cognitive declines that are otherwise associated with neurological illness or brain injury, including epilepsy [42].

Finally, we would like to comment on our use of the MSVT. Symptom validity tests, such as the MSVT, are commonly utilized in medicolegal clinical examinations where a potential incentive to perform poorly exists. Recent studies have found associations between symptom validity performance and disability status in conditions classified as somatiform disorders [43]. Effort testing has also been carried out with people with PNES. One previous study carried out by Drake et al. had reported findings of suboptimal effort on neuropsychological evaluation of people with PNES [44]. However, this finding was not replicated in a subsequent study of PNES utilizing the same test and carried out by a different research group [45]. The authors of the latter study suggested that the high rates of suboptimal effort found by Drake et al. were likely related to sample bias, which they attributed to the inclusion of people with PNES who had severe psychiatric difficulties, including people with “hysteroid” personality disorder. Moreover, a recent study examined performance of people with PNES on a symptom validity test while investigating potential confounders and reported that failure on the Word Memory Test (WMT) was strongly associated with reported abuse but not with variables such as the presence of financial incentives or severity of reported psychopathology [46]. These results indicate that for people with PNES, factors underlying WMT failure cannot be assumed to be similar to those found in other medical populations, such as exaggeration of distress or financial or disability incentives and may be more related to clinical variables such as traumatic experience. In our study, we included only those people with PNES who passed a well-validated test of effort in an attempt to rule out the possibility of response bias in our study. However, on the one hand our clinical sample was found to have significant levels of psychopathology and cluster B type personality disorder and included people who continued to experience PNES despite treatment; on the other hand, there was no significant between-groups difference of reported traumatic experiences compared with controls. Therefore, further research studies are likely to be required to identify clinical and psychosocial variables that can help predict with confidence those people with PNES likely to perform suboptimally on clinical tests. In general, however, these studies highlight the importance of effort testing in medical populations including those with PNES.

In summary, we studied a relatively homogeneous group of people with PNES and found significant differences from healthy controls on psychopathological indices of depression, anxiety, and dissociation. We also found significant differences between groups on personality construct, indicating an increased prevalence of alexithymia, preoccupation with physical health, and disordered personality in people with PNES, consistent with results from previous studies. Nevertheless, this is, to our knowledge, the first study that reports abnormal neuropsychological functioning in PNES after controlling for effort. In addition, our correlation analysis results found dissociation to be positively associated with frequency of PNES events. However, we found no evidence that our finding of abnormal neuropsychological functioning is associated with a cognitive decline often found in people who have suffered neurological illness or neural injury. Therefore, although the cause of our findings is unknown, we suggest that, overall, our findings support the hypothesis that PNES manifest through an interaction effect involving attention deficits [12] and disrupted integration of emotional processing and perception [6]. Moreover, our results also support evidence that there are abnormally functioning neural circuits in PNES that subserve the relevant cognitive functions [47].

The main limitations of our study are the small sample size and an associated increased risk of type II error in interpretation of our findings. However, on the other hand, our study was adequately powered, and we employed a rigorous structured approach to assessment and analysis of data. We also did not include people with epilepsy in our study. Hence, we do not know if our findings will generalize when compared with other groups within the epilepsy spectrum. Therefore, we suggest that further carefully planned studies involving multimodal assessment techniques such as neuropsychological, neurophysiological, and neuroimaging modalities will be required to replicate our results and further delineate the neurobiological underpinnings of PNES.

5. Conclusion
This is the first study to report that, compared with healthy controls, people with PNES have abnormal cognitive functioning after controlling for effects of effort and FSIQ. People with PNES also have high levels of anxiety, depressive, and dissociative symptoms. In addition, they appear to particularly focus on health problems and show evidence of chronic emotional dysregulation. Further studies are required to replicate our results and to help clarify the pathogenic mechanisms underlying PNES.

Funding
This research was funded by Molecular Medicine Ireland. The grant code was 1121F.

