Prevalence of Psychiatric Morbidity and Behavioural Problems in 22q11.2DS: An Irish Population Study

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ABSTRACT

Introduction

This population study examines the prevalence of psychiatric morbidity, behavioural difficulties, autistic and schizotypal features in a sample of individuals with 22q11.2DS and in their sibling controls.

Methods

Forty-five individuals with 22q11.2DS and their 27 siblings were recruited and studied. Psychiatric morbidity was assessed by using the parent Diagnostic Interview Schedule for Children (DISC-P), Kiddie SADS-Present and Lifetime Version (K-SADS-PL) (psychotic supplement), Comprehensive Assessment of the At Risk Mental State (CAARMS), Schedule for Clinical Assessment in Neuropsychiatry (SCAN) and the parent Conners' rating scale. Behavioural difficulties were measured by the Strengths and Difficulties Questionnaire (SDQ) and the Child Behaviour Checklist (CBCL). The Social Responsiveness Scale (SRS) and the Social Communication Questionnaire (SCQ) were used to measure symptoms of autism. The Schizotypal Personality Questionnaire (SPQ) was used to measure for schizotypal features.

Results

Children and adolescents with 22q11.2DS were found to have more internalising and externalising behaviour compared to their siblings; 25% of children and adolescents with 22q11.2DS had social problems within the clinical range. Individuals with
INDEX OF FIGURES

Figure 1 - Flow Diagram representing the Recruitment of Case Subjects .................. 76
Figure 2 - The range of SOFAS Scores: Cases vs. Controls .................................. 79
Figure 3 - Flow Diagram of Participation with Assessments ............................... 97
Figure 4 - Connors' Parent Rating Scale between Cases and Controls ............ 103
Figure 5 - The SOFAS scores of case group ....................................................... 117
Figure 6 - The FSIQ scores of the case group ..................................................... 118

APPENDICES

1. Patient and Parent Information Leaflets and Consent Forms
2. Letters of Ethical Approval
3. Background K-SADS Interview
4. Neurodevelopmental Questionnaire
5. Psychotic Supplement K-SADS
6. Interview booklet: Comprehensive Assessment of the At Risk Mental State (CAARMS)
7. SAPS and SANS
8. Social and Occupational Functioning Assessment Scale (SOFAS)
9. Schizotypal Personality Questionnaire (SPQ)
10. Social Responsiveness Scale (SRS)
11. Social Communication Questionnaire (SCQ)
12. School Report Form
13. Conners Parent Rating Scale
15. Strength and Difficulties Questionnaire (SDQ)
CHAPTER 1 – INTRODUCTION
Overview

In this chapter I will begin by reviewing the general features of 22q11.2DS and then focus on the psychiatric disorders which are found in children, adolescents and adults with 22q11.2DS. Next I will review the neurodevelopment hypothesis of schizophrenia and the relationship of this hypothesis with 22q11.2DS. Following this, I will review the current understanding of schizotypal personality disorder and schizotypy in the general population and in individuals with 22q11.2DS.

1.1 Introduction

22q11.2DS is the most frequently occurring chromosomal microdeletion syndrome in man, with an estimated incidence of 1 in 4,000 live births (Botta et al., 2003). 22q11.2DS is also known as Velo-cardio-facial syndrome (VCFS), DiGeorge syndrome, Conotruncal anomaly face syndrome or Shprintzen syndrome. 22q11.2DS is a multiple anomaly syndrome with an extensive and variable phenotype in which over 180 clinical features have been described (Murphy and Scambler, 2005). There is significant variation in both the severity and type of clinical features between patients. The most common abnormalities include speech and palatal anomalies, cardiac outflow tract defects, facial dysmorphism, immune disorders, learning difficulties and psychiatric disorders. In particular, there is a large body of evidence which indicates an unequivocal association between 22q11.2DS and schizophrenia. There is an increased prevalence of schizophrenia in individuals with 22q11.2DS, a high frequency of 22q11 deletion in individuals with schizophrenia and identification of susceptibility loci for schizophrenia which map within the 22q11
region (International Schizophrenia Consortium, 2009, International Schizophrenia Consortium, 2008, Badner and Gershon, 2002, Murphy et al., 1999, Karayiorgou et al., 1995). This has led investigators to hypothesise that one or more genes in the deleted region may confer susceptibility to schizophrenia both in individuals with 22q11.2DS and in the non-deleted population. Deletion of 22q11 is recognised as the third highest risk for the development of schizophrenia, with only a greater risk conferred by being the child of two parents with schizophrenia or the monozygotic co-twin of an affected individual (Murphy and Owen, 2001).

The challenge for clinicians and researchers is to identify early vulnerability traits, symptoms or disorders which may be associated with or predict a later emerging psychotic disorder, so that early monitoring and treatment can be initiated to reduce the duration of untreated psychosis in those at risk. Identification of these early traits or symptoms firstly requires detailed analysis of the behavioural phenotype in individuals with 22q11.2DS. One of the aims of this thesis is to comprehensively assess and describe the psychiatric and behavioural characteristics of a population cohort of individuals with 22q11.2DS in Ireland. The data gained from this study will provide the foundation for future longitudinal studies of risk factors of psychosis in 22q11.2DS.

Recent advances in genetic technology have permitted researchers to conduct genome-wide association studies (GWAS) on large sample sizes which allows for the detection of common alleles of small effect (Owen et al., 2009). Studies based on these techniques have identified chromosomal regions which harbour structural
variations (typically >1000 base pairs) such as deletions and duplications and are collectively referred to as copy number variations (CNV). CNV have found to be significantly overrepresented in schizophrenia compared to controls (International Schizophrenia Consortium, 2008, Stefansson et al., 2008). It has been found that in addition to deletion at 22q11.2 that deletions at 1q21.1, 15q11.2, 15q13.3 are also significantly associated with schizophrenia (Stefansson et al., 2008, International Schizophrenia Consortium, 2008). In addition micro-duplication of 16p11.2, 16p13.1 and microdeletion of the gene neurexin-1 (NRXN1) have also been significantly associated with schizophrenia (McCarthy et al., 2009, Ingason et al., 2009, Rujescu et al., 2009). Therefore, with the emergence of CNV throughout the genome contributing to the risk of developing schizophrenia, it becomes increasingly important to identify the psychiatric phenotype of individual mutations. Phenotypic heterogeneity has been a confounding factor in clinical genetic research reflecting underlying genetic heterogeneity of psychiatric disorders and resulting in inconsistent research findings. Phenotypic clinical studies of individual mutations may provide an avenue to link clinical disorders and symptoms to specific genetic mutations. This may provide insight into pathophysiological mechanisms and pathways in the brain underlying clinical disorders and symptoms and which may then ultimately provide specific or targeted treatment(s).

Deletion at 22q11.2 was the first CNV which was found to be significantly associated with schizophrenia. With the discovery of the additional CNV being associated with schizophrenia, there is a growing need to gain a clear understanding of the psychiatric phenotype of 22q11.2DS. This thesis will build on previous clinical
psychiatric phenotype studies of 22q11.2DS by using specific clinical interviews which have not been used previously to gain more insight into the psychiatric phenotype of 22q11.2DS. It is also anticipated that the clinical research carried out in this thesis may provide methodological information which can be extrapolated to study the psychiatric phenotype of other chromosomal regions which are found to be significantly associated with schizophrenia.

1.2 Historical Overview of 22q11.2DS

Descriptions of the syndrome in medical literature have been found as early as the 1950's. In 1955 a case series described 28 children with palate abnormality, hypernasal speech and a characteristic facial appearance (Sedlackova, 1955). Angelo Di George in 1965 first described athymia and immune disorders in a young child with a right-sided aortic arch and than published a case series to describe the phenotype (DiGeorge, 1968). DiGeorge syndrome has been synonymous with immune disorders in individuals with the deletion. In 1968 a distinct syndrome was reported in a family with congenital heart anomalies and cognitive impairment (Strong, 1968). In Japan, attention was given to an association between conotruncal heart anomalies and an unusual facial appearance in medical literature from 1976 onwards. Following these early descriptions, the label conotruncal anomaly face syndrome later emerged from Japan to describe the syndrome (Momma et al., 1996, Kinouchi et al., 1976). Shprintzen in 1978 coined the term, ‘Velo-cardio-facial syndrome’ to describe a genetically caused multiple anomaly syndrome in 12 unrelated cases and one mother-daughter pair (Shprintzen et al., 1978). In 1992 the microdeletion of chromosome 22 at band q11.2 was identified as the specific genetic
cause for the syndrome (Scambler et al., 1992). More recently the syndrome is being referred to as 22q11.2 deletion syndrome (22q11.2DS); this term describes the genetic aetiology underlying this syndrome and also encompasses the various labels which have been used to describe the same genetic disorder.

1.3 Genetic Basis of 22q11.2DS

22q11.2DS is the most common microdeletion syndrome found in humans. It is caused by a heterozygous interstitial deletion in band 11 of the long arm of chromosome 22. Using fluorescence in situ hybridization (FISH) and/or PCR of polymorphic markers the size of the deletion has been determined in several large patient groups. It has been demonstrated that the majority of patients (>85%) have a ~3Mb (million base pair) typically deleted region (TDR). A minority of patients have a smaller 1.5-2Mb nested deletion and very rarely some patients have small atypical deletions, deletions that do not overlap the TDR, single mutation of genes within the TDR and balanced translocations (Paylor and Lindsay, 2006, Shaikh et al., 2000, Emanuel et al., 1998, Carey et al., 1992). It has been put forward that the deletions within this region are facilitated by the presence of low copy repeats (LCR22) at the boundaries of the various deletions (Shaikh et al., 2001).

The majority of deletions occur sporadically in the population and approximately 5-10% are inherited, suggesting that the 22q11 region may be prone to rearrangement (Ryan et al., 1997, Kaplan et al., 1987). The syndrome is highly variable and there is no evidence to date that the size of the underlying deletion has any influence on the
physical or behavioural phenotype. Phenotypic diversity, variable expressivity and incomplete penetrance may extend to individuals within the same family. Phenotypic discordance has also been described between monozygotic twins with 22q11.2DS (Murphy and Scambler, 2005, Yamagishi et al., 1998, Goodship et al., 1995). It is suggested that the phenotypic variability is likely to be due to stochastic, environmental and genetic factors (Aggarwal and Morrow, 2008).

1.4 Physical Phenotype of 22q11.2DS

22q11.2DS is a multiple anomaly syndrome with an extensive and variable phenotype in which over 180 clinical features have been described (Murphy and Scambler, 2005). The most common physical features are; dysmorphic facial features, congenital heart disease, palatal anomalies, speech and language impairment, thymic and parathyroid defects including hypocalcaemia and immune problems (Shprintzen, 2008).

22q11.2DS is the most common genetic syndrome associated with palatal clefts and congenital velopharyngeal dysfunction (Kirschner, 2005, Scambler et al., 1992). The most commonly occurring palatal anomalies are submucous and occult submucous cleft palate (Shprintzen, 2000). Cardiovascular defects affect 75% of individuals with 22q11.2DS and accounts for 90% of the mortality found in the syndrome (Matsuoka et al., 1998). 22q11.2DS is the second most common genetic cause of congenital heart disease following Down syndrome and occurs in 1 of 68 children born with congenital heart disease (Goodship et al., 1998, Wilson et al., 1994). The
characteristic cardiac defects occurring in individuals with 22q11.2DS are conotruncal defects in which there are anomalies associated with the outflow tracts of the heart (Mc Donald-McGinn and Zackai, 2008). Most individuals with 22q11.2DS have a mild to moderate immuno-deficiency commonly evident as a reduction of T-cell numbers which occurs commonly in infancy and resolves with increasing age. A profound immunodeficiency is rare and occurs in approximately 0.5-1% of individuals with 22q11.2DS with absent or very minimal T-cell count (Sullivan, 2005).

Many of the defects associated with 22q11.2DS derive from the pharyngeal apparatus which is an embryological structure lying lateral to the developing head. The pharyngeal apparatus consists of the pharyngeal arches and the neural crest cells. The neural crest cells migrate from the adjacent closing neural tube into the pharyngeal arches. Ablation of the neural crest cells in animal models results in phenocopies of the syndrome. It has been suggested that defects in the neural crest cells underlies the abnormalities of the derivatives of the pharyngeal apparatus. Therefore, it is likely that one or more genes in the deleted region may be involved in neuronal migration or differentiation of the pharyngeal arches and haploinsufficiency of these genes may result in the interruption of development leading to multiple abnormalities (Aggarwal and Morrow, 2008, Murphy and Owen, 2001).

It is not clear whether the phenotype is caused by a loss of a single gene within the deleted region, by the combined loss of several genes within the deleted region or by genes which may act as modifiers lying outside the deleted region which may all act on a common pathway during pharyngeal and neurodevelopment. In the mouse
model resembling 22q11.2DS (Df1 heterozygous Df1/+), haploinsufficiency of the T-box gene 1 (TBX1) is associated with a wide range of developmental anomalies resembling the phenotype including hypoplasia of the thymus and parathyroid glands, cardiac outflow tract defects, abnormal facial structures and cleft palate (Jerome and Papaioannou, 2001, Merscher et al., 2001). TBX1 is a member of the T-box family of transcription factors and had been found to have a role in the regulation of developmental processes (Smith, 1999). Three mutations of TBX1 in five individuals without the 22q11 deletion (two unrelated patients and three individuals from a family) were identified. These individuals had a range of physical anomalies found in 22q11.2DS and had the characteristic facial features associated with conotruncal anomaly face syndrome. These findings indicate that mutation of TBX1 underlies five major anomalies found in 22q11.2DS namely: abnormal facies, cardiac defects, thymic hypoplasia, velopharyngeal insufficiency with cleft palate and parathyroid dysfunction with hypocalcaemia. It is suggested that TBX1 is the leading genetic determinant of the pharyngeal derived physical anomalies of 22q11.2DS (Yagi et al., 2003). It has been suggested that TBX1 may regulate genes that signal to neural crest cells to promote their growth and differentiation and studies in mouse models suggest that FGF8, FGF10, PITX2 and CRKL lie in the genetic pathways of TBX1 and all may play a critical role in the development of the caudal pharyngeal apparatus (Aggarwal and Morrow, 2008).

1.5 Psychiatric Phenotype-Genotype Correlation

The study of 22q11.2DS, a known genetic disorder with a high prevalence of psychiatric disorders, offers an opportunity to identify susceptibility genes which may
contribute to the risk of psychiatric disorders in individuals with 22q11.2DS and those in the general population (Murphy & Owen 2001). Several genes have been identified as possible susceptibility genes in individuals with 22q11.2DS and in mouse models resembling 22q11.2DS, although their contribution to these disorders remains poorly understood. Studies of 22q11.2DS mouse models have suggested that large numbers of genes in the deleted region are differentially expressed during brain development and are candidates for the behavioural phenotype observed in individuals with 22q11.2DS (Maynard et al 2003, Meechan et al 2006, Sivagnanasundaram et al 2007). The evidence from these studies suggests that multiple genes in the deleted region may increase the risk of psychiatric disorders in individuals with 22q11.2DS.

A genome wide association study (GWAS) of 3322 European individuals with schizophrenia found that the 22q11.2 deletion region contributes significantly to the risk of developing schizophrenia (International Schizophrenia Consortium, 2009). Linkage and association studies of people with schizophrenia have implicated several susceptibility genes of which three are within the deleted region; catechol-o-methyltransferase (COMT), proline dehydrogenase (PRODH) and guanine nucleotide binding protein (G protein), beta polypeptide 1-like (GNB1L) (Williams et al., 2008, Liu et al., 2002b, Shifman et al., 2002). However contradictory and equivocal evidence has emerged thus far concerning COMT and PRODH and its associated risk for schizophrenia, both in the general population and also in individuals with 22q11.2DS (Fan et al., 2005, Li et al., 2004, Ohtsuki et al., 2004, Glatt et al., 2003, Shifman et al., 2002). Mice that were homozygous PRODH mutants had significant
decreased prepulse inhibition (PPI) of the startle reflex which may be suggestive of a
defect in sensorimotor gating an endophenotype of schizophrenia (Gogos et al.,
1999).

Similarly *TBX1* and *GNB1L* have been associated with the impairment of PPI in the
heterozygous states and may also contribute to the 22q11.2DS psychiatric
phenotype (Paylor et al., 2006). The zinc finger and DHHC domain-containing
protein 8 (*ZDHHC8*) which maps to the 22q11.2 region has been associated with
schizophrenia, particularly in woman and *ZDHHC8* female knock-out mice were
found to have significantly lower levels of PPI compared with wild types (Mukai et al.,
2004, Liu et al., 2002a). This gene also has been proposed as a plausible candidate
gene contributing to the behavioural phenotype of 22q11.2DS. The proposed
candidate genes in the 22q11 region may play a role in the development of
schizophrenia and other psychiatric disorders both in individuals with 22q11.2DS and
the non-deleted population. However, their role at present remains unclear based on
studies done to date.

1.6 Neurodevelopmental hypothesis of schizophrenia

Many researchers hold the view that schizophrenia is a neurodevelopmental
disorder, in which subtle brain lesions are acquired in early brain development
resulting in a course of developmental deviance and abnormalities and with eventual
development of psychosis (Weinberger, 1995). There is a body of evidence which
supports the neurodevelopmental hypothesis of schizophrenia. Studies have found
that the likelihood of developing schizophrenia is associated with hypoxia-associated obstetric complications (Cannon et al., 2000). Early neuro-motor abnormalities such as coordination defects and unusual movements in children and neurological deficits in adolescence (motor coordination, sensory integration and disinhibition) were found to be associated with adult schizophrenia (Rosso et al., 2000, Chen et al., 2000). Several longitudinal studies found that abnormal behaviour in childhood such as pervasive social isolation, abnormal social adjustment, suspiciousness and relationship difficulties with peers were predictive of schizophrenia in adulthood (Allen et al., 2001, Cannon et al., 2001). Neuropsychological studies have found abnormalities from an early age without associated decline in neuropsychological function in individuals that develop schizophrenia (Heaton et al., 2001).

Findings from neuroimaging studies indicate that structural abnormalities predate the onset of psychosis (Fannon et al., 2000). However, there have been conflicting neuro-imaging findings concerning progressive brain volume changes in schizophrenia that cannot be accounted for by normal ageing changes suggesting a process of neurodegeneration (Mathalon et al., 2001). However, neuropathological studies have not found increased markers of neurodegeneration, gliosis, apoptosis or other indicators of neuronal injury or death (Falke et al., 2000, Harrison, 1999, Arnold et al., 1998). Cortical cytoarchitectural abnormalities such as; variability in the axes of orientation of pyramidal neurons in the hippocampus, disturbed differentiation, density, clustering, dispersion and reduction in neuronal numbers in the superficial layers of the entorhinal cortex and other corticolimbic regions have been found (Arnold et al., 1997, Conrad et al., 1991, Arnold et al., 1991). Other studies have
suggested that the neuronal cell counts are not abnormal in schizophrenia, though the cells are much more densely packed resulting in relative dystrophy of the dendritic arborisation and extracellular neurophil due to a deviance of insertion into the neural network, synaptic pruning, myelination and apoptosis (Kalkman, 2009, Selemon and Goldman-Rakic, 1999). Linkage and association studies have found that the disrupted in schizophrenia-1 (DISC1) gene and mutation of the neuregulin-1 gene (NRG1) are significant genetic risk factors for schizophrenia (Chubb et al., 2007, Law et al., 2006). Suppression of DISC1 activity has been found to cause accelerated dendrite development and neuronal migration resulting in inadequate positioning and incorporation into the neuronal network. NRG1 is involved in the growth factor pathway and interacts with the ErbB family of tyrosine kinase receptors. Hyperactivity of the NRG1-ErbB4 may have a role in the premature differentiation, accelerated maturation of neuronal cells which may lead to abnormal neuronal integration and connectivity (Kalkman, 2009, Chubb et al., 2007). These findings support the neurodevelopmental hypothesis of schizophrenia and suggest that the abnormalities may have a genetic predisposition.

The morphogenesis of the face, limbs, heart and the forebrain depends on a complex process of inductive signalling which involves the actions of specific genes, such as Lim-1, Emx-1, signalling molecules such as Fibroblast growth factor (Fgf) and Sonic hedgehog (Shh) and environmental factors such as retinoic acid (Carlson, 2009). Induction is an embryological process that occurs when one embryonic cell group provides a signal that modifies gene expression, differentiation and fate of another group of cells. Induction at certain sites in the developing embryo is mediated by
mesenchymal cells which are apposed to adjacent epithelial structures. A substantial component of the mesenchyme required for the development of the face, lens, limbs and heart is of neural crest origin. The forebrain acts as a signalling centre for early facial development and much of the mesenchyme of the face is of neural crest origin from the forebrain. In mouse models it has been found that the neural crest-dependant inductive interactions that are crucial to the development of the face, heart and limbs may also be involved in the development of the forebrain. These experimental studies have found that this neural-crest derived mesenchyme may have a role in the formation of the sub-divisions of the forebrain. Furthermore, this embryological process is regulated by the signalling molecule retinoic acid, which modulates gene expression and has a pivotal role in embryonic development (Carlson, 2009, La Mantia, 1999).

It has been proposed that the abnormalities in craniofacial structures, the heart and psychiatric complications (forebrain involvement) which are evident in 22q11.2DS may reflect abnormal neural crest migration and subsequent development. Therefore it has been suggested that a gene(s) within the 22q11 region may be involved in the process of neural crest cell migration or differentiation and haploinsufficiency of the gene(s) in question disrupts development leading to multiple tissue and organ abnormalities. In the mouse model of 22q11.2DS, haploinsufficiency of the genes TBX1 and CRKL have been implicated in the aberrant developmental process of the pharyngeal apparatus. TBX1 may have a regulatory role of Shh and retinoic acid, suggesting that it may be involved in early
embryological development. *TBX1* may regulate genes that signal to neural crest cells to promote their growth and differentiation (Aggarwal and Morrow, 2008).

It has been suggested that the cognitive, perceptual and behavioural symptoms that characterise schizophrenia may stem from alterations of neuronal circuitry and function of the forebrain (Jones, 1997). It has also been suggested that abnormalities of the neural crest-dependant retinoic acid mediated mesenchymal/epithelial induction may be a common aetiology of 22q11.2DS and schizophrenia in the general population (La Mantia, 1999). Therefore the genes involved in this embryological process may be involved in the aetiology of schizophrenia in 22q11.2DS and schizophrenia in the general population.

### 1.7 Early Temperament and Psychiatric Disorders found in 22q11.2DS

#### 1.7.1 Temperament of Children with 22q11.2DS

Early studies of children and adolescents with 22q11.2DS reported common temperamental and behavioural features including: poor social skills, problems with social interaction, social withdrawal, a ‘bland affect with minimal facial expression’ and the display of extreme behaviours such as inhibition and impulsivity or seriousness and shyness (Swillen et al., 1999, Golding-Kushner et al., 1985). Swillen and colleagues (1999b) have proposed that the weak social skills and social withdrawal may in part be explained by the adolescent’s impaired communication abilities and visual-perceptual skills, difficulties adjusting to new situations and their non-verbal learning difficulties. In addition, more recent studies have found that
children with 22q11.2DS exhibit a significant attachment to the mother or other caregivers and display clinging behaviour which may be associated with separation anxiety. It has been proposed that these early childhood temperamental and behavioural difficulties may be early indicators of future psychiatric disorders and longitudinal studies are needed to test these hypotheses (Vogels et al., 2002, Swillen et al., 2000).

1.7.2 Sub-threshold Psychotic Symptoms and Schizophrenia

The onset of frank psychotic symptoms in schizophrenia is commonly preceded by a prodromal period in which there may be altered functioning or symptomatology prior to the onset of formal symptoms of schizophrenia. The prodromal symptoms and behaviours include; attenuated or subthreshold psychotic symptoms, mood symptoms (anxiety, dysphoria, irritability), cognitive symptoms (distractibility & concentration difficulties) and social withdrawal (Lieberman et al., 2001). The subthreshold psychotic symptoms are different from true or frank psychotic symptoms in their intensity (conviction), frequency and duration (Yung et al., 2005). The prodromal period is considered potentially crucial for early intervention and treatment. If the prodromal period could be identified in both the general population and in those with 22q11.2DS and treatment initiated at an early stage, this may have implications for the course of the illness by reducing the duration of untreated psychosis. A shorter duration of untreated psychosis is associated with better response to antipsychotics and improved functional recovery from the first psychotic episode (Perkins et al., 2005). However, limitations of the prodromal symptoms are their non-specificity, as these symptoms also tend to overlap with the range of mental
experiences and behaviours in those who do not subsequently develop schizophrenia and therefore lack predictive validity (Lieberman et al., 2001).

Therefore the prodromal period and associated symptoms have been described as a period of risk though not inevitable risk for the development of psychotic disorders (Yung et al., 2005, Lieberman et al., 2001). Instruments such as the Comprehensive Assessment of the At Risk Mental State (CAARMS) have been designed to assess psychopathology which may indicate the imminent development of a first-episode psychotic disorder. Individuals who were considered as ultra high risk according to the CAARMS were found to have a transition rate of 28% in the first 6 months and 35% within the course of the year of developing a first episode psychotic disorder. In addition, a long duration of prodromal symptoms, poor functioning, high levels of depressive symptoms, subthreshold psychotic symptoms, reduced attention and a family history of psychosis increased the likelihood of developing a psychotic disorder over the course of the year (Yung et al., 2005, Yung et al., 2004, Yung et al., 2003). There have been no studies identified to date which has implemented the CAARMS to identify the 'at risk mental state' in individuals with 22q11.2DS.

1.7.2.1 Subthreshold symptoms and Schizophrenia in 22q11.2DS

In 1992 psychotic symptoms were first reported in 12 out of 90 children and adults with 22q11.2DS where symptoms were described as resembling “chronic paranoid schizophrenia” (Shprintzen et al., 1992). Subsequently several studies have reported the presence of transient or sub-threshold psychotic symptoms in children and adolescents with 22q11.2DS (Gothelf et al., 2007, Debbane et al., 2006, Baker and
Skuse, 2005, Feinstein et al., 2002b). One study found that psychotic symptoms were present in 28% (n=12) of their sample of 43 children and adolescents, of which 17% (5 out of 30) were pre-adolescent. In addition, the children and adolescents that were found to have psychotic symptoms had reduced adaptive skills and significantly decreased verbal I.Q. (V.I.Q.) compared to children and adolescents without psychotic symptoms and the authors suggested that these core symptoms may constitute risk factors for psychosis (Debbane et al., 2006).

A longitudinal study comparing adolescents with 22q11.2DS and a control group with idiopathic developmental disability matched for age and I.Q. found that at initial evaluation both groups had similar symptoms (Gothelf et al., 2007). However at follow up, 32% (9 of 28) of individuals with 22q11.2DS had developed a psychotic disorder compared with 4% (1 of 23) of control individuals and the authors hypothesised that children with 22q11.2DS display more serious psychiatric symptoms as they go through adolescence compared to children with idiopathic learning disability. They suggested that the development of psychotic disorders in individuals with 22q11.2DS is a gradual process with the initial presentation of sub-threshold psychotic symptoms occurring in childhood.

The available evidence suggests that adults with 22q11.2DS have high rates of schizophrenia (Bassett et al., 2007, Bassett et al., 2005, Gothelf et al., 2004b, Murphy et al., 1999). An early study found that 30% (n=15) of a sample of 50 adults with 22q11.2DS had a psychotic disorder of which 24% (n=12) met DSM-IV criterion for schizophrenia (Murphy et al., 1999). However, studies have been conflicting on
the age of onset, the presence of negative symptoms and global functioning of individuals with schizophrenia and 22q11.2DS (Bassett et al., 2003, Murphy et al., 1999, Bassett et al., 1998) and larger and more representative samples are required to resolve the differences between these studies. In addition, studies of adults with 22q11.2DS may have been biased towards a less severe phenotype as these individuals have survived into adulthood. Therefore, the true prevalence of schizophrenia in 22q11.2DS may be higher than the 24% found in studies (Murphy et al., 1999).

The high rates of psychotic symptoms and schizophrenia identified in children and adults with 22q11.2DS could be explained by the underlying learning disability rather than the deletion itself. However it has been suggested that the prevalence of schizophrenia in individuals with learning disability is about 3% and therefore the high rates of schizophrenia found in adults with 22q11.2DS cannot be satisfactorily explained by an underlying learning disability (Murphy, 2002). Furthermore, an early study did not find a correlation between the presence of psychosis and intellectual impairment in individuals with 22q11.2DS and individuals with 22q11.2DS and schizophrenia had a mean I.Q. in the non-disability range (Murphy et al., 1999). A longitudinal study found that children and adolescents with 22q11.2DS had significantly more DSM-IV psychotic disorders compared to an age, gender and I.Q. matched control group (Gothelf et al., 2007). Therefore the evidence suggests that the underlying deletion contributes to the high rates of psychotic disorders in individuals with 22q11.2DS and these high rates cannot be adequately explained by the presence of a learning disability.
Gothelf and colleagues (2007a) reported that the presence of sub-threshold psychotic symptoms, any anxiety disorders (not including phobias), depression and lower verbal I.Q. at baseline are strong predictors of a subsequent diagnosis of psychotic disorders. Specifically, they found that baseline psychotic symptoms interacting with baseline symptoms of anxiety or depression and COMT genotype (Met 158) significantly increased the risk for the subsequent development of psychotic disorders. The authors suggest that children and adolescents with 22q11.2DS should be routinely screened for these high risk predictive symptoms and treated with antipsychotic medication if they display sub-threshold psychotic symptoms to improve the prognosis of a later emerging psychotic disorder.

1.7.3 Schizotypal Personality Disorder and Schizotypy

1.7.3.1 Definition, Diagnosis & Dimensions

There is a view that Schizotypal personality disorder (SPD) may represent a point on a spectrum of related disorders which consist of the severe ‘dementia praecox’ (chronic schizophrenia) on the one end of the spectrum and the milder related conditions, such as SPD on the other end (Tsuang et al., 2005). SPD is found in about 3% of the general population and is considered to be phenomenologically and genotypically related to schizophrenia but quantitatively less severe (Cadenhead and Braff, 2002). There is convincing evidence that SPD shares genetic risk factors with schizophrenia based on familial co-aggregation of the two disorders and may be a milder expression (phenotype) of the schizophrenia genotype (Jones et al., 2000,
Kendler et al., 1995, Kendler et al., 1981). However the nature of these genetic factors and their relationship to frank psychosis still remains unclear (Cadenhead and Braff, 2002).

Alternatively, the concept of 'schizotypy' may be regarded as a collection of traits which are expressed on a dynamic continuum from those that are psychologically well through to the schizophrenia-spectrum disorders and other pathological spectra such as bipolar affective disorders. This approach considers the continuity of the psychosis phenotype to be present across the general population as well as in the clinical populations (Nelson and Yung, 2009, Heron et al., 2003, Rossi and Daneluzzo, 2002, Claridge, 1997). Schizotypy is also referred to as 'psychosis proneness', a term that has been used to describe subclinical psychotic experiences which do not meet the clinical criteria for psychosis (Claridge, 1997). Evidence suggests that those subjects with high schizotypy scores may be at risk for developing schizophrenia-spectrum disorders (Gooding et al., 2005, Kwapis, 1998).

SPD can be measured by either a nosological or a dimensional approach (Battaglia et al., 1997, Raine et al., 1994). SPD is characterised by positive or psychotic-like symptoms (ideas of reference, odd-beliefs, magical thinking, unusual perceptual experiences and suspiciousness) which are reminiscent of the positive symptoms of schizophrenia and negative or deficit-like symptoms (odd-thinking, speech, behaviour, lack of close friends and excessive social anxiety). Factor analyses of the schizotypal symptoms using the Schizotypal Personality Questionnaire (Raine et al. 1994) reveal three factors; cognitive-perceptual deficits (positive dimensions) and
two separate factors from the broad deficit-like symptoms which are defined as social or interpersonal deficits (negative dimension) and cognitive disorganisation (disorganised dimension) (Reynolds et al., 2000, Raine et al., 1994). These dimensions have been consistently replicated and stable across age, sex, religious inclination, cultural and social background (Reynolds et al., 2000, Battaglia et al., 1997). The multi-dimensional construct of SPD bears resemblance to Liddle’s three-dimensional construct of schizophrenia, providing support for the dimensionality or continuity of symptoms between schizophrenia and SPD (Liddle, 1987).

There is evidence that indicates that the psychotic-like symptoms and the deficit-like symptoms may have independent heritability both in normal subjects and in those within the schizophrenic spectrum, therefore suggesting independent transmission of genetic factors (liability) that contribute to the social and cognitive deficits and another set of genetic factors that may contribute to the psychotic-like symptoms (Tsuang et al., 2002). Several studies have shown that high disorganisation dimension scores in probands is associated with a familial risk for psychosis and other studies have found intra-familial (between affected schizophrenic siblings) resemblance of the disorganised symptom dimension. It has been suggested that the disorganised dimension may be a vulnerability trait or marker for psychosis in general and may be the core deficit of psychotic disorders (Schurhoff et al., 2005, Kendler et al., 1997, Cardno et al., 1996). However these findings are not consistent, with other studies which did not find the presence of familiality across symptom dimensions (Schurhoff et al., 2005). Studies have also found sex differences in the expression of schizotypal traits in which woman have been found to score higher in
the positive and social anxiety dimensions of schizotypy and men score higher in the negative and disorganised dimensions (Mata et al., 2005, Fossati et al., 2003, Raine, 1992).

1.7.3.2 Brain Structure & Psychophysiological findings in SPD

Consistent with the understanding of SPD being a related and less severe phenotype of the schizophrenia spectrum disorders, evidence shows many similar structural imaging and psychophysiology findings which are found in schizophrenia being apparent also in SPD.

Individuals with SPD show brain abnormalities in the superior temporal gyrus, Heschl’s gyrus, inferior and middle temporal gyrus and thalamus that are similar to those seen in people with schizophrenia (Dickey et al., 2002, Byne et al., 2001, Gur et al., 2000, Dickey et al., 1999). In comparison reduction of the medial temporal regions including the amygdala and/or hippocampal complex which is a consistent finding in schizophrenia is not found in SPD. In addition frontal cortical volume seems to be preserved in studies done to date on individuals with SPD in contrast to reduction in frontal volumes in many studies on individuals with schizophrenia (Seidman et al., 2002, Dickey et al., 1999). It has been suggested that these structural differences may result in the phenomenological differences that separate the two disorders (Tsuang et al., 2005).
Individuals with SPD have a number of psychophysiological abnormalities that are found in chronic schizophrenia, such as a failure of P50 suppression (sensory gating deficits), deficits in prepulse pulse inhibition (PPI) (capacity to inhibit the startle response), reduced P300 and N400 evoked potentials, (measure of auditory attention & failure of recurrent inhibition respectively) and abnormalities in antisaccade tasks (Cadenhead and Braff, 2002, Cadenhead et al., 2000b, Cadenhead et al., 2000a, Siever et al., 1994, Siever et al., 1982). It has been suggested that these physiological abnormalities are heritable and may be susceptible to common genetic factors across the schizophrenic spectrum which may serve as endophenotypes for genetic studies (Cadenhead and Braff, 2002).

Endophenotypes can be regarded as a stable and quantifiable biological variation or deficits of presumed inherited vulnerability to a disease which may be intermediate between the disease state and the associated genetic vulnerability. They are associated with the illness, co-segregate within families and are also found in unaffected relatives of individuals with the disease. Endophenotypes may have more straightforward inheritance patterns compared to the complex inheritance patterns of schizophrenia and may be used to identify abnormal brain function in schizophrenia spectrum disorders which are linked to abnormal proteins that impair neural function. Furthermore the use of neuro-biological endophenotypes to delineate subtypes within schizophrenia may reduce heterogeneity of a clinically defined disease and aid the identification of genetic determinants (Allen et al., 2009, Cadenhead and Braff, 2002).
Deficits in PPI have also been identified in children with 22q11.2DS, suggesting a common genetic liability between 22q11.2DS, schizophrenia and SPD perhaps at the 22q11 region (Sobin et al., 2006). It has been shown that homozygous PRODH and hemizygous TBX1 and GNB1L mutant mice have reduced PPI, suggesting that the genes in the 22q11 region may have a role in PPI in individuals with 22q11.2DS and in schizophrenia and SPD in the wider population (Paylor et al., 2006, Gogos et al., 1999).

1.7.3.3 Schizotypy and the 22q11 region

One study found that healthy males who were homozygous for the Val 158 COMT polymorphism had significantly higher schizotypy scores on the SPQ (Avramopoulos et al., 2002). Another study did not find any significant association between the COMT variants and PRODH genes in relation to any of the schizotypal components or factors on the SPQ in the population. However, weak associations were found between the low activity Met 158 COMT polymorphism and odd speech, unusual perceptual experiences and suspiciousness subscales. In contrast to the previous study, it was found that the low activity allele in males significantly influenced the total SPQ score, disorganisation factor and the constricted affect subscale (Ma et al., 2007). Although the findings from both studies are conflicting they both suggest that the COMT genotype may be associated with schizotypal traits in the general population.
Individuals with SPD provide an avenue to study the complex liability genes in schizophrenia spectrum disorders, perhaps without the confounding factors of chronic illness, hospitalisation and medication which are common in individuals with schizophrenia. The inclusion of schizotypal traits and/or dimensions in the characterisation of the phenotype may improve our understanding of the relationship between the genotype and phenotype and improve the power of linkage and association studies. By comparing and contrasting the commonalties and differences along the schizophrenic spectrum with phenomological, genetic, imaging and cognitive studies differences and similarities may be identified which may aid the identification of genes and their function which may be then unique to schizophrenia (Schurhoff et al., 2005, Siever and Davis, 2004, Heron et al., 2003, Cadenhead and Braff, 2002, Jones et al., 2000).

1.7.4 Autism Spectrum Disorders (ASD)

Autism spectrum disorders (ASD) encompass a continuum of traits diagnosed on the basis of impaired social interaction, difficulties in communication and the presence of repetitive and stereotyped behaviour (APA, 1994). ASD are etiologically complex and form a heterogeneous group of disorders. The aetiology of ASD remains unknown in more than 80% of affected individuals. Single gene defects, such as Fragile-X syndrome and Rett syndrome account for approximately 20% of the cause of ASD. Large chromosomal abnormalities have been identified by traditional cytogenetic approaches and have been estimated to account for 7% of cases of ASD. However, the improvement of cytogenetic methods and analysis has allowed for the screening of chromosomal abnormalities with increased resolution resulting in
the identification of cryptic microdeletions or microduplications (copy number variations). These findings suggest that the proportion of cases due to chromosomal structural variants may be much higher than the 7% identified by standard cytogenetic analysis alone. It has been suggested that there is a need to identify a homogenous subgroup of individuals (such as those with underlying CNV) with specific behavioural and physical phenotypes which may decrease heterogeneity and may ultimately assist in the identification for an underlying genetic cause of ASD (Lo-Castro et al., 2010).

One study investigated 28 candidate loci in 247 individuals with intellectual disability, 260 individuals with autism spectrum disorders, 236 individuals with schizophrenia or schizoaffective disorder and 236 controls. Recurrent copy number variations (CNV) were found in cases at 39.3% of the selected loci and found at significantly increased rates compared to controls. An interesting finding was that there was a significant association (p=.02) found between autism and a 350-kilobase deletion located at 22q11 which spanned the PRODH and DGCR6 genes (the authors only selected PRODH loci in the 22q11 region). The authors suggest that the recurrent CNV contain genes that are predominantly involved in neurotransmission, synapse formation and maintenance. In addition they suggest that the CNV may contribute to the disease process in the three conditions and supports the basis of a shared biological pathway in these neurodevelopmental disorders (Guilmatre et al., 2009). It is likely that other loci on the 22q11 region may also be associated with autism spectrum disorders and these findings lend support to genes within the 22q11 region being involved in ASD and neurodevelopment.
Several studies have found a high prevalence of autistic spectrum disorders (ASD) in children with 22q11.2DS (Vorstman et al., 2006, Fine et al., 2005, Niklasson et al., 2001). By the use of strict screening measures and a structured diagnostic interview in 98 children with 22q11.2DS, one study found that 14% (14) of the children met criteria for an autistic spectrum disorder (ASD) (Fine et al., 2005). Using similar methodologies another study found 50% (n=30) of a sample of 60 children and adolescents with 22q11.2DS met criteria for an ASD. In addition, the authors reported psychotic symptoms in 27% (n= 16) of the sample in which 12% (n=7) met criteria for a psychotic disorder and 5 of the 7 individuals who had a psychotic disorder also fulfilled a diagnosis of an ASD. The authors suggest that autistic and psychotic disorders are major features of the behavioural phenotype in children with 22q11.2DS. However, the authors also suggest that the autistic symptoms identified in this study may be a reflection of the neurodevelopmental abnormalities identified in individuals with schizophrenia and that the autistic symptoms identified may represent prodromal features of psychosis rather than exclusively an ASD (Vorstman et al., 2006). However, recent studies using whole genome technologies have identified some genetic overlap between ASD and schizophrenia (one study as mentioned above identified CNV in the 22q11 region at the PRODH gene), which suggest that these disorders may share underlying pathophysiological mechanism and may also share behavioural phenotypes (Spek and Wouters, 2010, Guilmatre et al., 2009). Therefore, it has been suggested that studies should consider the relationship of genes to a dimensional characterisation of psychopathology across the diagnostic categories and which also includes ASD and cognitive impairment.
(Carroll and Owen, 2009). There are limited studies done to date in individuals with 22q11.2DS to identify the overlap and differences in psychiatric and behavioural problems in individuals with autistic spectrum disorders/traits.

1.7.5 Attention-Deficit Hyperactivity Disorder (ADHD)

ADHD is the most commonly occurring and heritable childhood-onset psychiatric disorder. It is characterised by inattention with/or without hyperactivity-impulsive behaviour leading to impaired social, academic or occupational functioning. There are three subtypes of ADHD described; inattentive subtype, hyperactive/impulsive subtype and a combined subtype (APA, 1994). The estimated world-wide prevalence of ADHD is 5.3% in children and adolescents with boys having higher rates of ADHD compared to girls (Pastor and Reuben, 2008, Polanczyk et al., 2007). ADHD has been found to decline with age, though continues into adulthood affecting between 2.5%-4.4% of adults (Fayyad et al., 2007). ADHD has been found to have a high degree of co-morbidity with other psychiatric disorders. Studies of children and adolescents with a diagnosis of bipolar affective disorder have found rates of ADHD ranging from 60-90%. One study found that lifetime ADHD is a frequent co-morbid condition in adults with bipolar disorder and another found that bipolar disorder in adults is frequently preceded by ADHD in childhood (Henin et al., 2007, Nierenberg et al., 2005, Biederman et al., 1996, West et al., 1995). One study found that children with ADHD had more symptoms of autism compared to siblings or normal controls and in addition found a genetic subgroup of ADHD with increased rates of autistic symptoms, neurodevelopmental, conduct and motor disorders (Mulligan et al., 2009). Difficulties with attention are frequently found in individuals with
Schizophrenia and also in their high risk relatives and proposed as a marker of risk for the later development of the disorder. It has been reported that the motor and attention difficulties seen in children of individuals with schizophrenia resemble DSM ADHD. Similarly, studies have shown that ADHD and conduct disorders are found in high rates in young relatives of patients with schizophrenia (Keshavan et al., 2005, Keshavan et al., 2002, Erlenmeyer-Kimling et al., 2000). Prospective studies have found that children who develop schizophrenia have increased rates of attention impairments and retrospective studies have found that 40% of individuals with childhood schizophrenia had a history of pre-morbid attention problems and hyperactivity suggestive of ADHD (Cornblatt and Kelpp, 1994, Russell et al., 1989). Therefore it has been questioned whether difficulties with attention and clinically diagnosed ADHD represents a risk factor for the emergence of psychosis. One prospective study of children with ADHD who were followed up 15-21 years later found that none of the sample developed psychosis (Mannuzza et al., 1998). It has been suggested that as ADHD is a heterogeneous disorder, that only a small proportion of individuals with ADHD and familial risk may be at risk of developing schizophrenia and longitudinal studies are required to determine whether ADHD predicts an increased risk for the emergence of psychosis (Keshavan et al., 2005, Keshavan et al., 2002).

1.7.5.1 ADHD and 22q11.2DS

Attention Deficit Hyperactivity Disorder (ADHD) is the most prevalent psychiatric disorder in children with 22q11.2DS, occurring in approximately one third to half of all children (Antshel et al., 2006, Zagursky et al., 2006, Gothelf et al., 2004). In contrast,
conservative estimates indicate prevalence rates of ADHD in non-deleted school aged children to be around 3.5% (Solanto, 2001). One study compared 28 children with 22q11.2DS to 29 age and cognitively matched controls and found that both groups had a high prevalence of psychopathology including ADHD without statistical significance being found between the groups (Feinstein et al., 2002a). This suggests that the high rates of psychopathology reported in individuals with 22q11.2DS may be a reflection of their cognitive impairment rather than it being specific to a 22q11 deletion. However, the authors acknowledged that ascertainment bias and small sample size may have confounded these results.

In a larger sample of 51 individuals with 22q11.2DS, 41% (n=21 age range 6-20 years) received a diagnosis of ADHD. In addition there was a significant 6:1 male to female ratio of ADHD in this sample and a greater proportion received a diagnosis of the combined type ADHD (hyperactive-impulsive and inattentiveness). Furthermore, there was a significantly larger prevalence of ADHD in the first-degree relatives of patients with ADHD compared with those without ADHD, though the two groups had similar I.Q. scores, degree of facial dysmorphism and cardiac and cleft anomalies. It was suggested that ADHD in 22q11.2DS may have a genetic basis and that developmental and physical factors may play a smaller role (Gothelf et al., 2004). Another study found in a sample of 84 children with 22q11.2DS that 43% (n=36) received a diagnosis of ADHD, mostly of the inattentive subtype, with no gender differences identified and in contrast to Gothelf and colleagues (2004a), they did not find a high prevalence rate of ADHD in the first or second degree relatives of individuals with 22q11.2DS and ADHD (Antshel et al., 2006).
A longitudinal study of individuals with 22q11.2DS did not find the presence of ADHD to be associated with a greater risk of the later development of psychosis, despite ADHD being the most common psychiatric disorder found in individuals with the disorder (Gothe1f et al., 2007). However, as ADHD is a common disorder in individuals with 22q11.2DS, perhaps a subtype of ADHD with specific co-morbidities may be associated with greater risk of psychosis in 22q11.2DS. Longitudinal studies will be required to study whether attention problems and ADHD are risk factors for the later development of psychosis in individuals with 22q11.2DS. Consideration should be given to the evaluation of subtypes of ADHD and co-morbid psychiatric and behavioural problems to determine whether there is an association with the emergence of a later psychosis.

1.7.6 Affective, Anxiety and Obsessive Compulsive Disorders

Several studies have reported high rates of affective disorders, anxiety disorders, phobic disorders and obsessive-compulsive disorders in children and adults with 22q11.2DS (Antshel et al., 2006, Gothe1f et al., 2004b, Feinstein et al., 2002a, Murphy et al., 1999). Initially early studies reported high rates of bipolar disorder (47%) in a group of children and adolescents with 22q11.2DS, although subsequent studies failed to replicate this finding (Papolos et al., 1996). In a study of 50 adults with 22q11.2DS, 12% (n=6) met DSM-IV criteria for major depression (Murphy et al., 1999). Several studies have found that, compared to controls, adolescents with 22q11.2DS have high rates of depression, dysthymia and anxiety disorders and it has been suggested that the combination of pubertal changes, increased social
changes and genetic predisposition may place these individuals at a heightened risk of developing anxiety and depressive disorders (Antshel et al., 2006, Arnold et al., 2001, Swillen, 2001, Swillen et al., 2001, Swillen et al., 1999). In a sample of 43 people with 22q11.2DS, it was found that 33% (n=16; mean age 18) had obsessive compulsive disorder (OCD) which occurred at an early age and was unrelated to the presence of a learning disability. The authors suggest that the high rates of OCD found in individuals with 22q11.2DS may provide an insight to the genetic basis of OCD (Gothelf et al., 2004b).

1.8 Summary of Review

22q11.2DS is a known genetic disorder with high rates of psychiatric disorders. Individuals represent a homogenous model in which specific behavioural phenotypes may be linked to the underlying known genetic mutation providing an avenue to understanding the link between clinical disorder and pathophysiological mechanisms. However, the delineation of the psychiatric phenotype and particularly knowledge concerning the risk factors for the development of psychiatric disorders in 22q11.2DS remains unclear. In addition recent genetic advances have identified other CNV in other chromosomal regions to be significantly associated with schizophrenia, therefore there is a growing need to characterise the psychiatric symptoms/disorders associated with the different genetic mutations as this may provide insight to the role of these genetic abnormalities and pathophysiological mechanism in the development of these disorders. In 22q11.2DS there remains the ongoing need for systematic research to examine the psychiatric disorders and to identify vulnerability
or risk factors of these disorders so that comprehensive monitoring and treatment protocols can be established in Ireland for this high risk group of individuals.

This thesis seeks to examine the prevalence and association of psychiatric disorders, vulnerability factors and behavioural difficulties in a sample population of individuals with 22q11.2DS. In addition this thesis aims to identify individuals with 22q11.12DS who may be at a heightened risk of developing a psychotic disorder and deemed to be at an 'at risk mental state' with comprehensive psychiatric assessment tools and then to characterise the co-morbid psychiatric, behavioural and physical health profile of this group. Furthermore, the thesis aims to examine the prevalence of autism spectrum symptoms/disorders and schizotypal features and their associations with other psychiatric disorders and behavioural problems in individuals with 22q11.2DS. It is anticipated that the findings could be used to delineate the psychiatric phenotype in individuals with 22q11.2DS. The research aims to increase current understanding of the behavioural (psychiatric) phenotype of 22q11.2DS with the use of systematic interviews and questionnaires. It is anticipated that this work may serve as the foundation for future longitudinal studies of 22q11.2DS in Ireland and may facilitate genetic research, neuroimaging studies and service development for individuals with 22q11.2DS in Ireland and provide a source of investigating the psychiatric correlates of emerging CNV which are significantly associated with schizophrenia.
CHAPTER 2 – AIMS & HYPOTHESES
Overview

In this chapter I will outline the aims and hypotheses tested in this thesis.

2.1 Objectives of the study and Hypotheses

The review of the literature at the time of carrying out the study guided the formulation of the hypothesis and the development of the methodology. The general aim of this thesis is to comprehensively assess and describe the psychiatric and behavioural phenotype of a population cohort of individuals with 22q11.2DS in Ireland. The specific aims of the study are:

1. To examine the prevalence and association of psychiatric disorders and behavioural problems in a sample population of cases with 22q11.2DS.

2. To measure the prevalence of schizotypy in a sample population of cases with 22q11.2DS and the association of schizotypy with other psychiatric disorders.

3. To identify cases with 22q11.12DS who may be at a heightened risk of developing a psychotic disorder and deemed to be at an ‘at risk mental state’ with comprehensive psychiatric assessment tools and then to characterise the co-morbid psychiatric, behavioural and physical health profile of this group.

4. To identify questionnaire elements and scores that can discriminate cases with 22q11.2DS from their sibling controls
In this thesis, I tested the following hypotheses:

1. In a sample of cases with 22q11.2DS, the prevalence of behavioural problems will be higher compared to the sibling control group.

2. Schizotypy scores will be higher in a sample of cases with 22q11.2DS compared to the sibling control group.

3. In a sample of cases with 22q11.2DS the prevalence of psychiatric disorders will be higher compared to the sibling control group.

4. Behavioural problems will be higher in a sample of cases with 22q11.2DS and subthreshold psychotic symptoms compared to those cases with 22q11.2DS and without subthreshold psychotic symptoms.

5. Schizotypy scores will be higher in a sample of cases with 22q11.2DS and with subthreshold psychotic symptoms compared to those cases with 22q11.2DS and without subthreshold psychotic symptoms.

6. Schizotypy scores will be higher in a sample of cases with 22q11.2DS and with 'any psychotic symptoms' (includes subthreshold psychotic symptoms or psychotic disorders) compared to those individuals with 22q11.2DS and without 'any psychotic symptoms'.

7. In a sample of cases with 22q11.2DS and sub-threshold-psychotic symptoms the prevalence of co-morbid psychiatric disorders will be higher compared to those cases with 22q11.2DS and without subthreshold psychotic symptoms.

8. There is an association between physical disorders and psychiatric disorders in individuals with 22q11.2DS.
CHAPTER 3 – METHODS
Overview

In this chapter I will outline the methodology used in this thesis.

3.1 Recruitment of Cases & Controls

Subjects that were recruited into the study were residing either in Northern Ireland or in the Republic of Ireland. At the time of the study 32 subjects were identified with 22q11.2DS at the Northern Ireland Regional Genetics Centre and 76 subjects were identified with 22q11.2DS at the National Centre for Medical Genetics (Our Lady’s Hospital for Sick Children, Dublin). Therefore it was known at the time of the study that 108 subjects had a confirmed diagnosis of 22q11.2DS in Ireland.

Subjects were recruited from two main sources:

1. Data-base at the two genetic centres as above.

2. 22q11.2DS Support groups (22q11.2DS Ireland & Max Appeal (U.K))

The author did not have access to the data-base in the genetic centres containing the contact details of eligible participants due to reasons of medical confidentiality. Information concerning the study with contact details and invitation to participate in the study with an enclosed response sheet was sent to eligible participants aged 18 years and above and to parents of those below 18 years of age by the Consultant Geneticist from both Genetic Centres. Participants/parents that were willing to participate in the study either contacted the author directly or sent the enclosed response sheet and were then contacted by the author to arrange a visit to their
homes to commence the assessment. Questionnaires were sent by post prior to the assessment.

The assessment commenced with a detailed explanation of the study and its purpose. Participants and parents were informed that the data collected was for scientific use only and would remain strictly confidential and that they were also free to leave the study if they so wished. Informed consent was taken from participants who were 18 years of age and above. If the author had concerns about the capacity of an adult participant to give informed consent, this was discussed with their parents/guardians and they were nominated to provide informed permission for participation in the study on behalf of the adult participants. For participants who were younger than 18 years of age informed permission to participate in the study was obtained by their parents/guardians and assent from the child was obtained. The author interviewed all participants who were recruited into the study and their parent(s) / guardian.