Declaration of interest
The authors have no competing interests to report.
We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Conflict of interest

Authors declared that there are no known conflicts of interest associated with this publication and that there has been no significant financial support for this work that could have influenced its outcome.

References


[5] Dinene C, Delanty N, O’Keane V, Meaney AM, McMackin D. Patients with nonepileptic seizures show higher levels of alexithymia, emotional control, and stressful adult experiences than do patients with epilepsy and matched controls. Epilepsia 2001;42(Suppl. 7):137–8.


The Prevalence & Management of Psychogenic Non-Epileptic Seizures in an Irish Tertiary Referral Centre for Epilepsy

Finian M. O’Brien, Norman Delanty, Catherine Dineen, Kieran C. Murphy

Abstract

Objectives: To examine the prevalence, psychiatric co-morbidity and management of psychogenic non-epileptic seizures (PNES) in patients admitted to a tertiary referral Epilepsy Monitoring Unit (EMU).

Methods: Medical records of patients admitted to the EMU between 2003 and 2005 were examined and data from neurological, neuropsychiatric and neuropsychological assessments was analysed.

Results: Two hundred and twenty four patients were referred to the EMU over a three year period and 44 (20%) were diagnosed with PNES. Thirteen people (6%) were diagnosed with both PNES and epilepsy. Thirty four (75%) of people diagnosed with PNES were referred to psychology services for cognitive behavioural therapy (CBT) and 26 (58%) were followed-up by psychiatry services.

Conclusions: The prevalence rates for PNES and co-existing PNES and epilepsy are consistent with previous reports. Rates of psychiatric co-morbidity were less than would be expected in this clinical population. Clear evidence-based guidelines to manage people with PNES are required.

Key words: Psychogenic; Non epileptic convulsions; Conversion disorder; Prevalence; Epilepsy.
*Dr. Finian M. O’Brien, MB, MRCPsych, MSc. Research Fellow in Neuropsychiatry, Beaumont Hospital, Beaumont Road, Dublin 9, Ireland. E-mail: finobrien@rcsi.ie; Telephone: 01-2090009; Fax: 01-2109893.

Dr. Norman Delanty, FRCPI. Consultant Neurologist, Beaumont Hospital, Dublin 9, Ireland.

Catherine Dineen, BA. Psychologist, Beaumont Hospital, Dublin 9, Ireland.

Professor Kieran C. Murphy, M Med Sci, PhD, FRCPI, FRCPsych. Department of Psychiatry, Royal College of Surgeons in Ireland, Education and Research Centre, Beaumont Hospital, Dublin 9, Ireland.

*Correspondence
Introduction

Epilepsy is a common, chronic and disabling disorder with a lifetime prevalence rate of 1-2%. Several studies report that up to 20% of patients who attend neurology centres for treatment of epilepsy have psychogenic non-epileptic seizures (PNES)\textsuperscript{1,2}. PNES are episodes of altered movement, sensation or experience which resemble epileptic seizures, but are associated with patho-psychological processes and not with ictal discharges in the brain\textsuperscript{3}. They are classified under Dissociative (Conversion) disorder in ICD-10 and are a physical manifestation of psychological distress\textsuperscript{4}. However, approximately 5 to 10% of patients with PNES have concurrent epilepsy, which can make accurate characterisation of seizure-events clinically challenging\textsuperscript{5,6}.

It can be difficult to distinguish PNES from epileptic seizures. For example, no clinical signs of PNES exclude a diagnosis of epilepsy and, besides ictal electroencephalogram (EEG) abnormalities, there are no signs unique to epilepsy. However, assessment is facilitated by obtaining a comprehensive medical (and psychiatric) history from the patient, detailing features of typical seizures and carrying out appropriate investigations, particularly video-EEG (VEEG)\textsuperscript{7}. VEEG monitoring of seizure-events is the gold standard investigation for diagnosis of PNES and is carried out on an inpatient basis. During VEEG monitoring, the patient wears an EEG transmitter connected to a wall outlet by co-axial cable and both EEG and video signals are displayed simultaneously for on-line observation and recording of typical events. Epileptic events, but not PNES, will generally show characteristic clinical and diagnostic changes.
Patients with PNES have a significantly reduced quality of life and suffer a significantly increased risk of suffering adverse physical and mental health consequences from receiving inappropriate medical treatments and interventions for epilepsy\textsuperscript{8-10}. Therefore, it is important that once a patient is diagnosed with PNES, referral is made to specialised neuropsychiatry services for appropriate assessment and treatment and a co-ordinated multidisciplinary plan for managing the condition is agreed. Beaumont Hospital, an academic teaching hospital in Dublin, has the most comprehensive Neurology service in Ireland and includes specialist facilities for inpatient evaluation of seizures, including an epilepsy monitoring unit (EMU). Patients are admitted to the EMU for pre-surgical evaluation and localisation of seizures, to clarify diagnosis in cases of suspected nonepileptic seizures and to classify seizure type when their clinical differentiation is difficult or unclear. Definitive diagnosis is made on the basis of VEEG capturing “typical” seizures and if these do not occur during one period of inpatient assessment, the patient may be brought back for further assessment in the EMU. All patients admitted to the EMU undergo continuous VEEG evaluation of seizure activity and receive routine multidisciplinary assessment by the neurology, neuropsychiatry and neuropsychology teams. However, only one previous study has examined the prevalence of PNES among patients admitted to an Irish Neurology Centre\textsuperscript{11} and none have previously examined the immediate follow-up of these patients. Therefore, in this study we examined (1) the prevalence of PNES in people admitted to a tertiary referral EMU (2) the co-morbidity of psychiatric illness among people with PNES and (3) the management of people with a diagnosis of PNES.
Methods
The medical records for all those patients who were admitted to Beaumont Hospital’s EMU for a continuous 3 year period (2003-5) were examined retrospectively. The charts of those patients were reviewed to obtain appropriate information on referral, assessment and management of the patient by the neurology, neuropsychiatry and neuropsychology services. The data collected were entered into a database and analyzed using the SPSS statistical software programme.

Results
Two hundred and twenty five patients were admitted to the EMU for assessment over the three year period of study. Two hundred and twenty patients (98%) admitted to the EMU were assessed by the neuropsychiatry team and the remainder either were found to have non-epileptic seizures caused by medical reasons other than epilepsy (n=1), refused psychiatric assessment (n=2) or self-discharged before assessment could occur (n=2). Ninety seven patients (44%) had a current and/or previous history of psychiatric illness and had an average age (S.D.) of 34.8 (+/- 11.4) years. Sixty five patients (67%) were female, 32 (33%) were male and age did not differ significantly between genders (p = 0.47). PNES had an overall prevalence rate of 20% (Table 1) and was the most frequent psychiatric diagnosis (42%) in those found to have an acute psychiatric disorder (Figure 1).

(Figure 1: Psychiatric Diagnosis in EMU Patients)
Thirty six (80%) of those with PNES were female and the average age (S.D.) of people presenting with PNES was 36 (+/-11) years. One third of people diagnosed with PNES
also had a past history of psychiatric illness, with depressive disorder being the most common disorder (20%) (Figure 2) (Figure 2: Past Psychiatric Disorder in people with PNES). PNES and epilepsy co-existed in 6% of patients attending the EMU (Table 1).

All those diagnosed with PNES were initially reviewed by the neurology team to explain the diagnosis and to plan tapered reduction and stopping of their anticonvulsant drugs if appropriate (i.e., if no co-existing epilepsy). Subsequently, each patient was reviewed by the neuropsychiatry team to formally diagnose PNES (conversion disorder) and formulate a treatment plan. In addition, patients were reviewed by the psychology team to provide cognitive behavioural therapy (CBT).