Details of the study and contact information were placed on the website of Max Appeal (support group for individuals with 22q11.2DS and their family) and participants / parents who were interested in participating in the study contacted the author directly. Details of the study were announced at the 22q11.2DS Ireland support group conference and those participants/parents who were interested in participating in the study contacted the author directly.
The author had no clinical involvement with either of the two sources of recruitment of subjects.

A sibling control group was also recruited who were closest in age to the case with 22q11.2DS. Information was given to the sibling and parent(s) and the author further explained to the sibling and parent(s) the details and purpose of the study. If the sibling was willing to participate, informed consent was obtained from sibling participants who were 18 years of age or above. For sibling participants who were younger than 18 years of age informed permission to participate in the study was obtained by their parents/guardians and assent from the child was obtained. Due to the length of the assessment process usually the siblings were assessed on a different day to the cases.

A sibling control was chosen due to several reasons; firstly due to the assumption of shared environment between the cases and sibs, secondly siblings provide the closest genetic match to the case without having the genetic deletion and they are easily accessible to recruit. Therefore the siblings do not have the deletion in question but are otherwise closely comparable to the case due to shared environment and being the closest genetic match.

The author prepared the information leaflets, response sheets and consent forms which were distributed to study participants and these are included in Appendix 1.
3.2 Inclusion/Exclusion Criteria

The inclusion criteria required participants to be six years and above at the time of the study, to have an established diagnosis of 22q11.2DS prior to entry into the study and had to be residing in Ireland at the time the study. Individuals who had other chromosomal abnormalities were excluded from the study.

Individuals with either a de-nova or an inherited deletion were included in the sample. If a family had more than one individual with 22q11.2DS, all affected members were invited to participate in the study. Therefore it was anticipated that some subjects within the 22q11.2DS sample would be non-independent. However, it was viewed by the author that the inclusion of subjects in the sample with both a de-nova and an inherited deletion would be representative of the population as 10% of individuals with 22q11.2DS have an inherited deletion (Ryan et al., 1997). Furthermore, the exclusion of non-independent subjects would reduce the sample size.

3.3 Ethical Approval

All aspects of the project were approved by the Ethical and Research Committees at Beaumont Hospital, Our Lady’s Hospital for Sick Children in Dublin, The City Belfast Hospital and the Office for Research Ethics Committees Northern Ireland (Letters of ethical approval, see Appendix 2)
3.4 Demographic, Personal, Medical, Psychiatric, Social & Family History Data

Background information about each participant was collected from the parent(s) using the standardised background information in the introductory interview: scoring sheet in the Kiddie-SADS-Present and Lifetime Version (K-SADS-PL). This standardised format contains the date of birth, age, sex, race, home environment (who is at home), number of siblings and age, health care history (where health care received, last visit, illness/conditions, hospitalisations, surgery, medication history, current medications, allergies, immunisation history), developmental history, history of abuse, psychiatric treatment history, family history of medical/psychiatric illness and finally social adaption and social relations (Kaufman et al., 1997). This format was also administered to participants who were 18 years and above and/or their parents if they were available. This standardised format allowed a systematic approach to collecting background information on all participants (see Appendix 3).

Details of the physical disorders were obtained by parents as detailed above. In addition further information was obtained from letters made available by parents and/or general practitioners of previous hospitalisations / outpatient letters etc. Patient’s consent or parental permission was provided to obtain medical records from the participant’s general practitioners.

3.5 Obstetric History & Neurodevelopmental Details

The Neurodevelopmental Questionnaire was given to the parents of all participants to complete if they were available. This questionnaire aims to elicit data on a wide
range of areas; family history, antenatal history, obstetric history, early infancy, developmental milestones, developmental coordination disorder, play, sensory difficulties and attention control (see Appendix 4). This questionnaire was developed by a child & adolescent psychiatrist, though at the time of the study had not been used in a published study (Dr Sarah Buckley, Child and Adolescent Consultant Psychiatrist, St Patrick’s Hospital, Dublin 8).

From the information that was made available by parents and detailed in the Neurodevelopmental Questionnaire, birth complication(s) were considered when the following events occurred; instrumental delivery, emergency caesarean section/delivery, prolonged labour (>18hrs) and foetal distress.

3.6 Clinical Evaluation

The parent(s) of participants who were below 18 years of age were administered a structured interview, the computerised National Institute of Mental Health Diagnostic Interview Schedule for Children version IV for parents (NIMH-DISC-P-IV 1997). This instrument was administered by the author. This structured interview covers over 30 psychiatric disorders of children and adolescents which meets diagnostic criteria as specified in DSM-IV, DSM-III-R and the ICD-10. The interview is organised into six diagnostic sections: Anxiety Disorders, Mood Disorders, Disruptive Disorders, Schizophrenia and Miscellaneous Disorders. Within each section the diagnosis is assessed for the presence of the symptom(s) within the past year and also currently (last four weeks). The parental responses to the computer interview is then
automatically tabulated and scored by the DISC software using a computer algorithm programmed in Statistical Analysis Software (SAS). Specific DSM-IV diagnoses and a list of reported/absent symptoms as reported by parents is automatically generated (Shaffer et al., 2000, Jensen et al., 1995).

The DISC-P-IV interview was supplemented with the Psychosis module of the Kiddie-SADS-Present and Lifetime Version for parents (K-SADS-PL). Supplementation with the psychosis module from the K-SADS-PL facilitated a semi-structured interview with the parents and allowed the author to gain more detailed information about responses both systematically and flexibly. A scoring system based on the interview was: 0 indicates no delusion or hallucination, 1 indicates subthreshold, 2 indicates definite hallucinations or delusions (see Appendix 5).

Following the parent interview participants who were less than 18 years of age were administered the psychosis module of the K-SADS and the Comprehensive Assessment of the At Risk Mental State (CAARMS) (2006) (see Appendix 6). The CAARMS aims to provide a comprehensive assessment of psychopathology which may indicate the imminent development of a first-episode psychotic disorder and to assess whether a participant may meet ultra high risk (UHR) status based on the CAARMS criteria. The CAARMS includes the following subscales: disorders of thought content, perceptual abnormality, conceptual disorganisation, motor changes, concentration & attention, emotion & affect, negative symptoms, behavioural change and general psychopathology. Scores for each subscale are rated as a global score and a frequency/duration score from 0-6. The CAARMS has been found to have an
excellent inter-rater reliability, shows good predictive, concurrent and discriminant validity (Yung et al., 2005). As individuals with 22q11.2DS are at high risk of developing psychosis compared to the general population, the CAARMS was chosen for this study to determine whether a possible 'at risk mental state' could be identified in participants with 22q11.2DS.

The CAARMS defines the 'at risk mental state' with an operationally set of clinical features that may precede a first psychotic episode. The features may either comprise of state or trait factors. The state factors are either the 'attenuated psychotic group' ('this criterion identifies young people at risk of psychosis due to subthreshold psychotic symptoms. The symptoms do not reach threshold levels for psychosis due to subthreshold intensity, that is they are not severe enough or they have psychotic symptoms but at a subthreshold frequency, the symptoms do not occur often enough') or the brief limited intermittent psychotic symptoms (BLIPS) group ('this criterion identifies young people at risk of psychosis due to recent history of frank psychotic symptoms that resolved spontaneously (without antipsychotic medication) within one week'). The trait-based criteria include a combination of trait factors of psychosis, which are a family history of psychotic disorders or the individual meeting diagnostic criteria for schizotypal personality disorder.

At the time of the study, the CAARMS had not been validated for those below 14 years of age or in individuals with intellectual disability (Yung et al., 2005, Yung et al., 2004, Yung et al., 2003). Individuals with 22q11.2DS most commonly have a learning disability in the borderline-mild range and therefore it was assumed that
participation with the interview was valid for the majority of subjects. The CAARMS was also administered to those younger than 14 in this study though the author was aware that it was not yet validated in this younger age group. It was decided as the CAARMS provides a systematic method of assessment for possible prodromal or 'at risk mental state' this approach would be applied to all participants despite age to ensure a degree of uniformity in the assessment or identification of possible prodromal symptoms. In addition it was determined that the administration of the CAARMS in the younger age group with 22q11.2DS may offer a method to assess the age of the commencement of prodromal or any subtle psychotic symptoms given the high risk of psychosis. It was anticipated that the younger age group may have difficulties with this interview process, due to cognitive or linguistic disabilities and also due to the length of the interview itself. The psychotic supplement of the K-SADS was also administered in conjunction with the CAARMS; an interview which is validated in young children. If there was a lack of understanding with any of the questions it was marked as 0 and not rated. If there was significant difficulty (cognitive or linguistic) the interview was not carried out.

Participants who were 18 years or older were administered the computer based interview, Schedule for Clinical Assessment in Neuropsychiatry (SCAN) (Wing et al., 1990). The data from the interview is processed by the computer software to provide an automated diagnosis based on the ICD-10 and DSM categories. A list of items which were rated as present was provided. In addition the CAARMS was administered to those individuals without an established diagnosis of a psychotic disorder prior to entry into the study. Where a diagnosis of schizophrenia was made
the versions of the Schedule for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984) and the Schedule for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983) was also administered (see Appendix 7).

The individual's level of general functioning over the past year, six months and the last month was determined based on all the available clinical information (clinical evaluation, parents interview and school report) and with additional brief unstructured interview with parents/carers. The level of functioning was rated with The Social and Occupational Functioning Assessment Scale (Goldman et al., 1992) (see appendix 8). The level of functioning for the past month was used in the analysis for the study.

The clinical evaluation was administered by the author to the sibling control group in the same manner as was administered to the 22q11.2DS case group.

The author received one day training by a recognised trainer on the use of the K-SADS-PL (Professor Mc Nicholas, Child and Adolescent Psychiatrist, Lucena Clinic, Dublin). The author received two days of training on the use of the CAARMS by a recognised trainer (Ms Magenta Simmons, PACE Clinic, Australia). The author received five days of training on the use of the SCAN interview by recognised trainers (Dr TS Brugha, Ms Irene Cheney and Dr A Cardno, University of Leicester, U.K).
3.7 Questionnaires

3.7.1 Schizotypal Personality Questionnaire (SPQ)

The Schizotypal Personality Questionnaire (SPQ) was given to participants 12 years and older to complete. The SPQ is a self-rating questionnaire which contains 74 items with yes/no answers and identifies the three factors of schizotypy (Cognitive-Perceptual, Interpersonal and Disorganised) which can be derived by summation of the nine sub-scale schizotypal traits raw scores. All items endorsed as ‘yes’ are scored as 1. In the original population on which the instrument was developed a ten percent high-low cut-off on the distribution of the total score were 41 and 8 respectively. It is recommended that researchers should develop their own-high-low cut offs based on normative data on the population of interest. As there has not been any published data on cut-off scores for subjects with 22q11.2DS, a cut-off of 41 and 8 was used in this study. The SPQ has been found to have high internal reliability (coefficient alpha between 0.90 to 0.91), sampling validity (all nine schizotypal traits assessed), test-retest reliability (0.82), convergent validity (Pearson correlation r=0.59-0.81) and discriminant validity (Pearson correlation 0.63). Concerning criterion validity, it was found that of the 11 subjects who scored on the top ten percent of the total SPQ scores, 6(55%) were given a clinical SCID-II diagnosis of schizotypal personality disorder according to the DSM-III-R criterion. No subjects that received a low SPQ score fulfilled a clinical diagnosis of Schizotypal personality disorder according to the SCID-II (Raine, 1991). The SPQ is also available in an abbreviated format, the SPQ-B, which consists of 22 items that were most reliable and valid from the full SPQ. The abbreviated form has been validated in the adolescent population, although it has been shown that the correlation between
SPQ-B total/factor scores and the clinical interview of Schizotypal personality disorder are poor for the disorganised factor (r=.36) (Fonseca-Pedrero et al., 2009, Raine and Benishay, 1995). As the disorganised factor has been considered a vulnerability marker for the development of psychosis, the extended version of the SPQ was chosen in this high risk group, although it has not been validated in the adolescent population (Cardno et al., 1996). The administration of the SPQ in participants aged 12-18 took place under supervision by the author who read each of the questionnaire items verbatim. If the participant required clarification of questions this was briefly done by the author. The participants placed their own choice on the questionnaire and if he/she did not understand the question the participant was instructed to mark the response with a ‘No’ (see Appendix 9).

3.7.2 Social Responsiveness Scale (SRS)

The Social Responsiveness Scale (SRS) (Constantino et al., 2003) is a 65-item questionnaire which was given to the parent(s) of participants aged 6-18 years of age to complete. The SRS covers the various dimensions of interpersonal behaviour, communication and repetitive/stereotypic behaviour that are a feature of autism spectrum disorders. A Likert scale response format is used that has been found to be sensitive and reliable over a range of symptom severity. The SRS has been used as a screening tool and to assist clinical diagnosis. The SRS is designed to assess autistic impairment on a quantitative scale across a wide range of severity. The SRS includes items that identify autistic impairment in social awareness, social cognition, social communication, social motivation and mannerisms characteristic of autism spectrum disorders.
The psychometric properties of the SRS has been evaluated and it has been found that the total score alpha reliability estimates are above .90 for both males and females rated by both parents. The alpha coefficients for the subscales range from .76 to .91 (median .85). Scores on the SRS have been shown to discriminate between children with and without autistic-spectrum disorders and have been shown to correlate strongly with the Autism Diagnostic Interview-Revised (ADI-R) (r=0.65-0.77) and were unrelated to I.Q (Constantino et al., 2003). However one study found that the SRS showed lowered specificity in a sub-sample with elevated behavioural problems (Charman et al., 2007). In males a cut-off at 70 for the SRS Total raw score is recommended for the purpose of screening for any autism spectrum condition in schools or other general population groups. Use of this cut-off results in identifying 77% of cases where a previous diagnosis had been established (sensitivity of .77). For females a cut of point at 65 is recommended when screening in schools or the general population, with similar level of specificity (.75). In children with developmental problems a higher threshold/cut of point is recommended to reduce the chance of over identification. A cut-off of 85 is recommended, which may decrease the sensitivity, though increase the specificity in this group of children to 90% for both males and females. It is suggested that in most clinical and educational settings that SRS scores at or above 85 from two separate informants provides very strong evidence of the presence of an autism spectrum disorder.

In addition the questionnaire allows for the conversion of the raw scores to T-scores with similar interpretation for both genders. Total T-score of 76T or higher, is
suggestive of a strong association with a clinical diagnosis of autism spectrum disorders. Scores in this range also suggest a severe interference in everyday social interaction. Total $T$-score of $60T$ through $75T$, suggests deficiencies in reciprocal social behaviour that are clinically significant and may result in mild to moderate interference in everyday social interactions. Total $T$-score of $59T$ or less suggests the absence of an autism spectrum disorder and any psycho-social dysfunction (Constantino and Gruber, 2005). Both raw scores and $T$-scores are analysed in the study (see Appendix 10).

3.7.3 Social Communication Questionnaire (SCQ)

The Social Communication Questionnaire (SCQ) (Rutter et al., 2003), lifetime form was given to available parent(s) of all participants to complete. The SCQ is a 40-item parent-report screening measure that draws on the symptomatology associated with autism spectrum disorders. The items are administered in a yes/no response format. Each item is scored 0 or 1, with 1 being the support of each symptom. The SCQ was developed from the Autism Diagnostic Interview-Revised (ADI-R) and is parallel to the longer interview. Validation studies of the psychometric properties of the SCQ have indicated that the alpha index of internal consistency ranges from .84 to .93 with increasing age. Studies have shown that the SCQ correlates with the ADI-R at both total scores and domain score levels and largely unaffected by age, gender, language level and performance I.Q and validates the SCQ as a screening questionnaire. Similar to the SRS the SCQ also was found to have lower specificity in a subsample with elevated behavioural problems (Charman et al., 2007, Rutter et al., 2003). It is recommended that a cut-off score of 15 or greater be used as an
indication of possible autism spectrum disorders and a lower threshold be used if there are other risk factors, such as language impairment so that a comprehensive assessment can be done on these individuals. The total SCQ score of 15 or more for differentiating Autism spectrum disorders from other diagnoses has a sensitivity of .85 and a specificity of .75 (Rutter et al., 2003). The SCQ can also be used to determine sub-scores that match the *Reciprocal Social Interaction* domain, the *Restricted, Repetitive domain* and the *Communication domain* of the ADI-R. The SCQ sub-scores have been found to agree well with the ADI-R scores, although the factorial structure of the SCQ does not provide a close fit with the ADI-R domains and the subscales have not been extensively researched at the time of the study (Rutter et al., 2003). Therefore, only the total SCQ are analysed in this study (see Appendix 11).

### 3.7.4 School Report Form

The *School Report Form* was given to the parents of the school aged children to be given to the participant's teacher to compete. This questionnaire is divided into 9 sections. It asks the teacher to compare general ability of the child in relation to peers, the attention, and activity level of child in comparison to peers, attendance level, response to rules, self-esteem and peer relationships. Descriptive information from this questionnaire was obtained to provide information predominantly concerning the child's functioning at school (McKenna and McNicholas, 1999) (see Appendix 12).
3.7.5 Conners' Parent Rating Scale- Revised (S)

The Conners' Parent Rating Scale- Revised (S) was given to parents of children aged 6-17 to complete. The Conners' Parent Rating Scale is a screening tool to assist in determining whether children have ADHD. The parents' short version contains 27 items with four possible answers (0-3) and covers a subset of the subscales and items on the long-parent form. The scales on the short version include; oppositional, cognitive problems/inattention, hyperactivity and Conners' ADHD Index. T-Scores of greater than 60 are considered a cause for concern with a score of greater than 61 mildly atypical and scores of greater than 70 markedly atypical in the general population (Conners, 2000)(see Appendix 13).

3.8 Behavioural Evaluation

3.8.1 Child Behaviour Check-list (CBCL)

Parents of participants aged 6-17 years of age completed the Child Behaviour Check-list (CBCL) (Achenbach, 1991). The first section of the questionnaire consists of 20 competence items and the remainder of the questionnaire consists of 120 items on behaviour and emotional problems over the past 6 months. The 20 competence items are grouped into three scales (activities, social and school). The CBCL measures the following constructs/syndromes: social withdrawal, somatic complaints, anxiety/depression, social problems, thought problems, attention problems, delinquent behaviour and aggressive behaviour. The CBCL examines the eight constructs/syndromes under two broad groupings of internalizing and externalizing problems. Internalizing problems combines the social withdrawal, somatic
complaints and anxiety/depression scales. The externalizing problems combines the delinquent behaviour and aggressive behaviour scales.

Normative data for the CBCL was obtained from a sample of 2,368 children aged 4-18. None of the children in the sample had received mental health services or special remedial school classes in the 12 months preceding assessment with the CBCL. Test-retest reliability assessments resulted in correlation coefficients of .87 for the Social Competence scale and .89 for the Behaviour Problems Scale. Inter-parent agreement was found to be high ranging on average from .74-.78 for the social competence scales and from .65-.75 on average for the behaviour problems scales. Cronbach’s alpha values for the different scales ranged from .46 on the activities subscale to .93 on the externalising subscale for boys and from .54 on the activities subscale to .93 on the externalising subscale for girls. Among the eight syndromes, cronbach’s alpha values ranged from .62 to .92 for boys and from .66 to .92 for girls. Construct, content and criterion related validity was assessed by correlating CBCL scale scores with the Conners Parent Questionnaire and with the Revised Behaviour Problem Checklist. The correlations between the CBCL and the Conners scale ranged from .59 to .86 and the correlations between the CBCL and the Revised Behaviour Problem Checklist were between .59-.88 (Achenbach, 1991) (see Appendix 14).
3.8.2 *Strengths and Difficulties Questionnaire (SDQ)*

The *Strengths and Difficulties Questionnaire (SDQ)* was given to the parents of individuals aged 6-16 to complete. The SDQ is a brief questionnaire which covers common areas of emotional and behavioural difficulties. 25 items are present which are divided between five scales of five items each. Scores are generated for conduct problems, hyperactivity, emotional symptoms, peer problems and pro-social behaviour. The SDQ was evaluated on 403 Caucasian parents of children attending child psychiatric clinics in London and it was found that the range of test-retest values were 0.70 to 0.85 and the range of internal consistency were 0.51 to 0.76 (Goodman, 1997). One study found that the scores from the SDQ and CBCL were highly correlated and equally able to discriminate psychiatric from dental cases. The SDQ was judged against a semi-structured interview, and it was found to be significantly better than the CBCL at detecting inattention and hyperactivity, and at least as good at detecting internalising and externalising problems (Goodman and Scott, 1999)(see *Appendix 15*).

It was anticipated that the use of several evaluation tools and questionnaires to gather data on the participants would provide a comprehensive method of gaining information and facilitating comparisons between the different evaluations and questionnaires.
3.9 Full Scale I.Q. (FSIQ)

General intellectual functioning in individuals aged 6-17 years of age was assessed using the *Wechsler Intelligence Scale for Children-Fourth Edition* (Wechsler, 2003). Those individuals who were 18 years of age and older were assessed using the *Wechsler Abbreviated Scale of Intelligence* (Wechsler, 1999). The assessments of general intellectual functioning were performed by a research psychologist (S.H) who provided the author with the results of the FSIQ.

3.10 Statistical Analyses for the Psychiatric and Behavioural Data

The data was analysed using the statistical package SAS® Version 9.1. To determine associations, non-parametric statistical analyses were performed. Fisher’s exact test (for binary outcome data) and the Wilcoxon Rank-Sum test (for ordinal outcome data) were used to compare:

- The cases with controls
- Cases with specific psychiatric diagnosis compared with cases without the psychiatric disorder
- The case group with subthreshold psychotic symptoms were compared with cases without any sub-threshold psychotic symptoms
- Case group with schizophrenia and sub-threshold psychotic symptoms were compared with cases without these symptoms/diagnosis (the presence of any suspected early psychotic symptoms and psychotic disorder)
The frequency/occurrence of psychiatric psychopathology and behavioural problems were compared between the cases and control groups. Associations were made between the different psychiatric diagnoses, physical problems, obstetric complications, FSIQ and family history in the case group.

Medians and the Hodges-Lehmann confidence interval were given for ordinal variables. The strength of associations between variables was assessed using the Pearson/Spearman rank correlation coefficient. A multi-variate discriminate analysis was performed to determine which variables discriminated between the different groups analysed.

Multiple comparisons adjustments were made for sub-items of each questionnaire using the Bonferroni adjustment. However, multiple comparison adjustments were not made across questionnaires due to the high dependence/inter-correlations between them. It may be viewed that it is the inter-correlations within the data that are of primary interest. Due to the high inter-correlation between some questionnaires and/or their sub-items (e.g. Connor’s, CBCL, SDQ), many approaches to the multiple comparisons problem are inappropriate due to the independence assumption required of them: one statistically significant result is not required to be adjusted for another statistical result since they may in fact be demonstrating the same finding. While statistical tests are used throughout the study, the primary focus of the statistical analyses is discrimination between the groups of interest.
Six subjects in the 22q11.2DS group were related to existing cases in the study (non-independent. The relationships were varied (mother-daughter, father-daughter, sister-brother, refer to Section 4.1.8, page 75). The statistical analysis did not take into account familial relationships in the analysis. Methods which take into such correlations within the data are relatively complex (i.e. generalised linear mixed models with family relationship as random effects) and require large (familial) samples to have sufficient explanatory ability. For this reason, the analysis was kept as relatively simple (i.e. two-sample tests) due to the small sample size in the study.
CHAPTER 4 – RESULTS
4.1 Demographic Data and Background

4.1.1 22q11.2DS Group (Cases)

The demographic data is summarised in Table 1. All the cases had a 22q11 deletion which was confirmed by fluorescence-in-situ-hybridisation prior to recruitment into the study. The sample consisted of 45 cases with 22q11.2DS. Forty-three cases were Caucasian and all had been born in Ireland and were living in Ireland at the time of the study. One case had a biological father from Cyprus (Greek origin) and another had a biological father from Iran. The case group consisted of 20 (44%) males and 25 (56%) females. The mean age of the sample was 14.6 years (SD=8.94). Forty-four per cent of the cases were between 6-12 years of age (N=20), 36% of the cases were between 13-17 years of age (N=16) and 20% were 18 years old and over (N=9).

4.1.2 Sibling Control Group

Siblings that were closest in age to the case were chosen for the study. The control group consisted of 27 siblings. Twenty-five case subjects were Caucasian and all subjects had been born in Ireland. One control subject had a biological father from Cyprus (Greek origin) and another had a biological father from Iran. The control group consisted of 13 (48%) males and 14 (52%) females. Sixty-three per cent of cases were between 6-12 years of age (N=17), 30% were between 13-17 years of age (N=8) and 7% were 18 years of age or older (N=2).
4.1.3 Comparison of age and gender between cases and control

The gender and age distribution was comparable between the case group (44% males, 56% females, mean age of 14.6 years) and the sibling group (48% males, 52% females, mean age of 12.2 years) and was statistically non-significant (Wilcoxon sum test; gender p-value=0.8102, age p-value=0.1314)

<table>
<thead>
<tr>
<th>Demographic Variables</th>
<th>22q11.2DS group (N=45)</th>
<th>Sibling group (N=27)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>20 (44%)</td>
<td>13 (48%)</td>
<td>0.8102</td>
</tr>
<tr>
<td>Female</td>
<td>25 (56%)</td>
<td>14 (52%)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>14.6 (8.94)</td>
<td>12.2 (4.12)</td>
<td>0.1314</td>
</tr>
<tr>
<td>Range</td>
<td>6-49</td>
<td>6-22</td>
<td></td>
</tr>
</tbody>
</table>

Table 1: Demographic Data

4.1.4 Origin of Deletion

In 78% (N=35) of cases the 22q11 deletion was of de nova origin. In 15% of cases (N=7) the deletion was of familial origin, which included: a sib pair (maternal origin, mother did not participate in this study), father and two daughters, mother, son and
daughter and a mother-daughter pair. The basis of the three parents’ deletions was not confirmed.

Siblings are also tested for chromosomal abnormality following the diagnosis of 22q11.2DS in an affected sibling. The siblings that participated in the study were found not to have any chromosomal abnormalities.

4.1.5 Physical Phenotype

Cases had a range of physical problems/disorders. The most commonly occurring abnormality was found to be palatal anomalies/velopharyngeal dysfunction. Fifty-eight per cent (N=26) of cases had one or more abnormality of the palate/velopharynx of whom 96% (N=25) required pharyngoplasty/cleft palate repair. Forty-nine per cent (N=22) of cases had varying severity of congenital heart defects. Further description of the physical phenotype of the case group is summarised in Table 2. The sibling control group did not have any known underlying physical disorders. Details of the physical disorders were obtained by parents and letters made available by parents and/or general practitioners on previous hospitalisations/outpatient letters (patient’s consent or parental permission was provided to obtain medical records from the participant’s general practitioners.)
4.1.6 Birth Complications

Sixteen per cent (N=7) of cases were described by parents to have had complicated deliveries. Three cases were delivered by emergency caesarean section due to foetal distress. Four cases had a history of instrumental delivery. There was no reported incident of birth complications for sibling controls.

4.1.7 Family History of Mental Health Problems

Sixty-two per cent (N=28) of cases had at least one known family member with a history of mental health disorders and/or completed suicide. Five cases (11%) had a first or second degree family member with a history of probable schizophrenia or schizoaffective/bipolar affective disorder. Nineteen cases (42%) had a first or second degree family member with a history of depression. Four cases (9%) had a first or second degree relative commit suicide. Three cases (7%) had a first or second degree relative with a probable diagnosis of an autism spectrum disorder. Two case subjects (4%) had a family member with alcohol dependence syndrome. Of note, this information was obtained by history from parents/guardians and not confirmed by medical records.

4.1.8 The Recruitment of the Case Sample

At the time of the study, 108 subjects had a confirmed diagnosis of 22q11.2DS in Ireland. Twenty-eight subjects/parents responded to letters that were sent from the genetic centres. Of the 28 subjects/parents, 26 participated in the study. One adult subject and a parent of a subject below 18 years of age decided not to participate in
the study. Eighteen subjects were recruited based from the 22q11 support groups and the website advertisement and one subject was recruited following tertiary referral to the centre. Therefore, 58% of cases were recruited following letters that were received from the genetics centres, 40% of cases were recruited following information that they received from the 22q11.2DS support groups and 2% of cases were recruited following tertiary referral. The response rate to the study was 44% and the participation rate was 42% (See Figure 1).

The 22q11.2DS case group had 10 (22%) subjects that were related; a sib pair, father and two daughters, mother, son and daughter and a mother-daughter pair. Therefore, 39 (87%) subjects with 22q11.2DS were independent of each other in the sample and six subjects (13%) were related to the existing participants (See Figure 1).
Figure 1 – Flow Diagram representing the Recruitment of Case Subjects

RECRUITMENT

At the time of the study there were 108 confirmed cases of 22q11.2DS in the island of Ireland. Subjects were recruited through (a) databases in the genetics centres, (b) patient support groups and (c) following tertiary referral.

RESPONSE RATE 44%

RESPONSE TO LETTERS from GENETICS CENTRES
58%
(N=20)

PATIENT SUPPORT GROUPS
40%
(N=18)

TERTIARY REFERRAL
2%
(N=1)

WITHDRAWN DUE TO PATIENT CHOICE
N=2

PARTICIPATION RATE 42%

22q11 SUBJECTS PARTICIPATING IN STUDY
N=45

DENNOVO DELETION
N=35

FAMILIAL INHERITED DELETION
N=10

SIBLING PAIR
N=2

FATHER & TWO Daughters
N=3

MOTHER, SON & DAUGHTER
N=3

MOTHER & DAUGHTER
N=2

Figure 1: Shows the registered number of cases in the population and the response and participations rate based on the registered number of cases in the genetic databases. The composition of denovo and inherited deletions in the sample is indicated.
<table>
<thead>
<tr>
<th>Physical Phenotype</th>
<th>N (%)</th>
<th>Types of abnormalities</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palatal Anomalies &amp; velopharyngeal</td>
<td>26 (58%)</td>
<td>Velopharyngeal insufficiency</td>
<td>2</td>
</tr>
<tr>
<td>dysfunction</td>
<td></td>
<td>Submucous cleft palate</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Overt Cleft palate</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High arched palate</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ventricular septal defect</td>
<td>6</td>
</tr>
<tr>
<td>Congenital Heart Defects</td>
<td>22 (49%)</td>
<td>Tetralogy of Fallot</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Atrial septal defect</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patent Ductus Arteriosus</td>
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<tr>
<td></td>
<td></td>
<td>Interrupted aortic arch</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Pulmonary artery atresia</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mitral Incompetence</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MAPCA</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Multiple congenital heart defect (MCHD)</td>
<td>1</td>
</tr>
<tr>
<td>Orthopaedic Problems</td>
<td>4 (8%)</td>
<td>Scoliosis</td>
<td>2</td>
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<tr>
<td></td>
<td></td>
<td>Triphalangeal thumbs</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Calcaneo-naviclar coalition</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>On medications</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not on medications (seizure free &gt;5yrs without medications)</td>
<td>1</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>3 (7%)</td>
<td>Non-functional kidney (R alde)</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Atopic bladder</td>
<td>1</td>
</tr>
<tr>
<td>Urology Defects</td>
<td>2 (4%)</td>
<td>Hypoplasia of thymus gland</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Deficient T-cell response</td>
<td>1</td>
</tr>
<tr>
<td>Immune Problems</td>
<td>2 (4%)</td>
<td>Insulin dependent diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Endocrine</td>
<td>1 (2%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
4.2 Social & Occupational Functioning Assessment Scores (SOFAS)

The SOFAS score was present for 44 cases (permission not given by parents for the author to interview one case subject to assess the level of social & school functioning; parents did not want author to ask about psychiatric symptoms and levels of functioning with the subject) and 26 siblings (permission was not given by parents for the author to interview one control subject to assess the level of social & school functioning; parents did not want author to ask about psychiatric symptoms and levels of functioning with the subject). The SOFAS scores for the previous month were analysed.

It was found that there was a significant difference in the median SOFAS scores between cases and controls (Wilcoxon Rank p-value < 0.0001). The median SOFAS score for cases was found to be 60 compared to 82.5 for controls (H-L estimate of the difference = -25, 95% CI = -20 to -30). Median SOFAS score of 60 indicates a moderate difficulty in social, occupational or school functioning compared to a SOFAS score of 82.5 which would indicate no more than a slight impairment in social, occupational or school functioning (See Figure 2).

**SOFAS Scores & Age, Gender, Physical disorders-Birth Complications**

There was no significant association between SOFAS scores and age, gender, a history of physical disorders or birth complications in the case group.
Figure 2: The boxplots show the difference in the range of SOFAS scores between cases and controls. Higher scores indicate superior social, occupational and school functioning. There was a significant difference (Wilcoxon p-value<0.0001) in the social and occupational/school functioning scores found between cases and controls.

4.3 Full Scale I.Q Scores (FSIQ)

The results of the FSIQ are summarised in Table 3. Forty cases participated with the FSIQ assessments. Thirty-one cases were age 6-17 years and nine were 18 and older. Five cases did not participate with the FSIQ assessments and were all below 18 years of age (I was informed by S.H that two children had significant attention problems and would not comply with testing and three children declined to participate). Twenty-three controls participated with the FSIQ assessments (four controls declined to participate with testing and all were below 18 years of age). Twenty-one controls were 6-17 years of age and two were 18 years and older. There was a significant difference in the FSIQ scores between cases and controls aged 6-
17 years (Wilcoxon Rank p-value = <0.0001). There was no significant difference in the FSIQ scores between cases and sibling controls aged 18 years and older (Wilcoxon rank p-value = 0.0724). The lack of statistical significance between the cases and controls aged 18 years and older was likely due to the small sample size of the adult group.

<table>
<thead>
<tr>
<th>Age 6-17</th>
<th>FSIQ</th>
<th>22q11.2DS Group</th>
<th>Sibling Group</th>
<th>p-value (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=52</td>
<td>Median (n)</td>
<td>72 (31)</td>
<td>99 (21)</td>
<td>&lt;0.0001* (-11, -30)</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>52-89</td>
<td>87-112</td>
<td></td>
</tr>
<tr>
<td>Age 18+</td>
<td>FSIQ</td>
<td>22q11.2DS Group</td>
<td>Sibling Group</td>
<td>p-value (95% C.I.)</td>
</tr>
<tr>
<td>N=11</td>
<td>Median (n)</td>
<td>67 (9)</td>
<td>121 (2)</td>
<td>0.0724 (-39, -63)</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>60-78</td>
<td>115-127</td>
<td></td>
</tr>
</tbody>
</table>

Table 3: *Statistical significance at the 5% level, p-value < 0.05 (Wilcoxon Rank Sum test)

**Correlation between FSIQ Scores & SOFAS Scores**

There was a moderate positive correlation ($r_s 0.5$ p-value = 0.0042) which was of statistical significance found between the total SOFAS scores and the FSIQ scores in the cases. Therefore, cases with higher FSIQ scores had higher social, occupational and school functioning.
FSIQ Scores & Age, Gender, Physical disorders, Birth Complications

There was no significant association found between FSIQ scores and age, gender, a history of physical disorders or birth complications in the case group.

4.4 Behavioural Evaluations

4.4.1 Child Behavioural Checklist (CBCL)

The CBCL was completed by 36 parent(s) of cases who were between 6-18 years of age, the remaining seven individuals were 19 years of age or older. The CBCL was completed for 21 sibling controls, four were not completed by the parent(s) and the remaining two individuals were adults.

The T-scores of the CBCL Total problems, externalising and internalising scales and the syndrome scales were compared between cases (N=38) and controls (N=21) using the Wilcoxon Rank sum test.

For the externalizing, internalizing and total problems scale; T-scores less than 60 are considered in the normal range, scores 60-63 are borderline and scores greater than 63 are in the clinical range. For the syndrome scales, T scores less than 67 are considered in the normal range, T-scores ranging from 67-70 are considered to be borderline clinical and T scores above 70 are in the clinical range.
4.4.2 Comparison of CBCL scores Between Cases and Controls

It was found that the case group had significantly higher T-scores than the sibling control group on the total problem, externalising and total problem scales. These significant differences remained after adjusting for multiple comparisons (See Table 4 for further details). The median T-scores for the case group for the externalizing and internalising problems were 51 and 57 respectively and therefore considered within the normal range. However, 22% of cases scored ≥60 for externalizing problems; 8% of cases scored 60-63 (borderline range) and 14% of cases scored >63 (clinical range). It was found that 42% of cases scored ≥60 for internalizing problems; 11% scored 60-63 (borderline range) and 31% of cases scoring >63 (clinical range). The median total problem T-scores was 60, which is considered within the borderline range, it was found that 25% of cases had total problems in the clinical range. The median score for the control group for externalising and internalising problems was 40 and 43 respectively. It was found that 5% of the controls scored 60-63 (borderline range) for externalising problems and 5% scored >63 for internalising problems (clinical range).
Table 4 - CBCL Problems Scale T-scores: 22q11.2DS vs. Sibling Controls

<table>
<thead>
<tr>
<th>CBCL Variable</th>
<th>22q11.2DS (N=38) Median T-scores [Range]</th>
<th>% of Cases With T-score 60-63</th>
<th>Sibling Controls (N=21) Median T-scores [Range]</th>
<th>% of Control With T-score 60-63</th>
<th>p-value (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Externalising Problems</td>
<td>51 [33,82]</td>
<td>8</td>
<td>40 [34,60]</td>
<td>5</td>
<td>0.002** (6.14)</td>
</tr>
<tr>
<td>Internalising Problems</td>
<td>57 [33,88]</td>
<td>11</td>
<td>43 [33,65]</td>
<td>0</td>
<td>0.0001** (13,20)</td>
</tr>
<tr>
<td>Total Problems</td>
<td>60 [34,91]</td>
<td>28</td>
<td>37 [24,54]</td>
<td>0</td>
<td>&lt;0.0001** (18,24)</td>
</tr>
</tbody>
</table>

Table 4: **Statistical significance at the Bonferroni adjusted 0.455 level (p-value<0.0045)

It was found that the case group scored significantly higher than the sibling control group on all the CBCL Syndrome scales. After adjusting for multiple comparisons, significant differences remained for the syndrome scales of: withdrawn/depressed, somatic complaints, social problems, thought problems, attention problems and rule-breaking behaviour.

The median T-scores for all the syndrome scales for the cases and controls were less than 67 and therefore considered within the normal range. However, when the distribution of scores was examined, it was found that a high proportion of cases scored within the clinical range for the syndrome scales. The most notable was found for the social problem scale in which 25% of cases scored within the clinical range followed by 19% of cases scoring within the clinical range for the syndrome of
withdrawn/ depressed. In contrast, none of the sibling controls scored within the clinical range for any of syndrome scale problems (See Table 5 for further details).

<table>
<thead>
<tr>
<th>CBCL Variable</th>
<th>22q11.2DS (N=38) Median T-score [Range]</th>
<th>% of Cases With T-score 67-70</th>
<th>Sibling Controls (N=21) Median T-scores [Range]</th>
<th>% of Control With T-score 67-70</th>
<th>p-value (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxious/Depressed</td>
<td>53.5 [50.90]</td>
<td>11</td>
<td>50 [50.66]</td>
<td>0</td>
<td>0.009 (1.4)</td>
</tr>
<tr>
<td>Withdrewn/Depressed</td>
<td>57 [50.89]</td>
<td>0</td>
<td>50 [50.54]</td>
<td>0</td>
<td>0.0004** (4.7)</td>
</tr>
<tr>
<td>Somatic Complaints</td>
<td>61 [50.92]</td>
<td>6</td>
<td>50 [50.67]</td>
<td>5</td>
<td>0.0001** (6.11)</td>
</tr>
<tr>
<td>Social Problems</td>
<td>59.5 [50.96]</td>
<td>3</td>
<td>50 [50.58]</td>
<td>0</td>
<td>&lt;0.0001** (8.12)</td>
</tr>
<tr>
<td>Thought Problems</td>
<td>58 [50.90]</td>
<td>6</td>
<td>50 [50.54]</td>
<td>0</td>
<td>0.0001** (4.10)</td>
</tr>
<tr>
<td>Attention Problems</td>
<td>59 [50.100]</td>
<td>3</td>
<td>50 [50.51]</td>
<td>0</td>
<td>&lt;0.0001** (9.11)</td>
</tr>
<tr>
<td>Rule-Breaking Behav</td>
<td>52 [50.73]</td>
<td>3</td>
<td>50 [50.62]</td>
<td>0</td>
<td>0.003** (1.2)</td>
</tr>
<tr>
<td>Aggressive Behaviour</td>
<td>51 [50.97]</td>
<td>3</td>
<td>50 [50.58]</td>
<td>0</td>
<td>0.007 (1.4)</td>
</tr>
</tbody>
</table>

Table 5: **Statistical significance at the Bonferroni adjusted 0.455% level (p-value<0.0045)

**Multivariate Discriminate Analysis of CBCL Scores: Cases vs. Controls**

Significance level was set at 1%. Multivariate analysis found that the case group discriminated significantly from the control group on the CBCL syndrome scale of attention problems (F-value=28.08, DF 1, 53, p-value<0.0001).
4.4.3 Strengths & Difficulties Questionnaire (SDQ)

The Strengths and Difficulties Questionnaire (SDQ) was completed by 36 parent(s) of cases who were 6-16 years of age, the remaining nine subjects were older than 16 years. The questionnaire was completed for 23 sibling controls. Two were not completed by the parent(s) and the remaining two subjects were adults. The scores for the five scales: conduct problems, hyperactivity, emotional symptoms, peer problems, pro-social behaviour and total scores (prosocial behaviour scores are not included in the total scores) were compared for cases and controls using the Wilcoxon Rank sum test.

4.4.4 Comparison of SDQ scores: Cases vs. Controls

The case group had significantly more difficulties with emotional symptoms, hyperactivity and peer problems compared to the sibling control group. The case group had significantly higher total scores compared to the sibling control group. The sibling control group had significantly higher pro-social scores compared to the case group. A large proportion of the case group scored within the abnormal range for emotional symptoms (57%), in contrast to the control group (9%). There was no significant difference between the case group and the control group for conduct related problems, although 30% of the case group scored within the abnormal range compared to 9% of the control group. It was found that 27% of the case group scored within the abnormal range for pro-social behaviour compared to 4% of the control group (See Table 6 for further details).
Table 6 - Results from the Strengths and Difficulties Questionnaire

<table>
<thead>
<tr>
<th>Strengths &amp; Difficulties Scale</th>
<th>22q11.2DS Group (N=36)</th>
<th>% of cases scoring &gt;Borderline Range</th>
<th>Sibling Controls (N=23)</th>
<th>% of controls scoring &gt;Borderline Range</th>
<th>p-value (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conduct Problems</td>
<td>1 [0,8]</td>
<td>5 30</td>
<td>1 [0,4]</td>
<td>0 9</td>
<td>0.2159 (0,5)</td>
</tr>
<tr>
<td>Emotional Symptoms</td>
<td>5 [0,10]</td>
<td>16 57</td>
<td>1 [0,5]</td>
<td>9 9</td>
<td>0.0001** (4,8)</td>
</tr>
<tr>
<td>Hyperactivity</td>
<td>5 [0,10]</td>
<td>5 30</td>
<td>1 [0,4]</td>
<td>0 0</td>
<td>&lt;0.0001** (4,9)</td>
</tr>
<tr>
<td>Peer Problems</td>
<td>3 [0,10]</td>
<td>5 46</td>
<td>0 [0,4]</td>
<td>4 4</td>
<td>&lt;0.0001** (2,8)</td>
</tr>
<tr>
<td>Total Scores</td>
<td>13 [1,36]</td>
<td>3 35</td>
<td>3 [0,15]</td>
<td>0 0</td>
<td>&lt;0.0001** (10,25)</td>
</tr>
<tr>
<td>Pro-social Behaviour</td>
<td>3 [1,10]</td>
<td>5 27</td>
<td>13 [4,10]</td>
<td>4 4</td>
<td>0.002** (2,6)</td>
</tr>
</tbody>
</table>

Table 6: **Statistical significance at the Bonferroni adjusted 0.833 level (p-value<0.0083)

Multivariate Discriminate Analysis

Multivariate analysis between cases and controls found that emotional symptoms (F-value=12.13, DF, 1, 56, p-value=0.0010), conduct problems (F-value=0.0009, DF, 1, 56, p-value=0.0009) and hyperactivity (F-value=24.43, DF, 1,56, p-value <0.0001) together significantly discriminated cases from controls.
4.4.5 Relationship between the SOFAS scores and the CBCL & SDQ Questionnaires

Correlation between the CBCL problem scale, syndrome scale and the SOFAS scores were determined by Spearman test. There was no significant strength of correlation found between the CBCL scores and SOFAS scores. There was a moderate degree of negative correlation between the total SDQ scores and the SOFAS scores ($r_s$ -0.5, p-value=0.0030).

4.4.6 Relationship between the FSIQ scores and the CBCL & SDQ Questionnaires

Correlation between the CBCL problem scale, syndrome scale and the FSIQ scores were determined by Spearman test (N=33). There was no significant strength of correlation found between the CBCL scores and FSIQ scores. Similarly correlation between the SDQ and the FSIQ were determined by the Spearman test (N=33). There was no significant strength of correlation found between the SDQ scores and the FSIQ scores.

4.5 Screening tools for Autism Spectrum Disorders

The Social Responsiveness Scale (SRS) and the Social Communication Questionnaire (SCQ) are screening tools for autism spectrum disorders. These questionnaires provide a dimensional measure of autism spectrum symptomatology and also cut-off scores which can be used to indicate the likelihood of a subject having a possible autism spectrum disorder.
In this study, the questionnaires are used to measure the level of autism spectrum disorder symptomatology in both cases and controls and to identify subjects who score above a specified cut-off on the screening tools.

4.5.1 The Social Responsiveness Scale (SRS)

The SRS was completed by 38 parent(s) of cases and 23 controls age 6-18 years. There were 17 males and 21 females in the case group with completed SRS. There were 11 males and 12 females in the sibling control group who had completed the SRS. For males a cut-point of 70 and for females a cut-point of 65 for the SRS total raw score is recommended for the purpose of screening for any autism spectrum disorders in school or other general population groups. In settings where there may be a higher presumptive base rate of autism spectrum disorders, it is recommended a cut-point of 85 used for both males and females.

It was found that seven males cases (41%, Mean Age 12.7 years (S.D 3.4)) scored 70 or above when using a raw score cut-off of 70. Seven females cases (33%, Mean Age 8.3 (S.D 2.6)) scored 65 or above when using a raw score cut-point of 65. Therefore 14 (39%) cases scored above the specified cut-off. Twelve cases (32%, 6 males and 6 females,) scored 85 or above when the cut-off was increased to 85. Therefore of the cases that scored at or above the cut-point of 70 or 65, 86% also scored 85 or higher. None of the siblings scored above the cut-point of 70 or 65. It
was found that the case group were significantly more likely to score ≥ 85 and have a probable ASD compared to the sibling control group (Fisher's exact \( p \) value=0.0020).

Similarly it was found that six males (35%, Mean age 13, S.D 3.6) had a T-score of 76 or higher. Two males (12% Mean age, 10.5 (S.D 0.7)) had a T-score of 60-75. Nine males (53%, Mean age 11.7(S.D 2.6) had a T-score of 59 or less. Six females (29% Mean Age 8.7 (S.D 2.7)) had a T-score of 76 or higher. Four females (19% Mean Age 10.8 (S.D 5.0)) had a T-score of 60-75 and eleven females (52%, Mean age 12.9(S.D 3.1)) had a T-score of 59 or less. There was no statistical significance found in the frequencies in the categories between males and females (Fisher exact \( p \)-value=0.9076). Although, this could be due to the small sample size of the group analysed.

4.5.2 The Social Communication Questionnaire (SCQ)

The SCQ was completed by 40 parent(s) of cases and 25 controls. Three adults with 22q11.2DS did not have a parent to complete the questionnaire and it was not completed by two parents. Two questionnaires were not completed for the sibling control group. The total scores were determined for cut-offs and compared between cases and controls.

Six cases were found to have a total score > 15 (15%, median 17.0, range 16-23), suggesting that these subjects may have a possible autism spectrum disorder. The higher total scores were not gender specific as it was found that three males and
three females scored ≥15. It is advised in the SCQ manual that a lower cut-off score be used in groups who may have underlying developmental disorders or marked language impairment to allow for a comprehensive assessment. Therefore, a cut-off score of ≥14 was chosen. It was found that two cases scored 14. Therefore, eight cases (20%) scored ≥14 (4 males and 4 females). When the cut-off was further reduced to ≥13, three more cases scored at or above the cut-off and therefore 11 cases (28%) scored at or above the cut-off. There were no controls scoring 13 or over. There was a significant difference in the occurrence of autistic symptoms/probable ASD between cases and controls when the cut-off was 14 (Fisher’s exact $p$-value=0.0193) and when reduced to 13 (Fisher’s exact $p$-value=0.0045). There was no significant difference found between cases and controls when the cut-off was ≥15 (Fisher’s exact $p$-value=0.0743).

4.5.3 Correlation between the SRS and the SCQ

A higher rate of possible autism spectrum disorders was found with the SRS at a cut-off at 85 (32%) compared to the SCQ at a cut-off at 15 (15%). When the cut-off score for the SCQ was reduced to ≥14 a higher rate of possible autism spectrum disorder was found at 20% and when the cut-off was further reduced to ≥13 a rate of 28% was found. It was found that when the cut-off of 85 was used on the SRS and 13 used on the SCQ, this gave rise to a high agreement between the two questionnaires; a simple kappa coefficient of 0.63 was found between the questionnaires which corresponds to a substantial agreement. When a cut-off of 14 was used on the SCQ and a cut-off at 85 on the SRS a simple kappa coefficient of 0.53 was found. When the SCQ cut-off was increased to 15 the simple kappa
coefficient was 0.49. The kappa correlation coefficient between the total scores for the SRS and the SCQ was found to be \( \kappa 0.76 \), which indicates a very strong agreement between the two questionnaires.

### 4.5.4 SRS Scores and Total SCQ Score: Cases vs. Controls

The SRS raw scores were analysed with the Wilcoxon rank Sum test and significant differences were found between cases and controls across the five subscales and total score of the SRS. The median total score raw score for the case group was 50 compared to 6 for the control group (See Table 7 for further details).

<table>
<thead>
<tr>
<th>SRS Subscale and Total Variables</th>
<th>22q11.2DS (N=38) Median Values [Range]</th>
<th>Sibling Controls (N=23) Median Values [Range]</th>
<th>p-value (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autistic Mannerisms</td>
<td>6.0 [0.38]</td>
<td>0 [0.6]</td>
<td>&lt;0.0001** (4.11)</td>
</tr>
<tr>
<td>Social Communication</td>
<td>16.0 [0.55]</td>
<td>1 [0.13]</td>
<td>&lt;0.0001** (12.27)</td>
</tr>
<tr>
<td>Social Motivation</td>
<td>8.5 [2.26]</td>
<td>0 [0.12]</td>
<td>&lt;0.0001** (5.12)</td>
</tr>
<tr>
<td>Social Awareness</td>
<td>8.0 [3.20]</td>
<td>2 [0.9]</td>
<td>&lt;0.0001** (5.9)</td>
</tr>
<tr>
<td>Social Cognition</td>
<td>12.5 [2.20]</td>
<td>1 [0.15]</td>
<td>&lt;0.0001** (7.15)</td>
</tr>
<tr>
<td>Total Scores</td>
<td>50.0 [12.159]</td>
<td>6 [0.36]</td>
<td>&lt;0.0001** (33.73)</td>
</tr>
</tbody>
</table>

Table 7: **Statistical significance at the Bonferroni adjusted 0.83% level (p-value<0.0083)
There were significant differences found between the case group and the sibling control group on the total score of the SCQ. The case group had significantly higher total SCQ scores and therefore higher autistic symptoms/scores compared to the sibling control group (See Table 8 for further details).

Table 8 - SCQ: Total scores: Comparison between Cases and Sibling Controls

<table>
<thead>
<tr>
<th>Total score</th>
<th>Case Group (N=40)</th>
<th>Control Group (N=25)</th>
<th>p-value (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Score</td>
<td>7 [1,23]</td>
<td>2 [0.8]</td>
<td>&lt;0.0001*</td>
</tr>
</tbody>
</table>

Table 8: *Statistical significance at the 5% level (p-value < 0.05) (Wilcoxon rank sum test).

4.5.5 Autistic Symptoms & Age, Gender, Physical Disorders, Birth Complications

There was no significant association found between age, gender, physical disorders, birth complications and the total SRS score and the SCQ score (Wilcoxon sum p-value>0.05).

4.5.6 Autistic Symptoms and SOFAS Scores

The correlation between the SRS total scores with SOFAS scores was examined by the Spearman Correlation coefficient. There was a moderate significant strength of correlation between the SRS total score and the SOFAS scores. Total SRS score
and SOFAS, $r_s$ -0.46324, p-value=0.0039. Therefore, higher SRS total scores correlate significantly with lower social, occupational and school functioning for cases. Similarly the strength of association between the SCQ total scores with the SOFAS scores was examined with Spearman’s rank correlation. It was found that the total SCQ score did not have a significant correlation with the SOFAS score ($r_s$ 0.29913, p-value=0.0643).

**4.5.7 Autistic Symptoms and FSIQ Scores**

Correlation between autistic symptoms scores and FSIQ scores was determined by the Spearman’s rank correlation. It was found that there was no significant strength of correlation between the SRS total score and FSIQ scores in the cases. There was no significant strength of correlation found between the total SCQ score and the FSIQ scores; the Spearman’s rank coefficient values were found to be low ($r_s$ values between 0.0-0.2).

**4.6 Measure of Schizotypy with the SPQ**

The schizotypy personality questionnaire (SPQ) was administered to participants who were 12 years old and over. The SPQ was administered to 29 cases and 14 controls. The SPQ was completed by 27 cases. Two cases did not complete the questionnaire (1 could not due to learning difficulties and the other did not have parental consent). Fourteen questionnaires were completed by controls.