Eleven people (73%) diagnosed with PNES and with a previous history of psychiatric disorder were followed up by their local community mental health team and the remainder (27%) by the specialist neuro-psychiatry service in Beaumont Hospital (Table 2). Eleven (36%) people diagnosed with PNES and with no previous history of mental illness were formally followed-up by psychiatry services: seven (23%) by a specialist neuropsychiatry service and four (13%) by local psychiatry services.

Overall, thirty four people (75%) diagnosed with PNES were referred to psychology services for follow-up treatment: twenty six (58%) to a specialist neuropsychology service in Beaumont Hospital and eight (18%) to community-based psychology services.

Twenty three people (77%) newly diagnosed with PNES and with no previous contact with psychiatric services and three (20%) of those with a previous history of mental illness were referred for CBT to Beaumont Hospitals specialist neuropsychology service.
Two patients (7%) diagnosed with PNES refused all specialist treatment recommendations.

**Discussion**

We found that almost 20% of patients who attended an Irish specialist neurology inpatient unit for evaluation of seizures had PNES. This prevalence rate is consistent with that (20-50%) reported in the few previous studies carried out in specialist neurology centres in other countries.\(^2\,^5\). Also, our finding that 6% of patients attending the EMU had co-existing PNES and epileptic seizures is within the range reported (5-50%) from other similar studies.\(^5\,^6\,^13\,^14\). However, these rates are likely to underestimate the true prevalence of PNES in patients attending the general epilepsy service as only those who were referred for video EEG monitoring were included in this study. Also, it is difficult to reliably extrapolate the prevalence rates we report to those present in other specialist epilepsy services as admission criteria to VEEG facilities may differ according to local resources and other pressures (for example, assessment of suitability for neurosurgery).

We found that only four out of the forty-five patients (4%) diagnosed with PNES refused specialist follow-up treatment with mental health services. This is a significantly lower rate of follow-up with specialist treatment than that (23%) reported in the one previous study examining reactions of patients with PNES to diagnosis and referral for treatment.\(^15\). However, although the reason for our low finding is unknown, recent studies suggest that patients with PNES are more likely to have a positive outcome with a multidisciplinary
approach to treatment including specialised neuropsychiatry and neuropsychology input\textsuperscript{3,16}. The management model of PNES outlined in this study is consistent with this multi-disciplinary approach so that all patients receive standard assessments by neurology, neuropsychiatry and neuropsychology teams, both pre- and post-characterisation of seizures. Also, these assessments are reviewed routinely and discussed at regular ward rounds and inter-disciplinary meetings to help formulate appropriate plans, so that management of people with PNES is consistent and co-ordinated. Therefore, this approach may serve to improve therapeutic alliance and patient compliance with treatment recommendations\textsuperscript{17}. Nevertheless, further studies examining modes of management and long-term outcome in these patients are necessary.

Our finding that one third of people with PNES had other co-morbid psychiatric disorder is less than other reports suggesting prevalence rates of 43-100\%\textsuperscript{18,19}. The reason for this finding is unknown. However, our study was retrospective and data were obtained from psychiatric assessments based on clinical interview and available collateral information. In contrast, those studies which reported higher prevalence rates were prospective in nature and employed structured clinical interview schedules and standard rating scales to evaluate psychopathology using, for example, the Structured Clinical Interview Schedule (SCID) and Minnesota Multiphasic Personality Inventory (MMPI)\textsuperscript{18,19}. Thus, the discrepancy in prevalence rates may be explained by heterogeneity in study methodology. For example, evaluation of psycho-symptomatology using standardized semi-structured interviews is likely to increase sensitivity to detection of co-morbid psychiatric disorder. Also, duration of admission to the EMU was quite short in some cases (3-5 days) so that
it is possible that a more detailed history of, for example, abnormal illness behaviour and previous psychiatric contact may have been under-reported or unavailable for some patients interviewed during their period of admission. Nevertheless, our study adds to current evidence of high rates of psychiatric co-morbidity in people with PNES.