**4.6.1 Categorical Evaluation of SPQ scores**

A cut-off score of $\geq 41$ on the SPQ was used to identify subjects who may have a possible schizotypal personality disorder. It was found that 17% (N=5) of the case group scored $\geq 41$ on the SPQ and therefore indicating a possible schizotypal
personality disorder (age range 12-49). No individuals in the sibling group scored greater than 41.

4.6.2 Total SPQ scores and background data

The total SPQ score was examined with the Wilcoxon Rank-Sum test to determine if there was a significant association between the psychiatric disorders, physical disorders and birth complications in the case group. There was no significant association between total SPQ score and age, gender, FSIQ, a history of physical disorders or birth complications.

4.6.3 Dimensional Evaluation of SPQ scores: Case vs. Controls

The median SPQ scores of the nine subscales, three schizotypy factors and total scores are presented in Table 9. There was a trend for the cases to have higher median scores for the SPQ subscales, total score and the schizotypy factor/dimensions. After adjusting for multiple comparisons a significant difference was found between cases and controls on the subscale of excessive social anxiety, odd speech, the total score and the disorganised factor (p-value<0.0038).

Multivariate analysis of the subscales, total score and factors between the case group and control group found that the subscale of odd speech (F-value 25.69, DF 1,56, p-value<0.0001) significantly discriminated the case group from the control group.
<table>
<thead>
<tr>
<th>SPQ subscales, total and dimension scores</th>
<th>22q11.2DS</th>
<th>Sibling Control</th>
<th>p-values (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=29</td>
<td>N=14</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>Median</td>
<td></td>
</tr>
<tr>
<td></td>
<td>[Range]</td>
<td>[Range]</td>
<td></td>
</tr>
<tr>
<td>Excessive social anxiety</td>
<td>5</td>
<td>2</td>
<td>0.0015** (2.5)</td>
</tr>
<tr>
<td>Unusual perceptual experiences</td>
<td>1</td>
<td>0</td>
<td>0.0094* (0.2)</td>
</tr>
<tr>
<td>Odd speech</td>
<td>3</td>
<td>0</td>
<td>0.0011** (1.5)</td>
</tr>
<tr>
<td>Constricted affect</td>
<td>2</td>
<td>0</td>
<td>0.0088* (1.3)</td>
</tr>
<tr>
<td>No close friends</td>
<td>2</td>
<td>0</td>
<td>0.0157* (0.3)</td>
</tr>
<tr>
<td>Odd or eccentric behaviour</td>
<td>1</td>
<td>0</td>
<td>0.0213* (0.2)</td>
</tr>
<tr>
<td>Ideas of reference</td>
<td>2</td>
<td>0</td>
<td>0.0349* (0.3)</td>
</tr>
<tr>
<td>Paranoid ideation</td>
<td>1</td>
<td>0</td>
<td>0.0865 (0.4)</td>
</tr>
<tr>
<td>Odd Beliefs</td>
<td>0</td>
<td>0</td>
<td>0.2087 (0.1)</td>
</tr>
<tr>
<td>Total scores</td>
<td>16</td>
<td>4</td>
<td>0.0014** (7.25)</td>
</tr>
<tr>
<td>Cognitive/perceptual Factor</td>
<td>3</td>
<td>1</td>
<td>0.0169* (1.7)</td>
</tr>
<tr>
<td>Interpersonal factor</td>
<td>4</td>
<td>1</td>
<td>0.0062* (1.8)</td>
</tr>
<tr>
<td>Disorganised Factor</td>
<td>4</td>
<td>0</td>
<td>0.0018** (2.7)</td>
</tr>
</tbody>
</table>

Table 9: **Statistical significance at the Bonferroni adjusted 0.384% level (p-value<0.0038)
4.7 Prevalence of Psychiatric Disorders

4.7.1 An overview of the Prevalence of Psychiatric Disorders

The prevalence of psychiatric disorders is summarised in Table 10. It was found that 62% (N=28) of cases had at least one psychiatric disorder, 29% (N=13) were found to have two or more disorders, 16% (N=7) had three or more disorders and 4.4% (N=2) of cases had five psychiatric disorders (specific phobias, enuresis and encopresis were excluded from this analysis). In contrast it was found that 19% (N=5) of controls had at least one psychiatric disorder and 4% (N=1) of controls had two psychiatric disorders (specific phobias, enuresis and encopresis excluded from this analysis). There were no control subjects that had three or more psychiatric disorders. It was found that the case group had significantly higher prevalence of psychiatric disorders collectively compared to the control group (Fishers exact p-value=0.005) (p-value<0.00625, after adjusting for multiple comparisons).
Figure 3: Shows the participation of children and adults with the SOFAS, FSIQ and Psychiatric Evaluations. * please refer to text section page 79. ** please refer to page 111. *** please refer to page 111 for the reasons for non-participation of subjects.
<table>
<thead>
<tr>
<th>Psychiatric Disorder</th>
<th>22q11.2DS group (N=45)</th>
<th>Sibling group (N=27)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specific phobias</td>
<td>36% (16)</td>
<td>19% (3)</td>
<td>0.1811</td>
</tr>
<tr>
<td>Other Anxiety disorder</td>
<td>31% (14)</td>
<td>7% (2)</td>
<td>0.0212</td>
</tr>
<tr>
<td>Attention Deficit Hyperactivity Disorder</td>
<td>29% (13)</td>
<td>0</td>
<td>0.0012**</td>
</tr>
<tr>
<td>Oppositional defiant disorder</td>
<td>22% (10)</td>
<td>4% (1)</td>
<td>0.0439</td>
</tr>
<tr>
<td>Major Depressive Disorder</td>
<td>11% (5)</td>
<td>4% (1)</td>
<td>0.3996</td>
</tr>
<tr>
<td>Obsessive Compulsive disorder</td>
<td>4% (2)</td>
<td>0</td>
<td>0.3246</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>2% (1)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Asperger’s Syndrome</td>
<td>2% (1)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Enuresis</td>
<td>18% (8)</td>
<td>4% (1)</td>
<td>0.1397</td>
</tr>
<tr>
<td>Encopresis</td>
<td>0</td>
<td>4% (1)</td>
<td>0.375</td>
</tr>
<tr>
<td>Motor Tic Disorder</td>
<td>2% (1)</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 10: **Statistical significance at the Bonferroni adjusted 0.454% level (p-value<0.00454)

In general, cases tended to have higher occurrences of psychiatric illnesses across a range of disorders compared to controls. It was found that the specific phobias and other anxiety disorders were the most prevalent psychiatric disorders in the cases. Thirty-six per cent (N=16) of cases met the diagnostic criteria for specific phobias and 31% (N=14) of cases met the diagnostic criteria for ‘other anxiety disorders’. However, there was no significant difference in the prevalence of specific phobias or other anxiety disorders between cases and controls. Although the case group had significantly more psychiatric disorders together compared to controls and were
found to have a higher prevalence of psychiatric disorders, Attention Deficit Hyperactivity Disorder (ADHD) was the only psychiatric disorder in the cases which was found to be significantly prevalent compared to controls. Twenty-nine per cent (N=13) of the case group met the diagnostic criteria for ADHD; there were no control subjects that met the diagnostic criteria for ADHD (p-value<0.00454).

One case (Male, 26 years, FSIQ 78) subject had received a diagnosis of schizophrenia prior to being recruited into the study. He also had a history of epilepsy and was on antipsychotic and anti-epileptic medication at the time of the study. He was diagnosed with schizophrenia at the age of 25 and epilepsy at the age of six. He was assessed with the SAPS and SANS and received a SAPS score of 23 and a SANS score of 49. He had a family history of psychiatric disorders; an uncle on his father's side with a history of possible psychotic disorder. He admitted to smoking cannabis on one occasion, though denied any illicit substance use in the last year. There was no history of birth complications, feeding problems, congenital heart defects, or palate problems. This individual was referred from a psychiatric service for tertiary assessment of his psychiatric disorder, was then provided information about the study and agreed to participate.

Another case (Male, 16 years, FSIQ 75) had received a diagnosis of Asperger's syndrome at the age of 14. He displayed an intense preoccupation with certain interest such as golf, computers and astronomy. His focused interests had changed over the years, though he had displayed this behaviour from a very early age. He did not have an interest in interacting with peers and avoided social interaction. He
preferred to stay in his own room and had no friends. There was a history of birth complications (premature delivery at 34 weeks and emergency c-section), velopharyngeal insufficiency and triphalangeal thumbs. There was no other history of any other physical disorders. This subject was found to have a total score of 20 on the SCQ and a total score of 110 on the SRS, therefore scoring above the cut-off score for both the questionnaires.

Cases were found to have higher rates of enuresis compared to controls, although this difference was found not to be statistically significant (Fishers exact $p$-value=0.1397) There was no occurrence of encopresis in the cases. A six year old male control was found to have encopresis based on symptoms reported by mother. A 12 year old female case had symptoms consistent with a chronic motor tic disorder.

There were no subjects that were found to have Bipolar Affective Disorder. There were no subjects that were found to have alcohol dependence or were regular users of illicit substances in the past year or prior to this period.

4.7.2 Attention Deficit Hyperactivity Disorder (ADHD)

It was found that the prevalence of ADHD was significantly higher in the case group (29%) than the controls (0%). The case sample with ADHD consisted of nine males and four females ($p$-value=0.1915) with a mean age of 11 years (SD= 3.3, age range 6-16 years). Six (4 males, 2 females) subjects received a diagnosis of the inattentive
subtype, another six (4 males, 2 females) subjects received a diagnosis of the combined sub-type and one (male, age 13) subject received a diagnosis of the hyperactive subtype. None of the subjects had a known family history of ADHD. One subject in this sample was diagnosed with ADHD prior to entry into the study and had been treated with stimulant medication, although was not on stimulant treatment at the time of the study.

4.7.2.1 Conners Parent Rating Scale

The Conners Parent Rating Scale-Revised (S) was completed by 36 parent(s) of cases who were between 6-17 years of age, the remaining eight were 18 years of age or older. The Conners Scale was completed for 23 controls, two were not completed by the parent(s) and the remaining two cases were adults. The T-scores of the Conners Rating scales were compared between cases and controls using the Wilcoxon Rank sum test.

It was found that cases scored significantly higher on the four scales of the Conners Parent questionnaire compared to the controls. The results are detailed in Table 11 and Figure 4 below. T-scores of greater than 60 are considered a cause of concern, 61 and above mildly typical and 70 and over markedly atypical (general population estimates). It was found that the case group had a median T score of 67 for the Conners' ADHD Index scale, which could be interpreted as moderately atypical (Identifies children/adolescents at risk of ADHD). The median T-score for the case group for inattention was found to be 70, suggesting significant problems in this area.
The median T-scores for the case group on the hyperactivity and the oppositional scales were 59 and 50 respectively, which is considered below the score for concern. The median scores for the four scales were below 50 for the controls.

Therefore, the results from the Conners Questionnaire suggest that the case group have significantly more difficulties with inattention, hyperactivity, oppositional behaviour and are significantly more likely to be identified as having ADHD compared to the control group. The case group were found to have most difficulty with symptoms related to inattention compared to hyperactivity or oppositional behaviour. Therefore the results suggest that symptoms related to inattention may cause more difficulties than symptoms related to hyperactivity or opposition and the symptoms of inattention may contribute predominantly to the diagnosis of ADHD compared to hyperactivity in cases.

<table>
<thead>
<tr>
<th>Scales</th>
<th>22q11.2DS (N=36) Median T-scores [Range]</th>
<th>Sibling Controls (N=23) Median T-scores [Range]</th>
<th>P-values (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperactivity</td>
<td>59 [44,90]</td>
<td>48 [45,64]</td>
<td>0.0031** (12, 42)</td>
</tr>
<tr>
<td>Inattention</td>
<td>70 [42,90]</td>
<td>46 [42,62]</td>
<td>&lt;0.0001** (21, 38)</td>
</tr>
<tr>
<td>Oppositional</td>
<td>50 [40,90]</td>
<td>46 [40,90]</td>
<td>0.008** (8, 41)</td>
</tr>
<tr>
<td>ADHD Index</td>
<td>67 [40,90]</td>
<td>46 [40,68]</td>
<td>&lt;0.0001** (16, 40)</td>
</tr>
</tbody>
</table>

Table 11: **Statistical significance at the Bonferroni adjusted 1.25% level (p-value<0.0125)
Figure 4 - Connors' Parent Rating Scale between Cases and Controls

Figure 4: The boxplots show the distribution of T-scores and median values of the Conner's parent rating scales (S) between cases and controls. There is a significant difference in the scales between cases and controls. Interpretation of T-scores based on the general population suggests that inattention and the Conners ADHD index scale are moderately atypical and indicates a significant problem. The median T-scores of the oppositional and hyperactivity scales for cases are below 60. The median T-scores of the four scales for controls where below 60.

4.7.2.2 ADHD and Background Data

There was no association found between ADHD and the presence of palatal abnormalities, cardiovascular defects, epilepsy, family history of psychiatric disorders, birth complications or age (Fisher's exact p-value=1.000, p-value=0.5136, p-value=0.4990, p-value=0.7512 p-value=0.1676, p-value=0.1263 respectively).

4.7.2.3 SOFAS Scores in Cases with ADHD

It was found that cases with ADHD had significantly lower SOFAS scores compared to cases without ADHD (Wilcoxon rank p-value= 0.0067). Cases with ADHD (N=13,
29%) had a median SOFAS score of 55 compared to cases without ADHD with a median SOFAS score of 65 (H-L estimate of the difference = -10, 95% CI = -5 to -15). Both a score of 55 and 65 would correspond to approximately a moderate difficulty in social and social functioning.

4.7.2.4 FSIQ Scores in Cases with ADHD

Although, the median FSIQ of the sample of cases with ADHD was 73.5 compared to 71 for cases without ADHD, there was no statistical difference found between these two groups (Wilcoxon rank p-value 0.6777 95% CI -3, 24). However, the FSIQ scores were not available for three of the cases with ADHD. Therefore, the median FSIQ score of the sample with ADHD may not be a reflection of the true sample rate due to non-participation bias.

4.7.2.5 ADHD & Behavioural Evaluations

An association between ADHD and the CBCL problems and syndromes scales and the SDQ was determined with the Wilcoxon rank sum test for the case group. A 1% level of significance was set for the statistical tests in order to reveal the most important differences in the relatively small sample size. There was no significant association found between ADHD and the CBCL problems and syndrome scales. It was found that there was a significant association with ADHD and the conduct problem and hyperactivity scale of the SDQ (Wilcoxon rank p-value=0.003, p-value=0.0010). ADHD was found to be significantly associated with the total score of

104
the SDQ (Wilcoxon p-value=0.005). Therefore cases with ADHD scored significantly higher on the total SDQ.

4.7.2.6 ADHD and Autism Symptoms

An association between ADHD and the SRS total score in the case group was determined by using the Wilcoxon Rank Sum test. It was found that cases with ADHD had significantly higher total SRS scores compared to cases without ADHD (Wilcoxon p-value=0.0004); cases with ADHD had a median total SRS score of 94 compared to cases without ADHD with a median SRS score of 24.5. Of the 12 cases with a total SRS ≥85, eight (67%) had a diagnosis of ADHD. Of the 13 cases with ADHD eight (62%) scored ≥85 on the total SRS. Four of the subjects had the inattentive subtype and four had the combined subtype. Therefore 18% (N=8) of the case group had the combination of ADHD and high autism scores.

4.7.2.7 ADHD & Co-morbid Psychiatric Disorders

ADHD was found to be significantly associated with oppositional defiant disorder (Fisher’s exact p-value=0.0002) in the case group. ADHD was not associated with any other psychiatric disorders, though 38% (N=5) of the sample with ADHD had a co-morbid anxiety disorder.
4.7.3 Oppositional Defiant Disorder (ODD)

The prevalence of ODD in cases was found to be 22% (N=10). There was no significant difference in the prevalence of ODD between cases and controls. There was no significant association between ODD and gender, FSIQ scores, age, physical disorders, family history of psychiatric disorders or birth complications.

4.7.3.1 ODD & Co-morbid Psychiatric Disorders

ODD was found to be significantly associated with ADHD (Fisher's exact p-value=0.0002) in the case group. ODD was not associated with any other psychiatric disorders.

4.7.3.2 ODD, ADHD & Autism Symptoms

It was found that cases with Oppositional Defiant disorder (ODD) had significantly higher symptoms of autism (Median SRS score 102) compared to cases without ODD (Median SRS scores 36) (Wilcoxon p-value=0.0035). It was found that of the 10 cases with ODD, eight had total SRS scores of ≥85 (80%). Of these subjects, 6 (13%) had a combination of ADHD, ODD and total scores SRS scores of ≥ 85. Therefore, only two case subjects with ODD did not have SRS scores of ≥ 85. Therefore, 50% of cases with high autistic symptoms (≥85) had ADHD and ODD. Of note there was a significant association found between ADHD and ODD (Fisher’s exact p-value=0.0002) and it was difficult to determine the independence of the symptoms of autism, ADHD and ODD due to the overlap of symptoms between these three disorders.
4.7.4 Anxiety Disorders

Thirty-six per cent (N=16) of the case group were diagnosed with a specific phobia compared to 19% (N=5) of the control group (Fisher’s exact $p$-value=0.1811). The most common phobia in the case group was an insects/spiders phobia (n=10), followed by fear of the dark (n=5) and one subject had a needle phobia. In the control group three subjects had a specific phobia for spiders/insects and the other two had a specific phobia for the dark. Specific phobias were excluded in the analysis, as they commonly occur in children.

Thirty-one percent (N=14, mean age 13.64, S.D 9.4) of cases met criteria for ‘other anxiety disorders’. The term ‘other anxiety disorders’ in this study encompasses the following disorders; separation anxiety, social anxiety/phobia (anxiety symptoms related to social situations, peer interactions which causes distress, worry and avoidance of these situations) and generalised anxiety disorders. There was a significant difference in the prevalence of anxiety disorders between cases and controls (Fishers exact $p$-value=0.0212), though after adjusting for multiple comparisons the difference did not remain. Eight cases met the criteria for social anxiety disorder, eight cases met the criteria for separation anxiety disorders and three met the criteria for generalised anxiety disorder. Two cases also had an associated panic disorder. Three cases met criteria for more than one anxiety disorders.
Seven per cent (N=2) of controls met the criteria for social anxiety disorder. One control was 16 years of age and the other was 22 years of age. Both the controls had a co-morbid diagnosis; one with a history of recurrent depressive disorder and the other with sub-threshold psychotic symptoms.

4.7.4.1 Age and Anxiety Disorders in Cases

There were six cases with anxiety disorders who were 11 years of age or below, four had social anxiety, two had separation anxiety and one had both separation and social anxiety disorders. There were seven cases who were aged 12-17 with anxiety disorders, three had separation anxiety, two had social anxiety disorders and two had all three of the anxiety disorders with one also with associated panic disorder. Ninety-three per cent (N=13) of cases with an anxiety disorder were below 18. It was found that only one adult case had an anxiety disorder; generalised anxiety disorder associated with panic disorder. Therefore the prevalence of anxiety disorder in cases >18 was found to be 11%. In this sample, anxiety disorders were found predominantly in cases below 18 years of age. However there was no significant association between anxiety disorders and age in the case group (Wilcoxon rank sum p-value=0.3).

4.7.4.2 Anxiety Disorders and Co-morbidity in Cases

The anxiety disorders were not found to be significantly associated with a co-morbid psychiatric disorders, palatal anomalies, congenital cardiac defects, gender, birth complications or family history of psychiatric disorders in cases (Fisher's exact p-
values >0.5) (analysis excludes specific phobias). It was found that 35% (N=5) of cases with anxiety disorders had a co-morbid diagnosis of ADHD.

4.7.4.3 Anxiety Disorders and Behaviour & Evaluations

An association between anxiety disorders and the CBCL problems and syndromes scales and the SDQ was determined with the Wilcoxon rank sum test for the case group. A 1% level of significance was set for the statistical tests in order to reveal the most important differences in the relatively small sample size. There was a borderline level of significant association found between anxiety disorders and the anxious/depressed syndrome scale of the CBCL (p-value=0.0119). Anxiety disorders were significantly associated with the emotional scale of the SDQ (p-value=0.0087).

4.7.5 Obsessive Compulsive Disorder (OCD)

Four per cent (N=2) of cases met the criteria for an obsessive compulsive disorder (OCD). One case had compulsion of checking that things were in a certain order and the other had compulsion of touching parts of her body (nose, ears) to prevent something untoward happening to her father. There was no significant association found between OCD and any other psychiatric disorder, palatal disorders, congenital heart disorders, gender, age, FSIQ scores, birth complications or family history of psychiatric disorders.
The cases that were identified as having an anxiety disorder or OCD were not previously diagnosed and were not currently or previously receiving any psychological or pharmacological treatments. One control did not receive a prior diagnosis of anxiety disorder and the other control had received a prior diagnosis of anxiety disorder in association with depression.

4.7.6 Affective Disorders

Eleven per cent (N=5) of cases had a history of depression in which, four had a history of recurrent depressive disorder and one had a history of moderate depressive episode within the last year. Three cases with recurrent depressive disorder were on antidepressant medication at the time of the study, one was found to be moderately depressed at the time of the study and the other two had a relapse of depression within the past 8 months and at the time of the study were found to be euthymic. The remaining case had co-morbid schizophrenia and a history of recurrent depression and was found to be euthymic at the time of the study, though reported to have intermittent periods of low mood over the course of the year. The mean age of cases with depression was 29 years (SD=13.5, age range 16-49 years). There were nine cases in the study who were ≥18 and four were found to (44%) have had a history of depression. Older age was significantly associated with depression in the case group (Wilcoxon rank p-value=0.0024). The case group with a history of depression consisted of three females and two males with no significant association found between gender and depression. There was no significant association found between depression and FSIQ, the physical disorders, history of birth complications or family history of psychiatric disorders.
4.8 Subthreshold Psychotic Symptoms

4.8.1 Study Participants

Forty-one cases were assessed by the author (1 child refused to participate, 1 child was unable to participate because of significant speech impediment/hearing difficulties, parental consent not given for the other and the other individual had an established diagnosis of schizophrenia) with the CAARMS and 33 cases (<18 years of age)( 1 children refused to participate, 1 child was unable to participate because of significant speech impediment/hearing difficulties and parental consent not given for one child) were supplemented with the psychosis module of the schedule for affective disorders and schizophrenia for school-age children-present and life-time (K-SADS-PL). All cases who were 18 years and above were also administered the SCAN.

Twenty six controls were assessed by the author (parental consent not given for one child) with the CAARMS. Twenty-four controls (<18 years of age) (parental consent not given for one child) were supplemented with the psychosis module of the schedule for affective disorders and schizophrenia for school-age children-present and life-time (K-SADS-PL). All cases who were above 18 years were also administered the SCAN

All parents of participants (<18 years) were administered with the DISC followed by the psychosis module of the K-SADS-PL.
4.8.2 Sub-threshold Psychotic Symptoms

It was found that 20% of cases and 4% controls had subthreshold psychotic symptoms. See Table 12 for further details of the prevalence of subthreshold psychotic symptoms in cases and controls. Refer to Table 13 for the characteristics of the subthreshold psychotic symptoms and co-morbid physical and psychiatric disorders in cases. There were 9 case subjects and one control subject that met the K-SADS criteria for having subthreshold psychotic symptoms. Eight of these case subjects also met the criteria for attenuated psychotic symptoms on the CAARMS interview. One control subject met the CAARMS criteria and was also defined as ‘high risk’. The case subject (N=1) that met the K-SADS criteria but not the CAARMS criteria was labelled as having fleeting/transient hallucinations. Therefore, 20% (N=9) of the case group were defined as having subthreshold psychotic symptoms and eight subjects (18% of the case group) in this group also met the criterion for the ‘attenuated psychosis group’ on the CAARMS interview and were categorized as having ‘attenuated psychotic symptoms’ or the ‘high risk group’ in this study.
Table 12: Prevalence of Fleeting and Subthreshold Psychotic Symptoms in Cases (22q11.2DS) and Controls

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>22q11.2DS Group (N=44)</th>
<th>Sibling Group (N=27)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Attenuated psychotic symptoms</td>
<td>8 (18%)</td>
<td>1 (4%)</td>
<td>0.1391</td>
</tr>
<tr>
<td>(High Risk Group)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 Fleeting/Transient Hallucinations</td>
<td>1 (2%)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>3 Subthreshold Psychotic</td>
<td>9 (20%)</td>
<td>1 (4%)</td>
<td>0.0773</td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 12: Statistical significance at the 5% level, p-value < 0.05 (Fisher exact test)

1 Subjects who met criteria for attenuated psychosis group according to the CAARMS assessment.

2 Subject did not meet the intake criteria of sub-threshold psychotic symptoms according to the CAARMS. Individual reported experiencing auditory hallucinations in last year which received a global rating of 4, though received a frequency score of 1 without any associated 30% drop in SOFAS scores and/or a SOFAS score of less than 50 for the past 12 months. Found to have subthreshold psychotic symptoms according to K-SADS interview.

3 Subthreshold Psychotic Symptoms- is defined in the study as either fleeting/transient hallucinations or attenuated psychotic symptoms. The subject with schizophrenia is omitted from this analysis.
Table 13 - A Description of the Characteristics of the Subjects with Sub-Threshold Psychotic Symptoms

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age</th>
<th>Symptom Characteristic of Delusions &amp; hallucinations</th>
<th>Co-morbid psychiatric Disorders</th>
<th>Physical phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>M</td>
<td>16</td>
<td>Persecutory/ referential type</td>
<td>Anxiety Disorder, Specific phobia, Depressive episode,</td>
<td>V.P.I, Tri-phalangeal thumbs</td>
</tr>
<tr>
<td>M</td>
<td>14</td>
<td>Persecutory/ referential type, Auditory hallucinations</td>
<td>Anxiety Disorder, Specific phobia, ODD</td>
<td>V.P.I, Bladder hypoplasia</td>
</tr>
<tr>
<td>F</td>
<td>13</td>
<td>Referential type</td>
<td>Specific phobias, ADHD</td>
<td>Submucous cleft palate, Ventral septal defect, NIDDM</td>
</tr>
<tr>
<td>M</td>
<td>10</td>
<td>Persecutory/ passivity type</td>
<td>Specific phobia</td>
<td>TOF, Hypoplastic thymus and immune problems, V.P.I</td>
</tr>
<tr>
<td>F</td>
<td>12</td>
<td>Persecutory type, Auditory hallucinations</td>
<td>Specific phobia, Anxiety disorder, ODD, OCD</td>
<td>V.P.I, MAPCA's, Non-functional R-kidney, Caleacaneo-navicular coalition</td>
</tr>
<tr>
<td>F</td>
<td>12</td>
<td>Auditory hallucinations</td>
<td>Specific phobia, Anxiety disorder, ADHD, ODD, OCD, tic disorder</td>
<td>Epilepsy</td>
</tr>
<tr>
<td>F</td>
<td>7</td>
<td>Persecutory type, Auditory hallucinations</td>
<td>Specific phobia, Anxiety disorder, ADHD, ODD</td>
<td>Submucous cleft palate, Interrupted aortic arch, Hypoplastic thymus gland with immune problem</td>
</tr>
<tr>
<td>F</td>
<td>13</td>
<td>Auditory hallucinations</td>
<td>nll</td>
<td>V.P.I</td>
</tr>
<tr>
<td>F</td>
<td>12</td>
<td>Auditory hallucinations</td>
<td>Specific Phobia</td>
<td>Velopharyngeal anomalies, Ventral septal defect</td>
</tr>
</tbody>
</table>

Table 13: Descriptive details of the case subjects with subthreshold psychotic symptoms
One control subject (male, aged 16 yrs) met criteria for attenuated psychotic symptoms and was categorised as high risk. He expressed persecutory and referential ideas which met criteria for the attenuated psychosis group of the CAARMS. This subject also had co-morbid psychiatric disorders which were specific phobia and generalised anxiety disorder and a family history of psychiatric disorders.

### 4.8.3 Background Data of Subthreshold Group

The mean age of the case group with subthreshold psychotic symptoms was 12.1 years (S.D=2.7, age range 7-16). There was no significant association found between age or gender and subthreshold psychotic symptoms. At the 1% level of significance there was no significant association between subthreshold psychotic symptoms and physical disorders. At the 5% level of significance, a significant association was found between subthreshold psychotic symptoms and immune delay (Fisher’s exact p-value=0.0364). There was a non-significant trend found between subthreshold psychotic symptoms and palatal abnormalities (Fisher’s exact p-value=0.0578). There was no significant association between family history of psychiatric disorder (Fisher’s exact p-value=1.000) or birth complications (Fisher’s exact p-value=0.0943) and subthreshold psychotic symptoms.

### 4.8.4 Subthreshold Psychotic Symptoms and SOFAS Scores

The SOFAS scores were compared between the case group with subthreshold psychotic symptoms (N=9) and the case group without subthreshold psychotic
symptoms (N=34, excluding schizophrenia). The case group with subthreshold psychotic symptoms (N=9) had significantly lower SOFAS scores compared to the case group without attenuated psychotic symptoms (N=34) (Wilcoxon rank p-value=0.0072). The case group with subthreshold psychotic symptoms had a median SOFAS score of 45 compared to cases without subthreshold psychotic symptoms with a median SOFAS score of 60 (H-L estimate of the difference= -15, 95% CI= -5 to -20). SOFAS score of 45 corresponds to a serious impairment in social or school functioning compared to a score of 60 which corresponds to moderate difficulty in social, school or occupational functioning. However it must be noted that to meet the intake criteria for the attenuated psychotic group, the subject should have either a 30% drop in SOFAS scores from pre-morbid levels which has been sustained for a month or SOFAS score of 50 or less for the past 12 months or longer. The subject with schizophrenia was excluded in this analysis (See Figure 5 for further details).
Figure 5 - The SOFAS scores of case group with subthreshold psychotic symptoms (STPS) and case group without STPS.

Figure 5: The boxplots show the range of SOFAS scores (previous month) between cases with subthreshold psychotic symptoms (STPS) and cases without STPS (excluding case with schizophrenia).

4.8.5 Subthreshold Psychotic Symptoms and FSIQ Scores

The FSIQ scores of the case group with subthreshold psychotic symptoms (N=6, 3 individuals did not participate with the FSIQ analysis in this group) were compared with the case group without subthreshold psychotic symptoms (N=32). It was found that the median FSIQ in cases with subthreshold psychotic symptoms was 72 (Range 52-79) compared to 70 (Range 54-89) in cases without subthreshold psychotic symptoms (H-L estimate of the difference=2, 95% CI=0 to 2). There was no significant difference in the FSIQ scores between the case group with subthreshold psychotic symptoms and the case group without subthreshold psychotic symptoms (Wilcoxon rank p-value=0.6912). The subject with schizophrenia was excluded from this analysis (See Figure 6 for further details).
Figure 6 - The FSIQ scores of the case group with subthreshold psychotic symptoms (STPS) and case group without STPS

Figure 6: The boxplots show the range of the FSIQ scores of cases with STPS compared to cases without STPS (excluding case with schizophrenia). There was no significant difference in the FSIQ scores between the case group with subthreshold psychotic symptoms (STPS) and case group without STPS.

4.8.6 Co-morbid Psychiatric Disorders

The case group with subthreshold psychotic symptoms (N=9) were compared with the case group without these symptoms (N=35, excluding subject with schizophrenia). It was found that 67% (N=6) of cases with subthreshold psychotic symptoms had at least one psychiatric disorder compared to 63% (N=22) of cases without these symptoms. It was found that the case group with subthreshold psychotic symptoms had a median number of co-morbid psychiatric disorders of 2.0 compared to a median score of 1 in the case group without subthreshold psychotic symptoms. The case group with subthreshold psychotic symptoms had significantly more co-morbid psychiatric disorders compared to those without these symptoms.
(log linear regression p-value= 0.0067). Subject with schizophrenia and the diagnosis of specific phobias were excluded in this analysis.

The most frequently occurring co-morbid psychiatric disorder in the case group with subthreshold psychotic symptoms was the ‘other anxiety disorders’ (excluding specific phobias); five subjects were found to have one or more of the anxiety disorders; five had a social anxiety disorder, three had separation anxiety disorder and two had generalised anxiety disorders. Despite the high rates of anxiety disorders in the case group with subthreshold psychotic symptoms, there was no significant association found between subthreshold psychotic symptoms and anxiety disorders (Fisher’s exact p-value=0.09).

It was found that four per cent (N=2) of cases met the criteria for an obsessive compulsive disorder (OCD); both of the subjects also were found to have subthreshold psychotic symptoms. The OCD symptoms were distinct from the subthreshold psychotic symptoms. Both cases experienced auditory hallucinations. However, the hallucinations were not related to the OCD symptoms (these subjects did not have repeated thoughts to check or touch which could be mistaken for ‘voices’). A significant association between subthreshold psychotic symptoms and OCD was found only at the 5% level of significance (Fisher’s exact p-value=0.0283) in the case group.
4.8.7 Subthreshold Psychotic Symptoms and Behavioural Evaluation

4.8.7.1 CBCL Questionnaire

The CBCL T-scores were compared between the case group with subthreshold psychotic symptoms (N=9) and the case group without these symptoms (N=29) using the Wilcoxon Rank Sum test.

It was found that the case group with subthreshold psychotic symptoms had higher median T-scores for the problem scores and all the syndrome scales compared to the cases group without any subthreshold psychotic symptoms. After adjusting for multiple comparisons there were no significant differences found between the two groups. Refer to Table 14 for details. It was found that the case group with subthreshold psychotic symptoms had median T-scores within the clinical range for internalizing problems (median T-score 72) compared to a median T-score within the normal range for the case group without subthreshold psychotic symptoms (median T-score 55). In addition the case group with subthreshold psychotic symptoms had median externalising scores within the borderline range (median T-score 60) compared to a median T-score within the normal range for the case group without subthreshold psychotic symptoms. It was found that 33% of the case group with subthreshold psychotic symptoms had externalising problems within the clinical range compared to 7% of the case group without subthreshold psychotic symptoms. The median total problem scale was found to be within the clinical range for the case group with subthreshold psychotic symptoms, though within the normal range for the
case group without subthreshold psychotic symptoms. Sixty-seven per cent of the case group with subthreshold psychotic had total problems within the clinical range compared to 15% of the case group without subthreshold psychotic symptoms, though these differences were no statistically significant after adjusting for multiple comparisons.

<table>
<thead>
<tr>
<th>CBCL Variable</th>
<th>Cases Group With STPS (N=9)</th>
<th>% of Cases With STPS T-score 60-63 &gt;63</th>
<th>Case Group without STPS (N=29)</th>
<th>% of Cases w/o STPS T-score 60-63 &gt;63</th>
<th>p-value (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Externalising Problems</td>
<td>60 [40,82]</td>
<td>22 33</td>
<td>50 [33,66]</td>
<td>4 7</td>
<td>0.1238 (0.20)</td>
</tr>
<tr>
<td>Internalising Problems</td>
<td>72 [33,88]</td>
<td>11 56</td>
<td>55 [34,80]</td>
<td>11 22</td>
<td>0.0606 (2.22)</td>
</tr>
<tr>
<td>Total Problems</td>
<td>67 [37,91]</td>
<td>11 57</td>
<td>55 [34,74]</td>
<td>30 15</td>
<td>0.0393 (3.21)</td>
</tr>
</tbody>
</table>

Table 14: Statistical significance at the Bonferroni adjusted 0.455 level (p-value<0.0045)

It was found that the case group with subthreshold psychotic symptoms had higher median scores across the syndrome scales. Refer to Table 15 for details. The median scores of the withdrawn/depressed and social problems scales for the case group with subthreshold psychotic symptoms were found to be within the borderline clinical range at 70 (>70 is considered within the clinical range). It was found that 56% of the case group with subthreshold psychotic symptoms scored within the
clinical range for being withdrawn / depressed and having social problems compared to 7% and 15% respectively for the case group without subthreshold psychotic symptoms. There was a significant difference found between the two groups for the anxious depressed and thought problem scales, though after adjusting for multiple comparisons these problem scales were not significantly different between the two groups. It was found that 33% of the cases group with subthreshold psychotic symptoms scored within the borderline range and 22% scored within the clinical range for the anxious/depressed scale. It was found that 33% of the case group with subthreshold psychotic symptoms scored within the clinical range for having thought problems compared to 7% of cases without subthreshold psychotic symptoms. The case group with subthreshold psychotic symptoms were identified to have more problems with aggressive and rule-breaking behaviour compared to the case group without subthreshold psychotic symptoms. Eleven per cent of the case group with subthreshold psychotic symptoms scored within the clinical range for rule breaking behaviour compared to no subjects in the case group without subthreshold psychotic symptoms. In addition 11% of the case group with subthreshold psychotic symptoms scored within the borderline range and 11% scored within the clinical range for aggressive behaviour compared to 4% of the case group within the clinical range without subthreshold psychotic symptoms. However, these differences were not significant.
Table 15 - CBCL Syndrome Scale T-scores

<table>
<thead>
<tr>
<th>CBCL Variable</th>
<th>Cases with STPS (N=9) Median T-scores [Range]</th>
<th>% of Cases With STPS T-score 67-70 &gt;70</th>
<th>Cases without STPS (N=29) Median T-scores [Range]</th>
<th>% of Cases w/o STPS T-score 67-70 &gt;70</th>
<th>p-value (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxious/Depressed</td>
<td>68 [50,90]</td>
<td>33</td>
<td>52 [50,72]</td>
<td>7</td>
<td>0.0438 (0.18)</td>
</tr>
<tr>
<td>Withdrawn/Depressed</td>
<td>70 [50,89]</td>
<td>0</td>
<td>57 [50,80]</td>
<td>0</td>
<td>0.2236 (-2.25)</td>
</tr>
<tr>
<td>Somatic Complaints</td>
<td>66 [50,92]</td>
<td>0</td>
<td>57 [50,78]</td>
<td>7</td>
<td>0.0969 (0.16)</td>
</tr>
<tr>
<td>Social Problems</td>
<td>70 [50,96]</td>
<td>0</td>
<td>59 [50,82]</td>
<td>4</td>
<td>0.1779 (-1.18)</td>
</tr>
<tr>
<td>Thought Problems</td>
<td>64 [50,90]</td>
<td>0</td>
<td>52 [50,78]</td>
<td>7</td>
<td>0.0202 (3.18)</td>
</tr>
<tr>
<td>Attention Problems</td>
<td>62 [50,100]</td>
<td>11</td>
<td>59 [50,76]</td>
<td>0</td>
<td>0.3189 (-2.10)</td>
</tr>
<tr>
<td>Rule-Breaking</td>
<td>55 [50,73]</td>
<td>11</td>
<td>52 [50,68]</td>
<td>4</td>
<td>0.351 (1.2)</td>
</tr>
<tr>
<td>Aggressive Behaviour</td>
<td>60 [50,97]</td>
<td>11</td>
<td>51 [50,72]</td>
<td>4</td>
<td>0.0689 (0.15)</td>
</tr>
</tbody>
</table>

Table 15: Statistical significance at the Bonferroni adjusted 0.455 level (p-value<0.0045)

**Multivariate discriminate analysis**

Significance was considered at the 1% level of significance. There was evidence of borderline level of significance; it was found that thought problems on the CBCL syndrome scale showed a borderline level of discrimination between cases with subthreshold psychotic symptoms from cases without subthreshold psychotic symptoms (F-value=9.13, DF 1, 34, p-value=0.0047).
4.8.7.2 Strengths and Difficulties Questionnaire (SDQ)

The case group with subthreshold psychotic symptoms were found to have significantly higher median score on conduct problems compared to the case group without subthreshold psychotic symptoms (Wilcoxon p-value=0.04, p-value<0.05). It was found that 67% of the case group with subthreshold psychotic symptoms had scores within the abnormal range for conduct problems in contrast to 18% of the case group without subthreshold psychotic symptoms. However, after adjusting for multiple comparisons there were no significant differences found between the two groups. A large proportion (67%) of the case group with subthreshold psychotic symptoms had peer problems in the abnormal range in comparison to the case group without subthreshold psychotic symptoms (40%). In addition a higher proportion of the case group with subthreshold psychotic symptoms had total scores within the abnormal range (56%), in contrast to the case group without subthreshold psychotic symptoms (32%). Refer to Table 16 for details.
Table 16: Statistical significance at the Bonferroni adjusted 0.83 level (p-value<0.0083)

**Multivariate Analysis**

Significance was considered at the 1% level of significance. There was evidence of borderline level of significance in the peer problems scale of the SDQ discriminating the case group with subthreshold psychotic from the case group without subthreshold psychotic symptoms (F-value=6.73, DF, 1,35, p-value=0.0137).
4.8.8 Subthreshold Psychotic Symptoms & Autism Symptoms

There was no significant difference found in the total or sub-scale score of the SRS Questionnaire and the total score of the SCQ between the case group with subthreshold psychotic symptoms and the case group without subthreshold psychotic symptoms.

4.8.9 Subthreshold Psychotic Symptoms and SPQ Analysis

Using quantitative clinical cut-off scores; it was found that of the seven cases who had subthreshold psychotic symptoms and completed the SPQ, two of these subjects also met the cut-off (≥41) on the SPQ for potential schizotypal personality disorder.

The total SPQ, subscale scores and factor scores were compared between the case group with subthreshold psychotic (N=7) and case group without subthreshold psychotic symptoms (N=21) (schizophrenia excluded). There was no significant difference found between the total SPQ score, subscale or factor scores between the two groups.

To evaluate whether schizotypy scores were associated with psychotic disorders or with subjects in a possible prodromal state who may develop psychotic disorders, the subject with schizophrenia was grouped with the subjects with sub-threshold psychotic symptoms and categorised as the group with ‘psychotic symptoms’. The SPQ scores were compared between cases with psychotic symptoms (N=8) versus
cases without these psychiatric symptoms (N=21). Refer to Table 17 for detailed results. It was found that the case group with psychotic symptoms showed a trend towards higher median scores across the subscales and total scores, though there was no statistically significant difference found. Cases without psychotic symptoms were found to have a higher median score for the disorganized factor compared to those with ‘psychotic symptoms’. However, this difference was not statistically significant.

Multivariate analysis of the SPQ subscales, total scores and factors between cases with psychotic symptoms compared to cases without psychotic symptoms did not reveal any significant difference between the two groups.
<table>
<thead>
<tr>
<th>SPQ sub-scales, total and dimension scores</th>
<th>Cases with any psychotic symptoms N=8 Median [Range]</th>
<th>Cases without any psychotic symptoms N=21 Median [Range]</th>
<th>p-values (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ideas of reference</td>
<td>4 [0,6]</td>
<td>2 [0,7]</td>
<td>0.52 (-1,4)</td>
</tr>
<tr>
<td>Excessive social anxiety</td>
<td>4 [1,7]</td>
<td>5 [0,9]</td>
<td>0.44 (-2,3)</td>
</tr>
<tr>
<td>Odd Beliefs</td>
<td>1 [0,5]</td>
<td>0 [0,6]</td>
<td>0.39 (0,0)</td>
</tr>
<tr>
<td>Unusual perceptual experiences</td>
<td>2 [1,5]</td>
<td>0 [0,9]</td>
<td>0.034 (1,3)</td>
</tr>
<tr>
<td>Odd or eccentric behaviour</td>
<td>1.5 [0,9]</td>
<td>1 [0,6]</td>
<td>1.00 (-1,0)</td>
</tr>
<tr>
<td>No close friends</td>
<td>2 [0,8]</td>
<td>2 [0,8]</td>
<td>0.52 (-1,8)</td>
</tr>
<tr>
<td>Odd speech</td>
<td>2 [0,7]</td>
<td>3.5 [0,9]</td>
<td>0.56 (-3,4)</td>
</tr>
<tr>
<td>Constricted affect</td>
<td>2.5 [0,5]</td>
<td>2 [0,7]</td>
<td>0.93 (-1,0)</td>
</tr>
<tr>
<td>Paranoid ideation</td>
<td>2 [0,7]</td>
<td>1 [0,8]</td>
<td>0.55 (-1,5)</td>
</tr>
<tr>
<td>Total scores</td>
<td>18 [4,47]</td>
<td>14 [1,66]</td>
<td>0.87 (-8,34)</td>
</tr>
<tr>
<td>Cognitive/perceptual Dimension</td>
<td>6 [1,14]</td>
<td>2 [0,21]</td>
<td>0.36 (0,0)</td>
</tr>
<tr>
<td>Social anxiety Dimension</td>
<td>7.5 [0,13]</td>
<td>3.5 [0,14]</td>
<td>0.61 (-1,0)</td>
</tr>
<tr>
<td>Disorganised Dimension</td>
<td>3.5 [0,10]</td>
<td>5 [1,15]</td>
<td>0.55 (-3,0)</td>
</tr>
</tbody>
</table>

Table 17: Statistical significance at the Bonferroni adjusted 0.384% level (p-value<0.0038)
4.9 Analysis of the CAARMS Subscales

In addition to determining whether an individual met the inclusion criteria on the CAARMS, each of the symptom scales on the CAARMS were considered to determine whether there was a significant association in the occurrence of these symptoms between cases and controls and between the case group with subthreshold psychotic symptoms vs. the case group without subthreshold psychotic symptoms. Each of the symptoms were analysed by the global rating scores and considered for analysis when the symptoms received a global scores score of two or more.

4.9.1 Case Group vs. Control Group

Univariate analysis by using the Wilcoxon rank sum test, found that cases were significantly more likely to score higher on symptoms of: alogia, blunted affect, disorders of concentration and attention, disorganized speech, non-bizzare ideas and social isolation compared to siblings. Refer to Table 18 which details only the significantly occurring symptoms (1% level of significance for the statistical tests was set in order to reveal the most important differences in the relatively small sample size and large number of items and sub-items in the CAARMS assessment). After adjusting for multiple comparisons it was found that blunted affect, concentration & attention and disorganised speech was found to be significantly different between cases and controls (p-value<0.0018).
Table 18 - Significantly occurring symptoms identified by CAARMS interview

Cases (22q11.2DS) vs. sibling control (no of individuals scoring 2 or more on the Global Rating Scale)

<table>
<thead>
<tr>
<th>Symptoms measured By CAARMS</th>
<th>22q11.2DS Group (n=41)</th>
<th>Control Group (n=26)</th>
<th>p-value**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alogia</td>
<td>13</td>
<td>0</td>
<td>0.0025*</td>
</tr>
<tr>
<td>Blunted affect</td>
<td>19</td>
<td>0</td>
<td>0.0002**</td>
</tr>
<tr>
<td>Concentration &amp; attention</td>
<td>16</td>
<td>0</td>
<td>0.0003**</td>
</tr>
<tr>
<td>Disorganised speech</td>
<td>16</td>
<td>0</td>
<td>0.0016**</td>
</tr>
<tr>
<td>Non-bizarre ideas</td>
<td>11</td>
<td>0</td>
<td>0.0059</td>
</tr>
<tr>
<td>Social isolation</td>
<td>10</td>
<td>0</td>
<td>0.0091</td>
</tr>
</tbody>
</table>

Table 18: **Statistical significance at the Bonferroni adjusted 0.18% level (p-value<0.0018)

Multivariate analysis using step-wise discriminant analysis was performed on the global rating scores for each of the symptom (1% significance level set) between cases (N=40) and controls (N=26). It was found that blunted affect (F-value= 13.66, DF 1,63, p-value<0.0001) and observed cognitive inattentiveness during the interview (F-value=10.46, DF 1,63, p-value=0.0005) together significantly discriminated cases and controls. Therefore these results suggest that the case group could be identified from the sibling group based on the presence of blunted affect and cognitive inattentiveness. These two items give complete discrimination between the case and control group, there is no uncertainty and therefore odds ratios from a similar logistic regression analysis are non-estimable.
4.9.2 Case Group with Subthreshold Psychotic Symptoms

Univariate analysis by using Wilcoxon rank sum test was performed on the global rating scores for the case group with subthreshold psychotic symptoms vs. case group without subthreshold psychotic symptoms. It was found that the case group with subthreshold psychotic symptoms scored significantly higher than the case group without subthreshold psychotic symptoms on the global rating scale for anxiety symptoms, avolition/apathy, disorganized/odd behaviour, perceptual abnormalities* and inappropriate behaviour. Refer to Table 19 for details of the significantly occurring symptoms between case group with/without subthreshold psychotic symptoms (1% level of significance for the statistical tests was set in order to reveal the most important differences in the relatively small sample size and large number of items and sub-items in the CAARMS assessment). After adjusting for multiple comparisons it was found that the case group with subthreshold psychotic symptoms scored significantly higher than the case group without subthreshold psychotic symptoms for disorganised odd behaviour and perceptual abnormalities (p-value<0.0018).

*Of note, perceptual abnormalities is one of the symptoms used to identify the ‘at risk mental state’, therefore cases with ‘any subthreshold psychotic symptoms’ would have been categorised based on the presence of perceptual abnormalities, so therefore, significantly higher scores for perceptual abnormalities would have been expected.
Table 19 - Comparison of Significantly occurring CAARMS Symptoms
Case group with Subthreshold Psychotic Symptoms (STPS) vs. Case group without Subthreshold Psychotic Symptoms
(Significantly occurring symptoms only detailed)

<table>
<thead>
<tr>
<th>CAARMS subscales</th>
<th>Cases with STPS (n=9)</th>
<th>Cases without STPS (n=32)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety symptoms</td>
<td>Median</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>% Scoring ≥ 2</td>
<td>89%</td>
<td>34%</td>
</tr>
<tr>
<td>Aversion / apathy</td>
<td>Median</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>% Scoring ≥ 2</td>
<td>44%</td>
<td>6%</td>
</tr>
<tr>
<td>Perceptual abnormalities</td>
<td>Median</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>% Scoring ≥ 2</td>
<td>56%</td>
<td>3%</td>
</tr>
<tr>
<td>Disorganised / Odd</td>
<td>Median</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>behaviour</td>
<td>% Scoring ≥ 2</td>
<td>33%</td>
<td>0</td>
</tr>
<tr>
<td>Inappropriate affect</td>
<td>Median</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>% Scoring ≥ 2</td>
<td>33%</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 19: **Statistical significance at the Bonferroni adjusted 0.18% level (p-value<0.0018)

Multivariate analysis using step-wise discriminant analysis was performed on the global rating scores for each of the symptom (1% significance level set). Case group with subthreshold psychotic symptoms (N=8 as data from one individual was
not included due to numerous missing items) were compared with the case group without subthreshold psychotic symptoms (N=32). The presence of hallucinations, delusions and the SOFAS scores determined whether an individual was categorized as having subthreshold psychotic symptoms based on the CAARMS interview. In addition to these core diagnostic symptoms of the CAARMS, it was found that the case group with subthreshold psychotic symptoms were significantly more likely to display aggression/dangerous behaviour (F-value = 41, DF 1, 34, p-value = 0.0002), disorganized/odd behaviour (F-value = 65, DF 1, 34, p-value = 0.0001) and motor difficulties (informant)(F-value = 31, DF 1, 34, p-value < 0.0001) compared to the case group without subthreshold psychotic symptoms.

Therefore the case group with subthreshold psychotic symptoms were reported by parents/guardians to be clumsy, have problems related to coordination and have abnormal motor movements (motor difficulties). They were reported by parents to be irritable and confrontational towards peers/parents (aggression/dangerous behaviour scale, no subject scored greater than 4). They were reported by individuals/parents to be more socially isolative, requiring direction to maintain self care and social commitments and displaying eccentric/bizarre behaviour that attracts attention (disorganized/odd behaviour). Therefore these results suggest that the case group with subthreshold psychotic symptoms could be identified from the case group without subthreshold psychotic symptoms based on the presence of disorganised/odd behaviour, motor difficulties and the display of aggressive behaviour. These three items gave complete discrimination between the case group
with and without subthreshold psychotic symptoms, there is no uncertainty and therefore odds ratios from a similar logistic regression analysis are non-estimable.

4.10 Relationship between the SPQ and CAARMS

To determine whether the SPQ and the CAARMS were measuring similar attenuated symptoms of schizophrenia or whether these instruments were measuring independent constructs, correlations between SPQ scores and the CAARMS dimensions were examined with the Spearman Rank test. It was determined that a correlation would be considered between the scores and dimensions of at least 0.7 (or less than -0.7).

It was found that only the subscale of ‘No close friends’ of the SPQ correlated significantly with the CAARMS dimension of Alogia $r_s 0.83 \ p-value<0.0001$. The Interpersonal dimension factor (Suspiciousness/paranoid ideation, Social anxiety, No close friends & Constricted Affect) also correlated significantly in a positive manner with the CAARMS dimension of Alogia $r_s 0.76 \ p-value<0.0001$). Therefore cases scoring highly on the Alogia subscale of the CAARMS also scored highly on the SPQ subscale of no close friends. The subscale of ‘No close friends’ of the interpersonal factor was found to contribute significantly to the correlation of Alogia on the CAARMS and the interpersonal dimension factor of the SPQ. None of the other symptoms of the CAARMS showed any significant correlation with the SPQ.
The CAARMS and SPQ assess similar attenuated symptoms of schizophrenia, though the findings from this study suggest that the similar symptoms identified between the two measures do not show a significant degree of correlation between each other in this sample.

Using quantitative clinical cut-off scores; it was found that of the six cases who were identified as having subthreshold psychotic symptoms on the CAARMS assessment and completed the SPQ, two of these subjects also met the cut-off on the SPQ. Five subjects met the cut-off on the SPQ. Therefore nine cases who met the cut-off for one construct, did not meet the construct for the other, suggesting that there may be a degree of discrimination between the two measures for subjects with 22q11.2DS. However, this requires to be tested in a large sample size.
CHAPTER 5 – DISCUSSION
Overview
The general aim of this thesis was to assess the prevalence of psychiatric morbidity and behavioural difficulties in a sample of cases with 22q11.2DS and then to explore possible associations between psychiatric disorders, behavioural difficulties and physical problems by (1) comparing psychiatric and behavioural findings between individuals with 22q11.2DS and their siblings; (2) comparing individuals with specific psychiatric diagnosis with those without the specified psychiatric disorder; (3) comparing individuals with 22q11.2DS and with subthreshold psychotic symptoms compared with those individuals without subthreshold psychotic symptoms (4) investigating for associations and correlations between physical disorders, general functioning, intellectual functioning, psychiatric disorders, behavioural problems, autism symptoms, schizotypal features and subthreshold psychotic symptoms. The findings of the study are examined and considered in relation to the hypotheses formulated at the outset of the study.

5.1 Summary of the Behavioural and Psychiatric Findings
This is the first Irish population study of the psychiatric and behavioural profile of individuals with 22q11.2DS. This was the first study at the time to use the Comprehensive Assessment of the At Risk Mental State (CAARMS) to assess individuals with 22q11.2DS for the presence of preclinical psychotic symptoms.

The main findings from this study show that (1) children and adolescents with 22q11.2DS have more internalising and externalising behaviour than their siblings;
(2) individuals with 22q11.2DS have more symptoms of autism than their siblings; (3) individuals with 22q11.2DS have more schizotypy features than their siblings; (4) individuals with 22q11.2DS have higher rates of psychiatric disorders and in particular ADHD compared to their siblings; (5) individuals with 22q11.2DS have more difficulties with social and school/occupational functioning and more difficulties with mental performance compared to their siblings; (6) Children and adolescents with 22q11.2DS who exhibited sub-threshold psychotic symptoms were found to have much more difficulty with social and school performance, had higher rates of co-morbid psychiatric disorders, display aggressive, odd behaviour and have more motor difficulties compared to children and adolescents with 22q11.2DS and without sub-threshold psychotic symptoms.

5.1.1 Behavioural Profile of Children and Adolescents with 22q11.2DS

The present study found that children and adolescents with 22q11.2DS had significantly more difficulties in both internalising and externalising problems compared to their siblings. On the Child Behaviour Checklist (CBCL) questionnaire children and adolescents with 22q11.2DS were found to have significantly more problems with withdrawn/depressed behaviour, somatic complaints, social problems, thought problems, attention problems and rule breaking behaviour compared to siblings. However, the median CBCL scores for both the 22q11.2DS group and their siblings were within CBCL norms, a finding which has also occurred in other studies (Swillen 2001), though the prevalence of behavioural problems within the clinical range was proportionally higher for the 22q11.2DS group (Table 4.4 & 4.5 pg 80, 84). Within the 22q11.2DS group, the most prevalent behavioural difficulty was social
problems; 25% of children and adolescents with 22q11.2DS were found to have social problems within the clinical range. Nineteen percent of children and adolescents with 22q11.2DS exhibited withdrawn/depressed behaviour within the clinical range compared to none of their siblings. Results from the Strengths and Difficulties Questionnaire (SDQ) indicated that children and adolescents with 22q11.2DS had significantly more emotional symptoms, hyperactivity problems, peer problems and more difficulties with pro-social behaviour compared to siblings.

Further multi-variate analysis of the CBCL scores found that attention problems alone significantly discriminated the 22q11.2DS group from the sibling group and is in keeping with the significantly high rates of ADHD found in children and adolescents with 22q11.2DS. Multi-variate analysis of the SDQ scores indicated that children and adolescents with 22q11.2DS could be significantly discriminated from siblings on the presence of emotional, hyperactivity and conduct related behaviour and these findings are in keeping with the high prevalence of anxiety disorders, oppositional defiant disorder and ADHD found in children and adolescents with 22q11.2DS.

A significant difference in intellectual functioning was found between children and adolescents with 22q11.2DS compared to their siblings (p-value<0.0001). This difference may underlie or contribute to the significantly higher rates of behavioural problems, psychiatric disorders, autism scores and schizotypal features in the 22q11.2DS group. However, the contribution of intellectual functioning can only be adequately assessed with the use of an I.Q. matched control group. One of the limitations of the design of this study is the failure to include an I.Q. matched control.
group and therefore the effect of intellectual functioning on behaviour and psychopathology between the groups could not be adequately determined. An intra-group (22q11.2DS) correlation analysis of the FSIQ scores, the behaviour and psychiatric data was performed to determine the relationship between these variables.

An intra-group correlation analyses between FSIQ scores and behavioural problems did not reveal any significant correlation. These results suggest that differences in intellectual functioning/level in children and adolescents with 22q11.2DS may not be related to behavioural problems. Previous studies have found that behavioural problems in children and adolescents with 22q11.2DS were higher compared to the general population though comparable to I.Q matched controls, suggesting that differences in behaviour may be explained by differences in mental behaviour (Feinstein et al., 2002b). Therefore, the finding from the present study of a significant difference in behaviour between the 22q11.2DS group and their siblings may be explained by the difference in intellectual functioning. However, the present study found that the level of intellectual functioning within the 22q11.2DS group was not related to the severity of behavioural difficulties.

The high prevalence of withdrawn/depressed behaviour found in children and adolescents with 22q11.2DS in this study support the findings of an earlier study in which children with 22q11.2DS were significantly more likely to be withdrawn/depressed behaviour compared to I.Q. matched controls (Swillen, 2001). There was a significant difference in the prevalence of rule breaking behaviour
between children and adolescents with 22q11.2DS compared to their siblings. Previous studies have found that children and adolescents with 22q11.2DS have significantly lower rates of externalising behaviour compared to I.Q. matched controls (Feinstein et al., 2002b, Swillen, 2001). The results from this present study and those from I.Q. matched controls suggest that children and adolescents may have higher rates of externalising symptoms compared to siblings though have lower rates of externalising symptoms compared to children with other learning disabilities. This present study found that attention problems discriminated children and adolescents from their siblings. However, it is difficult to determine from the study whether the attention difficulties may be due to differences in intellectual performance between individuals with 22q11.2DS and their siblings. Future studies should include an I.Q. matched control group to assess for these differences.

The majority of previous studies on children and adolescents with 22q11.2DS have used the CBCL questionnaire to identify behavioural problems. The present study found that children and adolescents with 22q11.2DS who had high total scores on the SDQ particularly in the hyperactivity scales were likely to have a diagnosis of ADHD (\( p\)-value=0.005). It was also found that children and adolescents scoring highly on the emotional scale of the SDQ were likely to have anxiety disorders (\( p\)-value=0.0087). Furthermore, it was found that children and adolescents who had difficulties with social and school functioning were found to have higher total scores on the SDQ, suggesting that the total SDQ score in children and adolescents with 22q11.2DS may also identify those that are having functional difficulties. These findings suggest that the SDQ may be used as a screening tool to identify children
and adolescents with 22q11.2DS who may have ADHD, anxiety disorders or difficult social/school functioning. Children and adolescents with 22q11.2DS obtaining total SDQ scores within the abnormal range (20-40) should be considered for further comprehensive psychiatric assessments.

The findings from this present study support the 1st hypothesis - that individuals with 22q11.2DS have a higher prevalence of behavioural problems compared to their siblings.

5.1.2 Autism Symptoms in individuals with 22q11.2DS

5.1.2.1 Categorical Evaluation of Autism Screening Tool Scores

This present study found that individuals with 22q11.2DS were much more likely to score at or above specified cut-off points on Autism Screening Questionnaires compared to their siblings. Thirty-two percent of children and adolescents with 22q11.2DS scored ≥85 on the Social Responsiveness Scale (SRS), suggesting that these identified children and adolescents may have an Autism Spectrum Disorder (ASD). Twenty-eight percent of individuals with 22q11.2DS scored ≥ 13 with the use of the Social Communication Questionnaire (SCQ), suggesting that these identified individuals may have an ASD. There was no gender difference in those scoring above the specified cut-off mark for the questionnaires; both questionnaires identified an equal proportion of males and females. These results suggest that there may be no gender difference in the occurrence of ASD in individuals with 22q11.2DS, findings which have been found in other genetic syndromes such as Tuberous
Sclerosis, though in contrast to findings from the general population in which males are predominantly affected (De Vries et al., 2007, Summ, 2007, MMWR, 2007). An earlier study by Niklasson and colleagues (2009) found that the rate of ASD with the use of the Autism Spectrum Screening Questionnaire (ASSQ), a tool similar to the SRS and SCQ was 23%. This rate is comparable, though marginally lower compared to both of the rates obtained in this study, though much closer to the rates obtained by the SCQ in this present study when the cut-off was at 14.

The rates of individuals scoring at or above specified cut-offs on autism screening tools in this present study and the study by Niklasson and colleagues (2009) are much lower compared to other earlier studies in which the Autism Diagnostic Interview-Revised (ADI-R) was used; the prevalence of ASD in these studies were found to range from 41%-50% (Antshel et al., 2007, Vorstman et al., 2006). If the true rate of ASD in 22q11.2DS is around 41-50%, this suggests, based on the findings from the present study that the SRS and the SCQ may not be sensitive as screening tools to identify autistic symptoms in individuals with 22q11.2DS. However Fine and colleagues (2005) with the use of the ADI-R found that the rate of ASD in individuals with 22q11.2DS was 14%, suggesting a large variability in the occurrence of ASD (14%-50%) in individuals with 22q11.2DS. The variability found in the prevalence of ASD in the different studies of 22q11.2S may be due: to intellectual differences between the different groups (discussed further below), genetic factors within the deleted region, genetic factors outside the 22q11 region and environmental factors (services available, home situation, social factors).
The results from the present study indicate that a higher rate of possible ASD was found with the Social Responsiveness Scale (SRS) at 32% compared to a rate of 15% at a cut-off at 15 and 20% at a cut-off at 14 with the Social Communication Questionnaire. These results suggest that the SRS may be more sensitive than the SCQ in identifying possible ASD in individuals with 22q11.2DS. However, one study found that a lower cut-off for ASD with the SCQ was required for younger children compared to older children (Corsello et al., 2007). As the SCQ may be influenced by age effects, it is therefore uncertain whether the underestimate of the rates of ASD found with the SCQ may by due to these age effects in the younger population. In addition, it is not certain whether the inclusion of adults with the same cut-off scores as the younger children with the SCQ is appropriate given the influence of age on the SCQ. Therefore the differences between the two screening tools may be due to age effects and the inclusion of screening adults with the SCQ.

The sensitivity and specificity of these instruments in identifying autism spectrum disorders in the 22q11.2DS sample is required by assessing the sample with the Autism Diagnostic Interview-Revised (ADI-R), which is regarded as the gold standard instrument for the diagnosis of autism spectrum disorders (Lord et al., 1994). Due to the imposition on time with the assessments with the DISC, K-SADS and CAARMS, it was not feasible to also include the ADI-R in the assessment process. This is a limitation of the study; perhaps the ADI-R should have been administered to the carers of the individuals who scored above the specified cut-off for either the SCQ or SRS.
5.1.2.2 Dimensional Evaluation of Autism Screening Tool Scores

This present study found that children and adolescents with 22q11.2DS had increased symptoms of autism compared to their siblings (refer to Table 4.7 & 4.8 pages 91, 92). Children and adolescents with 22q11.2DS had higher SRS subscale scores in each of the domains of autism compared to their siblings. Findings from one population based study suggests that different aetiological pathways may underlie the different diagnostic domains of ASD (Ronald et al., 2006). The results from the present study suggest that children and adolescents with 22q11.2DS have impairments in each of the domains rather than a specific domain and have a wide range in severity of autistic symptoms.

It has been suggested that intellectual impairment, which is associated with many genetic disorders including 22q11.2S may increase the likelihood of autistic symptoms being found and the genetic syndromes which are associated with more severe intellectual impairment will be more likely to manifest autistic symptoms (Skuse, 2007). Furthermore several studies in other genetic disorders such as Fragile X and Tuberous sclerosis have found that the individuals who meet the criteria for ASD are more likely to have more severe intellectual functioning (De Vries et al., 2007, Lewis et al., 2007). The significantly higher autism symptoms in children and adolescents with 22q11.2DS compared to their siblings as found in the present study could be due to differences in intellectual functioning. However, the present study found that the level of intellectual functioning within the 22q11.2DS group was not related to the severity of autistic symptoms. These findings do not support
findings from previous studies on other genetic disorders as discussed above. Similarly other studies of individuals with 22q11.2DS did not find a correlation between I.Q. level and severity of autistic symptoms and also these studies did not find a significant difference in the FSIQ scores of cases with 22q11.2DS and ASD and cases without ASD (Antshel et al., 2007, Vorstman et al., 2006).

The present study found that children and adolescents with 22q11.2DS and with higher autism symptoms (total scores on the SRS) had more difficulty in social and school functioning compared to those with lower autism scores. Social deficit is a core symptom of autism spectrum disorders and may explain the difficulty that these children and adolescents with high autism scores have in social and school functioning. However, it was found in this present study that 18% of the sample with 22q11.2DS had the combination of ADHD and also high autism scores and therefore it was difficult to determine whether the difficulty in social and school functioning was due to the high autism scores, ADHD or the combination of both difficulties (discussed further in Section 5.1.4.2 page 156).

The identification of ASD symptoms and the diagnosis of ASD can be difficult in children and adolescents with 22q11.2DS due to communication problems, social problems (possibly due to anxiety disorders), behavioural problems, attention problems and intellectual difficulties. In addition, instruments such as the ADI-R, which are considered gold standard for the diagnosis of ASD were not developed to discriminate between the social-communication deficits which are present in genetic disorders such as 22q11.2DS and regarded by some authors to be different to the
deficits of idiopathic autism. These difficulties may also underlie the variability in rates of ASD in 22q11.2DS. Furthermore, as difficulties in communication in children and adolescents can stem from palatal and velopharyngeal abnormalities, these deficits can be difficult to discriminate from the speech difficulties of idiopathic ASD in the ADI-R interview.

5.1.3 Schizotypy in Adolescents and Adults with 22q11.2DS

Symptoms of schizotypy were measured in adolescents and adults with 22q11.2DS with the Schizotypal Personality Questionnaire (SPQ). It was found that adolescents and adults with 22q11.2DS had significantly more symptoms of schizotypy (median total SPQ=16, range 1, 66) compared to their siblings (median total SPQ=4, range 0, 39). In particular, it was found that there was a significant difference between the 22q11.2DS group and their siblings in the subscales of excessive social anxiety and odd speech of the SPQ, these two subscales contributed predominantly to the total SPQ score. It was also found that scoring highly on the subscale of odd speech significantly discriminated adolescents and adults with 22q11.2DS from their siblings (p-value<0.0001). Furthermore, it was found that there was a significant difference in the disorganized factor between adolescents and adults with 22q11.2DS compared to their siblings.

It has been suggested that high scores on the disorganized factor/dimension may be a vulnerability marker for psychotic disorders(Schurhoff et al., 2005, Cardno et al., 1996). The results from the present study show that adolescents and adults with
22q11.2DS have significantly higher scores for the disorganized factor/dimension (median disorganized score=4, range 0, 15) than their siblings (median disorganized score=0, range 0, 11). Individuals with 22q11.2DS have an increased risk of developing a psychotic disorder compared to the general population, therefore, higher scores for the disorganized dimension in the 22q11.2DS group support previous findings in the general population and suggest that the disorganized dimension may also be a general vulnerability factor for psychosis in 22q11.2DS. Follow-up studies of the cohort will provide understanding of the relationship between schizotypy scores, the disorganized dimension and the development of psychosis in individuals with 22q11.2DS. Furthermore, the interplay between high disorganized factor scores, environmental factors (stress) and other psychopathological symptoms and disorders should be examined in individuals that develop psychotic disorders.

The significant findings for the total schizotypy scores and the disorganized dimension scores between adolescents and adults with 22q11.2DS compared to their siblings in the present study demonstrates a lack of familiality in the schizotypy scores/disorganized dimension. In the general population, studies have found that factors composed of symptoms which form the disorganized dimension are associated with an increased risk of illness in relatives (Cardno et al., 1996). The present study found an absence of familiality in the disorganized dimension which suggests that the higher disorganized dimension scores/features in the 22q11.2DS group may stem primarily from haploinsufficiency of genes within the 22q11 region.
The disorganized dimension of schizotypal personality is constructed with the sum of the odd behaviour and odd speech subscales of the SPQ. In the current study the symptoms which appear to drive the significant finding for the disorganized dimension is odd speech. Three of the nine questions pertaining to the odd speech subscale may be endorsed entirely due to the speech difficulties which may be present in individuals with 22q11.2DS due to underlying palatal/velopharyngeal anomalies (*people sometimes find it hard to understand what I am saying*, *I find it hard to communicate clearly what I want to say to people* and *people occasionally comment that my conversation is confusing*). Therefore the subscale of *odd speech* may not be a valid measure of the odd speech of schizotypal personality particularly in individuals with 22q11.2DS and the high scores may be an over-estimate. Over-estimation of scores for the odd speech subscale also results in over-estimation for the disorganized factor scores. Therefore, future studies using the SPQ in 22q11.2DS may require modifying questions or scores to reduce the possibility of overestimation of the odd speech subscale. Therefore significant difference in the disorganized dimension between the 22q11.2DS and the sibling group should be interpreted with caution and replication with a larger and older sample size should be considered with modification of the questions to elicit symptoms of odd speech in the 22q11.2DS group.

The questions pertaining to the social anxiety subscale of the SPQ show some overlap with the questions asked in the assessment of anxiety disorders. It was found in the present study that anxiety disorders were the most commonly occurring psychiatric disorder in individuals with 22q11.2DS; hence this may explain the
particularly high scores for the excessive social anxiety subscale of the SPQ. Therefore, it is questionable as to whether the high schizotypy scores in the 22q11.2DS group reflect a measure of schizotypy or reflect the high rates of anxiety disorders. Correlation between the SPQ subscales and the symptoms measured by the CAARMS, including anxiety symptoms were investigated (discussed further in Sect 5.2.7 page 174). It was found that there was no significant strength of correlation between the excessive social anxiety sub-scale and the measure of anxiety symptom scale on the CAARMS. Therefore, these findings suggest that the subscale of excessive social anxiety of the SPQ does not simply reflect the high rate of anxiety disorders in individuals with 22q11.2DS; it is then assumed that the lack of correlation indicates that the subscale may measure a construct which is more specific with schizotypal personality disorder rather than a measure of anxiety disorders.

Studies of the general population have found that the mean total SPQ score varies between different samples and populations. The mean total SPQ score in 23 year old Mauritians was 24.2 and 26.4 in a sample of 18-45 year old from Los Angeles (Reynolds et al., 2000, Raine, 1992, Raine, 1991). In contrast it was found in the present study that the median total SPQ for the 22q11.2DS group was 16 and 4 for the siblings. One explanation for the lower total schizotypy scores in this current study compared to the general population studies may be due to age factors. Personality disorders become more apparent in early adulthood. Sixty-nine percent of participants in the 22q11.2DS group and 86% of participants in the sibling group were adolescents. Therefore the study may only be capturing developing
symptoms/features of schizotypy in the participants and therefore represent an underestimate of the true rate of schizotypal features in both the 22q11.2DS and sibling group. An estimation of the prevalence of schizotypy features/disorders in 22q11.2DS may require an older population.

The research findings do support the 2nd hypothesis; *individuals with 22q11.2DS had significantly higher total schizotypy scores compared to their sibling controls.* Furthermore this study found that the disorganized dimension of schizotypy is higher in the 22q11.2DS group, therefore supporting previous findings that the disorganized dimension may represent a general vulnerability marker for psychosis. However, significant differences in the disorganized dimension between the 22q11.2DS group and their siblings may be due to overestimation of the symptoms of odd speech in the 22q11.2DS group.

The characterization of symptoms on the schizophrenia spectrum in individuals with 22q11.2DS provides one avenue to examine possible candidate psychosis genes within the 22q11 region and specific symptom clusters. Identification of genes (both within and outside the 22q11 region) may provide insight into neurobiological models of aberrant pathways from the genotype to the expression of clinical symptoms. The study of schizotypal symptoms in individuals who are at risk of psychosis, such as those with 22q11 deletion provides a method of studying clusters of symptoms that are considered to be milder than frank psychotic symptoms of schizophrenia. This provides an opportunity to compare schizotypy scores/dimensions in a case control design between individuals who develop schizophrenia and those that do not do
identify for differences in clinical symptoms and possible underlying genetic differences.

5.1.4 Psychiatric Disorders in Individuals with 22q11.2DS

This study found that 62% of individuals with 22q11.2DS had at least one psychiatric disorder in contrast to 19% of their siblings (p-value=0.005). The most commonly occurring psychiatric disorders in individuals with 22q11.2DS were the specific phobias (36%) and other anxiety disorders (31%), though Attention Deficit Hyperactivity Disorder (ADHD) was found to be the most significantly occurring psychiatric disorder compared to siblings (p-value<0.00625). The results from this present study confirm findings from previous studies of high rates of anxiety disorders, ADHD, attention difficulties and autism symptoms in individuals with 22q11.2DS.

5.1.4.1 Attention Deficit Hyperactivity Disorder (ADHD)

The present study found that 29% of individuals with 22q11.2DS had ADHD. The prevalence of ADHD found in this study is a conservative estimate compared to other studies with rates between 30-50% (Zagursky et al., 2006, Antshel et al., 2006). Perhaps a sample with a higher mean age of 14.6 resulted in a conservative estimate compared to other studies of children and adolescents with 22q11.2DS.

There was no statistical difference found between the FSIQ scores of cases with ADHD and those without ADHD, suggesting that the level of intellectual functioning
may not entirely explain the high rates of ADHD found in children and adolescents with 22q11.2DS. These findings are consistent with an earlier study by Gothelf and colleagues (2004), in which they found no significant difference in the total FSIQ scores of those with ADHD compared to those without ADHD and no significant difference between verbal and performance I.Q. scores between subjects with ADHD and those without ADHD (Gothelf et al., 2004). Despite the presence of non-participation bias (non-participation of three cases with I.Q. testing) in the current study the results are consistent with other studies and therefore may reflect a true association.

The present study found that there was no significant gender difference in the occurrence of ADHD in the 22q11.2DS sample. These findings are consistent with a larger study of 84 children with 22q11.2DS in which no significant gender difference was also found (Antshel et al., 2006). However, these findings are in contrast to the findings in the general population and to the findings from two other studies of 22q11.2DS; one which found ADHD to be significantly present in males and the other study finding a female predominance of ADHD in 22q11.2DS (Niklasson et al., 2009, Zagursky et al., 2006, Gothelf et al., 2004). ADHD was not found in the first or second degree relatives of the affected individual, suggesting that ADHD in this sample may not have a familial basis, a finding consistent with Antshel and colleague (2006) though in contrast to Gothelf and colleagues (2004) findings of a significantly greater prevalence of ADHD in the first degree relatives of those affected by ADHD compared to those without ADHD. This present study also found that both the inattentive sub-type and the combined subtype of ADHD occurred equally in the
sample, without a gender bias. However, other studies have found either the combined (Gothelf et al., 2004) or inattentive subtype to predominate in the sample (Antshel et al., 2006, Zagursky et al., 2006).

This present study and other studies of 22q11.2DS show mixed findings related to ADHD occurring in 22q11.2DS. Studies to date have failed to find an ADHD subtype occurring in 22q11.2DS. The variable findings related to ADHD in individuals with 22q11.2DS may reflect an underlying genotypic heterogeneity which is also found in ADHD in the general population and suggests that multiple genes both within and outside the 22q11 region may contribute to symptoms of ADHD found in 22q11.2DS.

Findings from the present study indicate that symptoms underlying inattention is a significant problem in children and adolescents with 22q11.2DS and found to be markedly atypical compared to symptoms related to hyperactivity/impulsivity. It was found that attention problems significantly discriminated children and adolescents with 22q11.2DS from their siblings on the CBCL measures (p-value <0.0001). Similarly, observed cognitive inattentiveness significantly discriminated individuals with 22q11.2DS from their siblings on the CAARMS interview (p-value=0.0005) and problems of inattention were identified more of a concern then those related to hyperactivity on the Conners questionnaire. The findings from the present study suggest that inattention is a consistent difficulty in individuals with 22q11.2DS irrespective of whether they meet criteria for ADHD. These results are consistent with other studies which have also found that symptoms related to inattention are much more commonly endorsed or reported compared to the hyperactive symptoms.
in 22q11.2DS (Niklasson et al., 2009, Zagursky et al., 2006). These findings are further supported by neuropsychological studies which have found that youths with 22q11.2DS perform poorly on visual, auditory and computerised test of attention compared to control participants (Lewandowski et al., 2007, Sobin et al., 2004). It has been suggested that attention problems in individuals with 22q11.2DS may be associated with deficits in the prefrontal-striatal network and frontal-parietal dysfunction (Kates et al., 2005, Simon et al., 2005). Therefore, based on the findings from this study and other studies, inattention in children and adolescents with 22q11.2DS is a consistent finding and may comprise one of the core phenotypic symptoms of 22q11.2DS.

However, inattention is a broad symptom. Therefore, specific neuropsychological tests to identify cognitive dysfunction underlying impaired attention should be investigated in 22q11.2DS. These findings should be correlated with neuroimaging techniques which focus on investigating aberrant neural circuits and pathways. Abnormal neural-circuits may reflect defects of early development which may be related to haploinsufficiency of developmental genes within the 22q11 region and/or genes outside the 22q11 region.

A longitudinal study of individuals with 22q11.2DS did not find ADHD to be a risk factor for the later development of a psychotic disorder (Gothelf et al., 2007). However, several studies have found in the general population that difficulties with attention and hyperactivity consistent with ADHD may predate the onset of schizophrenia. Studies have also suggested that impairment of attention may be a
core abnormality in schizophrenia. It has been suggested that sustained impairment of attention may affect social interactions which may result in anxiety and social withdrawal which may then increase the levels of stress and may play a role in the development of psychosis in a susceptible individual (Cornblatt and Obuchowski, 1997). Yung and colleagues (2005) found that the CAARMS measure of disorders of concentration and attention were highly predictive of psychotic disorders. The follow-up of cases with ADHD and high inattention scores in association with neuropsychological test scores and neuroimaging data may provide information on whether difficulties of attention in individuals with 22q11.2DS may be a predictor of future psychotic disorders.

5.1.4.2 ADHD and Autism Symptoms

The current study found that there was a significant association found between autistic symptoms and ADHD in children and adolescents with 22q11.2DS (p-value=0.0004). It was found that 18% (1 in 6) of the sample, with 22q11.2DS had a combination of ADHD and high symptoms of autism (>85 on SRS). This finding is marginally higher compared to Niklasson and colleagues (2009) who found that 1 in 10 had the combination of ADHD and high symptoms of autism, with a greater proportion of the sample with a diagnosis of the combined ADHD. The current study did not find a particular subtype of ADHD to occur in individuals with high symptoms of autism. The current study also found children and adolescents with 22q11.2DS and oppositional defiant disorder to have significantly high symptoms of autism (p-value=0.0035). Furthermore, it was found that 13% (1 in 8) of the sample with 22q11.2DS had a diagnosis of ADHD, ODD and high symptoms of autism.
There is an overlap of the symptoms related to ODD, ADHD and ASD and therefore it is difficult to determine the relationship, contribution and independence of the different symptoms to each of the diagnosis based on the methodology and the small sample size in this study. A large sample size, with the use of the ADI-R and factor analysis of the different symptoms may provide more accurate information on the relationship of symptoms contributing to a diagnosis of ADHD and ODD and high symptoms of autism to determine whether these symptoms/disorders are independent of each other in individuals with 22q11.2DS. The current study shows that autism symptoms are associated with ADHD symptoms in a majority of children and adolescents with 22q11.2DS, though are not found in all children and adolescents with 22q11.2DS and ADHD. However, a larger sample size is required to replicate these preliminary findings and to also determine the level of functioning of children and adolescents with 22q11.2DS, ADHD, high symptoms of autism and ODD compared to those with ADHD alone. Follow-up studies are required to investigate the association of these symptoms for the future risk of psychosis in individuals with 22q11.2DS.

5.1.5 Anxiety Disorders

5.1.5.1 Prevalence of Anxiety Disorders in 22q11.2DS

The prevalence of specific phobias (36%) and anxiety disorders (31%) found in the current study are comparable to other studies of 22q11.2DS (Jolin et al., 2009, Feinstein et al., 2002a). In the general population, community prevalence estimates
of any anxiety disorders range from 3.1% to 17.5% in children and adolescents and 21.6% in adults (Leray et al., 2010, Pine et al., 2009). The results from the current study and other studies of 22q11.2DS indicate that the prevalence of anxiety disorders in children and adolescents with 22q11.2DS is higher compared to their siblings and general population findings. Findings from the current study indicate that the prevalence of anxiety disorders among adults with 22q11.2DS was 11%, this finding is marginally lower compared to another study of 22q11.2DS which found the prevalence of anxiety disorders around 19% in adults (Niklasson et al., 2009). Both these rates are lower than the rates of anxiety disorders in adults in the general population which is estimated at 21.6% (Leray et al., 2010). The prevalence of anxiety disorders in adults with 22q11.2DS found in the current study is lower compared to children and adolescents with 22q11.2DS and also lower compared to general population findings. One explanation could be related to the small sample size of adults present in this study compared to the larger numbers of children and adolescents in the study, resulting in an underestimate of the true prevalence of anxiety disorders found in adult with 22q11.2DS.

5.1.5.2 Treatment of Anxiety Disorders

The cases identified in the study as having anxiety symptoms did not receive a prior diagnosis or receive any prior treatment. Anxiety disorders may present in a diverse manner, including with the presentation of disruptive behaviour problems consistent with ODD and also ADHD (which are also found in significantly high rates in this study). Anxiety disorders are associated with distress and impairment in children and adolescents and are a risk factor for psychopathology in adult life, particularly
depression (Holzel et al., 2010). Early identification and treatment with appropriate interventions have been found to significantly improve anxiety symptoms and outcomes (Connolly and Bernstein, 2007). In the general population a combination of interventions is recommended to treat anxiety disorders in children and adolescents ranging from psycho-education, cognitive therapy, behavioural shaping and pharmacotherapy (Rockhill et al., 2010).

There are no studies published to date on treatments or interventions most suitable for the treatment of anxiety disorders in individuals with 22q11.2DS, despite the high rates of anxiety disorders found in children and adolescents with 22q11.2DS. Both parents and general physicians who may have initial contact with children with 22q11.2DS may need to be aware of the symptoms of anxiety so that appropriate and early referral can be made for appropriate treatment. Psychiatric assessment of children and adolescents with 22q11.2DS should aim to identify anxiety disorders and if identified close monitoring should be indicated and treatment with psychological or pharmacological approaches should be considered to improve coping, symptoms reduction and functioning for these individuals.

5.1.5.3 Anxiety and ADHD

Studies in the general population have found that ADHD and anxiety often occur together, studies have found that 25% of children with ADHD also meet the criteria for an anxiety disorder and 15-24% of children with anxiety disorders meet the criteria for ADHD (Anderson, 1994). It has been suggested that children with
underlying anxiety disorders/anxiety symptoms may have problems in relation to paying attention due to hypervigilance and preoccupation with worries and fears and therefore assessing for underlying anxiety disorders is an important element in the evaluation of ADHD (Rockhill et al., 2010). In this study it was found that 38% of cases with ADHD also had one or more anxiety disorders and 35% of cases with an anxiety disorder also had ADHD. These findings are higher than that found in the general population, it also supports the suggestion of the intrinsic relationship between problems related to attention and anxiety disorders and highlights the importance of evaluating for both disorders in children and adolescents with 22q11.2DS so that appropriate intervention may be implemented.

5.1.6 Affective Disorders

The prevalence of depression in individuals with 22q11.2DS was found to be 11%. This finding is comparable to other studies of adults with 22q11.2DS (Niklasson et al., 2009, Murphy et al., 1999). The current study found that depression was significantly associated with older age and there was no gender difference in the occurrence of depression.

5.1.7 Schizophrenia

There was one subject with 22q11.2DS and schizophrenia (2%). This subject was referred from a sector psychiatric service for tertiary assessment and was recruited into the study. It may be considered that the inclusion of this individual into the study
may reflect an ascertainment bias although this was the only subject to be recruited in this manner.

The prevalence of schizophrenia in individuals with 22q11.2DS is estimated to be 24% (Murphy et al., 1999). This study found the prevalence of schizophrenia to be 2%. This discrepancy may be predominantly due to mean age of the sample being 14.6 and therefore too young for the occurrence of schizophrenia. There were nine cases who were aged 18 or above in the study with only one having a diagnosis of schizophrenia, therefore the prevalence rate of psychotic disorders in adults was found to be 11%. The other eight cases denied any past experience of hallucinations or delusions. Similar to the findings of this study, a recent study which had a sample size of 100 cases with 22q11.2DS in which 16 were adults, found that only one subject had a psychotic disorder (6%), three adults had a history of psychotic symptoms which were determined by the presence of past occurrence of hallucinations, delusions or periods of confusion (Niklasson et al., 2009). The sample size of adults with 22q11.2DS in this study and the study by Niklasson and colleagues (2009) are too small to estimate the prevalence of schizophrenia.

The findings of the present study support the 3rd hypothesis, in a sample of cases with 22q11.2DS the prevalence of psychiatric disorders will be higher compared to the sibling control group. It was found that individuals with 22q11.2DS had higher prevalence of psychiatric disorders and higher symptoms of autism compared to their siblings. Attention Deficit Hyperactivity Disorder was the most significantly occurring psychiatric disorder in children and adolescents with 22q11.2DS compared to their
siblings. In addition it was found that attention difficulties were a core problem in individuals with 22q11.2DS irrespective of whether they had a diagnosis of ADHD.

5.2 Subthreshold Psychotic Symptoms

The current study found that 20% (N=9) of children and adolescents with 22q11.2DS and 4% (N=1) of siblings exhibited subthreshold psychotic symptoms. This was the first study at the time in which the Comprehensive Assessment of the At Risk Mental State (CAARMS) was used to identify preclinical psychotic symptoms in individuals with 22q11.2DS. Based on the structured approach of the CAARMS in identifying a possible prodromal state, it was found that eight subjects (18%) with 22q11.2DS and subthreshold psychotic also met the CAARMS criterion for having ‘attenuated psychotic symptoms’ and categorised as having an ‘at risk mental state’. Children and adolescents with subthreshold psychotic symptoms predominantly reported persecutory and referential delusion and auditory hallucinations. Subthreshold psychotic symptoms were found in children with 22q11.2DS as young as seven and ten years of age (Refer to Table 4.13 page 114), suggesting that children with 22q11.2DS should be assessed for pre-clinical psychotic symptoms.

5.2.2 General and Intellectual Functioning and Sub-Threshold Psychotic Symptoms in 22q11.2DS

The present study found that individuals with subthreshold psychotic symptoms had serious difficulties in social and school functioning compared to those without subthreshold psychotic symptoms (p-value=0.0072). The difference in the level of
general functioning was not found to be due to differences in intellectual functioning. There was no significant difference in FSIQ scores between individuals with subthreshold psychotic symptoms and those without subthreshold psychotic symptoms \( (p-value=0.6912) \), suggesting that serious deficits in school and social functioning are primarily due to the presence of subthreshold psychotic symptoms. Studies in the general population have suggested the presence of early psychotic symptoms for prolonged periods in young individuals disrupts their social and interpersonal developmental processes and has serious social damaging effects (Nordentoft et al., 2009).

However, only six of the nine individuals with subthreshold psychotic symptoms participated with psychological assessments. The remaining three subjects would not participate with testing, predominantly due to attention difficulties. Non-participation of these three subjects may have introduced an element of participant bias. The three subject's inability to participate could be due to underlying intellectual difficulties and therefore resulting in an over-estimation of the FSIQ scores of the group with subthreshold psychotic symptoms and non-significant differences in FSIQ scores. However, four subjects without subthreshold also did not participate with FSIQ testing. Non-participation with FSIQ test does introduce bias into the study, resulting in findings which may not be truly representative of the population. This is clearly a limitation of the study. The study by Murphy and colleagues (1999) of adults with 22q11.2DS found no difference in FSIQ scores between individuals with and without schizophrenia. These findings support the findings from the present study (based on the assumption that individuals with subthreshold psychotic
symptoms have an increased risk of developing schizophrenia). However, one previous study found that decreased/decline in verbal I.Q. scores is associated significantly with the presence of subthreshold psychotic symptoms and the emergence of psychotic disorders in 22q11.2DS (Gothelf et al., 2007, Debbane et al., 2006). The present study did not consider the association of either verbal or performance I.Q. scores in individuals with subthreshold psychotic symptoms or any other psychiatric disorders and is a limitation of the study. However, the effects of intellectual functioning can only be assessed adequately if there was an I.Q. matched control. An I.Q. matched control group in addition to the sibling control group was not considered simply due to the difficulties encountered in recruiting I.Q. matched controls.

5.2.3 **Behaviour and Autism Scores and Subthreshold Psychotic Symptoms**

The median group values for the behavioural measures on the CBCL and SDQ were largely higher for children and adolescents with subthreshold psychotic symptoms. However, these differences were not found to be significant. Previous studies have found that individuals with 22q11.2DS and subthreshold psychotic symptoms were more likely to be withdrawn/anxious depressed compared to those without subthreshold psychotic symptoms (Gothelf et al., 2007, Debbane et al., 2006). The lack of significance in the behavioural measures may be explained by the small sample size of individuals with subthreshold psychotic symptoms which lacked power to detect any statistical difference. Therefore, findings from this current study do not support the 4th hypothesis that *behavioural problems will be higher in a sample of*
cases with 22q11.2DS and sub-threshold-psychotic symptoms compared to those cases with 22q11.2DS and without sub-threshold psychotic symptoms.

There is one previous study of individuals with 22q11.2DS in which the rates of autism spectrum disorders were documented in those with psychotic disorders. Vorstman and colleagues (2006) found that 74% (N=5) of individuals with a psychotic disorder had co-morbid autism spectrum disorders. The author is not aware of other studies documenting similar findings. There are no published studies that the author is aware of on the relationship between autistic symptoms and subthreshold psychotic symptoms in individuals with 22q11.2DS. The present study compared autistic symptoms between individuals with subthreshold psychotic symptoms and those without subthreshold psychotic symptoms. There was no significant difference in the total autism scores or subscale scores between the two groups. Therefore, the present study found that individuals with 22q11.2DS had higher symptoms of autism compared to their siblings, though there was no significant difference in autism symptoms between individuals with/without subthreshold psychotic symptoms. The failure to find any statistical difference in the occurrence of autism symptoms between individuals with/without subthreshold psychotic symptoms may be explained by the sample size of individuals with subthreshold psychotic symptoms which lacked power to detect any difference.

Recent genetic studies in the general population have identified a genetic overlap between autism spectrum disorders, schizophrenia and intellectual impairment. These findings suggest that these disorders may share underlying pathophysiological
mechanism and behavioural phenotypes (Guilmatre et al., 2009). The findings from the present study support these suggestions; individuals with 22q11.2DS were found to have high autism scores and also have a general well documented risk of developing schizophrenia. Future follow-up studies should consider the relationship between autism symptoms and the development of psychotic disorders in individuals with 22q11.2DS. In addition, evaluation of autism symptoms in individuals who develop schizophrenia may facilitate the characterisation of a homogeneous genetic subgroup which may provide an avenue to link clinical symptoms to underlying genetic pathways and aberrant pathophysiological mechanisms.

5.2.4 Schizotypy and Subthreshold Psychotic Symptoms in 22q11.2DS

The present study did not find individuals with subthreshold psychotic symptoms to have higher subscale schizotypy scores, total schizotypy scores or schizotypy dimensional scores compared to individuals without subthreshold psychotic symptoms. Therefore, findings from the present study do not support the 5th hypothesis that schizotypy scores will be higher in a sample of cases with 22q11.2DS and with subthreshold psychotic symptoms compared to those cases with 22q11.2DS and without subthreshold psychotic symptoms. It has been suggested that individuals with high disorganized dimension scores may be at risk for developing psychotic disorders (Gooding et al., 2005, Kwapil, 1998, Cardno et al., 1996). Individuals with subthreshold psychotic symptoms are considered to be at high risk of developing a future psychotic disorder and therefore would have been expected to have higher disorganized dimension scores compared to those without subthreshold psychotic symptoms. Furthermore, the present study examined
schizotypy scores of individuals with an established psychotic disorder and those with subthreshold psychotic symptoms (possible prodromal state) and compared the schizotypy scores with those without any psychotic disorder or subthreshold psychotic symptoms and found no difference between the two groups (Refer to Table 4.17 page 128). Therefore, these findings do not support the 6th hypothesis that schizotypy scores will be higher in a sample of cases with 22q11.2DS and with 'any psychotic symptoms' (includes sub-threshold-psychotic symptoms or psychotic disorders) compared to those individuals with 22q11.2DS and without 'any psychotic symptoms'.

The failure to find any difference between the high risk/psychotic group vs. a group without any psychotic or possible preclinical psychotic symptoms may be due to; 1) deficits within the questionnaire itself particularly for questions related to the sub-factor of odd speech (discussed in Section 5.1.3); 2) age factors, individuals in the high risk group were children or adolescents (discussed in Section 5.1.3); 3) lack of power to detect a statistical difference due to the small sample size.

5.2.5 Psychiatric Disorders/Symptoms and Sub-Threshold Psychotic Symptoms in 22q11.2DS

The present study found that individuals with 22q11.2DS and subthreshold psychotic symptoms had more co-morbid psychiatric disorders compared to individuals with 22q11.2DS and without subthreshold psychotic symptoms (p-value=0.0067). These findings support the 7th hypothesis that, in a sample of cases with 22q11.2DS and sub-threshold-psychotic symptoms the prevalence of co-morbid psychiatric disorders
will be higher compared to those cases with 22q11.2DS and without sub-threshold psychotic symptoms. The most commonly occurring psychiatric disorder in individuals with subthreshold psychotic disorders was the ‘other anxiety disorders’, though there was no significant association found between anxiety disorders and subthreshold psychotic symptoms (p-value=0.09). One previous longitudinal study found that anxiety disorders were a risk factor for the development of a future psychotic disorder in individuals with 22q11.2DS (Gothelf et al., 2007). The course of anxiety disorders and the relationship of anxiety disorders to the development of psychotic disorders should be considered in the follow-up of this cohort.

At the five percent level of significance, there was a significant association found between obsessive compulsive disorder (OCD) and subthreshold psychotic symptoms (p-value=0.0283); the two subjects that were identified as having OCD were also identified as having subthreshold psychotic symptoms. Although this association was found only at the five percent level of significance, one previous study found that a diagnosis of OCD was a strong predictor of a subsequent diagnosis of a psychotic disorder (Gothelf et al., 2007).

In the general population there is evidence of a high rate of co-morbidity between schizophrenia, obsessive-compulsive symptoms and OCD. It has been suggested that individuals with schizophrenia, obsessive compulsive symptoms or OCD may be a distinct subgroup on the schizophrenia spectrum. The validity of this co-morbidity has been raised due to the overlap between obsessions and delusions; compulsions and abnormal stereotypies and mannerisms associated with schizophrenia. Several
studies have found that the symptoms of OCD occur independently to the symptoms of schizophrenia in those with a co-morbid diagnosis (Faragian et al., 2009, Poyurovsky et al., 2003). A meta-analysis of eight studies of schizophrenia and OCD in the general population found that OCD or even obsessive symptoms may predate the future development of schizophrenia (Devulapalli et al., 2008).

The findings from the present study of a significant association of OCD with subthreshold psychotic disorders, the findings from Gothelf and colleagues (2007) longitudinal study of an association between OCD and the future development of psychotic disorder and the findings of a temporal sequence of OCD with schizophrenia in the general population, suggests that individuals with 22q11.2DS and OCD should be assessed and monitored for subthreshold psychotic symptoms/psychotic disorders.

5.2.5.1 Associated Symptoms Assessed by the CAARMS

In addition to the symptoms that are used to determine high risk symptoms, other symptoms and psychopathological measures are evaluated on the CAARMS tool. The present study found that individuals with 22q11.2DS and subthreshold psychotic symptoms were more likely to display aggression / dangerous behaviour, disorganised / odd / stigmatising behaviour and to have motor difficulties (e.g. clumsiness, coordination difficulties, motor tics) compared to individuals with 22q11.2DS without subthreshold psychotic symptoms. It was found that individuals with 22q11.2DS and subthreshold psychotic symptoms were more likely to be
confrontational towards their siblings, parents and/or peers; these difficulties may be related to the individual's persecutory/paranoid thinking and misinterpretation of benign events and a tendency to respond in such a manner to benign stimuli. One recent study found that children in the general population with high levels of anxiety symptoms have a significant cognitive attention bias towards threat (Waters et al., 2010). Furthermore, Cornblatt and Obuchowski (1997) have suggested that sustained impairment of attention may affect social interactions and may result in anxiety, social withdrawal and increased levels of stress which may play a role in the development of psychosis in a susceptible individual. Therefore, the attention difficulties and the high rates of anxiety symptoms/disorders identified in individuals with 22q11.2DS may lead to hyperarousal and hypervigilance in social situations/interactions and may contribute to the development of persecutory / paranoid thought processes in vulnerable individuals with 22q11.2DS leading to irritable and aggressive responses to otherwise inert or benign situations.

The motor difficulties found in individuals with 22q11.2DS and subthreshold psychotic symptoms are reminiscent of the findings of early neuro-motor difficulties in individuals with schizophrenia in the general population (Rosso et al., 2000). The problems related to social isolation, self-care and odd behaviour in individuals with subthreshold psychotic symptoms are also indicative of findings in the general population which suggests that social isolation and abnormal social adjustment are predictive of schizophrenia in adulthood (Allen et al., 2001, Cannon et al., 2001).
Therefore the symptoms of irritability/aggression, motor difficulties and social isolation/odd behaviour in association with subthreshold psychotic symptoms may constitute early markers of a later psychotic disorder in individuals with 22q11.2DS. These findings are preliminary and are required to be replicated. Follow-up of the cohort will determine whether these symptoms are predictive of a later emerging psychotic disorder.

5.2.6 The use of the CAARMS and K-SADS

The CAARMS assessment tool has a well defined criterion to determine whether suspected pre-clinical psychotic symptoms could be considered as possible prodromal symptoms based on the intensity or frequency of symptoms and associated decline of functioning. The K-SADS interview rates symptoms on a scale of 0-2 and has no defined criteria to identify suspected pre-clinical psychotic symptoms compared to the CAARMS interview. Individuals with suspected subthreshold psychotic on the K-SADS interview may not meet the inclusion criteria for subthreshold psychotic symptoms on the CAARMS interview, as occurred in the case of ‘fleeting hallucinations’ in the present study. At present it is not certain whether using a strict criterion to define ‘subthreshold psychotic symptoms’ as with the CAARMS or a more inclusive criteria as with the K-SADS is appropriate for the study of psychiatric phenomenology in individuals with 22q11.2DS. A broader definition may identify those who may not truly have subthreshold psychotic symptoms. A narrow criterion may identify those who truly have subthreshold psychotic symptoms, be replicable, though, exclude those with less subtle symptoms who may also be at risk of developing a psychotic disorder. The CAARMS has been
designed and tested for use in the general population and one of the limitations in its use in this study is a question of its applicability to individuals with 22q11.2DS. To my knowledge the CAARMS has not been tested on a sample with chromosomal disorders or mild intellectual disability. It is not tested as yet whether the intake criterion of the CAARMS based on intensity and frequency of the core psychotic symptoms and associated functioning levels are valid for this group with mild intellectual disability. Furthermore, it was found from the present study that the baseline functioning of individuals with 22q11.2DS is significantly impaired compared to sibling controls; therefore the criterion of functioning based on scores from the general population may not be valid in individuals with 22q11.2DS.

As individuals with 22q11.2DS have a higher risk of developing psychotic disorders compared to the general population, the presence of pre-clinical psychotic symptoms regardless of the intensity, frequency or associated functioning of the individual could be advocated as ‘high risk’ so that close monitoring of these individuals can be ensured. Therefore a broader concept of ‘subthreshold’ may be advocated in individuals with 22q11.2DS. The counter-argument to this would be that a narrow instrument may identify those who truly have subthreshold psychotic symptoms and are much more likely to develop a psychotic disorder and therefore could be commenced on early treatment. However, even specific instruments such as the CAARMS has been found to detect high rates of false-positives in general population community samples with only 35% of individuals found to be ‘at risk mental state’ at initial assessment developing a psychotic disorder at 12-month follow-up (Yung et al., 2004). The detection of false-positives is a problem and studies aimed at therapeutic
intervention in individuals with 22q11.2DS who are considered to have an 'at risk mental state' may include many individuals who may not develop a psychotic disorder and poses a dilemma of whether to commence adolescents on antipsychotic treatment with potential side-effects. The follow-up of children and adolescents with subthreshold psychotic symptoms in the current study is required to determine the positive predictive value of the CAARMS and K-SADS in identifying subthreshold psychotic symptoms in individuals with 22q11.2DS who then develop a psychotic disorder. The positive predictive value of the CAARMS and the K-SADS in individuals with 22q11.2DS may then guide clinicians as to whether antipsychotic treatment should be initiated when an individual is identified with subthreshold psychotic symptoms.

One of the important reasons for the identification of individuals with subthreshold psychotic symptoms who may be at risk of developing psychosis is for the initiation of early treatment. At present it is uncertain when treatment should commence. Furthermore, studies of individuals with 22q11.2DS have approached the identification of subthreshold psychotic symptoms by different methods and therefore to date there is no uniform systematised approach resulting in different findings with no clear determination of when treatment should commence. Studies of treatment options in individuals with subthreshold psychotic symptoms or those considered to be at high risk should also consider alternatives to pharmacological treatment which have been studied in the general population. One study found that cognitive based therapy reduced the transition rate to psychosis and a recent study found that long chain fatty acids effectively reduced the risk of progression to psychotic disorders.
(Amminger et al., 2010, Morrison et al., 2004). These interventions have not yet been studied in individuals with 22q11.2DS with suspected pre-clinical psychotic symptoms who may be at risk of developing psychotic disorders.

5.2.7 SPQ and CAARMS

Schizotypal personality disorder is characterized by symptoms reminiscent of schizophrenia and which may overlap with the more subtle, attenuated and heterogeneous symptoms of prodromal schizophrenia. An interesting finding from the present study was the lack of significant correlation between the Schizotypal Personality Questionnaire (SPQ) and the Comprehensive Assessment of the At Risk Mental State (CAARMS). There was evidence of a significant correlation only between the measure of Alogia on the CAARMS and the Interpersonal dimension of the SPQ, contributed significantly by the subscale of ‘no close friends’. There was no significant correlation with any of the other measures and subscales. It would have been expected that other measures on the CAARMS such as perceptual experience to correlate with unusual perceptual experience on the SPQ or the measure of delusions on the CAARMS to correlate with subscales of ideas of reference, odd beliefs or paranoid ideation on the SPQ.

There may be an explanation for the lack of correlation between the two instruments. 1). The SPD is a distinct and independent syndrome on the schizophrenia spectrum sharing genetic links with schizophrenia, which is measured by the SPQ. Subthreshold psychotic symptoms are symptoms which may possibly indicate the
beginning of schizophrenia, which is measured by the CAARMS. Although there may be an overlap of the symptoms, in essence the two instruments measure different constructs. This study found that 67% of the individuals that met the cut-off for one did not meet the cut-off for the other, suggesting that there is a moderate degree of discrimination between the two different instruments to measure the two different constructs and hence the limited evidence of significant correlation, despite the overlap of symptoms. A large study in the general population found that the SPQ-B, which is based on the SPQ showed moderate degree of discrimination validity between the Abbreviated Youth Psychosis At Risk Questionnaire, a screening instrument based on the CAARMS; 75% of participants that met the cut-off for one instrument did not meet the cut-off for the other (Bedwell and Donnelly, 2005). 2). The SPQ is a respondent questionnaire. The CAARMS is a semi-structured interview. The difference in obtaining the information may also account for the lack of significant correlation between the two instruments. Other explanations for non-significant correlations may be due to: 3) deficits of the SPQ (discussed in Section 5.1.3); 4) age factors, individuals were predominantly adolescents (discussed in Section 5.1.5); 5) lack of power to detect a statistical difference due to the small sample size.

5.3 Physical Symptoms and Psychiatric Disorders

In view of the neurodevelopmental hypothesis of schizophrenia and the early embryological abnormalities which may underlie the physical and psychiatric abnormalities in 22q11.2DS, an association was tested between birth complications, cardiac defects and palatal abnormalities in individuals with 22q11.2DS and
subthreshold psychotic symptoms (based on the assumption that individuals with subthreshold psychotic symptoms are at increased risk of developing schizophrenia). There were no significant association found between congenital cardiac defects, palatal abnormalities, a history of birth complications and subthreshold psychotic symptoms.

There was some evidence of an association between early immune problems/disorders and subthreshold psychotic symptoms, though only at the 5% level of significance (Fisher's exact p-value=0.0364). These findings could be a chance association given the small sample size. However it is an interesting finding as there is an emerging body of evidence which supports an immunological contribution to the pathogenesis of schizophrenia (O'Brien et al., 2008). Given the small sample size, cross-sectional nature of the study and the lack of direct laboratory investigations of immunological factors it is unclear what the role of early immunological deficiency may have on the development of schizophrenia in 22q11.2DS. Future studies should investigate the relationship between immunological factors and the development of schizophrenia in 22q11.2DS.

Attention Deficit Hyperactivity Disorder (ADHD) is considered to be a neurodevelopmental disorder. Therefore an assumption was made that the early embryological developmental deviance underlying the aberrant physical phenotype in 22q11.2DS may also underlie the difficulties associated with ADHD. Therefore associations were considered between the physical disorders and ADHD. To determine whether the possibility of early brain insults from birth complications or
congenital heart defects (possible cyanosis) had an influence on the development of ADHD, associations were determined between these factors and ADHD. There was no significant association found between birth complications or congenital heart defects, suggesting that early brain insults may not provide an explanation for the high rates of ADHD found in the sample. In addition, there was no significant association found between the physical disorders and ADHD. These findings are consistent with other studies (Niklasson et al., 2009, Gothelf et al., 2004).

Similarly, the relationship between early brain insults, physical disorders and autism symptoms were considered in the present study. There were no significant associations found. There was no significant association found between physical disorders and other psychiatric disorders. In addition, there was no significant association found between social, occupational/school and intellectual functioning and physical disorders.