We found that many (58%) newly diagnosed patients with PNES were followed-up by Beaumont Hospital’s psychology service alone and not formally referred to the Neuropsychiatry services for later review. Further, only 23% (n = 7) of those newly diagnosed with PNES with no previous psychiatric history and 27% (n = 4) of patients with PNES and a previous history of psychiatric disorder were followed up by the specialist Neuropsychiatry service. However, while most patients were offered specialist treatment within the our epilepsy service framework, many were referred to their local community mental health teams (CMHT) for follow-up on the basis of patient preference (many were living outside Dublin and could not easily access the Beaumont Hospital service) and whether they were already engaged with their local CMHT for treatment of previously existing mental health problems.

In our study, 75% (n=34) of all people diagnosed with PNES were referred for psychological therapy. However, a recent Cochrane Review of behavioural treatments for PNES concluded that there is no reliable evidence to support the use of any behavioural treatment of PNES and recommended that randomised studies of all behavioural interventions are required\textsuperscript{20}. 

Page | 9
Stone and colleagues reported that patients with PNES were less likely than those with epilepsy to see psychological factors as relevant to their symptoms, more likely to deny that they have suffered from life stress and also to have a more external locus of control\textsuperscript{21}. They suggested that psychological treatment specifically designed to modify denial and locus of control may be useful although randomised controlled trials are required to test this hypothesis.

In this current study, the specialist neuropsychiatry service were more likely to follow-up those people with PNES who had a co-morbid psychiatric disorder requiring change in psychotropic medication and ongoing psychiatric monitoring (40\% of those with co-morbid disorder). In contrast, only two (12\%) of those followed up by their general practitioner had co-morbid psychiatric disorder (all depressive disorder) and neither had a previous psychiatric history. Nevertheless, available evidence suggests that over 44\% of these patients continue to have seizures and be dependant on healthcare services 10 years after diagnosis (if untreated)\textsuperscript{22}. Also, people with PNES have an increased risk of developing further psychiatric co-morbidity if psychological and psychiatric treatment is not available or unsuccessful\textsuperscript{23}. Therefore, it is necessary to formulate a clear multidisciplinary framework and international best practice guidelines for acute management and follow-up for these patients.

In common with people with other neuropsychiatric disorders, people with PNES benefit most from treatment within the context of a multidisciplinary team that includes psychiatrists, neurologists and psychologists\textsuperscript{24}. In our experience, such a model
facilitates a comprehensive and co-ordinated approach to diagnosis and treatment. We suggest that the approach outlined in Table 3 may be useful in guiding management and follow-up of people with PNES and we have now adopted this model in our Centre. However, more research, particularly involving randomised controlled trials of treatment interventions, is urgently required for this vulnerable patient group.

Acknowledgements
We would like to express thanks to the patients and staff of the Epilepsy Monitoring Unit

Competing Interests: None

Funding: Department of Psychiatry, Beaumont Hospital.
References


17. Aboukasm A, Mahr G, Gahry BR, Thomas A and Barkley GL. Retrospective analysis of the effects of psychotherapeutic interventions on outcomes of


Tables and Figures

*Table 1: Results of Video Electroencephalography Assessment of Patients in the Epilepsy Monitoring Unit*

<table>
<thead>
<tr>
<th>Epilepsy and NES</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epilepsy</td>
<td>180</td>
<td>80.4</td>
</tr>
<tr>
<td>NES of medical cause (syncope)</td>
<td>1</td>
<td>0.4</td>
</tr>
<tr>
<td>PNES &amp; Epilepsy</td>
<td>14</td>
<td>6.3</td>
</tr>
<tr>
<td>PNES alone</td>
<td>30</td>
<td>13.4</td>
</tr>
</tbody>
</table>

*Table 2: Referrals for specialist treatment of people diagnosed with Psychogenic Non-Epileptic Seizures*