Therefore, hypothesis eight, which stated that there is an association between physical disorders and psychiatric disorders in 22q11.2DS is not supported based on the findings from the present study. A lack of association may be due to the small sample size. There was some evidence of an association between a history of early immune problems and subthreshold psychotic symptoms. This preliminary finding should be investigated with direct lab investigations in individuals with schizophrenia and 22q11.2DS.
5.4 Critique of the Study Design, Methods, Sample & Limitations

5.4.1 Was the Sample Representative of the Population?

This study is an Irish population based cross-sectional assessment of the psychiatric and behavioural profile of individuals with 22q11.2DS. The study aimed to recruit a representative sample of the Irish population with a diagnosed 22q11.2DS. Ninety-eight percent of the sample was recruited by participants responding to letters from the genetic centres or due to information from the 22q11.2DS support groups. As the majority of the sample was recruited in this manner it could be assumed that the only way in which the sample may differ from the population will be due to chance. However, there may have been bias introduced into the random sampling; six subjects that were recruited were related to existing participants. It has been found in a previous study that children with 22q11.2DS who have inherited the deletion from a parent frequently do worse in cognitive testing compared to children with a de-nova deletion (Swillen et al., 1999). The recruitment of these cases may be considered an ascertainment bias and may have introduced selection bias (over-estimation or under-estimation of findings) which was not adjusted for in the analysis due to the small sample size of the study population. However, as familial inheritance of the syndrome occurs in 5-10% of cases, exclusion of these cases may lose representativeness and reduce an already very small size of 45 to 35. Further analysis of this familial group was not done to identify any differences in psychopathology between familial vs. de-nova inheritance, because of the heterogeneity within a small sample (wide age range, gender difference and different modes of inheritance e.g. maternal vs. paternal inheritance, mother-daughter). One subject was recruited following hospital referral and the inclusion of this subject is an
ascertainment bias, particularly as the subject's psychiatric history of schizophrenia was known and therefore could be considered as an artificial means of increasing the prevalence of psychiatric disorders, particularly psychotic disorders in the case group.

The response rate appears to be low at 42%; it was assumed that one of the reasons may be due to identified cases being too young to meet the inclusion criteria. Eighty percent of the case sample was below 18 years of age. Higher proportion of children and adolescents compared to adults in the case sample may be representative of the population at the time of the study as the genetic basis of the syndrome was only discovered in 1992 and affected individuals prior to this would not have been diagnosed. A small case sample of adults in this study limits the characterisation of psychopathology and the true estimation of the prevalence of psychiatric disorders in the adult group.

An advantage of the study is the inclusion of a sibling control group. Siblings are assumed to be a close match to the case in terms of genetic make-up and environment and therefore the assumption in this study is that any significant difference found between cases and controls may be explained by the underlying 22q11 deletion itself. However, it cannot be assumed that a sample of cases with 22q11.2DS are homogeneous; there are common polymorphism in the non-deleted allele and polymorphism in other chromosomal regions and familial vs. de-nova origin of deletion which may result in phenotypic differences between cases in the sample.
This study has made an attempt to recruit a representative sample of cases with a rare genetic disorder from the population. It is not certain how representative the sample is of the population, as the details of all those diagnosed are not known. Ascertainment bias, small sample size and a heterogeneous case group are factors which may have obscured differences between the groups in the study and consequently obscured the true population estimates.

5.4.2 Critique of Evaluation and Measures implemented in study

The validity of the CAARMS in 22q11.2DS and the purpose of its implementation already has been discussed. There were limited difficulties in the use of this tool in the adolescent and adult population with 22q11.2DS. The younger participants, particularly those below eight years of age (22q11.2DS and siblings) had difficulty understanding some of the more subtle questions and high proportion were marked as ‘0’ by the author. Therefore this may have been an under-estimation of the true prevalence of the symptoms assessed by the CAARMS, particularly in the younger participants.

The Autism Diagnostic Interview-Revised (ADI-R) was not used in the present study and is one of the limitations of the study as the prevalence of autism spectrum disorders could not be accurately determined in the sample. However, it has been suggested that genetic studies should consider the relationship of genes to a dimensional characterisation of psychopathology (Carroll and Owen, 2009).
is an increasing focus in genetic research to characterise psychopathology in a dimensional approach, several different spectrums of psychopathology may need to be considered in participants (psychotic spectrum, autism spectrum, affective spectrums and cognitive spectrums) which may only be feasible with brief, valid and appropriate questionnaires for the population to be tested.

The limitations of the Schizotypal Personality Questionnaire (SPQ) in 22q11.2DS had been discussed under Section 5.1.3 page 147.

### 5.4.3 Other Limitations of the Study

Within the 22q11.2DS group there was no significant association found between physical disorders, psychiatric disorders, autism symptoms, behavioural features, subthreshold psychotic symptoms and intellectual functioning as assessed by the FSIQ. However, there was a significant difference in the intellectual functioning between individuals with 22q11.2DS and their siblings. The present study did not control for this difference and therefore differences found between cases and controls can be assumed due to differences in intellectual functioning. The present phase of the study aimed to provide descriptive data of the psychiatric and behavioural functioning of individuals with 22q11.2Ds and their siblings. Further analysis of the data should consider controlling for FSIQ differences between cases and controls.
Chapter 5 - Discussion

The present study does not include an I.Q. matched control as discussed in Section 5.2. This is a limitation of the study. However, the effects of I.Q. on the development of psychiatric disorders in particular schizophrenia can be evaluated when the cohort are re-assessed and if there is uncertainty regarding the effects of I.Q., an I.Q. matched controls could be recruited at that stage.

The present study provides a descriptive account of the prevalence of psychiatric disorders and behavioural problems and their association with general functioning, intellectual functioning, physical disorders and birth complications. The present does not attempt to determine whether the data could be grouped into homogeneous sub-groups or clusters and one of the reasons is due to the small sample size. Cluster analysis of the data may provide further information on whether the data falls into distinct subgroups with specific psychiatric, behavioural and physical characteristics. In a larger sample size, this approach may assist genetic research in linking specific group of symptoms (phenotype) to specific gene(s) within and outside the 22q11 region.

The author was not blinded to the disease status of participants and this may have lead to interviewer bias; the author either unconsciously or not may have attempted to detect behavioural or psychiatric problems in participants with 22q11.2DS compared to their siblings and may have tended to make observations that may have coincided with expectations. These biases may increase the prevalence of psychiatric symptoms, psychiatric disorders and behavioural problems in participants with 22q11.2DS compared to their siblings. However, the use of structured
interviews, self-administered questionnaires and computer-based assessments may reduce interviewer bias. In addition, parents/guardians completing questionnaires may have either reported the presence of more symptoms/difficulties in affected individuals compared to siblings ('search for meaning') resulting in an over-estimation of symptoms/disorders or may normalise or minimise any deviation of symptoms, resulting in recall bias. The use of structured questionnaires/interviews may minimise recall bias. The use of structured and semi-structured interviews and questionnaire material may reduce interviewer and recall bias in the study.

5.5 Implications for Clinical Practice

Children and adolescents with 22q11.2DS have high rates of Attention Deficit Hyperactivity Disorder (ADHD) and should be assessed for these symptoms routinely. It was found that the Strengths and Difficulties Questionnaire (SDQ) could be used as a screening tool to identify children and adolescents with 22q11.2DS who may have underlying ADHD and require a more comprehensive assessment.

The association between motor problems and subthreshold psychotic symptoms may assist the early identification of children at risk of developing these disorders and possibly schizophrenia at a future stage. The association between subthreshold psychotic symptoms and motor problems supports the model of children and adolescents with subthreshold psychotic symptoms having more neurodevelopmental problems and therefore a greater risk of developing psychotic disorders. Children with motor problems could be identified and referred for
comprehensive assessment and regular monitoring of their mental state. However this is a cross-sectional study and prospective studies are required to ascertain if children with early motor problems (such as motor tics) are more likely to develop psychotic disorders.

The findings of an association between disorganised/stigmatising/odd behaviour, irritability/aggression and subthreshold psychotic symptoms may assist the identification of children and adolescents with subthreshold psychotic symptoms. In particular a recent change towards disorganised/stigmatising/odd behaviour and increased levels of irritability/aggression may guide clinicians to explore for subthreshold psychotic symptoms and regular monitoring of the mental state.

5.6 Implications for future clinical research

This study found that attention difficulties are a significant problem in individuals with 22q11.2DS. It would be interesting to correlate data from the current study with neuropsychological data testing deficits in attention and then determine whether these findings may have a functional basis with structural and functional neuroimaging studies. A neuroimaging study of individuals with 22q11.2DS and their siblings is currently underway. Deficits in attention will be correlated with neuroimaging findings as part of this study to determine whether there are associations with any specific cortical/striatal network deficits.
This study found a relationship between autism symptoms and 22q11.2DS. It would be interesting to correlate scores from the Social Responsiveness Scale (SRS) with neuroimaging findings. A further study could be performed to compare these findings with I.Q. matched controls in the general population to assess for the effects of I.Q. on autism symptoms.

This study and previous studies have found that anxiety disorders are the most prevalent disorders in individuals with 22q11.2DS. The present study found that individuals with anxiety disorders (excluding specific phobias) had more difficulties with social/school/occupational functioning compared to individuals without anxiety disorders and anxiety disorders were a common co-morbid disorder in children and adolescents with subthreshold psychotic symptoms. There have been no studies to date which has considered a specific treatment strategy in individuals with functionally impairing anxiety disorders. There is a large body of evidence in the general population which shows that cognitive behavioural techniques are effective in treating anxiety disorders. It may be beneficial to consider these options in a randomised trial to determine whether these techniques alleviate symptoms, reduce distress and improve functioning in individuals with 22q11.2DS.

The present study is a cross-sectional descriptive study of the psychiatric and behavioural characteristics of a population sample with 22q11.2DS. Prospective studies require to be performed to determine the association of baseline variables with the development of future psychiatric disorders, particularly schizophrenia. Furthermore, prospective studies are required to determine the predictive validity of
instruments such as the CAARMS in indentifying individuals who may develop a future psychotic disorder. The predictive validity of baseline symptoms has significant implications for early intervention. At present there are no published early intervention treatment trials in individuals with 22q11.2DS. Studies should consider the benefits of acceptable treatment options such as fatty-acids particularly in individuals identified with high risk symptoms.

22q11.2DS is a relatively rare genetic disorder. This poses a major difficulty in clinical and genetic research of 22q11.2DS due to the small population of individuals with the disorder. Large sample sizes are required to determine predictive markers, to test effectiveness of treatments and to undertake substantial genome-wide studies. There is a need for greater consensus on assessment protocols between different research centres so that comparisons between studies could be made.

5.7 Conclusions

This study has shown that children and adolescents with 22q11.2DS have a range of behavioural difficulties which include: withdrawn/depressed behaviour, somatic complaints, social problems, thought problems, attention problems and rule-breaking behaviour. In particular, it was found that social related behaviour problems were most prevalent, with 25% of children and adolescents with 22q11.2DS exhibiting social problems within the clinical range. The study found that the degree/severity of intellectual functioning of children and adolescents with 22q11.2DS could not account for the type or total behavioural problems exhibited, though may account for the
significant differences in behaviour compared to their siblings. It was therefore suggested that future studies should control for I.Q. effects or use I.Q. matched controls. This study found that the Strengths and Difficulty Questionnaire (SDQ) could be used as a valuable screening tool to identify possible ADHD in children and adolescents with 22q11.2DS and therefore it was recommended that the SDQ could be incorporated into the routine monitoring and/or follow-up of children and adolescents with 22q11.2DS.

This study found that individuals with 22q11.2DS were much more likely to score at or above specified cut-off points on Autism Screening Questionnaires and have increased symptoms of autism compared to their siblings. It was found that children and adolescents with 22q11.2DS had impairments in each of the autistic symptom domains rather than a specific domain and had a wide range in the severity of autistic symptoms. Autistic symptoms in 22q11.2DS were not found to be familial, gender or domain specific and the level of intellectual functioning within the 22q11.2DS group was not related to the severity of autistic symptoms.

Adolescents and adults with 22q11.2DS had more schizotypal features and were found to score highly on the disorganised dimension of schizotypy, supporting work based on the general population that the disorganized factor/dimension may be a vulnerability marker for psychosis, given the increased risk that individuals with 22q11.2DS have in developing a psychotic disorder.
Individuals with 22q11.2DS were found to have high rates of psychiatric disorders. It was found that 62% of individuals with 22q11.2DS had at least one psychiatric disorder in contrast to 19% of their siblings. The most commonly occurring psychiatric disorders were the anxiety related disorders. Attention Deficit Hyperactivity Disorder (ADHD) was found to be the most significantly occurring psychiatric disorder with 29% of the cohort receiving a diagnosis of ADHD. ADHD in 22q11.2DS was not found to be familial, gender or subtype specific. The level of intellectual functioning within the 22q11.2DS group was not associated with ADHD. In addition it was found that problems of inattention were a consistent difficulty in individuals with 22q11.2DS irrespective of whether they met a diagnosis of ADHD and it was suggested that deficits of attention may comprise one of the core phenotypic symptoms of 22q11.2DS.

This study found that 20% of children and adolescents with 22q11.2DS exhibited subthreshold psychotic symptoms, particularly persecutory and referential thinking and auditory hallucinations. Children and adolescents with 22q11.2DS and subthreshold psychotic symptoms were found to have more difficulties with social and school functioning compared to those without subthreshold psychotic symptoms; these differences were not related to differences in intellectual functioning, as there was no significant difference in intellectual functioning between those with and without subthreshold psychotic symptoms. In addition children and adolescents with 22q11.2DS and subthreshold psychotic symptoms were found to have more co-morbid psychiatric disorders. Anxiety disorders were the most commonly occurring psychiatric disorder in individuals with 22q11.2DS and subthreshold psychotic
symptoms. Furthermore, children and adolescents with 22q11.2DS and subthreshold psychotic symptoms were found to display aggressive/dangerous behaviour, disorganised/odd/stigmatising behaviour and were found to have more motor difficulties compared to those individuals without subthreshold psychotic symptoms. It was suggested that these symptoms in association with subthreshold psychotic symptoms may constitute early markers of a later psychotic disorder in individuals with 22q11.2DS.

There was evidence of an association with early immune problems and subthreshold psychotic symptoms. It is suggested that these preliminary findings warrant further investigation with direct laboratory investigations.

This study found that individuals with 22q11.2DS had high rates of psychiatric morbidity, behavioural problems, autism symptoms and schizotypal features. However due to the small sample size the study did not determine whether different symptoms/disorders clustered into specific sub-groups with distinct clinical features. It has been discussed in Section 1.5 page 19, that difficulties in identifying gene(s) for psychiatric disorders could be due to the heterogeneous description of the phenotype. Identification of clinical symptom(s) or a cluster of distinct symptoms may provide one avenue of identifying genes and underlying pathophysiological pathways which may be linked to specific clinical symptoms or a collection of symptoms. It may be interesting to pool clinical data from different centres to determine whether there are clustering of symptoms and if so whether there may be associated underlying candidate gene(s).
Follow-up of the present cohort of individuals is required to determine the association of behavioural symptoms, autism symptoms, schizotypal symptoms and base-line psychopathology in the development of psychotic disorders. Follow-up studies are required to determine early markers of a later emerging psychotic disorder so that protocols may be developed for early intervention in this high risk group of individuals. Consensus between different International centres on early intervention and treatment in 22q11.2DS should be determined and guided by pooled studies with large sample sizes and with similar assessment protocols.

The findings from this study have implications for current clinical practice and treatment. Preliminary findings from this study serve as the basis for future longitudinal studies and for hypothesis testing in associated studies of 22q11.2DS. The methodology employed in this study may provide guidance on the development of a uniform approach to the assessment of behavioural, autistic, schizotypal and psychiatric features of 22q11.2DS and other genetic syndromes. A uniform assessment approach may facilitate comparisons between different studies of relatively rare genetic syndromes which may then aid the development of effective treatment modalities and enhance the power of association and genome-wide studies.


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206

Appendices

1. Patient and Parent Information Leaflets and Consent Forms
2. Letters of Ethical Approval
3. Background K-SADS Interview
4. Neurodevelopmental Questionnaire
5. Psychotic Supplement K-SADS
6. Interview booklet: Comprehensive Assessment of the At Risk Mental State (CAARMS)
7. SAPS and SANS
8. Social and Occupational Functioning Assessment Scale (SOFAS)
9. Schizotypal Personality Questionnaire (SPQ)
10. Social Responsiveness Scale (SRS)
11. Social Communication Questionnaire (SCQ)
12. School Report Form
13. Conners Parent Rating Scale
15. Strength and Difficulties Questionnaire (SDQ)
Appendix 1
Dear (Name),

We are a team, who are finding out more about Velo-cardio-facial syndrome in children and young people. We would like you to help us in a project that we are doing.

We would like you to read this information first before you make up your mind whether you would like to be part of the project or not. If you have any problems, you can ask your parents, as they have received information about the project as well.

We want to find out how children and young people with velo-cardio-facial feel, behave and act in different situations. We would also like to test you in different things some of these things will be the way you draw, build things, spell and do maths.

If your parents and you decide to take part in the project, they will sign a form for you, saying that they give permission for you to take part in the project.

You do not have to take part if you do not want to.

If you don’t take part this will not affect the way that your doctors and other people are looking after you. If you do decide to take part and then change your mind or don’t like what is happening you can stop and you do not have to take part in the project.
anymore. This also will not change the way your doctors or others care for you.

If you do decide to take part, your parents will send all your details to us. We will then phone and speak to your parents and arrange a time that will fit in with yours. The project will take place in your own home so you do not have to travel.

What happens in the project?

- We need to speak to your parents and ask questions about you
- We will speak to you and ask you questions
- You need to do special test, some of which will test your memory, the way you spell, the way you build things, draw pictures and do maths
- We need to get a cheek swab from you. A cheek swab is similar to a cotton bud, but it is a little bit bigger and longer. We will scrape the inside of your cheek with this swab, it will not be painful
- The swab will collect special cells which are in the side of your cheek, don’t worry, taking this will not harm you in any way, as your body always replaces it
We will need to collect blood samples from both your parents during the interview. We will listen very carefully to what you and your parents will say, so we do not forget or miss anything, we will make notes as we go along.

Your name won't be used when we type up the project, this means, that nobody else will know what your parents or yourself said or how you did in the tests.

The assessment will take place with a doctor and a neuropsychologist (person who does all the special tests)

The assessments will take nearly two hours and the cheek swabs will take less than two minutes.

If you want to find out how you did in all the tests, you can ask your parents to contact us and we will give you and your parents the results.

If you are happy to help, we will look forward to meeting up with you.

Thanks for reading!
Dear (Name),

You are being invited to take part in a research study conducted by the Department of Psychiatry, Royal College of Surgeons in Ireland. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Please feel free to ask us anything that is not clear to you, or if you would like more information. Take time to decide whether you wish to take part. Thank you for reading this.

This study will look at the mental health, behaviour and neuropsychological profile of patients with velo-cardio-facial syndrome (VCFS). VCFS is an illness caused by an abnormality in one of the chromosomes (chromosome 22). Previous research has shown that some individuals with VCFS can encounter problems with their mental health. The aim of our research is to better understand the mental health problems that can occur in velo-cardio-facial syndrome.

Individuals with velo-cardio-facial syndrome who have had a blood test to confirm their diagnosis are being invited to participate. We will be including 100 children and adults from Northern Ireland and Ireland.

It is up to you to decide whether you wish to take part. If you do decide to take part, you will be given this information sheet to keep. You need to sign a consent form and you will be given a copy of this to keep. If you decide to take part, you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.
Individuals who agree to take part in the study will be interviewed at home. A small blood sample will be taken for genetic analysis; the equivalent of one tablespoon of blood. This can cause mild discomfort. You are asked to donate your sample, for use only in this and very similar research. We will ask your permission to store the blood sample so that it can be used for similar research in the future. In addition, we also require a small blood sample from both your parents for genetic analysis, for similar research in the future. We aim to examine for variation in a large number of genes to identify whether such genetic variation is associated with ill-health. We also wish to examine how the expression of protein might also be associated with ill-health.

The interview process takes approximately two hours and blood collection takes five minutes. The questions that will be asked will help us understand more fully the effects that this illness has on psychological health. All information which is collected about you during the course of the research will be kept strictly confidential. Access to this information will be limited to the research team from the Royal College of Surgeons in Ireland.

In addition to information obtained at interview, your permission will be sought for access to medical records which may be of relevance to the study.

Although there are no immediate benefits to you, this study will help us to better understand the causes of psychological problems that can occur as part of velo-cardio-facial syndrome. This may allow the development of better treatments in the future.

The results of the assessments will be made available to you upon request from the research team.

The results of the study will be published in scientific journals. Any publications can be made available upon request from Professor Murphy, Department of Psychiatry at The Royal College of Surgeons in Ireland. The results are likely to be available in 2007.

This study is funded and sponsored by The Health Research Board an independent organisation funding research to improve human health. This will pay for a research doctor who will conduct the interview, take the blood sample and will also cover laboratory expenses for analysing the blood sample. The research team are not receiving any other payment for this
study. The study has been approved by the Beaumont Hospital Medical Research and Ethics Committee.

Should you wish to be part of the study you can return the response form in the envelope provided. If you would like further information please feel free to contact Professor Murphy on 01-8093740 or Dr Sarah Prasad on 01-809 3361/01-8093740

Thank you for taking the time to read the information letter.

Professor K Murphy                         Dr Sarah-Evelyn Prasad

Department of Psychiatry, RCSI Education and Research Centre, Smurfit Building, Beaumont Hospital, P.O. Box 9063, Dublin 9.
Dear Parent or Carer (Name),

We understand from the Department of Medical Genetics in Our Lady's Hospital for Sick Children, that your son/daughter _____________ has velo-cardio-facial syndrome.

We are inviting you and _____________ to take part in a research study conducted by the Department of Psychiatry, Royal College of Surgeons in Ireland. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Please feel free to ask us anything that is not clear or if you would like more information. Please take time to decide whether you wish to take part in the study. Thank you for reading this.

This study will look at the mental health, behaviour and neuropsychological profile of patients with velo-cardio-facial syndrome (VCFS). VCFS is an illness caused by an abnormality in one of the chromosomes (chromosome 22). Previous research has shown that some individuals with VCFS can encounter problems with their mental health. The aim of our research is to better understand the mental health and psychological problems that can occur in velo-cardio-facial syndrome.

Individuals, who have had a blood test to confirm their diagnosis of velo-cardio-facial syndrome, are invited to participate in the study. We will be including 100 children and adults in total, from Northern Ireland and Ireland.

It is entirely up to you to decide whether you would like your son/daughter_______ and yourself to take part in this study. If you do decide to take part, you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

If you do decide to take part in the study, you can keep this information sheet and you will need to sign a consent form for participation in the study for yourself and ___________. You will be given a copy of the consent form to keep.
If you agree to take part in the study, both yourself and ________ will be interviewed at your home. The interviews will be conducted by a medical doctor and a neuropsychologist. A cheek swab will be taken from_______ for genetic material. This genetic material will be used only in this and very similar research. We will ask your permission to store the cheek swab so that it can be used for similar research in the future. In addition, a small blood sample, the equivalent of one tablespoon will be taken from both parents for genetic analysis. We also ask permission to store the blood sample so that it can be used for similar research in the future. We aim to examine for variation in a large number of genes to identify whether such genetic variation is associated with ill-health. We also wish to examine how the expression of protein might also be associated with ill-health.

The interview process takes approximately two hours and the cheek swab and blood collection ten minutes.

The questions that will be asked will help us understand more fully the effects that this illness has on psychological health. All information that is collected about you during the course of the research will be kept strictly confidential. Access to this information will be limited to the research team from the Royal College of Surgeons in Ireland.

In addition to information obtained at interview, your permission will be sought for access to medical records that may be of relevance to the study.

The results of the assessments will be made available to you and can be used to specifically tailor an educational programme with local professionals.

The results of the study will be published in scientific journals. Any publications can be made available upon request from Professor Murphy, Department of Psychiatry at The Royal College of Surgeons in Ireland. The results are likely to be available in 2007.

This study is funded and sponsored by The Health Research Board an independent organisation funding research to improve human health. This will pay for a research doctor who will conduct the interview, take the blood sample and will cover laboratory expenses for analysing the blood sample. The research team are not receiving any other payment for this study. This study has been approved by the Beaumont Hospital Medical Research and Ethics Committee.
Should you wish your son/daughter________ and yourself to be part of the study you can return the response form in the envelope provided. If you would like further information, please free to contact Professor Murphy on 01-8093740 or Dr Sarah Prasad on 01-8093361/01-8093740

Thank you for taking the time to read the information letter.

[Signature]

Professor K Murphy

Dr Sarah-Evelyn Prasad

Department of Psychiatry, RCSI Education and Research Centre, Smurfit Building, Beaumont
Agreement Form for Children and Young People

I have been asked by a research team to help with project about Velo-Cardio-Facial Syndrome.

I have an information sheet about the project.

I have been explained about the project by one of the research team.

I was given a chance to ask any questions I had about the project.

I know that the project will involve me being asked different questions.

I will be asked to do different tests, such as spelling and drawing.

I know that my name will not appear and that nobody will be able to tell that I was involved in the project, when it is later written.

I know that I will have to have a cheek-swab taken. This has been explained to me by the research team.

My Parents/Carer will also be involved in the project.

My Parents/Carer will sign a form that allows me to take part in the project.

I know that I can choose for myself whether I want to be part of this project.

Please sign below if you agree to be part of the project

_ X __________   ______   __________

Name        Date        Researcher's Name
Agreement Form for Patient's Representative

Name of patient: __________________________________________

Name of Representative ___________________ Relation to the Patient ______________

I have received an information sheet on the Study of Mental Health, Behaviour and Neuropsychological Profile of Velo-Cardio-Facial Syndrome. I have discussed the research and had the opportunity to ask any relevant questions concerning the study with ____________________.

I agree that the above-named individual may be interviewed and have a sample of blood taken.

I agree that contact can be made with the above-named individual's General Practitioner and any doctors who have treated him/her for a mental or physical illness.

I agree that other members of the above-named individual's family can be asked to take part in the study.

I understand that the above-named individually is free to withdraw from the study at any time without giving a reason or without affecting future medical care.

I agree that the above named individual will take part in the study.

Signed: Patient _______________________________________

Signed: Patient's representative _______________________________________

Relationship to Patient _______________________________________

Name of Witness: __________________________

Designation: ____________________

Signed: ______________________________________
Patient Consent Form

Patient Identification Number for this trial:

Title of Project: A Study of Mental Health, Behaviour and Neuropsychological Profile of Velo-Cardio-Facial-Syndrome

Name of Researcher: ____________________________

Name of Patient: ________________________________

1. I confirm that I have read and understand the information sheet for the study and have had the opportunity to ask questions. ☐

2. I understand that I am free to withdraw from the study at any time without giving a reason or without affecting my future medical care. ☐

3. I understand that sections of any of my medical notes may be looked at by responsible individuals from The Department of Psychiatry, Royal College of Surgeons in Ireland or from other regulatory authorities, where it is relevant to taking part in the research. ☐

4. I give permission for these individuals to have access to my records. ☐

5. I agree that contact can be made with my General Practitioner and any doctors who have treated me for a mental or physical illness. ☐

6. I have been informed that my name will not be used and I will not be identified in any part of the research or in the papers consequently published. ☐

7. I agree that I will take part in the study. ☐

Name of Patient ____________________________ Date ____________ Patient’s Signature ____________________________

Researcher ____________________________ Date ____________ Researcher’s Signature ____________________________

Form for patient, 1 for researcher and 1 to be kept with hospital notes
Appendix 2
Dr F Stewart
Belfast City Hospital HSS Trust (BCH)
Lisburn Road
Belfast
BT9 7AB

Dear Dr Stewart

ID: 05094FS-C  A novel high-risk study of schizophrenia susceptibility using a population-based cohort of people with velo-cardio-facial syndrome

The Belfast City Hospital Trust are pleased to inform you that the Trust will provide Sponsorship for the above project according to the requirements of the Research Governance Framework and subject to the project gaining ethical approval and, where necessary, MHRA Clinical Trial Authorisation.

The Belfast City Hospital Trust provides indemnity for negligent harm that may arise as a result of this study, according to the regulations given by the Department of Health in Northern Ireland. In relation to non-negligent harm, in NHS Indemnity: ‘Arrangements for Clinical Negligence Claims in the NHS’ (DoH, 1996), paragraph 16 in Annex A states “Apart from liability for defective products, legal liability does not arise where a person is harmed but no one has acted negligently. An example of this would be unexpected side-effects of drugs during clinical trials. In exceptional circumstances (and within the delegated limit of £50,000) NHS bodies may consider whether an ex-gratia payment could be offered. NHS bodies may not offer advance indemnities or take out commercial insurance for non-negligent harm”. It is therefore, only on this basis that indemnity for this research project will be provided by the Belfast City Hospital Trust.

You should now apply for Research Ethics Committee approval for your project and, if necessary, seek approval from MHRA. You can NOT start your research until you receive a ‘Start Certificate’ from the Trust. Should you require further clarification or advice, please do not hesitate to contact me.

Yours sincerely

Zoe Hunter
Research Co-ordinator

Copy to: Dr Sarah Prasad,
29 March 2006

Dr Fiona Stewart
Clinical Team Leader, Consultant in Medical Genetics
Belfast City Hospital
Lisburn Road
Belfast
BT9 7AB

Dear Dr Stewart

Full title of study: A novel high-risk study of schizophrenia susceptibility using a population-based cohort of people with velo-cardio-facial syndrome

REC reference number: 06/NIR03/38

The Research Ethics Committee reviewed the above application at the meeting held on 21 March 2006.

The documents reviewed at the meeting were:

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<th>Document</th>
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<td>5.0</td>
<td>23 February 2006</td>
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<td>Letter of invitation to participant</td>
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<td>GP/Consultant Information Sheets</td>
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<td>Participant information Sheet</td>
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<td>Participant Consent Form</td>
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<tr>
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<td>Other</td>
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<tr>
<td>Letter from Dr Stewart</td>
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Provisional opinion

The Committee would be content to give a favourable ethical opinion of the research, subject to receiving a complete response to the request for further information set out below.

Authority to consider your response and to confirm the Committee's final opinion has been delegated to a meeting of the Sub-Committee of the REC.

Further information or clarification required

The following need to be addressed:

- Participant information sheets and consent need headed paper, and terminology needs to be relevant to Northern Ireland e.g. "an HPSS Research Ethics Committee." Several typographical errors need corrected both in information sheets and the GP letter.
- Consent forms should list PIS version number and date.
- The committee requires that a Participant Information Sheet and consent form be provided for the participants in the control group.
- A24 answer should be corrected as the researchers explained that it would not be possible to conduct this study exclusively in patients capable of giving consent.
- A25 answer is inconsistent with the letter from the study sponsor stating that the latter accepts responsibility for negligent harm.
- A36 The committee require evidence of the extent of cover provided for non-negligent harm by the investigators' professional indemnity insurance.
- A45 answer should be corrected as the statistician cannot be regarded as independent of the research team since he is listed as PI in A41 and custodian in A42.
- A66 reassurance is required that the arrangements for DNA retention and disposal in Dublin fulfill the same standards as are required in the UK (since the patients from which they are derived are NHS patients).
- Review of the function/composition and planned analysis with respect to controls is needed. It was agreed that Dr Cran will provide statistical advice for the researchers.

The following statistical advice is provided:

The proposed study is based on a group of 100 VCF individuals, a control group of 50 siblings or relatives and a control group of 50 matched subjects. The sample size calculation (A51) comparing two groups, each of size 100, seems to infer that the two control groups would be combined. This would be inappropriate as they would be of quite different characteristics, possibly leading to substantial variation in the outcome measures. Hence the power calculation should be based on comparing a group of size 100 with a group of size 50.

When submitting your response to the Committee, please send revised documentation where appropriate underlining or making bold the changes you have made and giving revised version numbers and dates.

The Committee will confirm the final ethical opinion within a maximum of 60 days from the date of initial receipt of the application, excluding the time taken by you to respond fully to the above points. A response should be submitted by no later than 27 July 2006.
Attendance at Committee meeting on 21 March 2006

Committee Members:

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<tr>
<th>Name</th>
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<tr>
<td>Dr John Trinder</td>
<td>Consultant in Anaesthesia and Intensive Care Medicine</td>
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<td>Professor Jonathan Jackson</td>
<td>Principle Optometrist</td>
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<tr>
<td>Dr Marilyn Armstrong</td>
<td>Senior Lecturer, Dept of Microbiology and Immunobiology</td>
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<tr>
<td>Dr Kathryn Burnett</td>
<td>Pharmacist</td>
</tr>
<tr>
<td>Dr Gordon Cran</td>
<td>Senior Lecturer in Medical Statistics</td>
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<tr>
<td>Mr Paul Davidson</td>
<td>Senior Production Plant Manager</td>
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<td>Dr Stanley Hawkins</td>
<td>Consultant Neurologist</td>
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<td>Mrs Alleen Hutton</td>
<td>Community Adviser</td>
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<td>Dr Lorraine Martin</td>
<td>Lecturer in Pharmaceutics</td>
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<td>Dr Patrick McCrystal</td>
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<td>Mrs Catherine Milhench</td>
<td>Registered Nurse</td>
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<td>Mr Mark Miskelly</td>
<td>Engineer</td>
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<td>Mrs Gillian Murphy</td>
<td>Ward Sister</td>
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<tr>
<td>Dr Mark Reid</td>
<td>Consultant Paediatrician</td>
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Also in attendance:

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<tr>
<td>Jan Daley</td>
<td>HPSS REC 3 Administrator</td>
</tr>
</tbody>
</table>
Ethical review of research sites

The Committee agreed that all sites in this study should be exempt from site-specific assessment (SSA). There is no need to complete Part C of the application form or to inform Local Research Ethics Committees (LRECs) about the research. However, all researchers and local research collaborators who intend to participate in this study at NHS sites should notify the R&D Department for the relevant care organisation and seek research governance approval.

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

06/NIR03/38 Please quote this number on all correspondence

Yours sincerely

Dr John Trinder
Chair, HPSS REC 3

Email: daleyj@orec.n-i.nhs.uk

Enclosures: List of names and professions of members who were present at the meeting and those who submitted written comments.

Copy to: Ms Zoe Hunter
Belfast City Hospital NHS Trust
Lisburn Rd
Belfast
BT9 7AB
Dr. Sarah Prasad  
Research Fellow  
Department of Psychiatry  
Beaumont Hospital  
Dublin 9  
Email: sprasad@rcsi.ie

Office for Research Ethics Committees  
Northern Ireland (ORECNI)  
Office Suite 3, 1-4 Haslems Lane,  
Lisburn, Co. Antrim, BT28 1TW

REC Reference number: 06/NIR03/38

Dear Committee Members,

Thank you for approving the project titled, “A novel high-risk study of schizophrenia susceptibility using a population-based cohort of people with velo-cardio-facial syndrome”.

We have considered your kind suggestions and we have altered the various documentations accordingly.

1. We have enclosed participant information sheets and consent forms on headed paper  

2. We have included terminology which is relevant to Northern Ireland
3. We have altered typographical errors

4. We have included PIS version on consent forms

5. Participant information sheets and consent forms for control groups are enclosed (version 1)

6. With regards to A24-1, it has been corrected now to answer **no**, as it is not possible to conduct this study exclusively in patients capable of giving consent.

7. Evidence of the extent of cover provided for non-negligent harm by the investigators’ professional is enclosed

8. I do apologise for my oversight in answering this particular question. The statistical analysis was externally peer reviewed by the Health Research Board and the statistician Professor Peter Holmans, at the Biostatistics/Bioinformatics Unit (BB Unit), Cardiff University, Cardiff, Wales was involved in the statistic analysis. He is independent of the research team.

9.

I hope the relevant amendment is satisfactory to the committee.

Kind Regards,

Dr. Sarah Prasad.
Dear Committee Members,

The statistic analysis was performed by Professor Peter Holmans, at the Biostatistics/Bioinformatics Unit (BB Unit), Cardiff University, Cardiff, Wales.

The statistic analysis has also been peer-reviewed by the Health Research Board during the grant application process.

Please feel free to contact either Professor Holmans or Professor Murphy regarding the analysis.

Kind Regards,

Dr. Sarah Prasad.
Professor Gerry Mc Elvaney  
Chairperson  
Beaumont Hospital  
Ethics (Medical Research) Committee  
Beaumont Hospital, Dublin 5

26th September 2005

Re: 05/37, A novel high-risk study of schizophrenia susceptibility using a population-based cohort of people with Velo-cardio-facial syndrome

Dear Professor Mc Elvaney,

Thank-you for reviewing the above titled protocol at the recent Ethics Committee meeting.

We have considered the suggestions that were recommended by the committee and amended as follows:

1. The project will be titled as ‘A study of Mental Health, Behaviour and Neuropsychological Profile of Velo-Cardio-Facial Syndrome’, and we have amended and attached the information sheets.

2. We have amended the Study Information Leaflet for Parents/Carers (Patient Representative) to include more information regarding the susceptibility to mental health illness in those with Velo-Cardio-Facial syndrome.

3. We have enclosed a copy of the initial contact letter that will be sent by Professor Green to the participants.

4. We have considered the Committee’s suggestion in relation to specifying the tests that are to be done on the DNA collected in the consent forms. However in our view, we thought it may be more appropriate to include this detail in the information sheets provided to the participants and the General Practitioners.
5. DNA is being collected to examine for genetic variation in candidate genes and to determine an association with psychiatric and neuropsychological.

6. This is a prospective longitudinal study and consequent DNA storage is required

7. There is no question of stigmatisation as all individuals will already be aware of their deletion status and their 'chromosomal defect'.

8. We feel that as a separate consent form for DNA collection and storage has been created, there is no need for a separate protocol or amendment

9. We have removed reference to 'ownership' and replaced it with 'custodian' and also indicated that The Royal College of Surgeons in Ireland will be custodian of the data.

Kind Regards,

Yours sincerely,

-----------------------------
Professor Kieran C. Murphy

Department of Psychiatry, RCSI Education and Research Centre, Smurfit Building, Beaumont Hospital, P.O. Box 9063, Dublin 9.
SAC/74/06

2nd March 2006

Professor Andrew Green
Director of Genetics
National Centre for Medial Genetics
Our Lady’s hospital for Sick Children
Crumlin
Dublin 12

Re: A novel high risk study of schizophrenia susceptibility using a population based cohort of people with velo-cardio-facial syndrome
Chief Investigators: Professor Fiona McNicholas, Professor Andrew Green,
Professor Kieran Murphy, Professor Ian Robertson

Dear Professor Green

The above project was approved by the Research Ethics Committee at their meeting which was held on 21st February 2006.

The Committee requested minor alterations to the documentation e.g. advise patients/parents that results will not be given to them and to be more specific about mentioning the actual project throughout the documentation. The title of the project is not used on the Patient Information Leaflet, which contains a different title. The Committee felt that a consistent title should be used in all documentation and the title of the project used in patient information should reflect the actual aim of the project.

The project has been approved subject to receipt of copy of the amended documentation by the Secretary.

The Committee would like to thank Dr. Prasad for being present at the meeting.

Yours sincerely

Claire Rice
Secretary
Research Ethics Committee

CC: Dr Sarah Prasad, Research Fellow, Department of Psychiatry,
Beaumont Hospital, Dublin 9.
SAC/74/06

2nd March 2006

Professor Andrew Green
Director of Genetics
National Centre for Medial Genetics
Our Lady’s hospital for Sick Children
Crumlin
Dublin 12

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Chief Investigators: Professor Fiona McNicholas, Professor Andrew Green,
Professor Kieran Murphy, Professor Ian Robertson

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The Committee would like to thank Dr. Prasad for being present at the meeting.

Yours sincerely

Claire Rice
Secretary
Research Ethics Committee

CC: Dr Sarah Prasad, Research Fellow, Department of Psychiatry,
Beaumont Hospital, Dublin 9.
Dr. Sarah Prasad  
Research Fellow  
Department of Psychiatry  
Beaumont Hospital  
Dublin 9  
Email: sprasad@rcsi.ie  

Research Ethics Committee  
Our Lady’s Hospital for Sick Children  
Crumlin, Dublin 12  

Dear Committee Members,  

Thank you for approving the project titled, “A novel high-risk study of schizophrenia susceptibility using a population-based cohort of people with velo-cardio-facial syndrome”.  

We have considered your kind suggestions and we have altered the various documentations accordingly.  

With regards to your suggestions concerning the title of the project, we have now amended the title to “The Mental Health, Behaviour and Neuropsychological Profile of Velo-Cardio-Facial Syndrome”. It is our view that this title gives patients and parents a greater understanding of the nature of the project and it adequately reflects the aims of the project. We have included this title in all the documentations relevant to the project. As the new title mentions mental health, it is our view that this adequately addresses the concerns raised with regards to the mention of ‘schizophrenia’ in the former title.
As the project not only looks at schizophrenia/psychosis and also covers other areas such as behavioural and neuropsychological phenotypes it is our view that the study information leaflets reflect this aim (paragraph 3, Study Information Leaflet for Parents/Carers).

We hope that our advice to patients/parents in the feedback of results is adequate.

I hope the relevant amendments are satisfactory to the committee.

Kind Regards,

Dr. Sarah Prasad.
Appendix 3
BACKGROUND INFORMATION
INTRODUCTORY INTERVIEW: SCORING SHEET

DEMOGRAPHIC INFORMATION

1. Date of birth
   Month __    Day __    Year __

2. Age of child

3. Sex of child

4. Race (observed)
   1 = Caucasian  4 = Oriental
   2 = African American  5 = Biracial
   3 = Hispanic  6 = Other (Specify): ______________

5. Home environment of child (circle all that apply)
   Biological Mother  1  2
   Biological Father  1  2
   Stepmother  1  2
   Steppfather  1  2
   Adoptive/Foster Parents  1  2
   Siblings  1  2
   Grandparents  1  2
   Other Relative(s)  1  2
   Other Non-Relative(s)  1  2
   Residential Placement: ________________  1  2
   Other (Specify): ________________  1  2

6. If the child is not living with both of his/her biological parent(s), obtain information about whereabouts of non-residing parent, visitation, divorce history, out-of-home placements, etc.

7. List first names & ages of siblings:
   ___________________________  ___________________________
   ___________________________  ___________________________
   ___________________________  ___________________________
   ___________________________  ___________________________
   ___________________________  ___________________________
   ___________________________  ___________________________
   ___________________________  ___________________________
**BACKGROUND INFORMATION**
**INTRODUCTORY INTERVIEW: SCORING SHEET**

**DEMOGRAPHIC INFORMATION**

1. Date of birth
   - **Month** 
   - **Day** 
   - **Year**

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   - 1 = Caucasian
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   - 5 = Biracial
   - 6 = Other (Specify):

5. Home environment of child (circle all that apply)
   - Biological Mother
   - Biological Father
   - Stepmother
   - Stepfather
   - Adoptive/Foster Parents
   - Siblings
   - Grandparents
   - Other Relative(s)
   - Other Non-Relative(s)
   - Residential Placement:
   - Other (Specify):
   - **No**
   - **Yes**

6. If the child is not living with both of his/her biological parent(s), obtain information about whereabouts of non-residing parent, visitation, divorce history, out-of-home placements, etc.

   ____________________________________________________________
   ____________________________________________________________
   ____________________________________________________________
   ____________________________________________________________

7. List first names & ages of siblings:

   ____________________________________________________________
   ____________________________________________________________
   ____________________________________________________________
   ____________________________________________________________
   ____________________________________________________________

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CHILDA

DE AND ADOLESCENT HEALTH SCREENING

Name of Patient ____________________________ Hospital # ____________________________

Date of Assessment ____________________________ Age of Child ___________ D.O.B. ____________________________

Interviewed ____________________________ Relationship to Child ____________________________

Is there anyone who is more familiar with this child's health history than interviewee? _____ YES _____ NO

Name ____________________________ Relationship to child ____________________________ Telephone ____________________________

ADEQUACY OF CURRENT HEALTH CARE:

Where does child receive his/her regular health care?

____________________________________________________________

Approximate Date of Last Visit: _____ mo _____ year _____ don't know

Approximate Date of last physical exam: _____ mo _____ year _____ don't know

Does child have any illnesses or conditions for which he/she receives or should receive regular care? (Describe below)

[ e.g., asthma, allergies, diabetes, anemia, seizures] _____ NO _____ YES ____________________________

Significant Hospitalizations, Surgical or Invasive Procedures: __________________________________________________________

Medication History: ________________________________________________________________

Does child take any medications: _____ YES _____ NO _____ DON'T KNOW

Name and Dose of Medication: ________________________________________________ Daily _____ As Needed

Name and Dose of Past Medications: ___________________________________________ Date Started __/__/ Date Discontinued __/__/ 

Sensitivities or Allergies to ANY Drugs? _____ YES _____ NO

Drug Name __________________________________________ Reaction ____________________________

IMMUNIZATIONS: ______ COMPLETE ______ INCOMPLETE ______ INFOR. NOT PROVIDED ______ UNKNOWN to interviewee

____ DOCUMENTATION PROVIDED AND ATTACHED

DPT Dates: #1 ____________ #2 ____________ #3 ____________ #4 ____________ #5 ____________

OPV Dates: #1 ____________ #2 ____________ #3 ____________

Measles/Mumps/Rubella Vaccines Date(s): __________________________________________________________

OTHER ________________________________________________________________
DEVELOPMENTAL HISTORY:
Complications during pregnancy, labor, and/or delivery. ___ No ___ Yes
If yes, explain____________________

Drug and/or Alcohol use during pregnancy. ___ No ___ Yes
If yes, explain____________________

Social Relatedness during infancy and early childhood. ___ No ___ Yes
If no, explain____________________

Developmental milestones within normal limits. ___ No ___ Yes
If no, explain____________________

PAST HISTORY OF ABUSE?
___ Yes ___ No
If Yes, what kind(s) of abuse? ___ Physical ___ Neglect ___ Sexual ___ Psychological
If Yes, abuse was identified: ___ Prior to assessment ___ At assessment
The age of the patient at the time of the abuse:___________
CY47 was filed: ___ Yes ___ No ___ Not sure Approximate Date:________________=
Report was: ___ Founded ___ Unfounded ___ Not sure
Action taken if founded:_____________________________
Relationship of the perpetrator to the patient:_________________________
Does the child have any current contact with the perpetrator? ___ No ___ Yes ___ Not sure
Is CYS currently involved with this family? ___ Yes ___ No

COMMENTS:

CURRENT RISK FOR ABUSE:
___ precocious sexual play/talk ___ possible physical abuse ___ possible sexual abuse/risk ___ parental concern/fear of abuse

CLINICIAN ___ DATE ___ SUPERVISING PHYSICIAN ___

K-SADS-PL, version 1.0, October 1996
©1986, Kaufman, Birmaher, Brent. Rand ARB/yuan, All rights reserved
PSYCHIATRIC TREATMENT HISTORY

Record Lifetime Treatment History Below

<table>
<thead>
<tr>
<th>AGE</th>
<th>DATES OF TREATMENT</th>
<th>SYMPTOMS OR CONDITION</th>
<th>TREATMENT/LOCATION</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tr>
</tbody>
</table>

Age of First Outpatient Treatment

Age of First Psychiatric Hospitalization

No. of Psychiatric Hospitalizations

Psychotropic Medication:
- Sedatives or Minor Tranquilizers
- Major Tranquilizers
- Antidepressants
- Stimulants
- Lithium
- Other (Specify):

FAMILY HISTORY OF MEDICAL AND PSYCHIATRIC ILLNESS

NOTES:
SCHOOL ADAPTATION AND SOCIAL RELATIONS

Obtain information about the following domains. Some of this information may have already been acquired.

1. School
   Inquire about: (a) Current Grade (or last grade completed); (b) Repeated Grade(s); (c) Special Services (specify); (d) Grade Point Average; (e) Functioning (daily functioning and standardized tests results); (f) Complaints from teacher about child’s behavior; (g) Suspensions and detentions; and (h) Likes and Dislikes.

2. Peer Relations
   Inquire about: (a) Best Friend(s); (b) Relations with peers at school; (c) Relations with peers in home neighborhood; (d) Activities with friends; and (e) Problems (e.g. teased, in fights).

3. Family relations
   Inquire about: (a) Mother-Child relationship; (b) Father-Child relationship; (c) Marital relationship; (d) Sibling relationships; (e) Extended Family/Social Supports; and (f) Current or Past CYS involvement.

4. Other Activities
   Inquire about: (a) Hobbies; (b) spare time activities; (c) sports; (d) organizations; etc.
Appendix 4
**Neurodevelopmental Questionnaire**

Child's name: 
Address: 
Date of Birth: 

1. Male □ Female □

2. Age of referral to CAMHS

Informant (Mother, Father, Carer)

**A. Family History**

1. Father
   - Birth Date
   - Occupation
   - Highest education achieved

2. Mother
   - Birth Date

3. Are parents related?

4. Child's siblings; Number

5. Child's birth position (1st, 2nd, etc.)

6. Any other carers?
   If in care document the length of time in each placement.

7. Brothers and sisters (in order, including miscarriages, still births or abortions)
   - First name
   - Date of Birth
   - Present Occupation (School/job)


---

1
8. List any family members who have suffered from any of the following (Include only brothers and sisters of the child named herein, grandparents, uncles, aunts and cousins). 
   Give details: stage of relationship of affected relative and nature of disorder

<table>
<thead>
<tr>
<th>Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intellectual Disability</td>
</tr>
<tr>
<td>Specific Learning Disability</td>
</tr>
<tr>
<td>Speech Delay</td>
</tr>
<tr>
<td>Epilepsy</td>
</tr>
<tr>
<td>Mental Illness</td>
</tr>
<tr>
<td>Suicide</td>
</tr>
<tr>
<td>Alcoholism</td>
</tr>
</tbody>
</table>

**B. Antenatal**

1. Did you have an intrauterine device in place when you became pregnant? 
   __________________________

2. Were you on any contraception when you became pregnant?  ______________________

3. Was your baby’s conception assisted medically? eg. IVF, Clomidene  ______
   __________________________

4. Did you take any medication during the pregnancy (oral, topical, intramuscular)?  ______________________

<table>
<thead>
<tr>
<th>Medication</th>
<th>Amount (Dosage)</th>
<th>1st Trimester</th>
<th>2nd Trimester</th>
<th>3rd Trimester</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleeping Pills</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Recreational drugs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin supplements (Iron, Calcium)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Folic acid (for how long before and during pregnancy?)</td>
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<tr>
<td>Other (include over the counter preparations)</td>
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</tr>
</tbody>
</table>

5. Did you smoke cigarettes during the pregnancy?  ______________________
   Amount per day on average
   1st Trimester  ______________________
   2nd Trimester  ______________________
   3rd Trimester  ______________________
6. Was there anybody else living in the house smoking during the pregnancy?
   1st Trimester
   2nd Trimester
   3rd Trimester

7. Did you drink alcoholic beverages during the pregnancy? ————
   Amount per day on average
   1st Trimester
   2nd Trimester
   3rd Trimester
   (1 unit = 1 oz of hard liquor or 1 beer or 4 oz wine)

8. Did you obtain prenatal care? ———— (Where)

9. How was your health in general during the pregnancy? (physically, psychologically) ————

10. Did you experience any of the following during the pregnancy?

    Pre-eclampsia - treated with drugs?

    Pre-eclampsia requiring hospital admission?

    Pre-eclampsia requiring early induction?

<table>
<thead>
<tr>
<th></th>
<th>1st Trimester</th>
<th>2nd Trimester</th>
<th>3rd Trimester</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vomiting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding or spotting, ante partum haemorrhage?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excessive Swelling (of hands or feet)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sugar in urine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infectious episode including all illnesses, even minor viral, rubella, syphilis)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhesus incompatibility</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Falls, Trauma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Threatened abortion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not putting on weight as expected</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdomen not growing as expected</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Were you hospitalised for any reason during the pregnancy? If so describe</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
C. Obstetric history

1. Delivery at term?
2. Hospital delivery?
3. Home delivery?
4. Gestational age 
5. Birth Weight (kg)
6. Do you recall any of the following occurring? If yes record details:

<table>
<thead>
<tr>
<th>Duration of labour?</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Caesarean Section &lt; 37/40?</td>
<td></td>
</tr>
<tr>
<td>Premature Rupture of membranes?</td>
<td></td>
</tr>
<tr>
<td>Intrapartum Bleed?</td>
<td></td>
</tr>
<tr>
<td>Placenta Praevia?</td>
<td></td>
</tr>
<tr>
<td>Post partum Bleed?</td>
<td></td>
</tr>
<tr>
<td>Meconium Staining?</td>
<td></td>
</tr>
<tr>
<td>Labour induced ?(reason)</td>
<td></td>
</tr>
<tr>
<td>Prolapsed Cord?</td>
<td></td>
</tr>
<tr>
<td>Foetal Distress?</td>
<td></td>
</tr>
<tr>
<td>Assisted delivery ?(forceps, ventouse)</td>
<td></td>
</tr>
<tr>
<td>Apgar score?</td>
<td></td>
</tr>
<tr>
<td>Baby intubated?</td>
<td></td>
</tr>
<tr>
<td>Baby in incubator?</td>
<td></td>
</tr>
<tr>
<td>Baby ventilated?</td>
<td></td>
</tr>
<tr>
<td>Baby placed in Intensive Care Unit?</td>
<td></td>
</tr>
<tr>
<td>Twin Birth (if yes was proband 1st or 2nd born?)</td>
<td></td>
</tr>
<tr>
<td>Baby Jaundiced requiring phototherapy?</td>
<td></td>
</tr>
<tr>
<td>Did the baby have to have a blood transfusion at/soon after birth (details)?</td>
<td></td>
</tr>
<tr>
<td>Did the baby have any treatment / medication at/soon after birth (details)?</td>
<td></td>
</tr>
<tr>
<td>Did the baby have any infections at/soon after birth (details)?</td>
<td></td>
</tr>
<tr>
<td>How many days after the birth was the baby in hospital?</td>
<td></td>
</tr>
<tr>
<td>Did the baby stay in hospital after the mother went home?</td>
<td></td>
</tr>
</tbody>
</table>

4. Any congenital defect or disorder?

5. How was mother's health after the birth (physically, psychologically)?

6. If child has siblings, was there any difference in this child's development either in the antenatal or postnatal period of development?
D. Early Infancy

Feeding:
1. How did you feed the baby?
   Breast ------------ Formula ------------
2. Comment on any difficulties ----------------
3. Was suck strong and did the baby eat well?
4. Was the baby colicky?

Sleep
5. Was the baby a light -------- or a heavy -----------sleeper?
6. Was the baby easy to settle? ------------
6. Did the baby sleep between feedings?
7. Was the baby contented ------ or irritable ---------?
8. When the baby was awake, was he or she alert? --------- Or lethargic? ---------

Medical
9. Any major Illnesses during the first year of life?
   If so List
10. Any operations or hospitalisations?
11. Febrile convulsions?
12. Epilepsy?
13. Head Injury?
14. Visual Problems?
15. Hearing Problems?

Social interaction
1. Did your baby smile socially at 6 weeks?
2. Did your child ever use his/her index finger to point, to ask for something?
3. Did your child ever use his/her index finger to point, to indicate interest in something?
4. Did the baby like to be picked up?
5. Did the baby anticipate being picked up (look up in anticipation or hold up arms)?
6. Did the baby show an interest in his or her environment? ---------- Does your child show an interest in other children?
7. Was the baby unusually fearful (e.g. cry at loud noises or strangers, etc.)?
8. Does your child enjoy playing peek-a-boo/hide- and- seek?
9. Does your child show an interest in other children?
10. Does your child ignore conversational cues? e.g. If asked what they are making they may continue working as if nothing has happened?
11. Is your child aware of other people's feelings?
12. Does your child notice the effect of his/her behaviour on other members of the family?
E. Developmental Milestones

Motor Development (3DI)

1. How old was the baby when he/she sat without a firm surface? (months)
2. Babies start moving around the place in a variety of ways. How did the baby begin to move? (months)
3. At what age did this happen?
4. What about walking? At what age did the baby walk without holding on? (months)
5. Did the baby demonstrate any repetitive movement? (Rocking, Headbanging, other)
6. Age in months achieved bladder control
7. Age in months achieved bowel control

Speech and Language Development

1. Early babbling (months)
2. Age in months of first word other than mum/dad (months)
3. Speaking with 2-3 word sentences (months)
4. Abnormal speech: eg. echolalia, neologisms, abnormal phonology, (months)

Gross Motor Skills

1. Can he/she ride a bicycle?
2. How good is he/she at kicking a ball while moving him/herself? (Compare with children of his/her age)
3. How well does she negotiate an object which is in the way but below her line of vision such as a low table? Would he/she tend to walk into it?
4. What about dancing to music how does that work out from the point of view of coordination and so on?

Gait

1. Is there anything unusual about the way walks now? (For example: Bouncing, exaggeration of toe-heel, up on his/her toes)
(If > 5 years old)

*Fine Motor Skills*

1. How well does he/she use a pencil or pen to produce reasonably neat writing?

2. How good is he/she at using a crayon or pencil for drawing purposes?

3. How easily can he/she use a pair of scissors (without supervision)?

**F. Developmental coordination disorder**

1. How well can he/she use his/her hands to make things or to fit things together such as Lego?

2. Has your child ever had difficulties getting dresses the right way (putting things on the wrong way round, putting both legs in one trouser leg and the like?)

3. Was there any time that he/she appeared to lose coordination or other physical skills?

4. How well coordinated is he/she when filling a glass from a jug?

5. Which hand does he/she prefer to use when completing tasks?

6. Despite this preference, might he/she swap hands from time to time in the course of a task?

7. Abnormal movements (Tics)

---

**Please ask the following if child is > 5 years old**

8. Has your child ever had trouble turning a doorknob the right way to get through a door?

9. Can your child tie their own shoelaces without help?

10. Is your child able to use a knife and fork?

11. Has your child any difficulties turning a key the right way to get through a door?
G. Play
1. At ages 1-4 which types of toys did your child like? Favourite?
   Vehicles
   Blocks
   Puzzles
   Fantasy
   Dolls, house

2. Can your child play properly with small toys (eg. cars or bricks) without just mouthing, fiddling or dropping them?

3. Did your child use all toys in an oddly formal way e.g. ordering toys by size or colour?

4. Does your child ever pretend, for example, to make a cup of tea using a toy cup and tea-pot, or pretend other things? Describe

5. Did your child choose a favourite object to carry around (such as a teddy bear, other stuffed animals, a blanket)? If so specify

6. How long can your child stay focused on an activity of their own choosing?

7. Does your child ever bring objects over to you (parent) to show you something?

H. Sensory difficulties
1. Tactile
2. Auditory
3. Taste
4. Movement
5. Visual
6. Has your child ever shown any hand or finger mannerisms (e.g. Hand flapping or flicking fingers before his/her eyes) when excited or distressed?
7. Has he/she any more complex body mannerisms or whole body movements such as spinning round while hand flapping?
8. Does your child enjoy being swung, bounced on your knee, etc?
9. Does your child enjoy climbing on things, such as upstairs?
If child is > 5 years old

1. Has your child required any additional supports in school?

Attention Control

Stage 1 (approximate age 0-1 year)
Can pay fleeting attention but is highly distractible

Stage 2 (approximate age 1-2 years)
Pays rigid attention to an activity of his own choice

Stage 3 (approximate age 2-3 years)
Single channel attention. Can attend to activity of adults choice but is difficult to control

Stage 4 (approximate age 3-4 years)
Single channel attention. Can control his own attention

Stage 5 (approximate age 4-5 years)
Can attend fully, but for short spells only

Stage 6 (approximate age 5 years and over)
Integrated attention. Can play well controlled and sustained attention

Riley Motor Problems Inventory

References

Children’s Nonverbal Learning Disabilities Scale, Goldstein, D.

Lewis Murray Scale; Lewis, SW, Owen MJ, Murray, RM; Obstetric complications and schizophrenia: methodology and mechanisms, in schizophrenia: Scientific Progress. Edited by Schulz SC, Tramming, A., CA. New York, Oxford University Press, 1989, p.56-68


The CHAT, Geneva Centre for Autism (416) 322-7877
Appendix 5
PSYCHOTIC DISORDERS SUPPLEMENT

Subject's ID# and Initials

Date of Interview

Interviewer
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Topic</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychosis</td>
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<tr>
<td>Diagnostic Tree</td>
<td>12</td>
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PSYCHOSIS SUPPLEMENT

I. HALLUCINATIONS

Probes: In addition to the probes provided below for assessing the specific categories of hallucinations, use some of the following probes to further evaluate the validity of the reported hallucinations. These voices you hear (or other hallucinations), do they occur when you are awake or asleep? Could it be a dream? Do they happen when you are falling asleep? Waking up? Only when it is dark? Do they happen at any other time also? Were you sick with fever when they occurred? Had you been drinking beer, wine, liquor?, or taking any drugs when it happened? Was it like a thought or more like a voice (noise) or a vision? Was it like you were imagining things? Did you have any control over it? Could you stop it if you wanted to? Were you having a seizure?

Follow-up on data obtained during the screen interview. Use the language the child used earlier in discussing possible hallucinations to elicit the information below. Complete both the hallucinations and delusion sections for all subjects who scored positively on either the hallucinations or delusions screen items.

<table>
<thead>
<tr>
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</tr>
</tbody>
</table>

1. Auditory Hallucinations
   a. Non-Verbal Sounds (e.g., Music)
   
   Do you hear music or other noises that other people cannot hear?

   b. Command Hallucinations

   Do the voices tell you to do anything? (What?) (Good or bad?) Have they ever told you to hurt or kill yourself? How? Have they ever told you to hurt or kill someone else? Who? How?

   (Specify if content always related to depression or mania)

   DESCRIBE: ________________________________
c. Running Commentary (Commenting Voice)

Do you hear voices that talk about what you're doing? or feeling? or thinking? (Specify if content is always related to depression or mania)

<table>
<thead>
<tr>
<th>Parent CE</th>
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<th>Child CE</th>
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<td>3</td>
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</table>

d. Converging Voice

How many voices do you hear? What do they say? Do they talk with each other? (Specify if content always related to depression or mania)

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</table>

DESCRIPTOR:

e. Thoughts Aloud

Do you ever hear your thoughts spoken aloud? If somebody stood next to you, could they hear your thinking? Is it a real voice outside your head?

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<tr>
<th>Parent CE</th>
<th>Parent MSP</th>
<th>Child CE</th>
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<th>Summary CE</th>
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</table>

f. Other Verbal Hallucinations

Have there been other noises or voices you have heard that you have not told me about? Do the voices ever criticize you? Make fun of you? Say they are going to do bad things to you? Has God (Jesus), angels, demons, Virgin Mary, or saints ever talked to you? Are there any other people you know who had (______) talk to them? (Specify if content always related to depression or mania)

DESCRIPTOR:

Laughing/SCOURING
2. Location of Voices/Noises
   a. Inside head only
      Where did the voices come from? From inside your head? Was it your thoughts you heard? Could other people hear the voices?
      0 1 2 3 0 1 2 3 0 1 2 3 0 1 2 3 0 1 2 3
   b. Outside head only
      From outside your head, through your ears? Did it sound as clear as my voice does talking to you right now?
      0 1 2 3 0 1 2 3 0 1 2 3 0 1 2 3 0 1 2 3
   c. Combination
      Have the voices sometimes seemed to be inside your head, and other times outside your head? Sometimes like thoughts and other times like my voice now?
      0 1 2 3 0 1 2 3 0 1 2 3 0 1 2 3 0 1 2 3

3. Visual Hallucinations
   Do you
   Do you see things other children don't? What do you see? Did you see something real, or was it just like a shadow moving? How clear was it? Did you see it several times for several days in a row? (Specify if content always related to depression or mania)
   0 1 2 3 0 1 2 3 0 1 2 3 0 1 2 3 0 1 2 3
   DESCRIBE:

4. Tactile Hallucinations
   Do you ever feel like someone or something is touching you, but when you look there is nothing there? Tell me about it? (Specify if content always related to depression or mania)
   0 1 2 3 0 1 2 3 0 1 2 3 0 1 2 3 0 1 2 3
   DESCRIBE:
   2 days | 3 days
5. Olfactory Hallucinations

Do you ever smell things other people don't smell? What is it?

**DESCRIBE:**

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<tr>
<th>Parent CE</th>
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6. Illusions

False perceptions stimulated by a real perception which is momentarily transformed. They occur frequently due to poor perceptual resolution (darkness, noisy locale) or inattention and they are immediately corrected when attention is focused on the external sensory stimulus or perceptual resolution improves.

Have you ever seen things around your room at night that you thought were something else? Like did you ever look at one of your stuffed animals or a shirt and think it was something that could get you? Have you ever looked at a rope and thought it was a snake? Other things?

**Code for Remaining Items:**

0 = No information
1 = No
2 = Yes

7. Cultural Acceptance of Hallucinations

Does anyone else in your family or any members of your church experience the same (specify hallucination)?

8. Duration of Hallucinations

One or a combination of hallucinations lasted throughout the day for several days or several times a week for several weeks.

9. Association with Affective Illness

Hallucinations always occurred during or within 2 weeks of an affective illness (MDD or Mania).
10. Association with Trauma

Hallucination themes reflect past traumatic experiences. (Specify):

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<tr>
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11. Association with Substance Use or Organic Factor

Hallucinations always occurred after substance use or in the course of a medical condition. Specify:

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12. Evidence of a Precipitant (Specify): When:

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13. Duration of Symptoms one week or greater: Specifically

Specify Duration: _3 weeks_.

NOTES:
II. DELUSIONS

Probes: In addition to the probes provided below for assessing the specific types of delusions, use some of the following probes to further evaluate the validity of the reported delusions. Are you sure that this (. . . ) is this way? Could there be any other reason for it? How do you know that it happens as you say? Any other possible explanation? Is what you told me make believe or real? (You might suggest other possible explanations and see how the subject reacts to them.)

Follow-up on data obtained during the screen interview. Use the language the child used earlier in discussing possible delusions to elicit the information below.

<table>
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1. Grandiosity

Do you feel that you are a very important person or that you have special powers or abilities? What are they? Are you related to important people, like kings or the president or a sports figure? Do you have special powers like reading people's minds? Tell me more about it. Has God chosen you to perform any special tasks for him?

2. Guilt/Sin

Do you ever feel like you did something terrible? What is the worst thing that you ever did? Do you deserve punishment? Length of time (years).

3. Delusions of Control

Do you have the feeling that you are being controlled by some force of power outside yourself? Whose power? Do you feel sometimes that you are a puppet or a robot and can't control what you do? Or that you are forced to move or say things that you don't want to?
### Somatic Delusions

Do you think you have any serious diseases? How do you know? Are you sure? Has something happened to your body or insides? Tell me about it. Maybe you just feel these things but nothing is wrong with you. Could that be?

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### a. Only During Affective Episode

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### Nihilism

Do you feel that something terrible will happen or has happened? What will happen? Have you felt that the world is coming to an end? When?

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<th>Nihilism</th>
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### Thought Broadcasting

Do you ever feel that your thoughts are broadcast out loud so that other people know what you are thinking? Like on a radio, so that anyone listening could hear them? Have you actually heard your thoughts spoken out loud? Have others heard them?

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<thead>
<tr>
<th>Thought Broadcasting</th>
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### Thought Insertion

Do you feel that thoughts are put into your mind that are not your own? Who put them there? How? Why?

<table>
<thead>
<tr>
<th>Thought Insertion</th>
<th>0 1 2 3</th>
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### Thought Withdrawal

Have you had thoughts taken out of your mind by someone or some special force? Tell me what happened.

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<th>Thought Withdrawal</th>
<th>0 1 2 3</th>
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</table>

### Message from TV/Radio

Does the TV or radio ever talk about you or send you messages? What about songs?

<table>
<thead>
<tr>
<th>Message from TV/Radio</th>
<th>0 1 2 3</th>
<th>0 1 2 3</th>
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### Delusions of Persecution

Has anyone been making things hard, or purposely causing you trouble, or trying to hurt you, or plotting against you? How come?

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"\[
\text{lot of children.}
\]
11. Delusions That Others Can Read, His/Her Mind

Can people know what you are thinking in some strange way? Is that because the way you look or is it just because they know what you are thinking because they can read your mind?

<table>
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<th>Child CE</th>
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12. Delusions of Reference

Do people seem to drop hints about you? Do people say things with a double meaning? Do they do things in a special way to tell you something? Have things seemed especially arranged so only you understand the meaning?

| 0 1 2 3   | 0 1 2 3    | 0 1 2 3 | 0 1 2 3   | 0 1 2 3    | 0 1 2 3     |

13. Other Bizarre Delusions

Any other special thoughts that you want to tell me about?

| 0 1 2 3   | 0 1 2 3    | 0 1 2 3 | 0 1 2 3   | 0 1 2 3    | 0 1 2 3     |

**Code for Remaining Items:**

0 = No Information  
1 = No  
2 = Yes

14. Subcultural or Family Delusions

Do other people in your family also believe in what you say (ask the mother and if necessary other members of the family)? Do other members of your religion believe in that too? Do other children like your friends believe in what you believe?

| 0 1 2   | 0 1 2    | 0 1 2   | 0 1 2    | 0 1 2    | 0 1 2     |

15. Multiple Delusions

| 0 1 2   | 0 1 2    | 0 1 2   | 0 1 2    | 0 1 2    | 0 1 2     |

16. Delusions always occurred during or within 2 weeks of an affective illness (MDD or Mania)

<p>| 0 1 2   | 0 1 2    | 0 1 2   | 0 1 2    | 0 1 2    | 0 1 2     |</p>
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<td>17. Delusions always occurred in the context of substance use or during the course of a medical illness. Specify:</td>
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<tr>
<td>18. Content of Delusions always related to depressed or elated mood.</td>
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<td>19. Evidence of a Precipitant (Specify):</td>
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<td>20. Duration of Symptoms one week or more. Specify duration:</td>
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NOTES:
### OTHER PSYCHOTIC SYMPTOMS

Rate based on observation during interview.

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<tr>
<td>Deficit in emotional contact not explainable by severe mood disturbance or preoccupation, i.e., even with adequate efforts on the part of the interviewer to establish appropriate emotional contact, the subject does not give back signs of emotional response such as occasional smiling, tearfulness, laughing, or looking directly at the interviewer. At the &quot;moderate&quot; level or above, there is flatness of affect as indicated by monotonous voice, and facial expression lacking signs of emotion.</td>
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</table>

| **b. Inappropriate Affect** | 0 1 2 | 0 1 2 | 0 1 2 | 0 1 2 | 0 1 2 | 0 1 2 |
| Affect is incongruous with content of speech, for example, giggles while discussing reason for hospitalization. Do not include mere embarrassment or excessively strong affect, as when subject cries when discussing a minor disappointment. Incongruity does not mean excessive intensity but qualitative inconsistency with thought content and/or environmental circumstances. |

| **2. a. Incoherence**     | 0 1 2 | 0 1 2 | 0 1 2 | 0 1 2 | 0 1 2 | 0 1 2 |
| Speech that is generally not understandable, running together of thoughts or words with no logical or grammatical connection, resulting in disorganization. |

**DESCRIBE:**

| **b. Loosening of Associations** | 0 1 2 | 0 1 2 | 0 1 2 | 0 1 2 | 0 1 2 | 0 1 2 |
| Flow of thought in which ideas shift from one subject to another in a completely unrelated way. |

**DESCRIBE:**
3. **Catatonic Behavior**

Motor anomalies including immobility, stupor, rigidity, bizarre posturing, waxy flexibility, and excited movements (purposeless and stereotyped excited motor activity not influenced by external stimuli).

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<th>Parent CE</th>
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<th>Child CE</th>
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**IV. IMPAIRED FUNCTIONING DURING ACTIVE ILLNESS**

1. Impaired School Performance

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2. Impaired Peer Relations

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3. Impaired Family Relations

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<th>Parent MSP</th>
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<th>Child MSP</th>
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4. Impaired Self Care

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COMPLETE DIAGNOSTIC TREES BEGINNING ON PAGE 12 OF THIS SUPPLEMENT.
DIAGNOSTIC TREE: PSYCHOSIS

Ever had psychotic symptoms not associated with depression or mania

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DSM-III-R Criteria

FOR A DIAGNOSIS OF SCHIZOPHRENIA, the following criteria are required:

A. Characteristic psychotic symptoms of the active phase. Either (1), (2), or (3) for at least one week (or less if symptoms successfully treated):

1. Two of the following
   (a) delusions
   (b) prominent hallucinations (throughout the day for several days or several times a week for several weeks and each hallucinatory experience is not limited to a few brief moments)
   (c) incoherence or marked loosening of associations
   (d) catatonic behavior
   (e) flat or grossly inappropriate affect

2. bizarre delusions (i.e., involving a phenomenon that the individual's subculture would regard as totally implausible e.g., thought broadcasting, being controlled by a dead person) — F R S

3. prominent hallucinations (as defined in 1 (b) above) of a voice with content having no apparent relation to depression or elation, or a voice keeping up a running commentary on the individual's behavior or thoughts, or two or more voices conversing with each other.

B. During the course of the disturbance, functioning in such areas as work, social relations, and self-care is markedly below the highest level achieved prior to the disturbance (or with onset in childhood or adolescence, failure to achieve expected level of social development).

C. Major depressive or manic syndrome, if present during the active phase of the disturbance (symptoms in A), was brief relative to the duration of the disturbance. Schizoaffective disorder and mood disorder with psychotic features ruled out.

D. Continuous signs of disturbance for at least six months. The six-month period must include an active phase (of at least one week, unless symptoms have been successfully treated) during which there are psychotic symptoms characteristic of schizophrenia (symptoms in A), and either a prodromal or residual phase if the active phase was of less than six-months duration.

Prodromal phase: A clear deterioration in functioning before the active phase of the disturbance, not due to a disturbance in mood or to a Psychoactive Substance Use Disorder, and involving at least two of the symptoms listed below.

Residual phase: Following the active phase of the disturbance, persistence of at least two of the symptoms noted below, not due to a disturbance in mood or to a Psychoactive Substance Use Disorder.

Prodromal and Residual Symptoms

1. marked social isolation or withdrawal
2. marked impairment in role (functioning as wage-earner, student, or homemaker)
3. markedly peculiar behavior (e.g., collecting garbage, talking to self in public, hoarding food)
4. marked impairment in personal hygiene and grooming, blunted, flat or inappropriate affect
5. digressive, vague, overelaborate, or circumstantial speech, or poverty of speech, or poverty of content of speech
6. odd beliefs or magical thinking influencing behavior and inconsistent with subcultural norms, e.g., superstitiousness, belief in clairvoyance, telepathy, sixth sense, "others can feel my feelings.", overvalued ideas, ideas of reference
7. unusual perceptual experience, e.g., recurrent illusions, sensing the presence of a force or person not actually present
8. marked lack of initiative, interests or energy.

Examples: Six months of prodromal symptoms with one week of symptoms from A; no prodromal symptoms with six months of symptoms from A; no prodromal symptoms with one week of symptoms from A and six months of residual symptoms.
E. It cannot be established that an organic factor initiated and maintained the disturbance.

F. If there is a history of Autistic Disorder, the additional diagnosis of Schizophrenia is made only if prominent delusions or hallucinations are also present.

**FOR DIAGNOSES OF SCHIZOPRENFIFORM DISORDER**, the following criteria are required:

A. Meets criteria A and C of Schizophrenia.

B. An episode of the disturbance (including prodromal, active, and residual phase) lasts less than six months.

C. Does not meet the criteria for Brief Reactive Psychosis and not due to an Organic Mental Disorder.

**FOR DIAGNOSES OF BRIEF REACTIVE PSYCHOSIS**, the following criteria are required:

A. Presence of incoherence or marked loosening of associations, delusions, hallucinations, or catatonic or disorganized behavior;

B. Emotional turmoil (e.g. rapid shifts from one intense affect to another).

C. Appearance of the symptoms in A and B shortly after, and apparently in response to, one or more events that singly or together, would be markedly stressful to almost anyone in a similar situation.

D. Absence of prodromal symptoms of Schizophrenia.

E. Duration of episode **not more than one month**, with eventual return to premorbid level of functioning.

F. Not due to a psychotic Mood Disorder.
DSM-IV Criteria

FOR A DIAGNOSIS OF SCHIZOPHRENIA, the following criteria are required:

A. Characteristic psychotic symptoms: At least two of the following, each present for a significant portion of time during a one month period (or less if symptoms successfully treated):

1. delusions
2. hallucinations
3. disorganized speech (e.g. frequent derailment, incoherence or marked loosening of associations)
4. grossly disorganized or catatonic behavior
5. negative symptoms (e.g. affective blunting, alogia, or avolition).

Note: Only one A symptom is required if delusions are bizarre or hallucinations consist of a voice keeping a running commentary on the person's behavior or thoughts, or two or more voices conversing.

B. During the course of the disturbance, functioning in such areas as work, social relations, and self-care is markedly below the highest level achieved prior to the disturbance (or with onset in childhood or adolescence, failure to achieve expected level of social development).

C. Continuous signs of disturbance for at least six months. The six-month period must include an active phase (of at least one week, unless symptoms have been successfully treated) during which there are psychotic symptoms characteristic of schizophrenia (symptoms in A), and either a prodromal or residual phase if the active phase was of less than six-months duration.

D. Major depressive or manic syndrome, if present during the active phase of the disturbance (symptoms in A), was brief relative to the duration of the disturbance. Schizoaffective disorder and mood disorder with psychotic features ruled out.

E. Organic and pharmacological etiology ruled out.

FOR DIAGNOSES OF SCHIZOPRENFIFORM DISORDER, the following criteria are required:

A. Meets criteria A, D, and E of Schizophrenia.

B. An episode of the disturbance (including prodromal, active, and residual phase) lasts at least one month but less than six months.

FOR DIAGNOSES OF BRIEF REACTIVE PSYCHOSIS, the following criteria are required:

A. Presence of disorganized speech, delusions, hallucinations, or catatonic or disorganized behavior;

B. Duration of episode at least one day and not more than one month, with eventual return to premorbid level of functioning.

C. Not due to a psychotic Mood Disorder, schizophrenia, organic cause, or psychopharmacological etiology.

Specify if: With Marked Stressor(s); Without Marked Stressor(s); or Post-partum onset.

IF MEETS CRITERIA FOR SCHIZOPHRENIA OR SCHIZOPRENFIFORM DISORDER, OR CURRENTLY IN PRODROMAL OR RESIDUAL PHASE, DESCRIBE CLINICAL FEATURES IN THE CHARTS ON THE FOLLOWING PAGES.
If meets criteria for schizophrenia complete items below:

1. **Course**

   a. **Subchronic**: The time from the beginning of the disturbance, when the individual first begins to show signs of the disturbance (including prodromal, active, and residual phases), more or less continuously, is less than two years but at least six months.

   b. **Chronic**: Same as above, but greater than two years.

   c. **Subchronic with Acute Exacerbation**: Re-emergence of prominent psychotic symptoms in an individual with a chronic course who has been in the residual phase of the disturbance.

   d. **Chronic with Acute Exacerbation**: Re-emergence of prominent psychotic symptoms in an individual with a chronic course who has been in the residual phase of the disturbance.

   e. **In Remission**: This should be used when an individual with a history of Schizophrenia is now free of all signs of the disturbance (whether or not on medication). The differentiation of Schizophrenia In Remission from No Mental Disorder requires consideration of overall level of functioning, the length of time since the last period of disturbance, the total duration of the disturbance, and whether prophylactic treatment is being given.

For Prodromal or residual phases of illness, rate associated features:

2. **Associated Features**

   a. Social isolation or withdrawal

   b. Impaired school performance

   c. Markedly peculiar behavior

   d. Impaired personal hygiene/grooming

   e. Blunted, last, inappropriate affect

   f. Digressive, vague, overelaborate or circumstantial speech or poverty of speech or content of speech

   g. Odd beliefs or magical thinking which influence behavior

   h. Unusual perceptual experiences

   i. Marked lack of initiative, interests or energy

   j. Duration of Prodromal/Residual Phase (in weeks)
If meets criteria for schizophreniform disorder, complete items below:

Specify if good prognostic features are present, i.e., at least two of the following for good, one for fair, none for poor.

1. Prognostic Features:
   a. Onset of prominent psychotic symptoms within four weeks of first noticeable change in usual behavior or functioning.  
      RATING: 0 1 2
   b. Confusion, disorientation, or perplexity at the height of the psychotic episode.  
      RATING: 0 1 2
   c. Good premorbid social and occupational functioning.  
      RATING: 0 1 2

2. Prognosis
   a. Good: Two or more positive prognostic features present  
      RATING: 0 1 2
   b. Fair: Only one positive prognostic feature present  
      RATING: 0 1 2
   c. Poor: No positive prognostic features present  
      RATING: 0 1 2
Appendix 6

Name: __________________________

CRF #: _________________________

Rater: __________________________

Date: _____/_____/______

The PACE Clinic
Department of Psychiatry
The University of Melbourne
Melbourne, Australia

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INDEX

1: POSITIVE SYMPTOMS
1.1 UNUSUAL THOUGHT CONTENT  1
1.2 NON-BIZARRE IDEAS  3
1.3 PERCEPTUAL ABNORMALITIES  5
1.4 DISORGANISED SPEECH  7

2: COGNITIVE CHANGE ATTENTION/CONCENTRATION
2.1 SUBJECTIVE EXPERIENCE  9
2.2 OBSERVED COGNITIVE CHANGE  11

3: EMOTIONAL DISTURBANCE
3.1 SUBJECTIVE EMOTIONAL DISTURBANCE  12
3.2 OBSERVED BLUNTER AFFECT  14
3.3 OBSERVED INAPPROPRIATE AFFECT  15

4: NEGATIVE SYMPTOMS
4.1 ALOGIA  16
4.2 AVOLITION/APATHY  17
4.3 ANHEDONIA  18

5: BEHAVIOURAL CHANGE
5.1 SOCIAL ISOLATION  19
5.2 IMPAIRED ROLE FUNCTION  20
5.3 DISORGANISING/ODD/STIGMATING BEHAVIOUR  21
5.4 AGGRESSION/DANGEROUS BEHAVIOUR  22

6: MOTOR/PHYSICAL CHANGES
6.1 SUBJECTIVE COMPLAINTS OF IMPAIRED MOTOR FUNCTIONING  23
6.2 INFORMANT REPORTED OR OBSERVED CHANGES IN MOTOR FUNCTIONING  24
6.3 SUBJECTIVE COMPLAINTS OF IMPAIRED BODILY SENSATION  25
6.4 SUBJECTIVE COMPLAINTS OF IMPAIRED AUTONOMIC FUNCTIONING  26

7: GENERAL PSYCHOPATHOLOGY
7.1 MANIA  27
7.2 DEPRESSION  29
7.3 SUICIDALITY AND SELF-HARM  31
7.4 MOOD SWINGS/LABILITY  32
7.5 ANXIETY  33
7.6 OCD SYMPTOMS  34
7.7 DISSOCIATIVE SYMPTOMS  35
7.8 IMPAIRED TOLERANCE TO NORMAL STRESS  36

8: INCLUSION CRITERIA  37

9: PSYCHOSIS THRESHOLD  38

10: STUDY WITHDRAWAL  38
OVERVIEW OF THE CAARMS

Aims:
- To determine if an individual meets the criteria for an ‘At Risk Mental State’.
- To rule out, or confirm criteria for acute psychosis.
- To map a range of psychopathology and functioning factors, over time in young people at ultra high-risk of psychosis.

Structure of the CAARMS:
- Ratings are made on a range of subscales that target different areas of psychopathology and functioning. From these ratings it is then possible to extract information relating to the above aims.

Overview of Symptoms and Functioning - Longitudinal Change:
- At the first interview (not follow-up interviews), the CAARMS aims to obtain a general overview of the history of change from the premorbid state in the respondent. All available information should be used.
- Record the time of first noted change - date and age of respondent in years:
  Date: 
  Age: 
- Note first ever symptoms or signs:
  
- Overview of course since then - map on timeline e.g.:

![Timeline Diagram]

- Current time line:
1: POSITIVE SYMPTOMS

1.1 UNUSUAL THOUGHT CONTENT

Delusional Mood and Perplexity (‘Non Crystallized Ideas’)
- Have you had the feeling that something odd is going on that you can’t explain? What is it like?
- Do you feel puzzled by anything? Do familiar surroundings feel strange?
- Do you feel that you have changed in some way?
- Do you feel that others, or the world, have changed in some way?

Ideas of Reference
- Ideas of Reference: Have you felt that things that were happening around you had a special meaning, or that people were trying to give you messages? What is it like? How did it start?

Bizarre Ideas (‘Crystallized Ideas’)
- Made thoughts, feelings, impulses: Have you felt that someone, or something, outside yourself has been controlling your thoughts, feelings, actions or urges? Have you had feelings or impulses that don’t seem to come from yourself?
- Somatic Passivity: Do you get any strange sensations in your body? Do you know what causes them? Could it be due to other people or forces outside yourself?
- Thought Insertion: Have you felt that ideas or thoughts that are not your own have been put into your head? How do you know they are not your own? Where do they come from?
- Thought Withdrawal: Have you ever felt that ideas or thoughts are being taken out of your head? How does that happen?
- Thought Broadcasting: Are your thoughts broadcast so that other people know what you are thinking?
- Thoughts Being Read: Can other people read your mind?
## Unusual Thought Content - Global Rating Scale

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<tr>
<th></th>
<th>Never, absent</th>
<th>Questionable</th>
<th>Mild</th>
<th>Moderate</th>
<th>Moderately severe</th>
<th>Severe</th>
<th>Psychotic and Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No unusual thought content.</td>
<td>Mild elaboration of conventional beliefs as held by a proportion of the population</td>
<td>Vague sense that something is different, or not quite right with the world, a sense that things have changed but not able to be clearly articulated. Subject not concerned/ worried about this experience.</td>
<td>A feeling of perplexity. A stronger sense of uncertainty regarding thoughts than 2.</td>
<td>Referential ideas that certain events, objects or people have a particular and unusual significance. Feeling that experience may be coming from outside the self. Belief not held with conviction, subject able to question. Does not result in change in behaviour.</td>
<td>Unusual thoughts that contain completely original and highly improbable material. Subject can doubt (not held with delusional conviction), or which the subject does not believe all the time. May result in some change in behaviour, but minor.</td>
<td>Unusual thoughts containing original and highly improbable material held with delusional conviction (no doubt). May have marked impact on behaviour.</td>
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**Onset date:** __________  **Offset date:** __________

### Frequency and Duration

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<td>Less than once a month</td>
<td>Once a month to twice a week - less than one hour per occasion</td>
<td>Once a month to twice a week - more than one hour per occasion OR 3 to 6 times a week - less than one hour per occasion</td>
<td>3 to 6 times a week - more than one hour per occasion OR daily - less than one hour per occ.</td>
<td>Daily – more than an hour per occ. OR several times a day</td>
<td>Continuous</td>
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### Pattern of Symptoms

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<td>No relation to substance use noted</td>
<td>Occurs in relation to substance use and at other times as well</td>
<td>Noted only in relation to substance use</td>
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### Level of Distress (In Relation to Symptoms)

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<tbody>
<tr>
<td>0</td>
<td>Not At All Distressed</td>
<td></td>
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<td></td>
<td>Extremely Distressed</td>
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</tbody>
</table>

CAARMS- July 2006
1.2 Non-Bizarre Ideas

Non-Bizarre Ideas ('Crystallized Ideas')

- **Suspiciousness, Persecutory Ideas**: Has anybody been giving you a hard time or trying to hurt you? Do you feel like people have been talking about you, laughing at you, or watching you? What is it like? How do you know this?

- **Grandiose Ideas**: Have you been feeling that you are especially important in some way, or that you have powers to do things that other people can't do?

- **Somatic Ideas**: Have you had the feeling that something odd is going on with your body that you can't explain? What is it like? Do you feel that your body has changed in some way, or that there is a problem with your body shape?

- **Ideas of Guilt**: Do you feel you deserve punishment for anything you have done wrong?

- **Nihilistic Ideas**: Have you ever felt that you, or a part of you, did not exist, or was dead? Do you ever feel that the world does not exist?

- **Jealous Ideas**: Are you a jealous person? Do you worry about relationships that your spouse/girlfriend/boyfriend has with other people?

- **Religious Ideas**: Are you very religious? Have you had any religious experiences?

- **Erotomanic Ideas**: Is anyone in love with you? Who? How do you know this? Do you return his/her feelings?
# Non-Bizarre Ideas - Global Rating Scale

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<th>6</th>
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</thead>
<tbody>
<tr>
<td>Never, absent</td>
<td>Questionable</td>
<td>Mild</td>
<td>Moderate</td>
<td>Moderately severe</td>
<td>Severe</td>
<td>Psychotic and Severe</td>
</tr>
<tr>
<td>No non-bizarre ideas.</td>
<td>Subtle changes that could be reality based. Eg. Very self-conscious.</td>
<td>Increased self-consciousness. Eg. Feeling that others look at the subject, or talk about the subject. Or feeling of increased self-importance. Subject able to question.</td>
<td>Odd or unusual thoughts but whose content is not entirely implausible—may be some logical evidence. More evidence than rating of 3. Content of thoughts not original i.e. jealousy, mild paranoia.</td>
<td>Clearly idiosyncratic beliefs, which although 'possible' have arisen without logical evidence. Less evidence than rating of 3. Eg. Thoughts that others wish the subject harm, which can be easily dismissed. Thoughts of having special powers, which can be easily dismissed.</td>
<td>Unusual thoughts about which there is some doubt (not held with delusional conviction), or which the subject does not believe all the time. May result in some change in behaviour, but minor.</td>
<td>Unusual thoughts containing original and highly improbable material held with delusional conviction (no doubt). May have marked impact on behaviour.</td>
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**Onset date:** ___________  **Offset date:** ___________

## Frequency and Duration

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## Pattern of Symptoms

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<td>Noted only in relation to substance use</td>
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## Level of Distress (In Relation to Symptoms)

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<th>4</th>
<th>5</th>
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</tr>
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<tbody>
<tr>
<td>Not At All Distressed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Extremely Distressed</td>
</tr>
</tbody>
</table>

CAARMS- July 2006
1.3 PERCEPTUAL ABNORMALITIES

Visual Changes
- Distortions, illusions: Is there a change in the way things look to you? Do things somehow look different, or abnormal? Are there alterations in colour, or brightness of objects (things seeming brighter, or duller in colour)? Are there alterations in the size and shape of objects? Do things seem to be moving?
- Hallucinations: Do you have visions, or see things that may not really be there? Do you ever see things that others can’t, or don’t seem to? What do you see? At the time that you see these things, how real do they seem? Do you realise they are not real at the time, or only later?

Auditory Changes
- Distortions, illusions: Is there any change in the way things sound to you? Do things somehow sound different, or abnormal? Does your hearing seem more acute, or have increased sensitivity? Does your hearing seem muted, or less acute?
- Hallucinations: Do you ever hear things that may not really be there? Do you ever hear things that other people seem not to (such as sounds or voices)? What do you hear? At the time you hear these things, how real do they seem? Do you realise they are not real at the time, or only later?

Olfactory Changes
- Distortions, illusions: Does your sense of smell seem to be different, such as more, or less intense, than usual?
- Hallucinations: Do you ever smell things that other people don’t notice? At the time, do these smells seem real? Do you realise they are not real at the time, or only later?

Gustatory Changes
- Distortions, illusions: Does your sense of taste seem to be different, such as more, or less intense, than usual?
- Hallucinations: Do you ever get any odd tastes in your mouth? At the time that you taste these things, how real do they seem? Do you realise they are not real at the time, or only later?

Tactile Changes
- Distortions, illusions, hallucinations: Do you ever get strange feelings on, or just beneath, your skin? At the time that you feel these things, how real do they seem? Do you realise they are not real at the time, or only later?

Somatic Changes
NOTE: Probes also used to rate Impaired Bodily Sensation, p.26
- Distortions, illusions: Do you ever get strange feelings in your body (eg feel that parts of your body have changed in some way, or that things are working differently)? Do you feel/think that there is a problem with some part, or all of your body, i.e. that it looks different to others, or is different in some way? How real does this seem?
- Hallucinations: Have you noticed any change in your bodily sensations, such as increased, or reduced intensity? Or unusual bodily sensations such as pulling feelings, aches, burning, numbness, vibrations?
## Perceptual Abnormalities - Global Rating Scale

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never, absent</td>
<td>Questionable</td>
<td>Mild</td>
<td>Moderate</td>
<td>Moderately severe</td>
<td>Psychotic but not severe</td>
<td>Psychotic and severe</td>
</tr>
<tr>
<td>No abnormal perceptual experience.</td>
<td>Heightened, or dulled perceptions, distortions, illusions (eg lights/shadows). Not particularly distressing. Hypnagogic/hypnopompic experiences</td>
<td>More puzzling experiences: more intense/vivid distortions/illusions, indistinct murmuring, etc. Subject unsure of nature of experiences. Able to dismiss. Not distressing. Derealisation/ depersonalisation</td>
<td>Much clearer experiences than 3 such as name being called, hearing phone ringing etc, but may be fleeting/transient. Able to give plausible explanation for experience. May be associated with mild distress.</td>
<td>True hallucinations i.e. hearing voices or conversation, feeling something touching body. Subject able to question experience with effort. May be frightening or associated with some distress.</td>
<td>True hallucinations which the subject believes are true at the time of, and after, experiencing them. May be very distressing</td>
<td></td>
</tr>
</tbody>
</table>

Onset date: __________________ Offset date: __________________

### Frequency and Duration

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
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</tr>
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<tr>
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<tbody>
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</table>

### Level of Distress (In Relation to Symptoms)

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Not At All Distressed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Extremely Distressed</td>
</tr>
</tbody>
</table>

CAARMS- July 2006
1.4 DISORGANISED SPEECH

NOTE: Probes also used to rate Alogia, p. 16

Subjective Change:
- Do you notice any difficulties with your speech, or ability to communicate with others?
- Do you have trouble finding the correct word at the appropriate time?
- Do you ever use words that are not quite right, or totally irrelevant?
- Have you found yourself going off on tangents when speaking and never getting to the point? Is this a recent change?
- Are you aware that you are talking about irrelevant things, or going off the track?
- Do other people ever seem to have difficulty in understanding what you are trying to say/trouble getting your message across?
- Do you ever find yourself repeating the words of others?
- Do you ever have to use gesture or mime to communicate due to trouble getting your message across? How bad is this?
- Does it ever make you want to stay silent and not say anything?

Objective Rating of Disorganised Speech
- Is it difficult to follow what the subject is saying at times due to using incorrect words, being circumstantial or tangential?
- Is the subject vague, overly abstract or concrete? Can responses be condensed?
- Do they go off the subject often and get lost in their words? Do they appear to have difficulty finding the right words?
- Do they repeat words that you have used or adopt strange words (or ‘non-words’) in the course of regular conversation?
### DISORGANISED SPEECH - GLOBAL RATING SCALE

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<tr>
<th>Level</th>
<th>Description</th>
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<tbody>
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<td>Never, absent</td>
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<tr>
<td>1</td>
<td>Questionable</td>
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<tr>
<td>2</td>
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<tr>
<td>4</td>
<td>Moderately severe</td>
</tr>
<tr>
<td>5</td>
<td>Severe</td>
</tr>
<tr>
<td>6</td>
<td>Psychotic</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Level</th>
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</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal logical speech, no disorganisation, no problems communicating or being understood.</td>
</tr>
<tr>
<td>1</td>
<td>Slight subjective difficulties, e.g. problems getting message across. Not noticeable by others.</td>
</tr>
<tr>
<td>2</td>
<td>Somewhat vague, some evidence of circumstantiality, or irrelevance in speech. Feeling of not being understood.</td>
</tr>
<tr>
<td>3</td>
<td>Clear evidence of mild disconnect ed speech and thought patterns. Links between ideas rather tangential. Increased feeling of frustration in conversation.</td>
</tr>
<tr>
<td>4</td>
<td>Marked circumstantiality, or tangentiality in speech, but responds to structuring in interview. May have to resort to gesture, or mime to communicate.</td>
</tr>
<tr>
<td>5</td>
<td>Lack of coherence, unintelligible speech, significant difficulty following line of thought. Loose association in speech.</td>
</tr>
</tbody>
</table>

**Onset date:** __________  
**Offset date:** __________

### Frequency and Duration

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### Level of Distress (In Relation to Symptoms)

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<td>Not At All Distressed</td>
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<td>100</td>
<td>Extremely Distressed</td>
</tr>
</tbody>
</table>

CAARMS - July 2006
2: COGNITIVE CHANGE - ATTENTION/CONCENTRATION

2.1 SUBJECTIVE EXPERIENCE (HUBER'S BASIC SYMPTOM)

Concentration and Attention Problems:
- Have you had difficulty concentrating (difficulty listening to others, watching television, reading)?
- Is it more of an effort to think about, or concentrate on things?

Selective Attention Problems:
- Is it difficult to pay attention to just one thing?
- Are you distracted by other things easily?
- Have you been feeling overwhelmed, or confused by all the things that have been happening in the environment around you?

Thought Form Problems:
[NOTE: See also Alogia, p. 16]
- Do your thoughts ever seem to stop, get blocked, or disappear (e.g. do you have 'trances', or 'blank spells')? Can you describe this more fully?
- Do you ever experience racing or confused, jumbled thoughts?
- Do other things, as well as your thoughts, seem to stop e.g. attention, hearing, sight, memory, speech, or movement?
- Do you ever lose your sense of personal identity? What do you think was the cause of this?

Comprehension Difficulties:
- Do you have trouble following what others are saying?
- Do you sometimes require sentences to be repeated, especially long sentences?
- Do you sometimes not understand figures of speech and so on?
- Is this a change for you, or have you always had trouble with this?
- Do you ever have trouble picking up the emotional tone of conversations (eg. not recognising sarcasm, or irony)?
- Is it ever hard to understand non-verbal forms of communication i.e. gestures? How bad is this?

Memory Problems:
[NOTE: See also Dissociative Symptoms, p.36]
- Have you had memory problems?
- Have you ever felt as if there were large gaps in your memory?
- Are they present all the time, or do they come and go? Have you noticed if the memory problems come at times of stress?
## Subjective Cognitive Change - Severity Rating Scale

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</thead>
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<tr>
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<td>Mild</td>
<td>Moderate</td>
<td>Moderately severe</td>
<td>Severe</td>
<td>Extreme</td>
</tr>
<tr>
<td>No subjective difficulty with concentration /attention.</td>
<td>Subject aware of some changes, but attributable perhaps to extraneous factors. Subject has difficulty in pinpointing changes.</td>
<td>Mild, but definite problems eg some difficulty concentrating while reading, or watching TV. Concentrating requires more effort. OR Slight impairment in memory, but passing.</td>
<td>Subjectively feeling muddled, or confused, racing, or slowed thoughts, difficulty understanding conversations. Occ. episodes of thought blocking. OR Memory problems more evident but do not interfere with everyday functioning.</td>
<td>Subjective feeling of being unable to think properly, confused, unable to understand others. More regular episodes of thought blocking OR Memory difficulties impair conversation, results in frequent misplacing of items.</td>
<td>Marked inattentiveness, feeling confused and overwhelmed at times, distracted by other things in the environment. Frequent episodes of thought block. OR Memory difficulties noted by others, distressing.</td>
<td>Subject reports extreme difficulty focussing on interview. Interview suspended due to impossibility of patient to concentrate or severe thought blocking. OR Severe memory problems.</td>
</tr>
</tbody>
</table>

### Onset date: ____________________  Offset date: ____________________

### Frequency and Duration

<table>
<thead>
<tr>
<th>0</th>
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<td>Daily – more than an hour per occ. OR Continuous</td>
<td></td>
</tr>
</tbody>
</table>

### Pattern of Symptoms

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</tbody>
</table>

CAARMS - July 2005
2.2 OBSERVED COGNITIVE CHANGE

Observed Inattentiveness During Interview
- Subject appears inattentive - looks away during interview, does not pick up the topic during a discussion, shifts focus of attention.
- Attention may be drawn to noise in adjoining room, objects around the room, interviewer's clothing etc

Observed Inattentiveness During Mental Status Testing
- The subject may perform poorly on simple tests of intellectual functioning in spite of adequate education and intellectual ability.
- This is assessed by having the subject spell the word 'world' backwards and by serial 7s or serial 3s for a series of 5 subtractions.
  - D L R O W
  - 100, 93, 86, 79, 72
  - 100, 97, 94, 91, 88

OBSERVED COGNITIVE CHANGE – SEVERITY RATING SCALE

<table>
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<tr>
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<th>1</th>
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<th>5</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Never, absent</td>
<td>Questionable</td>
<td>Mild</td>
<td>Moderate</td>
<td>Moderately severe</td>
<td>Severe</td>
<td>Extreme</td>
</tr>
<tr>
<td>No abnormalities observed.</td>
<td>Some questionable inattentiveness - may be explained by other events.</td>
<td>Mild problems with concentration. Objectively may be observed to shift focus of attention from interview 1 to 3 times. Not quite understanding what others are saying or the emotional tone of the conversation.</td>
<td>Moderate concentration problems during interview. Mild disruption to flow of interview as a result.</td>
<td>Poor concentration and attention significantly affect ability to perform tasks. Distractibility clearly observed to interfere with flow of the interview.</td>
<td>Severe concentration and attention difficulties. Extremely difficult to conduct interview, or pursue a topic due to preoccupation with irrelevant stimuli.</td>
<td>Inability to concentrate at all. Impossible to conduct interview due to preoccupation with irrelevant stimuli.</td>
</tr>
</tbody>
</table>

CAARMS- July 2006
# 3: Emotional Disturbance

## 3.1 Subjective Emotional Disturbance (Huber's Basic Symptom)

**Impaired Emotional Functioning:**  
**Note:** See also Anhedonia, p. 18; Depression, p. 28

- Have you noticed any change in your feelings, or emotions e.g. feel like you have no feelings, feel your emotions are 'empty', or that your emotions are somehow not genuine?  
- Has there been any change in the way you are using your emotions?  
- Have you still been able to enjoy things, or experience pleasure?  
- Do you find that even when something sad happens, you are no longer able to feel sadness? Or when something happy happens, you can no longer feel happy?

**Change in Affect:**

**Facial expressions:**  
- Have you noticed any change in your facial expressions?  
- Have people commented on your facial expression, saying it is blank, or hard to know what you are thinking?

**Eye contact:**  
- Has there been a change in the way you interact with other people e.g. do you find it hard to look at people when you speak to them?  
- Has anyone commented on this?

**Speech:**  
- Have you noticed a change in the way you talk, such as your voice becoming monotonous?  
- Have people told you that you have a monotonous way of talking?  
- Do they seem to find you boring?

**Inappropriate affect:**  
- Have you ever felt different on the inside from the way you look to others?  
- Like your appearance was uncoordinated with your emotions? Would you smile, or laugh when talking about something that was sad, or not funny at all?
### Subjective Emotional Disturbance - Severity Rating Scale

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
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<td>Moderately severe</td>
<td>Severe</td>
<td>Extreme</td>
</tr>
<tr>
<td></td>
<td>No subjective change in feelings, or emotions.</td>
<td>Subjectively sporadic, mild, but definite problems reported eg not able to enjoy things as much as previously. Some feeling of blunting of emotional responses. Affect is inappropriate, but not sustained.</td>
<td>Subjectively more frequent, or continuous problems. Some feeling of blunting of emotional responses. More pervasive feeling of inappropriate affect, but subject able to control somewhat.</td>
<td>Subject describes more marked change in emotions eg not able to express, or experience feelings as before. Sense of distance when with others. Inappropriate affect more difficult to hide from others.</td>
<td>Subject describes feeling of having no feelings, or emotions feel empty, or not genuine. Unable to feel sad at all. Severe degree of distance from others. Inappropriate affect interferes with relationships.</td>
<td>Subject reports constant emotional blunting, OR Inappropriate affect.</td>
<td></td>
</tr>
</tbody>
</table>

**Onset date:** ______________  **Offset date:** ______________

### Frequency and Duration

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CAARMS- July 2006
3.2 OBSERVED BLUNTED AFFECT

**NOTE:** Incorporate informant information as well as interviewer’s impression.

- Rate observed evidence of blunting of affect. For example, diminished facial expressions, reduced emotional tone in speech, reduced expressive movements and gestures.
- The rater may also feel a diminished ability to engage the subject.

### OBSERVED BLUNTED AFFECT – SEVERITY RATING SCALE

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
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<th>3</th>
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</thead>
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<tr>
<td>Never, absent</td>
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<td>Moderate</td>
<td>Moderately severe</td>
<td>Severe, not psychotic</td>
<td>Extreme/psychotic</td>
</tr>
<tr>
<td>No abnormalities observed by interviewer, or others.</td>
<td>Slight degree of constriction of affect may be observed.</td>
<td>Observable constriction of emotional field. Avoidance or failure to display feelings. Reduced emotional expressivity. Interviewer feels a sense of ‘distance’, or decreased rapport.</td>
<td>More marked degree of dullness or blockade. Definite decrease in sense of rapport observed by interviewer. May have been reported, or commented on by informants.</td>
<td>Minimal evidence of affective display</td>
<td>Gross blunting of affect. No spontaneous emotional expression observed during interview. Definitely reported by informants.</td>
<td></td>
</tr>
</tbody>
</table>

Onset date: ___________________________  Offset date: ___________________________
(Do not score if relying on interviewer’s report only- -3 on database)

**Frequency and Duration**
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CAARMS- July 2006
### 3.3 Observed Inappropriate Affect

**NOTE:** Incorporate informant information as well as interviewer’s impression

- Also rate clear-cut inappropriate affect (affect clearly discordant from the content of speech, or ideation (e.g. giggling when speaking of something sad).

### Observed Inappropriate Affect - Severity Rating Scale

<table>
<thead>
<tr>
<th>0</th>
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<td>Extreme</td>
</tr>
<tr>
<td>No abnormalities observed by interviewer, or others.</td>
<td>Mild inappropriate affect during interview, or reported occasionally by others. Subject appears able to control.</td>
<td>More pervasive inappropriate emotion displayed. Does not dominate interview. Subject appears able to control somewhat.</td>
<td>More often reported by others - distracting during interview.</td>
<td>Inappropriate affect reported frequently. Interferes with social relationships and flow of interview.</td>
<td>Inappropriate affect throughout interview. Severely impacts on ability to conduct interview. Reported by others as occurring most of the time.</td>
<td></td>
</tr>
</tbody>
</table>

**Onset date:** ____________  **Offset date:** ____________
(Do not score if relying on interviewer’s report only- Enter-3 on database)

**Frequency and Duration**
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CAARMS- July 2006
4: NEGATIVE SYMPTOMS

4.1 ALOGIA

NOTE: Refer also to Cognitive Change, p.9; Disorganised Speech, p.7

- Have you noticed problems trying to form conversations - i.e. hard to find words, thought blocking?

- Are the subject’s responses to questions vague, or convey little information? Does the subject take a long time to respond to questions, but when prompted, displays an awareness of the question?

**ALOGIA - SEVERITY RATING SCALE**

<table>
<thead>
<tr>
<th>0</th>
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<tr>
<td>No observed, or reported changes in speech.</td>
<td>Subject unsure about recent changes. Changes may be attributable to external factors, but subject unsure.</td>
<td>Very mild changes in ability to speak spontaneously. Subject reports feeling “blocked” in their thinking. Difficulty finding words for thoughts. Not reported by others.</td>
<td>Difficulty expressing self in words - finding words, or more regular instances of thought blocking. Observable by others, but not constant difficulty. Subject responds to prompting.</td>
<td>More marked poverty of speech, or thought blocking. Does not significantly interfere with school, or work functioning.</td>
<td>Unable to express oneself adequately, or severe thought blocking. May experience infrequent periods of mutism as a result of word finding and expression difficulties.</td>
<td>Marked poverty of speech or thought blocking. Seriously hinders flow of interview. Subject may be mute at times. Interferes significantly with ability to perform in social, occupation and educational settings.</td>
</tr>
</tbody>
</table>

**Onset date:** ___________  **Offset date:** ___________

**Frequency and Duration**

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CAARMS- July 2006
### 4.2 Avolition/Apathy (Huber’s Basic Symptom)

**Subjective Experience:**
- Have you felt lacking in energy, mental and physical? Are you tired, or lacking in motivation, or ‘get up and go’? Lack of will power? Lack of physical strength?
- To what extent does this interfere with activities such as going to school/work and other everyday tasks? How are you spending your days?