<table>
<thead>
<tr>
<th>Referral for specialist treatment upon diagnosis of PNES</th>
<th>No previous Psychiatric Diagnosis before that of PNES (n=30)</th>
<th>Those with a previous Psychiatric Diagnosis before that of PNES (n=15)</th>
<th>Overall (n=45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct Referrals for Psychological follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beaumont Neuropsychology</td>
<td>77% (23)</td>
<td>20% (3)</td>
<td>58% (26)</td>
</tr>
<tr>
<td>Local Psychology Service</td>
<td>0% (0)</td>
<td>53% (8)</td>
<td>18% (8)</td>
</tr>
<tr>
<td>Direct Referrals to Psychology</td>
<td>77% (23)</td>
<td>73% (11)</td>
<td>75% (34)</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Direct Referrals for Psychiatric follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beaumont Neuropsychiatry</td>
<td>23% (7)</td>
<td>27% (4)</td>
<td>24% (11)</td>
</tr>
<tr>
<td>Local Psychiatry Service</td>
<td>13% (4)</td>
<td>73% (11)</td>
<td>33% (15)</td>
</tr>
<tr>
<td>Overall Direct Referrals for Psychiatric Follow-up</td>
<td>36% (11)</td>
<td>100% (15)</td>
<td>58% (26)</td>
</tr>
<tr>
<td>Refused Specialist Treatment</td>
<td>7% (2)</td>
<td>0% (0)</td>
<td>7% (2)</td>
</tr>
</tbody>
</table>
### Table 3: Suggested Management and Follow-up of people diagnosed with Psychogenic Non-Epileptic Seizures

<table>
<thead>
<tr>
<th>PNES diagnosed by VEEG monitoring</th>
</tr>
</thead>
</table>

**Patient’s Neurology team meets with patient +/- next of kin to deliver and explain:**
1. Assessment finding of PNES (clearly, positively and sympathetically)
2. That treatment for PNES will be delivered through neuropsychiatry and neuropsychology teams
3. That anti-epileptic medication will be tapered and stopped completely (if patient does not also have co-existing epileptic seizures)

**Neuropsychiatry team reviews patient to:**
1. Formally make psychiatric diagnosis of PNES (conversion disorder) using ICD-10 Criteria.
2. Confirm that no other co-morbid psychiatric disorder is present (e.g., post-traumatic stress disorder)
3. Explain diagnosis/diagnoses and recommended treatment(s), to the patient.
4. Decide if psycho-pharmacological intervention is appropriate
5. Decide if other psycho-social interventions/supports apart from psychological therapy are required.
6. Arrange follow-up with neuropsychiatry and patient’s psychiatric services (if appropriate).

**Neuropsychologist reviews patient to:**
1. Explain role of psychological therapy in treating PNES.
2. Explore possible aetiological issues of trauma/abuse, etc with patient
3. Assess patient for motivation and suitability for psychological therapy.
4. Decide which type of psychological intervention is appropriate to the patient needs (e.g., CBT).
5. Makes follow-up arrangements with patient.
6. Liaises regularly with neuropsychiatry regarding patient progress in therapy and to arrange neuropsychiatry review after psychological treatment is finished.

**Regular Multidisciplinary meetings (neurology, neuropsychiatry & neuropsychology) to:**
1. Discuss management and follow-up of patients with PNES.
2. Arrange discharge and liaison with GP/other community services as appropriate.
Figure 1: Psychiatric Diagnosis in EMU patients

- Depressive Disorder: 28%
- Learning Disability: 9%
- Anxiety: 6%
- Neurodevelopmental Conditions: 42%
- Other: 4%
- Personality Disorder: 6%
- Psychosis: 5%
- Psychosis: 5%
- Psychosis: 5%
- Psychosis: 5%

Figure 2: Past Psychiatric Disorder in people with PNES

- Depression: 20%
- Personality Disorder: 7%
- PTSD: 2%
- Subst. Abuse: 2%
- Eating Dis.: 2%
- Nil: 67%