**Observed Avolition/Apathy:**

**NOTE:** Refer also to Disorganising/Odd/Stigmatising Behaviours, p.21
- Has the subject indicated difficulty maintaining the level of his/her usual social, or occupational/educational commitments?
- Does the subject appear to be looking after him/herself adequately-cleanliness/hygiene/general self-care?

**Avolition/Apathy - Severity Rating Scale**

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<tbody>
<tr>
<td>Never, absent</td>
<td>Subject unsure about recent changes. Changes may be attributable to external factors, but unclear.</td>
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<td>Feeling fatigued, things are an effort. May not initiate activities as much as previously. Still able to perform everyday tasks. Does not interfere with schoolwork, or work attendance.</td>
<td>Feeling of reduced energy, or will power. Decreased attendance at school/work, or not performing usual tasks to usual ability. Not everyday and not reported by others.</td>
<td>More marked reduction in energy/ motivation. Some interference with normal functioning eg tasks take longer to do, subject doesn’t bother to do some things. May miss school, or work a few times a week or frequently run late.</td>
<td>Daily reduction in energy, drive, will power, physical strength, or motivation. Interferes with normal functioning eg missing school, or work most day. Spends significant portions of time lying around. Clear impact on personal hygiene</td>
<td>Extreme and continuous disability eg unable to perform normal tasks, confined to house, no will power, or volition. Unable to attend school/work at all due to motivation. Marked impact on personal hygiene</td>
</tr>
</tbody>
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**Onset date:**

**Offset date:**

### Frequency and Duration

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CAARMS- July 2006
4.3 ANHEDONIA

NOTE: Refer also to Depression, p. 29

- Have you been able to enjoy social activities/work/study as much as usual?
- Have you noticed a decrease in your level of interest in things you usually enjoy?
- Has this interfered with your ability to perform activities, e.g. going to school/work/participating in events?

ANHEDONIA - SEVERITY RATING SCALE

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<td>Mild</td>
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<tr>
<td>No observed, or reported changes in affect, speech, activity level, or attentiveness.</td>
<td>Some mild decrease in interest in events, but may be attributable to external cause (i.e. dislikes topic at school).</td>
<td>Some mild decrease in interest or enjoyment of activities.</td>
<td>Moderate reduction in interest or enjoyment of activities such as school/work. May affect school/work performance.</td>
<td>Some regular experience of pleasure or humour but decreased in extent and quality. May impact on work/school attendance. Others concerned by associated withdrawal and isolation.</td>
<td>Rarely gains sense of enjoyment/interest from tasks. At times able to enjoy something, but short lived. Poor attendance at school/work. Very noticeable by others.</td>
<td>No enjoyment or interest at all in tasks. Marked lack of interest. Isolated and withdrawn.</td>
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Onset date: ______________ Offset date: ______________

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CAARMS- July 2006
5: BEHAVIOURAL CHANGE
Consider informant information as well as subjective report

5.1 SOCIAL ISOLATION
- Have you stayed at home more often than usual recently? Has this been by choice?
- Have you felt uncomfortable around others recently?
- Have you wanted to be alone more than usual recently? Has there been a reason for this? Have others commented on this?
- Have you missed important social events/school/work due to this?

Questions for informants:
- Has the subject been staying at home, perhaps in their room alone, more often than in the past? If so, do you know the reason for this?
- Have they missed social events/work/school due to this?
- Do they appear to want to spend time alone at present (more so than usual)?

### SOCIAL ISOLATION - SEVERITY RATING SCALE

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- Never, absent: No change in level of social activity.
- Questionable: Subject feels that she/he does not want to fulfill all social/role functions. Wanting to be alone, but able to motivate self.
- Mild: Isolating self at times, but not marked. Able to fulfill main role functions involving interactions with others. May miss some social activities.
- Moderate: Intolerant of being around others for long periods of time. Social withdrawal commented on by others. May miss 2-3 days a week of school/work because of wanting to be alone.
- Moderately severe: Missing more days than not of work/school, spending greater part of day alone.
- Severe: Isolated from others for extended periods (i.e. days)

Onset date: __________ Offset date: __________

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CAARMS - July 2006
5.2 IMPAIRED ROLE FUNCTION

**NOTE:** See also Depression, p. 29

- Have you been able to attend school/work as usual recently?
- Has your school/work performance dropped recently?
- Have you been less interested in your work/school recently? Have others commented on this? Is there a reason for this? (Phrase questions appropriately i.e. for job seekers etc)

**Questions for Informants:**
- Have you noticed a change in attendance at work/school recently?
- Does the subject appear as capable at achieving normal tasks as usual?

### IMPAIRED ROLE FUNCTION - SEVERITY RATING SCALE

<table>
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<tr>
<th></th>
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</tr>
<tr>
<td>No recent change in role function.</td>
<td>Subject reports mild impairment in performance of usual activities. Not noted by informants.</td>
<td>Usual tasks performed with less care than usual. Missing occasional day of work/school. Noted as mild by informants.</td>
<td>Around half of usual time spent on normal daily tasks. Decreased quality of task performance noted by others.</td>
<td>Marked impairment of role functioning. Spending about half of day in aimless activity.</td>
<td>Subject attempting no role function whatsoever</td>
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**Onset date:** ____________  **Offset date:** ____________

### Frequency and Duration

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CAARMS- July 2006
5.3 Disorganising/Odd/Stigmatising Behaviour

NOTE: See also Avolition, p.17; OCD, p.34; Social isolation, p. 19

- Has there been anything about your lifestyle recently that others might regard as unusual, or odd? (Attempt to sensitively assess peculiar behaviours such as hoarding, talking to self, odd movements etc.)
- Have you been able to look after yourself as well as usual (Bathing, eating etc)? Has this been reported by others?

Questions for Informants:
- Have you noticed the subject behaving in an odd manner recently?
- Have you felt there is something strange about their behaviour? Has this been commented on by others?
- Have you noticed that they are hoarding goods, talking to self, moving in a bizarre fashion etc?

Disorganised/Odd/Stigmatising Behaviour - Severity Rating Scale

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<tr>
<td>No change in behaviour noted by subject, informants, or in interview.</td>
<td>Some reduction in self care, social isolation, but not marked. Subject able to motivate self to rectify this change. Slightly odd behaviour that would not normally attract attention of others, or conducted in private.</td>
<td>May require pressure from others to maintain social/occupational commitments, or self care. Able to be motivated. Occasional odd behaviour that is noticeable by others (ie giggling to self).</td>
<td>Mildly eccentric behaviour - clearly noticeable by others (ie talking to self/hoarding Not constant.</td>
<td>Clearly bizarre behaviour that attracts attention of others. Sometimes resulting in intervention by others.</td>
<td>Very poor self-care. Eccentric behaviours dominate clinical picture. May result in intervention by others. Odd behaviours may have negative impact on physical health. Extreme social isolation.</td>
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5.4 Aggression/Dangerous Behaviour

- Have you been feeling angry, or irritable recently? Has there been a reason for this? Have you felt more irritated than usual at small things? Have you been in more arguments with others than usual recently? Have you been taking more risks (i.e. when driving) recently than usual? Have others commented that your behaviour is becoming risky, or unsafe? Have you felt like striking out at people or objects recently (more so than usual)?
- Have you become so angry at someone that you have had thoughts of hurting them, or destroying their property? Have you acted on these thoughts?

Questions for Informants:
- Has the subject been acting in an aggressive or dangerous manner recently? Have there been any recent episodes of anger outbursts/physical confrontation? Is this how the subject normally behaves? Have others commented on a change in their level of anger, or irritability? Has the subject destroyed property lately (in association with anger)? Have you felt safe with the subject recently (i.e. when driving, at otherwise normal times)?

Aggression/Dangerous Behaviour - Severity Rating Scale

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<tr>
<td>No aggressive, or dangerous behaviour reported by the subject or others.</td>
<td>Slight irritability but not associated with rise in aggressive behaviour. May be attributed to events by subject.</td>
<td>More marked increase in irritability/anger towards self/others. May be expressed verbally, or physically in restrained manner (i.e. punching pillow etc). May be noted by subject only.</td>
<td>Marked increase in irritability towards others expressed in increased propensity to verbal confrontations with threat of physical aggression. Noted by others and subject.</td>
<td>Aggressive behaviour results in property damage, or harm to others. Subject reports some level of control over anger.</td>
<td>Dangerousness in conjunction with anger at very destructive level, resulting in some considerable physical damage to others, or property. Dominates clinical picture. May attract attention of police etc.</td>
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CAARMS- July 2006
6: MOTOR/PHYSICAL CHANGES

6.1 SUBJECTIVE COMPLAINTS OF IMPAIRED MOTOR FUNCTIONING
(HUBER’S BASIC SYMPTOM)

Disorganised Movement:
- Have you noticed any change in the way you are moving e.g. clumsiness, lack of coordination, trouble organising your activities, or movements, loss of spontaneous movements?
- Have you noticed if your ability to perform some movements is distracted by other things?
- Does it require more effort or energy to perform some movements?

Mannerisms, Posturing:
- Have you developed any new movements, or poses (e.g. developed a nervous habit, a characteristic way of doing something, mimicking others, assuming certain postures)? What is your explanation for this?

SUBJECTIVE MOTOR CHANGE - SEVERITY RATING SCALE

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<tr>
<td>No abnormal movements, or somatic difficulties reported by subject.</td>
<td>Mild changes only. Feeling clumsier, more uncoordinated than usual, feeling slightly slowed down. Occasional grimace, or mildly unusual gait</td>
<td>Experiences noted in column 1, but the subject feels a more noticeable change. Reports control over</td>
<td>Changes such as loss of coordination. Movements distracted by other things. Different gait, new poses, tics or mannerisms Loss of some previous abilities.</td>
<td>Experiences noted in column 4, but more distressing. May include episodes of mutism, bizarre postures, copying others movements.</td>
<td>Clearly distorted, or idiosyncratic movements, which dominate the clinical picture. Gross mannerisms, bizarre postures. Mute, or almost mute, with only very occasional spontaneous movements.</td>
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CAARMS- July 2006
**6.2 INFORMANT REPORTED OR OBSERVED CHANGES IN MOTOR FUNCTIONING**

**Disorganised Movement:**
- Have you noticed any change in the way you are moving e.g. clumsiness, lack of coordination, trouble organising your activities, or movements, loss of spontaneous movements?
- Have you noticed if your ability to perform some movements is distracted by other things?
- Does it require more effort or energy to perform some movements?

**Mannerisms, Posturing:**
- Have you developed any new movements, or poses (e.g. developed a nervous habit, a characteristic way of doing something, mimicking others, assuming certain postures)? What is your explanation for this?

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**OBSERVED MOTOR CHANGE - SEVERITY RATING SCALE**

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<tr>
<td>0</td>
<td>Never, absent</td>
</tr>
<tr>
<td>1</td>
<td>Questionable</td>
</tr>
<tr>
<td>2</td>
<td>Mild</td>
</tr>
<tr>
<td>3</td>
<td>Moderate</td>
</tr>
<tr>
<td>4</td>
<td>Moderately severe</td>
</tr>
<tr>
<td>5</td>
<td>Severe</td>
</tr>
<tr>
<td>6</td>
<td>Extreme</td>
</tr>
</tbody>
</table>

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CAARMS- July 2006
6.3 Subjective Complaints of Impaired Bodily Sensation
(Huber’s Basic Symptom)

**NOTE:** Refer also to p. 5 Perceptual Abnormalities

- Subjects say that there is something wrong with their bodily sensations.
- This includes disagreeable, but qualitatively normal sensations e.g. pulling sensations, aches, pains, itching, burning, numbness, or qualitatively abnormal, unusual, or bizarre sensations may be described such as 'rustling' sensations in the eyes, vibrations, crawling sensations.
- Do you ever get strange feelings in your body (e.g. feel that parts of your body have changed in some way, or that things are working differently)?
- Do you feel/think that there is a problem with some part, or all of your body, i.e. that it looks different to others, or is different in some way? How real does this seem?

**Impaired Bodily Sensation - Severity Rating Scale**

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent</td>
<td>Questionable</td>
<td>Mild, slight differences in bodily sensations.</td>
<td>Moderate</td>
<td>Moderately severe</td>
<td>Severe</td>
<td>Extreme</td>
</tr>
<tr>
<td>Subject reports no change noticed in bodily sensations.</td>
<td>Subject notices occasional slight differences in bodily sensations.</td>
<td>More intense changes to bodily sensations reported.</td>
<td>Less able to ignore.</td>
<td>Occasional bizarre bodily sensation.</td>
<td>Subject reports more unusual, or bizarre sensations.</td>
<td>Subject reports extremely bizarre and unusual bodily sensations.</td>
</tr>
</tbody>
</table>

**Onset date:** __________

**Offset date:** __________

**Frequency and Duration**

<table>
<thead>
<tr>
<th>0</th>
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<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent</td>
<td>Less than once a month</td>
<td>Once a month to twice a week - less than one hour per occasion</td>
<td>Once a month to twice a week - more than one hour per occasion OR 3 to 6 times a week - less than one hour per occasion</td>
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<td>Daily - more than an hour per occ. OR several times a day</td>
<td>Continuous</td>
</tr>
</tbody>
</table>

**Pattern of Symptoms**

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>No relation to substance use noted</td>
<td>Occurs in relation to substance use and at other times as well</td>
<td>Noted only in relation to substance use</td>
</tr>
</tbody>
</table>

CAARMS - July 2006
6.4 SUBJECTIVE COMPLAINTS OF IMPAIRED AUTONOMIC FUNCTIONING

(HUBER'S BASIC SYMPTOM)

Subjects may complain of something wrong with one, or more of their autonomic systems such as:
- The feeling of the heart racing, or going too slow, breathing too fast, or too deeply,
- Nausea,
- Increased sensitivity to the weather,
- Having to urinate more often, constipation,
- Poor sleep etc.

<table>
<thead>
<tr>
<th>IMPAIRED AUTONOMIC FUNCTIONING: SEVERITY RATING SCALE</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>Nothing reported.</td>
</tr>
</tbody>
</table>

Onset date: __________ Offset date: __________

Frequency and Duration

| 0 |Absent | 1 | Less than once a month | 2 | Once a month to twice a week | 3 | Once a month to twice a week – more than one hour per occasion OR 3 to 6 times a week – less than one hour per occasion | 4 | 3 to 6 times a week – more than an hour per occasion OR daily – less than an hour per occ. | 5 | Daily – more than an hour per occ. OR several times a day | 6 | Continuous |

Pattern of Symptoms

| 0 | No relation to substance use noted | 1 | Occurs in relation to substance use and at other times as well | 2 | Noted only in relation to substance use |

CAARMS- July 2006
7: GENERAL PSYCHOPATHOLOGY

7.1 MANIA

NOTE: See also Dangerous Behaviour/Aggression, p. 22

- Would you describe your mood as 'high', or 'hyper' recently?

- Have you been feeling excessively cheerful and had more energy than usual? How long has this feeling lasted?

- Have you felt out of control at these times?

- Has this feeling been in response to a substance, or event that has occurred (i.e. finished exams, new boyfriend/girlfriend etc)?

- Have you been able to stay awake doing things for longer periods of time than usual?

- Have you been sleeping less than usual?

- Have you found yourself spending more money than usual, or acting in ways you would not normally (i.e. heightened sexual drive, reckless behaviour etc)?

- Have you found your self, or have others described you, talking more than usual and faster than usual?

- Have people commented on your mood, or energy, saying you seem more energetic than usual, or out of control?

- Have you been feeling more irritable than usual recently? Has there been a reason for this?

- Have you been feeling better about yourself recently?

- Have you felt that you are special in some way, or have special powers, or skills?

CAARMS- July 2006
### MANIA - SEVERITY RATING SCALE

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never, absent</td>
<td>Questionable</td>
<td>Mild</td>
<td>Moderate</td>
<td>Moderately severe</td>
<td>Severe</td>
<td>Extreme</td>
</tr>
<tr>
<td>No observed, or reported elevation in mood.</td>
<td>No change in self-opinion/energy.</td>
<td>Cheerful without much reason.</td>
<td>Unaccountable feelings of well-being that persist or mild lability in mood.</td>
<td>Evidence of over-confidence with no real reason - within normal limits.</td>
<td>Reports excessive feelings of well-being, or cheerfulness without underlying reason.</td>
<td>More persistent feelings of optimism, happiness, or elevated mood.</td>
</tr>
<tr>
<td>&amp;/OR Some mild irritability</td>
<td>&amp;/OR</td>
<td>&amp;/OR</td>
<td>&amp;/OR</td>
<td>&amp;/OR</td>
<td>&amp;/OR</td>
<td>&amp;/OR</td>
</tr>
<tr>
<td>Moderate irritability</td>
<td></td>
<td></td>
<td></td>
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</table>

**Onset date:**  
**Offset date:**

### Frequency and Duration

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</tr>
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<tbody>
<tr>
<td>Absent</td>
<td>Less than once a month</td>
<td>Once a month to twice a week - less than one hour per occasion</td>
<td>Once a month to twice a week - more than one hour per occasion OR 3 to 6 times a week - less than one hour per occasion</td>
<td>3 to 6 times a week - more than an hour per occasion OR daily - less than one hour per occasion</td>
<td>Daily - more than an hour per occ. OR several times a day</td>
<td>Continuous</td>
</tr>
</tbody>
</table>

### Pattern of Symptoms

<table>
<thead>
<tr>
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<th>2</th>
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</thead>
<tbody>
<tr>
<td>No relation to substance use noted</td>
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<td>Noted only in relation to substance use</td>
</tr>
</tbody>
</table>
7.2 DEPRESSION

NOTE: Refer also to: Aversion, p.17; Anhedonia, p.18; Role Functioning, p.20; Suicidality, p.31

- How would you describe your mood recently?

- Have you been feeling sad, or low? How often have you felt this way?

- Out of 10, what would be your average mood? Your lowest mood?

- Have you been able to enjoy activities, or feel good about yourself at all?

- How have you been feeling about the future (assess helplessness/hopelessness)?

- Has your interest in activities/events been lower than usual?

- Have you been able to complete, or start tasks you have been set (assess motivation)?

- How has your sleep been recently (assess change in sleep pattern/insomnia)?

- What has your appetite been like recently? Have you lost any weight?

- Have any events occurred recently that might account for these feelings (death/relationship issues/job/school)?
## DEPRESSION - SEVERITY RATING SCALE

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Never, absent</td>
<td>Questionable</td>
<td>Mild</td>
<td>Moderate</td>
<td>Moderately severe</td>
<td>Severe</td>
<td>Extreme</td>
</tr>
<tr>
<td></td>
<td>No reported depressed mood. No physical signs of depression.</td>
<td>Some feelings of sadness. Does not dominate clinical picture. Able to distract self from depressive thoughts. Depressive themes not spontaneously volunteered.</td>
<td>Evidence of more sustained lowered mood. More difficult to shift mood. Lowered mood may be impacting on level of motivation, but not significantly interfering with role functioning. May be slightly tearful, or sad expression in interview.</td>
<td>Stronger observational evidence of lowered mood. Reduced ability to react to pleasurable events. More regular 'tearful episodes'.</td>
<td>Severe depression - mood not able to be shifted. No evidence of delusional component. Some suicidality, but not acted upon. Biological changes consistent with lowered mood evident (appetite/sleep disturbance). Very low energy.</td>
<td>Abject misery. Delusional component to mood - i.e. nihilistic. More marked feelings of suicidality and associated behaviour.</td>
<td></td>
</tr>
</tbody>
</table>

**Onset date:** ____________  **Offset date:** ____________

## Frequency and Duration

<table>
<thead>
<tr>
<th></th>
<th>0</th>
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<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Absent</td>
<td>Less than once a month</td>
<td>Once a month to twice a week - less than one hour per occasion</td>
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<td>3 to 6 times a week - more than an hour per occasion OR daily - less than an hour per occ.</td>
<td>Daily - more than an hour per occ. OR several times a day</td>
<td>Continuous</td>
</tr>
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## Pattern of Symptoms

<table>
<thead>
<tr>
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<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No relation to substance use noted</td>
<td>Occurs in relation to substance use and at other times as well</td>
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</tr>
</tbody>
</table>

CAARMS - July 2006
7.3 SUICIDALITY AND SELF HARM

- Have you had any thoughts recently about harming, or killing yourself? How often have you felt this way?
- Have you had any thoughts of what you would do to achieve this?
- Have you acted on those thoughts at all? What happened?

**SUICIDALITY- SEVERITY RATING SCALE**

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Never, absent</td>
<td>Questionable</td>
<td>Mild</td>
<td>Moderate</td>
<td>Moderately severe</td>
<td>Severe</td>
<td>Extreme</td>
</tr>
<tr>
<td></td>
<td>Not present.</td>
<td></td>
<td>Occasional thoughts of being tired of living.</td>
<td>Feeling of being better off dead.</td>
<td>Thoughts of suicide more frequent with associated plan.</td>
<td>Clear expression of wanting to kill self.</td>
<td>Specific plan and attempt. OR Serious attempt that clearly could have been fatal.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Occasional thought of self-harm.</td>
<td>Suicidal thoughts, with only vague plan.</td>
<td>May be more seriously considering attempt with specific plan.</td>
<td>OR Potentialy serious, or lethal attempt with knowledge of possible rescue.</td>
<td>OR Impulsive attempts using non-lethal method, or with knowledge of potential for being found.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No suicidal thoughts, or plans.</td>
<td>Able to be distracted from thoughts with some effort.</td>
<td>OR Minor actions of self-harm (slight scratches etc).</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Onset date: ______________ Offset date: ______________

**Frequency and Duration**

<table>
<thead>
<tr>
<th></th>
<th>0</th>
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<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Absent</td>
<td>Less than once a month</td>
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</tr>
</tbody>
</table>

**Pattern of Symptoms**

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No relation to substance use noted</td>
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</tr>
</tbody>
</table>

CAARMS- July 2006
7.4 Mood Swings/Lability

- Have you experienced mood swings recently?
- Have you felt that your moods have been up and down for no apparent reason?
- Do you find yourself happy one moment, and sad the next (or irritable), with no explanation?
- How often does this happen?
- Has this occurred in response to drugs, or events that have happened? Have others commented on this?
- How often has this occurred?

Mood Swings - Severity Rating Scale

<table>
<thead>
<tr>
<th></th>
<th>Never, absent</th>
<th>Questionable</th>
<th>Mild</th>
<th>Moderate</th>
<th>Moderately severe</th>
<th>Severe</th>
<th>Extreme</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No evidence, or reported mood swings.</td>
<td>Subject reports feeling mood changes more easily than usual.</td>
<td>More marked changes in response to external events.</td>
<td>Feeling that mood is out of control some of the time.</td>
<td>Not noticed/report-ed by others.</td>
<td>Mood swings experienced more days than not.</td>
<td>Subject reports that mood changes constantly and completely out of control.</td>
</tr>
</tbody>
</table>

Onset date: __________________ Offset date: __________________

Frequency and Duration

<table>
<thead>
<tr>
<th></th>
<th>0</th>
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<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
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<td>Less than once a month</td>
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Pattern of Symptoms

<table>
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<th></th>
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<th>2</th>
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</tr>
</tbody>
</table>

CAARMS- July 2006
### 7.5 Anxiety

- Have you been feeling nervous, or anxious recently? Has there been a reason for this? How often have you felt this way?
- How long does this feeling remain for?
- Have you felt panicky lately?
- Have you had times when you have felt breathless, heart racing, sweaty palms, tingling fingers, for no apparent reason?
- Do you have a phobia/are you afraid of dogs, spiders, enclosed places, crowds etc?
- Have you felt nervous around others recently (differentiate social anxiety from suspiciousness)?

### Anxiety - Severity Rating Scale

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score</td>
<td>Never, absent</td>
<td>Questionable</td>
<td>Mild</td>
<td>Moderate</td>
<td>Moderately severe</td>
<td>Severe</td>
<td>Extreme</td>
</tr>
<tr>
<td></td>
<td>No evidence, or reporting of anxiety.</td>
<td>Minor worries. Able to distract self from these. &amp;/OR Mild physical signs of anxiety.</td>
<td>Moderate concerns, but level of anxiety is within appropriate range for event &amp;/OR Moderate physical symptoms of anxiety.</td>
<td>Level of anxiety interfering slightly with normal activities. Some preoccupation with trigger. &amp;/OR More marked physical signs of anxiety.</td>
<td>More marked preoccupation with fears, sense of dread. &amp;/OR Intrusive, distressing physical symptoms of anxiety.</td>
<td>Level of anxiety disabling, feeling of panic, terrified.</td>
<td></td>
</tr>
</tbody>
</table>

**Onset date:** __________________**Offset date:** __________________

**Frequency and Duration**

<table>
<thead>
<tr>
<th></th>
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<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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<tr>
<td>Score</td>
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**Pattern of Symptoms**

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<thead>
<tr>
<th></th>
<th>0</th>
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</tr>
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<tbody>
<tr>
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</tr>
</tbody>
</table>

CAARMS- July 2006
### 7.6 OCD Symptoms

- Do you have distressing, or intrusive thoughts that go round and round in your head that you cannot stop?
- Do you have any repetitive behaviours that you feel compelled to perform?
- Do you have anything that you do to stop ‘bad things’ from occurring (rituals/superstitions etc)?
- Do you have to have things a certain way, or you feel extremely anxious?
- Do you repeatedly check things, like light switches/gas/electrical appliances are switched off/doors locked etc?

<table>
<thead>
<tr>
<th>OCD Symptoms - Severity Rating Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>0</strong></td>
</tr>
<tr>
<td>Never, absent</td>
</tr>
<tr>
<td>No obsessional thoughts, or ruminations. No compulsive behaviour.</td>
</tr>
</tbody>
</table>

**Onset date:** __________  
**Offset date:** __________

### Frequency and Duration

<table>
<thead>
<tr>
<th>0</th>
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<th>2</th>
<th>3</th>
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<tbody>
<tr>
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CAARMS- July 2006
**7.7 Dissociative Symptoms**

**Depersonalisation:**
Have you experienced yourself as being unreal, as if you were outside your own body?
Or that part of your body did not belong to you?

**Derealisation:**
NOTE: See also Nihilistic Ideas, p.3
Have you had the feeling that things around you were unreal?

**Dissociative Memory Problems:**
NOTE: See also Cognitive Change, p.9
Have you ever found yourself a long way from your usual range of travel without any memory of how you got there?
Were you under stress then?

**Dissociative Symptoms - Severity Rating Scale**

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Never, absent</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Questionable</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mild</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Moderate</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Moderately severe</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Severe</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Extreme</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No reported feelings of depersonalisation/ dissociation.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild feeling of depersonalisation/ derealisation.</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Not distressing, or distracting.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>More marked dissociative experiences.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Some concern expressed by subject about these, but not marked concern.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dissociative experiences associated with heightened concern/ Distress about these experiences.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distress as a result of dissociative experiences. Interferes somewhat with usual activities (i.e. has to leave work/school/social situation).</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feelings of depersonalisation/derealisation on extremely distressing. Feeling of extreme distance from others. Marked periods of time when subject not able to describe what they have been doing, where they have been etc.</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

**Onset date:** ___________  **Offset date:** ___________

**Frequency and Duration**

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Absent</strong></td>
<td>Less than once a month</td>
<td>Once a month to twice a week - less than one hour per occasion</td>
<td>Once a month to twice a week - more than one hour per occasion</td>
<td>3 to 6 times a week - more than one hour per occasion OR Daily - less than one hour per occasion</td>
<td>3 to 6 times a week - more than an hour per occasion OR Daily - more than an hour per occ. OR several times a day</td>
<td>Continuous</td>
<td></td>
</tr>
</tbody>
</table>

**Pattern of Symptoms**

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No relation to substance use noted</strong></td>
<td>Occurs in relation to substance use and at other times as well</td>
<td>Noted only in relation to substance use</td>
<td></td>
</tr>
</tbody>
</table>

CAARMS- July 2006
### 7.8 Impaired Tolerance to Normal Stress

**Huber’s Basic Symptom**

- Have you noticed a change in the way you have been coping with everyday stress?
- Have you felt less able to cope with, or tolerate everyday stress than before?
- When subjected to everyday stressors have you found yourself becoming excitable, uneasy, tense, nervous or anxious?
- Have you found that ordinary stressors increase other difficulties you have been experiencing?

#### Impaired Tolerance to Stress - Severity Rating Scale

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never, absent</td>
<td>Questionable</td>
<td>Mild</td>
<td>Moderate</td>
<td>Moderately severe</td>
<td>Severe</td>
<td>Extreme</td>
</tr>
<tr>
<td>No subjectively impaired tolerance to normal stress.</td>
<td></td>
<td>Mild, or rare feeling of not coping as well as before.</td>
<td>Feeling mildly stressed in response to situations which would normally be coped with easily. Mild anxiety with everyday stressors, but still able to cope with them.</td>
<td>More marked feeling of high anxiety, or tension with everyday stressors, but able to perform everyday tasks. Feeling unable to cope with more stressful situations. May feel anxious for no reason infrequently.</td>
<td>Feelings of high anxiety, or tension with everyday stressors. Sometimes anxious for no reason at all.</td>
<td>Extreme disability eg. even trivial events, or minor concerns result in feelings of being overwhelmed and panicked. Very anxious all of the time, even if there is no apparent reason. Unable to adapt to novel situations.</td>
</tr>
</tbody>
</table>

**Onset date:** _____________ **Offset date:** _____________

#### Frequency and Duration

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent</td>
<td>Less than once a month</td>
<td>Once a month to twice a week – less than one hour per occasion</td>
<td>Once a month to twice a week – more than one hour per occasion OR 3 to 6 times a week - less than one hour per occasion</td>
<td>3 to 6 times a week - more than one hour per occasion OR daily - less than an hour per occ.</td>
<td>Daily – more than an hour per occ. OR several times a day</td>
<td>Continuous</td>
</tr>
</tbody>
</table>

#### Pattern of Symptoms

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>No relation to substance use noted</td>
<td>Occurs in relation to substance use and at other times as well</td>
<td>Noted only in relation to substance use</td>
</tr>
</tbody>
</table>

CAARMS - July 2006
## 8: Inclusion Criteria

### Intake Criteria Checklist

#### Group 1: Vulnerability Group

This criterion identifies young people at risk of psychosis due to the combination of a trait risk factor and a significant deterioration in mental state and/or functioning.

- Family history of psychosis in first degree relative OR Schizotypal Personality Disorder in identified patient

  **PLUS**
  - 30% drop in SOFAS score from premorbid level, sustained for a month, occurred within past 12 months OR SOFAS score of 50 or less for past 12 months or longer

**Criterion met for Group 1 – Vulnerability Group**

#### Group 2: Attenuated Psychosis Group

This criterion identifies young people at risk of psychosis due to a subthreshold psychotic syndrome. That is, they have symptoms which do not reach threshold levels for psychosis due to subthreshold intensity (the symptoms are not severe enough) or they have psychotic symptoms but at a subthreshold frequency (the symptoms do not occur often enough).

2a) Subthreshold intensity:

- Global Rating Scale Score of 3-5 on Unusual Thought Content subscale, 3-5 on Non-Bizarre Ideas subscale, 3-4 on Perceptual Abnormalities subscale and/or 4-5 on Disorganised Speech subscales of the CAARMS

  **PLUS**
  - Frequency Scale Score of 3-6 on Unusual Thought Content, Non-Bizarre Ideas, Perceptual Abnormalities and/or Disorganised Speech subscales of the CAARMS for at least a week
  - OR Frequency Scale Score of 2 on Unusual Thought Content, Non-Bizarre Ideas, Perceptual Abnormalities and Disorganised Speech subscales of the CAARMS on more than two occasions (experienced a minimum of four times in total)

2b) Subthreshold frequency:

- Global Rating Scale Score of 6 on Unusual Thought Content, 6 on Non-Bizarre Ideas, 5-6 on Perceptual Abnormalities and/or 6 on Disorganised Speech subscales of the CAARMS

  **PLUS**
  - Frequency Scale Score of 3 on Unusual Thought Content, Non-Bizarre Ideas, Perceptual Abnormalities and/or Disorganised Speech subscales of the CAARMS

  **PLUS** (for both categories)
  - Symptoms present in past year

  **PLUS** (for both categories)
  - 30% drop in SOFAS score from premorbid level, sustained for a month, occurred within past 12 months OR SOFAS score of 50 or less for past 12 months or longer

**Criterion met for Group 2 – Attenuated Psychosis Group**

#### Group 3: BLIPS Group

This criterion identifies young people at risk of psychosis due to a recent history of frank psychotic symptoms that resolved spontaneously (without antipsychotic medication) within one week.

- Global Rating Scale Score of 6 on Unusual Thought Content subscale, 6 on Non-Bizarre Ideas, 5 or 6 on Perceptual Abnormalities subscale and/or 6 on Disorganised Speech subscales of the CAARMS

  **PLUS**
  - Frequency Scale Score of 4-6 on Unusual Thought Content, Non-Bizarre Ideas, Perceptual Abnormalities and/or Disorganised Speech subscales

  **PLUS**
  - Each episode of symptoms is present for less than one week and symptoms spontaneously remit on every occasion.

  **PLUS**
  - Symptoms occurred during last year

  **PLUS**
  - 30% drop in SOFAS score from premorbid level, sustained for a month, occurred within past 12 months OR SOFAS score of 60 or less for past 12 months or longer

**Criterion met for Group 3 – BLIPS Group**

CAARMS - July 2006
### 9: Psychosis Threshold / Anti-Psychotic Treatment Threshold

- **Severity Scale Score of 6 on Unusual Thought Content subscale, 6 on Non-Bizarre Ideas, 5 or 6 on Perceptual Abnormalities subscale and/or 6 on Disorganised Speech subscales of the CAARMS**

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
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<tbody>
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</table>

  **PLUS**

- **Frequency Scale Score of greater than or equal to 4 on Unusual Thought Content, Non-Bizarre Ideas, Perceptual Abnormalities and/or Disorganised Speech subscales**

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
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<tbody>
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</table>

  **PLUS**

- **Symptoms present for longer than one week**

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
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<tbody>
<tr>
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</table>

**Psychosis Threshold Criterion Met**

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
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<tbody>
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<td></td>
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</table>

### 10: Study Withdrawal (‘Break Blind’) Threshold

- **Severity Scales Score of 5 or above on Aggression/Dangerous Behaviour and/or Suicidality/Self Harm Subscales**

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
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</table>

- **NOTE:** This should be considered independently from level of psychosis

**Study Withdrawal Threshold Criterion Met**

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
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</tbody>
</table>

CAARMS- July 2006
June 2006 VERSION OF THE CAARMS: SUMMARY OF CHANGES

1. The first subscale (formerly ‘Disorders of Thought Content’) has been split into two subscales: ‘Unusual Thought Content’ and ‘Non-bizarre Ideas’. Hence, where there used to be three subscales in section one (Positive Symptoms), there are now four (Unusual Thought Content, Non-Bizarre Ideas, Perceptual Abnormalities and Disorganised Speech). Each subscale has its own questions/prompts and rating anchors. It is hoped that this will make it easier to rate interviewees who experience both bizarre and non-bizarre ideas.

2. The addition of a 0-100 Likert scale to measure levels of distress (for the first four subscales only). This is a subjective rating scale, whereby interviewers should ask the interviewee how distressed they feel in relation to that particular subscale. Eg. ‘When you hear your name being called, how distressed does this make you feel? If we were to look at this scale, where 0 equals not at all distressed, and 100 equals extremely distressed, where would you rate your own level of distress in relation to hearing your name being called?’

3. The ‘pattern of symptoms’ section of the CAARMS previously grouped substance use and stress together. ‘Stress’ has been removed, so this question now only relates to substance use.

4. The intake criteria have changed to reflect the aforementioned changes in section one (i.e. ‘Positive Symptoms’ now has four subscales instead of three).

5. All intake groups now require the interviewee to have experienced either a drop in functioning, or have experienced chronic low functioning (see intake criteria at end of CAARMS for specific SOFAS scores and time frames).

6. The intake criteria now use the SOFAS instead of the GAF as a measure of functioning.

7. ‘Psychosis Threshold’ and ‘Study Withdrawal Threshold’ have been separated in the exclusion criteria section. The criteria remain the same.

8. An index has been added at the start of the CAARMS to assist in finding the page number of each subscale.
SCALE FOR THE ASSESSMENT OF
POSITIVE SYMPTOMS

(SAPS)

Nancy C. Andreasen, M.D., Ph.D.

Department of Psychiatry
College of Medicine
The University of Iowa
Iowa City, Iowa 52242

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INTRODUCTION

This scale is designed to assess positive symptoms, principally those that occur in schizophrenia. It is intended to serve as a complementary instrument to the Scale for the Assessment of Negative Symptoms (SANS). These positive symptoms include hallucinations, delusions, bizarre behavior, and positive formal thought disorder.

As in the case of the SANS, the investigator using this instrument will need to decide on an appropriate "time set." The instrument was developed with the exception that, in general, the time set will cover the past month as in the case of SANS. This scale can also be used in psychopharmacologic research in order to make weekly ratings and chart the subject's response to treatment.

Investigators using this instrument, particularly in combination with the SANS, will need to use a standard clinical interview in order to evaluate the subject's symptoms. Since positive formal thought disorder is an important positive symptom, it is recommended that, in doing this interview, the investigator begin talking with the subject on a relatively neutral topic for five to ten minutes in order to observe the subject's manner of speaking and responding. Thereafter, he can begin to ask specific questions about the various positive symptoms. Suggested probes are provided in the interview guide.

In addition to using a clinical interview, the investigator should also draw on other sources of information, such as direct observation, reports from the subject's family, reports from nurses, and reports from the subject himself. In general, the subject can usually be considered a relatively reliable informant concerning delusions and hallucinations if he is able to communicate clearly and will comply with a clinical interview. On the other hand, the interviewer will usually have to rely on observation and reports from outside sources in order to evaluate bizarre behavior and positive formal thought disorder.

The last item describing each major type of positive symptom is an overall global rating. This should be a true global rating based on taking into account both the nature and the severity of the various types of symptoms observed. In some cases, a single symptom (e.g., extremely severe persecutory delusions) may lead to a very high global rating, even if other symptoms of this type are not present.
HALLUCINATIONS

Hallucinations represent an abnormality in perception. They are false perceptions occurring in the absence of some identifiable external stimulus. They may be experienced in any of the sensory modalities, including hearing, touch, taste, smell, and vision. True hallucinations should be distinguished from illusions (which involve a misperception of an external stimulus), hypnagogic and hypnopompic experiences (which occur when the subject is falling asleep or waking up), or normal thought processes that are exceptionally vivid. If the hallucinations have a religious quality, then they should be judged within the context of what is normal for the subject's social and cultural background. Hallucinations occurring under the immediate influence of alcohol, drugs, or serious physical illness should not be rated as present. The subject should always be requested to describe the hallucination in detail.

Auditory Hallucinations

The subject has reported voices, noises, or sounds. The commonest auditory hallucinations involve hearing voices speaking to the subject or calling him names. The voices may be male or female, familiar or unfamiliar, and critical or complimentary. Typically, subjects suffering from schizophrenia experience the voices as unpleasant and negative. Hallucinations involving sounds rather than voices, such as noises or music, should be considered less characteristic and less severe.

Have you ever heard voices or other sounds when no one is around?

What did they say?

Voices Commenting

Voices commenting are a particular type of auditory hallucination which phenomenologists such as Kurt Schneider consider to be pathognomonic of schizophrenia, although some recent evidence contradicts this. These hallucinations involve hearing a voice that makes a running commentary on the subject's behavior or thought as it occurs. If this is the only type of auditory hallucination that the subject hears, it should be scored instead of auditory hallucinations (No. 1 above). Usually, however, voices commenting will occur in addition to other types of auditory hallucinations.

Have you ever heard voices commenting on what you are thinking or doing?

What do they say?
<table>
<thead>
<tr>
<th>Voices Conversing</th>
<th>None</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Questionable</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Mild: Subject hears noises or single words; they occur only occasionally</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Moderate: Clear evidence of voices; they have occurred at least weekly</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Marked: Clear evidence of voices which occur almost every day</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Severe: Voices occur often every day</td>
<td>5</td>
</tr>
<tr>
<td>Somatic or Tactile Hallucinations</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>These hallucinations involve experiencing peculiar physical sensations in the body. They include burning sensations, tingling, and perceptions that the body has changed in shape or size.</td>
<td>Questionable</td>
<td>1</td>
</tr>
<tr>
<td>Have you ever had burning sensations or other strange feelings in your body?</td>
<td>Mild: Subject experiences peculiar physical sensations; they occur only occasionally</td>
<td>2</td>
</tr>
<tr>
<td>What were they?</td>
<td>Moderate: Clear evidence of somatic or tactile hallucinations; they have occurred at least weekly</td>
<td>3</td>
</tr>
<tr>
<td>Did your body ever appear to change in shape or size?</td>
<td>Marked: Clear evidence of somatic or tactile hallucinations which occur almost every day</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Severe: Hallucinations occur often every day</td>
<td>5</td>
</tr>
<tr>
<td>Olfactory Hallucinations</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>The subject experiences unusual smells which are typically quite unpleasant. Sometimes the subject may believe that he himself smells. This belief should be scored here if the subject can actually smell the odor himself, but should be scored among delusions if he only believes that others can smell the odor.</td>
<td>Questionable</td>
<td>1</td>
</tr>
<tr>
<td>Have you ever experienced any unusual smells or smells that others do not notice?</td>
<td>Mild: Subject experiences unusual smells; they occur only occasionally</td>
<td>2</td>
</tr>
<tr>
<td>What were they?</td>
<td>Moderate: Clear evidence of olfactory hallucinations; they have occurred at least weekly</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Marked: Clear evidence of olfactory hallucinations; they occur almost every day</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Severe: Olfactory hallucinations occur often every day</td>
<td>5</td>
</tr>
</tbody>
</table>
Visual Hallucinations
The subject sees shapes or people that are not actually present. Sometimes these are shapes or colors, but most typically they are figures of people or human-like objects. They may also be characters of a religious nature, such as the Devil or Christ. As always, visual hallucinations involving religious themes should be judged within the context of the subject's cultural background. Hypnogogic and hypnopompic visual hallucinations (which are relatively common) should be excluded, as should visual hallucinations occurring when the subject has been taking hallucinogenic drugs.

Have you had visions or seen things that other people cannot?

What did you see?

Did this occur when you were falling asleep or waking up?

Global Rating of Severity of Hallucinations
This global rating should be based on the duration and severity of hallucinations, the extent of the subject's preoccupation with the hallucinations, his degree of conviction, and their effect on his actions. Also consider the extent to which the hallucinations might be considered bizarre or unusual. Hallucinations not mentioned above, such as those involving taste, should be included in this rating.

None 0
Questionable 1
Mild: Subject experiences visual hallucinations; they occur only occasionally 2
Moderate: Clear evidence of visual hallucinations; they have occurred at least weekly 3
Marked: Clear evidence of visual hallucinations which occur almost every day 4
Severe: Hallucinations occur often every day 5

None 0
Questionable 1
Mild: Hallucinations definitely present, but occur infrequently; at times the subject may question their existence 2
Moderate: Hallucinations are vivid and occur occasionally; they may bother him to some extent 3
Marked: Hallucinations are quite vivid, occur frequently, and pervade his life 4
Severe: Hallucinations occur almost daily and are sometimes unusual or bizarre; they are very vivid and extremely troubling 5
DELUSIONS
Delusions represent an abnormality in content of thought. They are false beliefs that cannot be explained on the basis of the subject's cultural background. Although delusions are sometimes defined as "fixed false beliefs," in their mildest form delusions may persist only for weeks to months, and the subject may question his beliefs or doubt them. The subject's behavior may or may not be influenced by his delusions. The rating of severity of individual delusions and of the global severity of delusional thinking should take into account their persistence, their complexity, the extent to which the subject acts on them, the extent to which the subject doubts them, and the extent to which the beliefs deviate from those that normal people might have. For each positive rating, specific examples should be noted in the margin.

Persecutory Delusions
People suffering from persecutory delusions believe that they are being conspired against or persecuted in some way. Common manifestations include the belief that one is being followed, that one's mail is being opened, that one's room or office is bugged, that the telephone is tapped, or that police, government officials, neighbors, or fellow workers are harassing the subject. Persecutory delusions are sometimes relatively isolated or fragmented, but sometimes the subject has a complex set of delusions involving both a wide range of forms of persecution and a belief that there is a well-designed conspiracy behind them. For example, a subject may believe that his house is bugged and that he is being followed because the government wrongly considers him a secret agent for a foreign government; this delusion may be so complex that it explains almost everything that happens to him. The ratings of severity should be based on duration and complexity.

Have people been bothering you in any way?

Has anyone been trying to harm you?

Has anyone been watching or monitoring you?

Delusions of Jealousy
The subject believes that his/her mate is having an affair with someone. Miscellaneous bits of information are construed as "evidence." The person usually goes to great effort to prove the existence of the affair, searching for hair in the bedclothes, the odor of shaving lotion or smoke on clothing, or receipts or checks indicating a gift has been bought for the lover. Elaborate plans are often made in order to trap the two together.

Have you ever worried that your husband (wife) might be unfaithful to you?

What evidence do you have?

None

Questionable

Mild: Delusional beliefs are simple and may be of several different types; subject may question them occasionally

Moderate: Clear, consistent delusion that is firmly held

Marked: Consistent, firmly-held delusion that the subject acts on

Severe: Complex, well-formed delusion that the subject acts on and that preoccupies him a great deal of the time; some aspects of the delusion or his reaction may seem quite bizarre

_ _ 6
Delusions of Sin or Guilt
The subject believes that he has committed some terrible sin or done something unforgivable. Sometimes the subject is excessively or inappropriately preoccupied with things he did wrong as a child, such as masturbating. Sometimes the subject feels responsible for causing some disastrous event, such as a fire or accident, with which he in fact has no connection. Sometimes these delusions may have a religious flavor, involving the belief that the sin is unpardonable and that the subject will suffer eternal punishment from God. Sometimes the subject simply believes that he deserves punishment by society. The subject may spend a good deal of time confessing these sins to whomever will listen.

Have you ever felt that you have done some terrible thing that you deserve to be punished for?

Grandiose Delusions
The subject believes that he has special powers or abilities. He may think he is actually some famous personage, such as a rock star, Napoleon, or Christ. He may believe he is writing some definitive book, composing a great piece of music, or developing some wonderful new invention. The subject is often suspicious that someone is trying to steal his ideas, and he may become quite irritable if his ideas are doubted.

Do you have any special or unusual abilities or talents?

Do you feel you are going to achieve great things?
Religious Delusions
The subject is preoccupied with false beliefs of a religious nature. Sometimes these exist within the context of a conventional religious system, such as beliefs about the Second Coming, the Antichrist, or possession by the Devil. At other times, they may involve an entirely new religious system or a pastiche of beliefs from a variety of religions, particularly Eastern religions, such as ideas about reincarnation or Nirvana. Religious delusions may be combined with grandiose delusions (if the subject considers himself a religious leader), delusions of guilt, or delusions of being controlled. Religious delusions must be outside the range considered normal for the subject's cultural and religious background.

Are you a religious person?

Have you had any unusual religious experiences?

What was your religious training as a child?

Somatic Delusions
The subject believes that somehow his body is diseased, abnormal, or changed. For example, he may believe that his stomach or brain is rotting, that his hands or penis have become enlarged, or that his facial features are unusual (dysmorphophobia). Sometimes somatic delusions are accompanied by tactile or other hallucinations, and when this occurs, both should be rated. (For example, the subject believes that he has ball bearings rolling around in his head, placed there by a dentist who filled his teeth, and can actually hear them clanking against one another.)

Is there anything wrong with your body?

Have you noticed any change in your appearance?

None 0
Questionable 1
Mild: Delusional beliefs may be simple and may be of several different types; subject may question them occasionally 2
Moderate: Clear, consistent delusion that is firmly held 3
Marked: Consistent, firmly-held delusion that the subject acts on 4
Severe: Complex, well-formed delusion that the subject acts on and that preoccupies him a great deal of the time; some aspects of the delusion or his reaction may seem quite bizarre 5
Ideas and Delusions of Reference
The subject believes that insignificant remarks, statements, or events refer to him or have some special meaning for him. For example, the subject walks into a room, sees people laughing, and suspects that they were just talking about him and laughing at him. Sometimes items read in the paper, heard on the radio, or seen on television are considered to be special messages to the subject. In the case of ideas of reference, the subject is suspicious, but recognizes his idea is erroneous. When the subject actually believes that the statements or events refer to him, then this is considered a delusion of reference.

Have you ever walked into a room and thought people were talking about you or laughing at you?

Have you seen things in magazines or on TV that seem to refer to you or contain a special message for you?

Have people communicated with you in any unusual ways?

Delusions of Being Controlled
The subject has a subjective experience that his feelings or actions are controlled by some outside force. The central requirement for this type of delusion is an actual strong subjective experience of being controlled. It does not include simple beliefs or ideas, such as that the subject is acting as an agent of God or that friends or parents are trying to coerce him to do something. Rather, the subject must describe, for example, that his body has been occupied by some alien force that is making it move in peculiar ways, or that messages are being sent to his brain by radio waves and causing him to experience particular feelings that he recognizes are not his own.

Have you ever felt you were being controlled by some outside force?

None
Questionable
Mild: Occasional ideas of reference
Moderate: Have occurred at least weekly
Marked: Occurs at least two to four times weekly
Severe: Occurs frequently
Delusions of Mind Reading
The subject believes that people can read his mind or know his thoughts. This is different than thought broadcasting (see below) in that it is a belief without a percept. That is, the subject subjectively experiences and recognizes that others know his thoughts, but he does not think that they can be heard out loud.

Have you ever had the feeling that people could read your mind?

Thought Broadcasting
The subject believes that his thoughts are broadcast so that he or others can hear them. Sometimes the subject experiences his thoughts as a voice outside his head; this is an auditory hallucination as well as a delusion. Sometimes the subject feels his thoughts are being broadcast although he cannot hear them himself. Sometimes he believes that his thoughts are picked up by a microphone and broadcast on the radio or television.

Have you ever heard your own thoughts out loud, as if they were a voice outside your head?

Have you ever felt your thoughts were broadcast so other people could hear them?

Thought Insertion
The subject believes that thoughts that are not his own have been inserted into his mind. For example, the subject may believe that a neighbor is practicing voodoo and planting alien sexual thoughts in his mind. This symptom should not be confused with experiencing unpleasant thoughts that the subject recognizes as his own, such as delusions of persecution or guilt.

Have you ever felt that thoughts were being put into your head by some outside force?

Have you ever experienced thoughts that didn’t seem to be your own?

<table>
<thead>
<tr>
<th>None</th>
<th>0</th>
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<tbody>
<tr>
<td>Questionable</td>
<td>1</td>
</tr>
<tr>
<td>Mild:</td>
<td>2</td>
</tr>
<tr>
<td>Subject has experienced mind reading, but doubts it occasionally</td>
<td></td>
</tr>
<tr>
<td>Moderate:</td>
<td>3</td>
</tr>
<tr>
<td>Clear experience of mind reading which has occurred on two or three occasions in a week</td>
<td></td>
</tr>
<tr>
<td>Marked:</td>
<td>4</td>
</tr>
<tr>
<td>Clear experience of mind reading which occurs frequently; behavior may be affected</td>
<td></td>
</tr>
<tr>
<td>Severe:</td>
<td>5</td>
</tr>
<tr>
<td>Clear experience of mind reading which occurs frequently, pervades the subject’s life, and often affects his behavior</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>None</th>
<th>0</th>
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<tbody>
<tr>
<td>Questionable</td>
<td>1</td>
</tr>
<tr>
<td>Mild:</td>
<td>2</td>
</tr>
<tr>
<td>Subject has experienced thought broadcasting, but doubts it occasionally</td>
<td></td>
</tr>
<tr>
<td>Moderate:</td>
<td>3</td>
</tr>
<tr>
<td>Clear experience of thought broadcasting which has occurred on two or three occasions in a week</td>
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</tr>
<tr>
<td>Severe:</td>
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<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Questionable</td>
<td>1</td>
</tr>
<tr>
<td>Mild:</td>
<td>2</td>
</tr>
<tr>
<td>Subject has experienced thought insertion, but doubts it occasionally</td>
<td></td>
</tr>
<tr>
<td>Moderate:</td>
<td>3</td>
</tr>
<tr>
<td>Clear experience of thought insertion which has occurred on two or three occasions in a week</td>
<td></td>
</tr>
<tr>
<td>Marked:</td>
<td>4</td>
</tr>
<tr>
<td>Clear experience of thought insertion which occurs frequently; behavior may be affected</td>
<td></td>
</tr>
<tr>
<td>Severe:</td>
<td>5</td>
</tr>
<tr>
<td>Thought insertion which occurs frequently, pervades the subject’s life and affects behavior</td>
<td></td>
</tr>
</tbody>
</table>
Thought Withdrawal
The subject believes that thoughts have been taken away from his mind. He is able to describe a subjective experience of beginning a thought and then suddenly having it removed by some outside force. This symptom does not include the mere subjective recognition of alogia.

*Have you ever felt your thoughts were taken away by some outside force?*

<table>
<thead>
<tr>
<th>None</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Questionable</td>
<td>1</td>
</tr>
<tr>
<td>Mild: Subject has experienced thought withdrawal, but doubts it occasionally</td>
<td>2</td>
</tr>
<tr>
<td>Moderate: Clear experience of thought withdrawal which has occurred on two or three occasions in a week</td>
<td>3</td>
</tr>
<tr>
<td>Marked: Clear experience of thought withdrawal which occurs frequently; behavior may be affected</td>
<td>4</td>
</tr>
<tr>
<td>Severe: Clear experience of thought withdrawal which occurs frequently, pervades the subject's life and often affects his behavior</td>
<td>5</td>
</tr>
</tbody>
</table>

Global Rating of Severity of Delusions
The global rating should be based on duration and persistence of delusions, the extent of the subject's preoccupation with the delusions, his degree of conviction, and their effect on his actions. Also consider the extent to which the delusions might be considered bizarre or unusual. Delusions not mentioned above should be included in this rating.

<table>
<thead>
<tr>
<th>None</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Questionable</td>
<td>1</td>
</tr>
<tr>
<td>Mild: Delusion definitely present but, at times, the subject questions the belief</td>
<td>2</td>
</tr>
<tr>
<td>Moderate: The subject is convinced of the belief, but it may occur infrequently and have little effect on his behavior</td>
<td>3</td>
</tr>
<tr>
<td>Marked: The delusion is firmly held; it occurs frequently and affects the subject's behavior</td>
<td>4</td>
</tr>
<tr>
<td>Severe: Delusions are complex, well-formed, and pervasive; they are firmly held and have a major effect on the subject's behavior; they may be somewhat bizarre or unusual</td>
<td>5</td>
</tr>
</tbody>
</table>
BIZARRE BEHAVIOR

The subject's behavior is unusual, bizarre, or fantastic. For example, the subject may urinate in a sugar bowl, paint the two halves of his body different colors, or kill a litter of pigs by smashing their heads against a wall. The information for this item will sometimes come from the subject, sometimes from other sources, and sometimes from direct observation. Bizarre behavior due to the immediate effects of alcohol or drugs should be excluded. As always, social and cultural norms must be considered in making the ratings, and detailed examples should be noted and noted.

Clothing and Appearance
The subject dresses in an unusual manner or does other strange things to alter his appearance. For example, he may shave off all his hair or paint parts of his body different colors. His clothing may be quite unusual; for example, he may choose to wear some outfit that appears generally inappropriate and unacceptable, such as a baseball cap backwards with rubber galoshes and long underwear covered by denim overalls. He may dress in a fantastic costume representing some historical personage or a man from outer space. He may wear clothing completely inappropriate to the climatic conditions, such as heavy wools in the midst of summer.

Has anyone made comments about your appearance?

Social and Sexual Behavior
The subject may do things that are considered inappropriate according to usual social norms. For example, he may masturbate in public, urinate or defecate in inappropriate receptacles, or exhibit his sex organs inappropriately. He may walk along the street muttering to himself, or he may begin talking to people whom he has never met about his personal life (as when riding on a subway or standing in some public place). He may drop to his knees praying and shouting in the midst of a crowd of people, or he may suddenly sit in a yoga position while in the midst of a crowd. He may make inappropriate sexual overtures or remarks to strangers.

Have you ever done anything that others might thing unusual or that has called attention to yourself?
Aggressive and Agitated Behavior
The subject may behave in an aggressive, agitated manner, often quite unpredictably. He may start arguments inappropriately with friends or members of his family, or he may accost strangers on the street and begin haranguing them angrily. He may write letters of a threatening or angry nature to government officials or others with whom he has some quarrel. Occasionally, subjects may perform violent acts such as injuring or tormenting animals, or attempting to injure or kill human beings.

Have you ever done anything to try to harm animals or people?

Have you felt angry with anyone?

How did you express your anger?

Repetitive or Stereotyped Behavior
The subject may develop a set of repetitive actions or rituals that he must perform over and over. Frequently, he will attribute some symbolic significance to these actions and believe that they are either influencing others or preventing himself from being influenced. For example, he may eat jelly beans every night for dessert, assuming that different consequences will occur depending on the color of the jelly beans. He may have to eat foods in a particular order, wear particular clothes, or put them on in a certain order. He may have to write messages to himself or to others over and over; sometimes this will be in an unusual or occult language.

Are there any things that you feel you have to do?

| None | 0 |
| Questionable | 1 |
| Mild: Occasional instances | 2 |
| Moderate: For example, writing angry letters to strangers | 3 |
| Marked: For example, threatening people, public harangues | 4 |
| Severe: For example, mutilating animals, attacking people | 5 |
Global Rating of Severity of Bizarre Behavior

In making this rating, the interviewer should consider the type of behavior, the extent to which it deviates from social norms, the subject's awareness of the degree to which the behavior is deviant, and the extent to which it is obviously bizarre.

<table>
<thead>
<tr>
<th>Rating</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>None 0</td>
<td></td>
</tr>
<tr>
<td>Questionable 1</td>
<td>Occasional instances of unusual or apparently idiosyncratic behavior; subject usually has some insight</td>
</tr>
<tr>
<td>Moderate 2</td>
<td>Behavior which is clearly deviant from social norms and seems somewhat bizarre; subject may have some insight</td>
</tr>
<tr>
<td>Marked 3</td>
<td>Behavior which is markedly deviant from social norms and clearly bizarre; subject may have some insight</td>
</tr>
<tr>
<td>Severe 4</td>
<td>Behavior which is extremely bizarre or fantastic; may include a single extreme act, e.g., attempting murder; subject usually lacks insight</td>
</tr>
</tbody>
</table>

14
POSITIVE FORMAL THOUGHT DISORDER

Positive formal thought disorder is fluent speech that tends to communicate poorly for a variety of reasons. The subject tends to skip from topic to topic without warning, to be distracted by events in the nearby environment, to join words together because they are semantically or phonologically alike even though they make no sense, or to ignore the question asked and ask another. This type of speech may be rapid, and it frequently seems quite disjointed. It has sometimes been referred to as "loose associations." Unlike alogia (negative formal thought disorder), a wealth of detail is provided, and the flow of speech tends to have an energetic, rather than an apathetic, quality to it.

In order to evaluate thought disorder, the subject should be permitted to talk at length on some topic, particularly a topic unrelated to his psychopathology, for as long as five to ten minutes. The interviewer should observe closely the extent to which his sequencing of ideas is well connected. In addition, the interviewer should insist that he clarify or elaborate further if the ideas seem vague or incomprehensible. He should also pay close attention to how well the subject can reply to a variety of different types of questions, ranging from simple (Where were you born?) to more complicated (How do you think the present government is doing?)

The anchor points for these ratings assume that the subject has been interviewed for a total of approximately forty-five minutes. If the interview is shorter, the ratings should be adjusted accordingly.

Derailment (Loose Associations)
A pattern of spontaneous speech in which the ideas slip off one track onto another which is clearly but obliquely related, or onto one which is completely unrelated. Things may be said in juxtaposition which lack a meaningful relationship, or the subject may shift idiosyncratically from one frame of reference to another. At times there may be a vague connection between the ideas, and at others none will be apparent. This pattern of speech is often characterized as sounding "disjointed." Perhaps the commonest manifestation of this disorder is a slow, steady slippage, with no single derailment being particularly severe, so that the speaker gets farther and farther off the track with each derailment without showing any awareness that his reply no longer has any connection with the question which was asked. This abnormality is often characterized by lack of cohesion between clauses and sentences and by unclear pronoun references.

| None                                      | 0 |
| Questionable                              | 1 |
| Mild: Occasional instances of derailment, with only slight topic shifts | 2 |
| Moderate: Several instances of derailment; subject is sometimes difficult to follow | 3 |
| Marked: Frequent instances of derailment; subject is often difficult to follow | 4 |
| Severe: Derailment so frequent and/or extreme that the subject's speech is almost incomprehensible | 5 |

Example: Interviewer: "Did you enjoy college?"
Subject: "Um-hum. Oh hey well, I oh, I really enjoyed some communities I tried it, and the, and the next day when I'd be going out, you know, um, I took control like uh, I put, um, bleach on my hair in, in California. My roommate was from Chicago, and she was going to the junior college. And we lived in the Y.M.C.A., so she wanted to put it, um, peroxide on my hair, and she did, and I got up and looked at the mirror and tears came to my eyes. Now do you understand it, I was fully aware of what was going on but why couldn't I, l... why, why the tears? I can't understand that, can you?"
Tangentiality
Rephrasing a question in an oblique, tangential or even irrelevant manner. The reply may be related to the question in some distant way. Or the reply may be unrelated and seem totally irrelevant. In the past tangentiality has sometimes been used as roughly equivalent to loose associations or derailment. The concept of tangentiality has been partially redefined so that it refers only to answers to questions and not to transitions in spontaneous speech.

Example: Interviewer: “What city are you from?”
Subject: “That’s a hard question to answer because my parents... I was born in Iowa, but I know that I’m white instead of black, so apparently I came from the North somewhere and I don’t know where, you know, I really don’t know whether I’m Irish or Scandinavian or I don’t, I don’t believe I’m Polish but I think I’m, I think I might be German or Welsh.

Incoherence (Word Salad, Schizophrenia)
A pattern of speech which is essentially incomprehensible at times. Incoherence is often accompanied by derailment. It differs from derailment in that in incoherence the abnormality occurs within the level of the sentence or clause, which contains words or phrases that are joined incoherently. The abnormality in incoherence involves unclear or confusing connections between larger units, such as sentences or clauses.

This type of language disorder is relatively rare. When it occurs, it tends to be severe or extreme, and mild forms are quite uncommon. It may sound quite similar to Wernicke’s aphasia or jargon aphasia, and in these cases the disorder should only be called incoherence when history and laboratory data exclude the possibility of a past stroke, and formal testing for aphasia is negative.

Exclusions: Mildly ungrammatical constructions or idiomatic usages characteristic of particular regional or ethnic backgrounds, lack of education, or low intelligence.

Example: Interviewer: “What do you think about current political issues like the energy crisis?”
Subject: “They’re destroying too many cattle and oil just to make soap. If we need soap when you can jump into a pool of water, and then when you go to buy your gasoline, my folks always thought they should, get pop but the best thing to get, is motor oil, and, money. May, may as well go there and, trade in some, pop caps and, uh, tires, and tractors to group, car garages, so they can pull cars away from wrecks, is what I believed in.”

None 0
Questionable 1
Mild: One or two oblique replies 2
Moderate: Occasional oblique replies (three to four times) 3
Marked: Frequent oblique replies (more than four times) 4
Severe: Tangentiality so severe that interviewing the subject is extremely difficult 5

None 0
Questionable 1
Mild: Occasional instances of incoherence 2
Moderate: Frequent bursts of incoherence 3
Marked: At least half of the subject’s speech is incomprehensible 4
Severe: Almost all of the subject’s speech is incomprehensible 5
Illogicality
A pattern of speech in which conclusions are reached which do not follow logically. This may take the form of non-sequiturs (= it does not follow), in which the subject makes a logical inference between two clauses which is unwarranted or illogical. It may take the form of faulty inductive inferences. It may also take the form of reaching conclusions based on faulty premises without any actual delusional thinking.

Exclusions: Illogicality may either lead to or result from delusional beliefs. When illogical thinking occurs within the context of a delusional system, it should be subsumed under the concept of delusions and not considered a separate phenomenon representing a different type of thinking disorder. Illogical thinking which is clearly due to cultural or religious values or to intellectual deficit should also be excluded.

Example: "Parents are the people that raise you. Any thing that raises you can be a parent. Parents can be anything – material, vegetable, or mineral – that has taught you something. Parents would be the world of things that are alive, that are there. Rocks – a person can look at a rock and learn something from it, so that would be a parent."

Circumstantiality
A pattern of speech which is very indirect and delayed in reaching its goal idea. In the process of explaining something, the speaker brings in many tedious details and sometimes makes parenthetical remarks. Circumstantial replies or statements may last for many minutes if the speaker is not interrupted and urged to get to the point. Interviewers will often recognize circumstantiality on the basis of needing to interrupt the speaker in order to complete the process of history-taking within an allotted time. When not called circumstantial, these people are often referred to as "long-winded."

Exclusions: Although it may coexist with instances of poverty of content of speech or loss of goal, it differs from poverty of content of speech in containing excessive amplifying or illustrative detail and from loss of goal in that the goal is eventually reached if the person is allowed to talk long enough. It differs from derailment in that the details presented are closely related to some particular goal or idea and that the particular goal or idea must be, by definition, eventually reached.
Pressure of Speech
An increase in the amount of spontaneous speech as compared to what is considered ordinary or socially customary. The subject talks rapidly and is difficult to interrupt. Some sentences may be left uncompleted because of eagerness to get on to a new idea. Simple questions which could be answered in only a few words or sentences are answered at great length so that the answer takes minutes rather than seconds and indeed may not stop at all if the speaker is not interrupted. Even when interrupted, the speaker often continues to talk. Speech tends to be loud and emphatic. Sometimes speakers with severe pressure will talk without any social stimulation and talk even though no one is listening. When subjects are receiving phenothiazines or lithium, their speech is often slowed down by medication, and then it can be judged only on the basis of amount, volume, and social appropriateness. If a quantitative measure is applied to the rate of speech, then a rate greater than 150 words per minute is usually considered rapid or pressured. This disorder may be accompanied by derailment, tangentiality, or incoherence, but it is distinct from them.

Distractible Speech
During the course of a discussion or interview, the subject stops talking in the middle of a sentence or idea and changes the subject in response to a nearby stimulus, such as an object on a desk, the interviewer's clothing or appearance, etc.

Example: "Then I left San Francisco and moved to... where did you get that tie? It looks like it's left over from the 50's. I like the warm weather in San Diego. Is that a conch shell on your desk? Have you ever gone scuba diving?"
Clanging
A pattern of speech in which sounds rather than meaningful relationships appear to govern word choice, so that the intelligibility of the speech is impaired and redundant words are introduced. In addition to rhyming relationships, this pattern of speech may also include punning associations, so that a word similar in sound brings in a new thought.

Example: I'm not trying to make a noise. I'm trying to make sense. If you can make sense out of nonsense, well, have fun. I'm trying to make sense out of sense. I'm not making sense (cents) anymore. I have to make dollars.

Global Rating of Positive Formal Thought Disorder
In making this rating, the interviewer should consider the type of abnormality, the degree to which it affects the subject's ability to communicate, the frequency with which abnormal speech occurs, and its degree of severity.

Inappropriate Affect
Affect expressed is inappropriate or incongruous, not simply flat or blunted. Most typically, this manifestation of affective disturbance takes the form of smiling or assuming a silly facial expression while talking about a serious or sad subject. (Occasionally subjects may smile or laugh when talking about a serious subject which they find uncomfortable or embarrassing. Although their smiling may seem inappropriate, it is due to anxiety and therefore should not be rated as inappropriate affect.) Do not rate affective flattening or blunting as inappropriate.
SCALE FOR THE ASSESSMENT OF NEGATIVE SYMPTOMS
(SANS)

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Department of Psychiatry
College of Medicine
The University of Iowa
Iowa City, Iowa 52242

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AFFECTIVE FLATTENING OR BLUNTING

Affective flattening or blunting manifests itself as a characteristic impoverishment of emotional expression, reactivity, and feeling. Affective flattening can be evaluated by observation of the subject’s behavior and responsiveness during a routine interview. The rating of some items may be affected by drugs, since the Parkinsonian side-effect of phenothiazines may lead to mask-like facies and diminished associated movements. Other aspects of affect, such as responsivity or appropriateness, will not be affected, however.

Unchanging Facial Expression
The subject’s face appears wooden, mechanical, frozen. It does not change expression, or changes less than normally expected, as the emotional content of discourse changes. Since phenothiazines may partially mimic this effect, the interviewer should be careful to note whether or not the subject is on medication, but should not try to “correct” the rating accordingly.

<table>
<thead>
<tr>
<th>Rating</th>
<th>Description</th>
<th>Score</th>
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</thead>
<tbody>
<tr>
<td>Not at all</td>
<td>Subject is normal or labile</td>
<td>0</td>
</tr>
<tr>
<td>Questionable</td>
<td>Decrease</td>
<td>1</td>
</tr>
<tr>
<td>Mild</td>
<td>Occasionally the subject’s expression is not as full as expected</td>
<td>2</td>
</tr>
<tr>
<td>Moderate</td>
<td>Subject’s expressions are dulled overall, but not absent</td>
<td>3</td>
</tr>
<tr>
<td>Marked</td>
<td>Subject’s face has a flat ‘set’ look, but flickers of affect arise</td>
<td>4</td>
</tr>
<tr>
<td>Severe</td>
<td>Subject’s face looks “wooden” and changes little, if at all throughout the interview</td>
<td>5</td>
</tr>
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</table>

Decreased Spontaneous Movements
The subject sits quietly throughout the interview and shows few or no spontaneous movements. He does not shift position, move his legs, move his hands, etc., or does so less than normally expected.

<table>
<thead>
<tr>
<th>Rating</th>
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<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not at all</td>
<td>Subject moves normally or is overactive</td>
<td>0</td>
</tr>
<tr>
<td>Questionable</td>
<td>Decrease</td>
<td>1</td>
</tr>
<tr>
<td>Mild</td>
<td>Some decrease in spontaneous movements</td>
<td>2</td>
</tr>
<tr>
<td>Moderate</td>
<td>Subject moves three or four times during the interview</td>
<td>3</td>
</tr>
<tr>
<td>Marked</td>
<td>Subject moves once or twice during the interview</td>
<td>4</td>
</tr>
<tr>
<td>Severe</td>
<td>Subject sits immobile throughout the interview</td>
<td>5</td>
</tr>
</tbody>
</table>
Prurity of Expressive Gestures
The subject does not use his body as an aid in expressing his ideas, through such means as hand gestures, sitting forward in his chair when intent on a subject, leaning back when relaxed, etc. This may occur in addition to decreased spontaneous movements.

Not at all: Subject uses expressive gestures normally or excessively 0
Questionable decrease 1
Mild: Some decrease in expressive gestures 2
Moderate: Subject uses body as an aid in expression at least three or four times 3
Marked: Subject uses body as an aid in expression only once or twice 4
Severe: Subject never uses body as an aid in expression 5

Poor Eye Contact
The subject avoids looking at others or using his eyes as an aid in expression. He appears to be staring into space even when he is talking.

Not at all: Good eye contact and expression 0
Questionable decrease 1
Mild: Some decrease in eye contact and eye expression 2
Moderate: Subject’s eye contact is decreased by at least half of normal 3
Marked: Subject’s eye contact is very infrequent 4
Severe: Subject almost never looks at interviewer 5

Affective Nonresponsivity
Failure to smile or laugh when prompted may be tested by smiling or joking in a way which would usually elicit a smile from a normal individual. The examiner may also ask, “Have you forgotten how to smile?” while smiling himself.

Not at all 0
Questionable decrease 1
Mild: Slight but definite lack in responsibility 2
Moderate: Subject occasionally seems to miss the cues to respond 3
Marked: Subject seems to miss the cues to respond most of the time 4
Severe: Subject is essentially unresponsive, even on prompting 5
Lack of Vocal Inflections
While speaking the subject fails to show normal vocal emphasis patterns. Speech has a monotonic quality, and important words are not emphasized through changes in pitch or volume. Subject also may fail to change volume with changes of subject so that he does not drop his voice when discussing private topics nor raise it as he discusses things which are exciting or for which louder speech might be appropriate.

<table>
<thead>
<tr>
<th>Category</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not at all: Normal vocal inflections</td>
<td>0</td>
</tr>
<tr>
<td>Questionable decrease</td>
<td>1</td>
</tr>
<tr>
<td>Mild: Slight decrease in vocal inflections</td>
<td>2</td>
</tr>
<tr>
<td>Moderate: Interviewer notices several instances of flattened vocal inflections</td>
<td>3</td>
</tr>
<tr>
<td>Marked: Obvious decrease in vocal inflections</td>
<td>4</td>
</tr>
<tr>
<td>Severe: Subject’s speech is a continuous monotone</td>
<td>5</td>
</tr>
</tbody>
</table>

Global Rating of Affective Flattening
The global rating should focus on overall severity of affective flattening or blunting. Special emphasis should be given to such core features as unresponsiveness, inappropriateness, and an overall decrease in emotional intensity.

<table>
<thead>
<tr>
<th>Category</th>
<th>Rating</th>
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<tbody>
<tr>
<td>No flattening: Normal affect</td>
<td>0</td>
</tr>
<tr>
<td>Questionable affective flattening</td>
<td>1</td>
</tr>
<tr>
<td>Mild affective flattening</td>
<td>2</td>
</tr>
<tr>
<td>Moderate affective flattening</td>
<td>3</td>
</tr>
<tr>
<td>Marked affective flattening</td>
<td>4</td>
</tr>
<tr>
<td>Severe affective flattening</td>
<td>5</td>
</tr>
</tbody>
</table>
Alogia

Alogia is a general term coined to refer to the impoverished thinking and cognition that often occur in subjects with schizophrenia (Greek a = no, none; logos = mind, thought). Subjects with alogia have thinking processes that seem empty, turgid, or slow. Since thinking cannot be observed directly, it is inferred from the subject’s speech. The two major manifestations of alogia are nonfluent empty speech (poverty of speech) and fluent empty speech (poverty of content of speech). Blocking and increased latency or response may also reflect alogia.

Poverty of Speech

Restriction in the amount of spontaneous speech, so that replies to questions tend to be brief, concrete, and unelaborated. Unprompted additional information is rarely provided. Replies may be monosyllabic, and some questions may be left unanswered altogether. When confronted with such speech patterns, the interviewer may find himself frequently prompting the subject in order to encourage elaboration of replies. To elicit this finding, the examiner must allow the subject adequate time to answer and to elaborate his answer.

| No poverty of speech: A substantial and appropriate number of replies to questions include additional information | 0 |
| Questionable poverty of speech | 1 |
| Mild: Occasional replies do not include elaborated information even though this is appropriate | 2 |
| Moderate: Some replies do not include appropriately elaborated information, and some replies are monosyllabic or very brief. ("Yes," "No," "Maybe," "I don’t know." "Last week.") | 3 |
| Marked: Answers are rarely more than a sentence or a few words in length | 4 |
| Severe: Subject says almost nothing and occasionally fails to answer questions | 5 |
Poverty of Content of Speech

Although replies are long enough so that speech is adequate in amount, it conveys little information. Language tends to be vague, often over-abstract or over-concrete, repetitive, and stereotyped. The interviewer may recognize this finding by observing that the subject has spoken at some length but has not given adequate information to answer the question. Alternatively, the subject may provide enough information, but require many words to do so, so that a lengthy reply can be summarized in a sentence or two. Sometimes the interviewer may characterize the speech as "empty philosophizing."

Exclusions: This finding differs from circumstance in that the circumstantial subject tends to provide a wealth of detail.

Example: Interviewer: "Why is it, do you think, that people believe in God?"
Subject: "Well, first of all because he u.h., he are the person that is their personal savior. He walks with me and talks with me. And uh, the understanding that I have, um, a lot of peoples, they don't really, uh, know they own personal self. Because, uh, they ain't, they all, just don't know they personal self. They don't know that he uh, seemed like to me, a lot of 'em don't understand that he walks and talks with them."

Blocking

Interruption of a train of speech before a thought or idea has been completed. After a period of silence which may last from a few seconds to minutes, the person indicates that she/he cannot recall what he had been saying or meant to say. Blocking should only be judged to be present if a person voluntarily describes losing his thought or idea, upon questioning by the interviewer, the person indicates that that was the reason for pausing.
Increased Latency of Response
The subject takes a longer time to reply to questions than is usually considered normal. He may seem “distant” and sometimes the examiner may wonder if he has even heard the question. Prompting usually indicates that the subject is aware of the question, but has been having difficulty in formulating his thoughts in order to make an appropriate reply.

Global Rating of Alogia
Since the core features of alogia are poverty of speech and poverty of content of speech, the global rating should place particular emphasis on them.

<table>
<thead>
<tr>
<th>Rating</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not at all</td>
<td>0</td>
</tr>
<tr>
<td>Questionable</td>
<td>1</td>
</tr>
<tr>
<td>Mild: Occasional brief pauses before replying</td>
<td>2</td>
</tr>
<tr>
<td>Moderate: Often pauses several seconds before replying</td>
<td>3</td>
</tr>
<tr>
<td>Marked: Usually pauses at least ten to fifteen seconds before replying</td>
<td>4</td>
</tr>
<tr>
<td>Severe: Long pauses prior to nearly all replies</td>
<td>5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Rating</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>No alogia.</td>
<td>0</td>
</tr>
<tr>
<td>Questionable</td>
<td>1</td>
</tr>
<tr>
<td>Mild: Mild but definite impoverishment in thinking</td>
<td>2</td>
</tr>
<tr>
<td>Moderate: Significant evidence for impoverished thinking</td>
<td>3</td>
</tr>
<tr>
<td>Marked: Subject's thinking seems impoverished much of the time</td>
<td>4</td>
</tr>
<tr>
<td>Severe: Subject's thinking seems impoverished nearly all of the time</td>
<td>5</td>
</tr>
</tbody>
</table>
AVOLITION-APATHY

Avolition manifests itself as a characteristic lack of energy, drive, and interest. Subjects are unable to mobilize themselves to initiate or persist in completing many different kinds of tasks. Unlike the diminished energy or interest of depression, the avolitional symptom complex in schizophrenia is usually not accompanied by saddened or depressed affect. The avolitional symptom complex often leads to severe social and economic impairment.

Grooming and Hygiene
The subject displays less attention to grooming and hygiene than normal. Clothing may appear sloppy, outdated, or soiled. The subject may bathe infrequently and not care for hair, nails, or teeth—leading to such manifestations as greasy or uncombed hair, dirty hands, body odor, or unclean teeth and bad breath. Overall, the appearance is dilapidated and disheveled. In extreme cases, the subject may even have poor toilet habits.

How often do you bathe or shower?

Do you change your clothes every day?

How often do you do laundry?

Impersistence at Work or School
The subject has had difficulty in seeking or maintaining employment (or schoolwork) as appropriate for his or her age and sex. If a student, he/she does not do homework and may even fail to attend class. Grades will tend to reflect this. If a college student, there may be a pattern of registering for courses, but having to drop several or all of them before the semester is completed. If of working age, the subject may have found it difficult to work at a job because of inability to persist in completing tasks and apparent irresponsibility. He may go to work irregularly, wander away early, complete them in a disorganized manner. He may simply sit around the house and not seek any employment or seek it only in an Infrequent and haphazard manner. If a housewife or retired person, the subject may fail to complete chores, such as shopping or cleaning, or complete them in an apparently careless and half-hearted way.

Have you been having any problems at (work, school)?

Do you ever start some project and just never get around to finishing it?

No evidence of poor grooming and hygiene

Questionable

Mild: Some slight but definite indication of inattention to appearance, i.e., messy hair or disheveled clothes

Moderate: Appearance is somewhat disheveled, i.e., greasy hair, dirty clothes

Marked: Subject's attempts to keep up grooming or hygiene are minimal

Severe: Subject's clothes, body and environment are dirty and smelly

No evidence of impersistence at work or school

Questionable

Mild: Slight indications of impersistence, i.e., missing a couple days of school or work

Moderate: Subject often has poor performance at work or school

Marked: Subject has much difficulty maintaining even a below normal level of work or school

Severe: Subject consistently fails to maintain a record at work or school
Physical Anergia
The subject tends to be physically inert. He may sit in a chair for hours at a time and not initiate any spontaneous activity. If encouraged to become involved in an activity, he may participate only briefly and then wander away or disengage himself and return to sitting alone. He may spend large amounts of time in some relatively mindless and physically inactive task such as watching TV or playing solitaire. His family may report that he spends most of his time at home “doing nothing except sitting around”. Either at home or in an inpatient setting he may spend much of his time sitting in his room.

Are there times when you lie or sit around most of the day?
(Does this ever last longer than one day?)

Global Rating of Avolition - Apathy
The global rating should reflect the overall severity of the avolition symptoms, given expected normal norms for the subject’s age and social status or origin. In making the global rating, strong weight may be given to only one or two prominent symptoms if they are particularly striking.

No Evidence of Physical Anergia
Questionable
Mild Anergia
Moderate: Subject lies in bed or sits immobile at least a quarter of normal waking hours
Marked: Subject lies in bed or sits immobile at least half of normal waking hours
Severe: Subject lies in bed or sits immobile for most of the day

No Avolition
Questionable
Mild, But Definitely Present
Moderate Avolition
Marked Avolition
Severe Avolition

<table>
<thead>
<tr>
<th>Rating</th>
<th>Score</th>
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<tbody>
<tr>
<td>No Evidence of Physical Anergia</td>
<td>0</td>
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<tr>
<td>Questionable</td>
<td>1</td>
</tr>
<tr>
<td>Mild Anergia</td>
<td>2</td>
</tr>
<tr>
<td>Moderate</td>
<td>3</td>
</tr>
<tr>
<td>Marked</td>
<td>4</td>
</tr>
<tr>
<td>Severe</td>
<td>5</td>
</tr>
<tr>
<td>No Avolition</td>
<td>0</td>
</tr>
<tr>
<td>Questionable</td>
<td>1</td>
</tr>
<tr>
<td>Mild, But Definitely Present</td>
<td>2</td>
</tr>
<tr>
<td>Moderate Avolition</td>
<td>3</td>
</tr>
<tr>
<td>Marked Avolition</td>
<td>4</td>
</tr>
<tr>
<td>Severe Avolition</td>
<td>5</td>
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</table>
ANHEDONIA-ASOCIALITY

This symptom complex encompasses the schizophrenic subject's difficulties in experiencing interest or pleasure. It may express itself as a lack of interest in pleasurable activities, an inability to experience pleasure when participating in activities normally considered pleasurable, or a lack of involvement in social relationships of various kinds.

Recreational Interests and Activities

The subject may have few or no interests, activities, or hobbies. Although this symptom may begin insidiously or slowly, there will usually be some obvious decline from an earlier level of interest and activity. Subjects with relatively milder loss of interest will engage in some activities which are passive or non-demanding, such as watching TV, or will show only occasional or sporadic interest. Subjects with the most extreme loss will appear to have a complete and intractable inability to become involved in or enjoy activities. The rating in this area should take both the quality and quantity of recreational interests into account.

Have you felt interested in the things you usually enjoy?

(Do they seem as fun as usual?)

Have you been watching TV or listening to the radio?

Sexual Interest and Activity

The subject may show a decrement in sexual interest and activity, as judged by what would be normal for the subject's age and marital status. Individuals who are married may manifest disinterest in sex or may engage in intercourse only at the partner's request. In extreme cases, the subject may not engage in any sex at all. Single subjects may go for long periods of time without sexual involvement and make no effort to satisfy this drive. Whether married or single, they may report that they subjectively feel only minimal sex drive or that they take little enjoyment in sexual intercourse or in masturbatory activity even when they engage in it.

Have you noticed any changes in your sex drive?

No Inability to Enjoy Recreational Interests or Activities 0
Questionable 1
Mild Inability to Enjoy Recreational Activities 2
Moderate: Subject often is not "up" for recreational activities 3
Marked: Subject has little interest in and derives only mild pleasure from recreational activities 4
Severe: Subject has no interest in and derives no pleasure from recreational activities 5

No Inability to Enjoy Sexual Activities 0
Questionable Decrement in Sexual Interest and Activity 1
Mild Decrement in Sexual Interest and Activity 2
Moderate: Subject occasionally has noticed decreased interest in and/or enjoyment from sexual activities 3
Marked: Subject has little interest in and/or derives little pleasure from sexual activities 4
Severe: Subject has no interest in and/or derives no pleasure from sexual activities 5
Ability to Feel Intimacy and Closeness
The subject may display an inability to form close and intimate relationships of a type appropriate for his age, sex, and family status. In the case of a younger person, this area should be rated in terms of relationships with the opposite sex and with parents and siblings. In the case of an older person who is married, the relationship with spouse and with children should be evaluated while older unmarried individuals should be judged in terms of relationships with the opposite sex and any family members who live nearby. Subjects may display few or no feelings of affection to available family members. Or they may have arranged their lives so that they are completely isolated from any intimate relationships, living alone and making no effort to initiate contacts with family or members of the opposite sex.

Have you been having any problems with your (family, spouse)?

How would you feel about visiting with your (family, parents, spouse, etc.)?

Relationships with Friends and Peers
Subjects may also be relatively restricted in their relationships with friends and peers of either sex. They may have few or no friends, make little or no effort to develop such relationships, and choose to spend all or most of their time alone.

Have you been spending much time with friends?

Do you enjoy spending time alone, or would you rather have more friends?

No Inability to Feel Intimacy and Closeness 0
Questionable Inability 1
Mild, But Definite Inability to Feel Intimacy and Closeness 2
Moderate: Subject appears to enjoy family or significant others but does not appear to 'look forward' to visits 3
Marked: Subject appears neutral toward visits from family or significant others. Brighton only mildly 4
Severe: Subject prefers no contact with or is hostile toward family or significant others 5

No Inability to Form Close Friendships 0
Questionable Inability to Form Friendships 1
Mild, But Definite Inability to Form Friendships 2
Moderate: Subject able to interact, but sees friends/acquaintances only two to three times per month 3
Marked: Subject has difficulty forming and/or keeping friendships. Sees friends/acquaintances only one to two times per month 4
Severe: Subject has no friends and no interest in developing any social ties 5
Global Rating of Anhedonia-Asociality

The global rating should reflect the overall severity of the anhedonia-asociality complex, taking into account the norms appropriate for the subject’s age, sex, and family status.

- No Evidence of Anhedonia-Asociality 0
- Questionable Evidence of Anhedonia-Asociality 1
- Mild, But Definite Evidence of Anhedonia-Asociality 2
- Moderate Evidence of Anhedonia-Asociality 3
- Marked Evidence of Anhedonia-Asociality 4
- Severe Evidence of Anhedonia-Asociality 5

ATTENTION

Attention is often poor in schizophrenia. The subject may have trouble focusing his attention, or he may only be able to focus sporadically and erratically. He may ignore attempts to converse with him, wander away while in the middle of an activity or task, or appear to be inattentive when engaged in formal testing or interviewing. He may or may not be aware of his difficulty in focusing his attention.

Social Inattentiveness

While involved in social situations or activities, the subject appears inattentive. He looks away during conversations, does not pick up the topic during a discussion, or appears uninvolved or unengaged. He may abruptly terminate a discussion or a task without any apparent reason. He may seem “spacy” or “out of it”. He may seem to have poor concentration when playing games, reading, or watching TV.

- No Indication of Inattentiveness 0
- Questionable Signs 1
- Mild, But Definite Signs of Inattentiveness 2
- Moderate: Subject occasionally misses what is happening in the environment 3
- Marked: Subject often misses what is happening in the environment; has trouble with reading comprehension 4
- Severe: Subject unable to follow conversation, remember what he’s read, or follow TV plot 5

Inattentiveness During Mental Status Testing

The subject may perform poorly on simple tests of intellectual functioning in spite of adequate education and intellectual ability. This should be assessed by having the subject spell “world” backwards and by serial 7’s (at least a tenth grade education) or serial 3’s (at least a sixth grade education) for a series of five subtractions. A perfect score is 10.

- No Errors 0
- Questionable: No errors but subject performs in a halting manner or makes/_corrects an error 1
- Mild, But Definite (One Error) 2
- Moderate (Two Errors) 3
- Marked (Three Errors) 4
- Severe (More Than Three Errors) 5
Global Rating of Attention
This rating should assess the subject's overall ability to attend or concentrate, and include both clinical appearance and performance on tasks.

<table>
<thead>
<tr>
<th>Description</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Indications of Inattentiveness</td>
<td>0</td>
</tr>
<tr>
<td>Questionable</td>
<td>1</td>
</tr>
<tr>
<td>Mild, But Definite Inattentiveness</td>
<td>2</td>
</tr>
<tr>
<td>Moderate Inattentiveness</td>
<td>3</td>
</tr>
<tr>
<td>Marked Inattentiveness</td>
<td>4</td>
</tr>
<tr>
<td>Severe Inattentiveness</td>
<td>5</td>
</tr>
</tbody>
</table>
# Social and Occupational Functioning Assessment Scale (SOFAS)

Consider social and occupational functioning on a continuum from excellent functioning to grossly impaired functioning. Include impairments in functioning due to physical limitations, as well as those due to mental impairments. To be counted, impairment must be a direct consequence of mental and physical health problems; the effects of lack of opportunity and other environmental limitations are not to be considered.

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>Superior functioning in a wide range of activities.</td>
</tr>
<tr>
<td>91</td>
<td>Good functioning in all areas, occupationally and socially effective.</td>
</tr>
<tr>
<td>80</td>
<td>No more than a slight impairment in social, occupational, or school functioning (e.g., infrequent interpersonal conflict, temporarily falling behind in schoolwork).</td>
</tr>
<tr>
<td>70</td>
<td>Some difficulty in social, occupational, or school functioning, but generally functioning well, has some meaningful interpersonal relationships.</td>
</tr>
<tr>
<td>60</td>
<td>Moderate difficulty in social, occupational, or school functioning (e.g., few friends, conflicts with peers or co-workers).</td>
</tr>
<tr>
<td>50</td>
<td>Serious impairment in social, occupational, or school functioning (e.g., no friends, unable to keep a job).</td>
</tr>
<tr>
<td>40</td>
<td>Major impairment in several areas, such as work or school, family relations (e.g., depressed man avoids friends, neglects family, and is unable to work; child frequently beats up younger children, is defiant at home, and is failing at school).</td>
</tr>
<tr>
<td>30</td>
<td>Inability to function in almost all areas (e.g., stays in bed all day; no job, home, or friends).</td>
</tr>
<tr>
<td>20</td>
<td>Occasionally fails to maintain minimal personal hygiene; unable to function independently.</td>
</tr>
<tr>
<td>10</td>
<td>Persistent inability to maintain minimal personal hygiene. Unable to function without harming self or others or without considerable external support (e.g., nursing care and supervision).</td>
</tr>
<tr>
<td>0</td>
<td>Inadequate information.</td>
</tr>
</tbody>
</table>

Appendix 9
NAME:

MALE □ FEMALE □ (CHECK ONE)

DATE OF BIRTH (MM/DD/YY) __/__/__

PLACE OF BIRTH ____________________________

ETHNICITY ____________________________

Please answer each item by checking Y (Yes) or N (No). Answer all items even if unsure of your answer. When you have finished, check over each one to make sure you have answered them.

1. Do you sometimes feel that things you see on the TV or read in the newspaper have a special meaning for you? Y □ N □

2. I sometimes avoid going to places where there will be many people because I will get anxious. Y □ N □

3. Have you had experiences with the supernatural? Y □ N □

4. Have you often mistaken objects or shadows for people, or noises for voices? Y □ N □

5. Other people see me as slightly eccentric (odd). Y □ N □

6. I have little interest in getting to know other people. Y □ N □
7. People sometimes find it hard to understand what I am saying. Y □ N □

8. People sometimes find me aloof and distant. Y □ N □

9. I am sure I am being talked about behind my back. Y □ N □

10. I am aware that people notice me when I go out for a meal or to see a film. Y □ N □

11. I get very nervous when I have to make polite conversation. Y □ N □

12. Do you believe in telepathy (mind-reading)? Y □ N □

13. Have you ever had the sense that some person or force is around you, even though you cannot see anyone? Y □ N □

14. People sometimes comment on my unusual mannerisms and habits. Y □ N □

15. I prefer to keep to myself. Y □ N □

16. I sometimes jump quickly from one topic to another when speaking. Y □ N □

17. I am poor at expressing my true feelings by the way I talk and look. Y □ N □

18. Do you often feel that other people have got it in for you? Y □ N □

19. Do some people drop hints about you or say things with a double meaning? Y □ N □

20. Do you ever get nervous when someone is walking behind you? Y □ N □

21. Are you sometimes sure that other people can tell what you are thinking? Y □ N □

22. When you look at a person, or yourself in a mirror, have you ever seen the face change right before your eyes? Y □ N □

23. Sometimes other people think that I am a little strange. Y □ N □

24. I am mostly quiet when with other people. Y □ N □

25. I sometimes forget what I am trying to say. Y □ N □

26. I rarely laugh and smile. Y □ N □

27. Do you sometimes get concerned that friends or co-workers are not really loyal or trustworthy? Y □ N □

28. Have you ever noticed a common event or object that seemed to be a special sign for you? Y □ N □

29. I get anxious when meeting people for the first time. Y □ N □
30. Do you believe in clairvoyancy (psychic forces, fortune telling) ? Y □ N □

31. I often hear a voice speaking my thoughts aloud. Y □ N □

32. Some people think that I am a very bizarre person. Y □ N □

33. I find it hard to be emotionally close to other people. Y □ N □

34. I often ramble on too much when speaking. Y □ N □

35. My "non-verbal" communication (smiling and nodding during a Y N conversation) is poor. Y □ N □

36. I feel I have to be on my guard even with friends. Y □ N □

37. Do you sometimes see special meanings in advertisements, shop windows, or in the way things are arranged around you ? Y □ N □

38. Do you often feel nervous when you are in a group of unfamiliar people ? Y □ N □

39. Can other people feel your feelings when they are not there ? Y □ N □

40. Have you ever seen things invisible to other people ? Y □ N □

41. Do you feel that there is no-one you are really close to outside of your immediate family, Y □ N □ or people you can confide in or talk to about personal problems ?

42. Some people find me a bit vague and elusive during a conversation. Y □ N □

43. I am poor at returning social courtesies and gestures. Y □ N □

44. Do you often pick up hidden threats or put-downs from what people say or do ? Y □ N □

45. When shopping do you get the feeling that other people are taking notice of you ? Y □ N □

46. I feel very uncomfortable in social situations involving unfamiliar people. Y □ N □

47. Have you had experiences with astrology, seeing the future, UFOs, ESP or a sixth sense ? Y □ N □

48. Do everyday things seem unusually large or small ? Y □ N □

49. Writing letters to friends is more trouble than it is worth. Y □ N □

50. I sometimes use words in unusual ways. Y □ N □
51. I tend to avoid eye contact when conversing with others. Y □ N □

52. Have you found that it is best not to let other people know too much about you? Y □ N □

53. When you see people talking to each other, do you often wonder if they are talking about you? Y □ N □

54. I would feel very anxious if I had to give a speech in front of a large group of people. Y □ N □

55. Have you ever felt that you are communicating with another person telepathically (by mind-reading)? Y □ N □

56. Does your sense of smell sometimes become unusually strong? Y □ N □

57. I tend to keep in the background on social occasions. Y □ N □

58. Do you tend to wander off the topic when having a conversation. Y □ N □

59. I often feel that others have it in for me. Y □ N □

60. Do you sometimes feel that other people are watching you? Y □ N □

61. Do you ever suddenly feel distracted by distant sounds that you are not normally aware of? Y □ N □

Y N 62. I attach little importance to having close friends. Y □ N □

63. Do you sometimes feel that people are talking about you? Y □ N □

64. Are your thoughts sometimes so strong that you can almost hear them? Y □ N □

65. Do you often have to keep an eye out to stop people from taking advantage of you? Y □ N □

66. Do you feel that you are unable to get "close" to people? Y □ N □

67. I am an odd, unusual person. Y □ N □

68. I do not have an expressive and lively way of speaking. Y □ N □

69. I find it hard to communicate clearly what I want to say to people. Y □ N □

70. I have some eccentric (odd) habits. Y □ N □

71. I feel very uneasy talking to people I do not know well. Y □ N □

72. People occasionally comment that my conversation is confusing. Y □ N □
73. I tend to keep my feelings to myself. Y ☐ N ☐

74. People sometimes stare at me because of my odd appearance. Y ☐ N ☐

raine@usc.edu

Home Page

CONTINUE WITH SPQ
Appendix 10
<table>
<thead>
<tr>
<th>Statement</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Seems much more fidgety in social situations than when alone.</td>
<td></td>
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<tr>
<td>2. Expressions on his or her face don't match what he or she is saying.</td>
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<tr>
<td>3. Seems self-confident when interacting with others.</td>
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<tr>
<td>4. When under stress, he or she shows rigid or inflexible patterns of behavior that seem odd.</td>
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<tr>
<td>5. Doesn't recognize when others are trying to take advantage of him or her.</td>
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<tr>
<td>6. Would rather be alone than with others.</td>
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<tr>
<td>7. Is aware of what others are thinking or feeling.</td>
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<tr>
<td>8. Behaves in ways that seem strange or bizarre.</td>
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<tr>
<td>9. Clings to adults, seems too dependent on them.</td>
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<tr>
<td>10. Takes things too literally and doesn't get the real meaning of a conversation.</td>
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<tr>
<td>11. Has good self-confidence.</td>
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<tr>
<td>12. Is able to communicate his or her feelings to others.</td>
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<tr>
<td>13. Is awkward in turn-taking interactions with peers (e.g., doesn't seem to understand the give-and-take of conversations).</td>
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<tr>
<td>15. Is able to understand the meaning of other people's tone of voice and facial expressions.</td>
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<td>16. Avoids eye contact or has unusual eye contact.</td>
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<td>17. Recognizes when something is unfair.</td>
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<tr>
<td>18. Has difficulty making friends, even when trying his or her best.</td>
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<tr>
<td>19. Gets frustrated trying to get ideas across in conversations.</td>
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<tr>
<td>20. Shows unusual sensory interests (e.g., mouthing or spinning objects) or strange ways of playing with toys.</td>
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<tr>
<td>21. Is able to imitate others' actions.</td>
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<tr>
<td>22. Plays appropriately with children his or her age.</td>
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<tr>
<td>23. Does not join group activities unless told to do so.</td>
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<tr>
<td>24. Has more difficulty than other children with changes in his or her routine.</td>
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<tr>
<td>25. Doesn't seem to mind being out of step with or &quot;not on the same wavelength&quot; as others.</td>
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<tr>
<td>26. Offers comfort to others when they are sad.</td>
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<tr>
<td>27. Avoids starting social interactions with peers or adults.</td>
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<tr>
<td>28. Thinks or talks about the same thing over and over.</td>
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<td>29. Is regarded by other children as odd or weird.</td>
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<td>30. Becomes upset in a situation with lots of things going on.</td>
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<td>31. Can't get his or her mind off something once he or she starts thinking about it.</td>
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<tr>
<td>32. Has good personal hygiene.</td>
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<tr>
<td></td>
<td>NOT TRUE</td>
<td>SOMETIMES TRUE</td>
<td>OFTEN TRUE</td>
<td>ALMOST ALWAYS TRUE</td>
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<tr>
<td>33.</td>
<td>Is socially awkward, even when he or she is trying to be polite.</td>
<td>1 2 3 4</td>
<td></td>
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<tr>
<td>34.</td>
<td>Avoids people who want to be emotionally close to him or her.</td>
<td>1 2 3 4</td>
<td></td>
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<tr>
<td>35.</td>
<td>Has trouble keeping up with the flow of a normal conversation.</td>
<td>1 2 3 4</td>
<td></td>
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<tr>
<td>36.</td>
<td>Has difficulty relating to adults.</td>
<td>1 2 3 4</td>
<td></td>
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<tr>
<td>37.</td>
<td>Has difficulty relating to peers.</td>
<td>1 2 3 4</td>
<td></td>
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<tr>
<td>38.</td>
<td>Responds appropriately to mood changes in others (e.g., when a friend's or playmate's mood changes from happy to sad).</td>
<td>1 2 3 4</td>
<td></td>
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<tr>
<td>39.</td>
<td>Has an unusually narrow range of interests.</td>
<td>1 2 3 4</td>
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<tr>
<td>40.</td>
<td>Is imaginative, good at pretending (without losing touch with reality).</td>
<td>1 2 3 4</td>
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<tr>
<td>41.</td>
<td>Wanders aimlessly from one activity to another.</td>
<td>1 2 3 4</td>
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<tr>
<td>42.</td>
<td>Seems overly sensitive to sounds, textures, or smells.</td>
<td>1 2 3 4</td>
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<tr>
<td>43.</td>
<td>Separates easily from caregivers.</td>
<td>1 2 3 4</td>
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<tr>
<td>44.</td>
<td>Doesn’t understand how events relate to one another (cause and effect) the way other children his or her age do.</td>
<td>1 2 3 4</td>
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<tr>
<td>45.</td>
<td>Focusses his or her attention to where others are looking or listening.</td>
<td>1 2 3 4</td>
<td></td>
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<tr>
<td>46.</td>
<td>Has overly serious facial expressions.</td>
<td>1 2 3 4</td>
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<tr>
<td>47.</td>
<td>Is too silly or laughs inappropriately.</td>
<td>1 2 3 4</td>
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<td>48.</td>
<td>Has a sense of humor, understands jokes.</td>
<td>1 2 3 4</td>
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<tr>
<td>49.</td>
<td>Does extremely well at a few tasks, but does not do as well at most other tasks.</td>
<td>1 2 3 4</td>
<td></td>
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<tr>
<td>50.</td>
<td>Has repetitive, odd behaviors such as hand flapping or rocking.</td>
<td>1 2 3 4</td>
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<tr>
<td>51.</td>
<td>Has difficulty answering questions directly and ends up talking around the subject.</td>
<td>1 2 3 4</td>
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<tr>
<td>52.</td>
<td>Knows when he or she is talking too loud or making too much noise.</td>
<td>1 2 3 4</td>
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<tr>
<td>53.</td>
<td>Talks to people with an unusual tone of voice (e.g., talks like a robot or like he or she is giving a lecture).</td>
<td>1 2 3 4</td>
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<tr>
<td>54.</td>
<td>Seems to react to people as if they are objects.</td>
<td>1 2 3 4</td>
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<tr>
<td>55.</td>
<td>Knows when he or she is too close to someone or is invading someone’s space.</td>
<td>1 2 3 4</td>
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<tr>
<td>56.</td>
<td>Walks in between two people who are talking.</td>
<td>1 2 3 4</td>
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<tr>
<td>57.</td>
<td>Gets teased a lot.</td>
<td>1 2 3 4</td>
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<tr>
<td>58.</td>
<td>Concentrates too much on parts of things rather than seeing the whole picture. For example, if asked to describe what happened in a story, he or she may talk only about the kind of clothes the characters were wearing.</td>
<td>1 2 3 4</td>
<td></td>
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<tr>
<td>59.</td>
<td>Is overly suspicious.</td>
<td>1 2 3 4</td>
<td></td>
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<tr>
<td>60.</td>
<td>Is emotionally distant, doesn’t show his or her feelings.</td>
<td>1 2 3 4</td>
<td></td>
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<tr>
<td>61.</td>
<td>Is inflexible, has a hard time changing his or her mind.</td>
<td>1 2 3 4</td>
<td></td>
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<tr>
<td>62.</td>
<td>Gives unusual or illogical reasons for doing things.</td>
<td>1 2 3 4</td>
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<tr>
<td>63.</td>
<td>Touches others in an unusual way (e.g., he or she may touch someone just to make contact and then walk away without saying anything).</td>
<td>1 2 3 4</td>
<td></td>
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<tr>
<td>64.</td>
<td>Is too tense in social settings.</td>
<td>1 2 3 4</td>
<td></td>
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<tr>
<td>65.</td>
<td>Stares or gazes off into space.</td>
<td>1 2 3 4</td>
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</tbody>
</table>
Appendix 11
A few questions ask about several related types of behaviour; please tick the appropriate box if any one of these was present. Although you may be uncertain about whether some behaviours were present or not, please tick “yes” or “no” to every question on the basis of what you think.

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Is he or she able to talk using short phrases or sentences?</td>
<td>O</td>
<td>1</td>
</tr>
<tr>
<td>If NO, proceed to question 9</td>
<td></td>
<td></td>
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<tr>
<td>2. Does he/she ever talk with you just to be friendly (rather than to get something)?</td>
<td>O</td>
<td>1</td>
</tr>
<tr>
<td>3. Can you now have a to and fro “conversation” with him/her that involves taking turns or building on what you said?</td>
<td>O</td>
<td>1</td>
</tr>
<tr>
<td>R4. Has he/she ever used odd phrases or said the same thing over and over in almost exactly the same way? That is, either phrases he/she has heard other people use or the ones he/she has made up?</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>R5. Has he/she ever used socially inappropriate questions or statements? For example, has he/she ever regularly asked personal questions or made personal comments at awkward times?</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>R6. Does he/she ever get his/her pronouns the wrong way round, ie saying you or he for I?</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>R7. Has he/she ever used words that he/she seems to have invented or made up himself/herself, or ever put things in odd, indirect ways, or metaphorical ways of saying things? For example, saying “hot rain” for “steam”</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>R8. Has he/she ever said the same thing over and over in exactly the same way, or insist on you saying the same things over and over again?</td>
<td>1</td>
<td>0</td>
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<tr>
<td>R9. Has he/she ever had things that he/she seemed to have to do in a very particular way or order, or rituals that he/she has to have you do?</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>10. Does his/her facial expression usually seem appropriate to the particular situation, as far as you can tell?</td>
<td>O</td>
<td>1</td>
</tr>
<tr>
<td>R11. Has he/she ever used your hand like a tool, or as if it were part of his/her own body (e.g. pointing with your finger, putting your hand on a doorknob to get you to open the door)?</td>
<td>1</td>
<td>0</td>
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<tr>
<td>R12. Has he/she ever had any interests that pre-occupy him/her and might seem odd to other people (e.g. traffic lights, drainpipes or timetables)?</td>
<td>1</td>
<td>0</td>
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</tbody>
</table>
R13. Has he/she ever seemed to be more interested in a certain part of a toy (eg. spinning the wheels of a car) or an object rather than using the object as it was intended? Yes | No

R14. Has he/she ever had any special interests that were unusual in their intensity but otherwise appropriate for his/her age and peer group (eg. trains, dinosaurs)? Yes | No

R15. Has he/she ever seemed to be unusually interested in the sight, sound, taste or smell of things or people? Yes | No

R16. Has he/she ever had any mannerisms or odd ways of moving his/her hands or fingers, such as flapping, or moving his/her fingers in front of his/her eyes? Yes | No

R17. Has he/she ever had any complicated movements of his/her whole body, such as spinning or repeatedly bouncing up and down? Yes | No

R18. Does he/she ever injure himself/herself deliberately, such as by biting his/her arm or banging his head? Yes | No

R19. Does he/she have any objects (other than a soft toy or comfort blanket) that he/she has to carry around with him/her? Yes | No

20. Does he/she have any particular friends or a best friend? Yes | No

For some behaviours, it is most helpful to focus on the time period between 4th birthday and 5th birthday. You may find it easier to remember how things were at that time by fixing in your mind in relation to key happenings such as starting school, moving house, Christmas time, or any events that are particularly memorable for you as a family.

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
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<tbody>
<tr>
<td>21. When he/she was 4 to 5 did he/she ever spontaneously copy you (or other people), or what you were doing (such as Hoovering, gardening, mending things)?</td>
<td>0</td>
<td>1</td>
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<tr>
<td>22. When he/she was 4 to 5 did he/she ever spontaneously point at things around him/her just to show you things (not because he/she wanted them)?</td>
<td>0</td>
<td>1</td>
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<tr>
<td>23. When he/she was 4 to 5 did he/she ever use gestures, other than pointing or pulling your hand, to let you know what he/she wanted?</td>
<td>0</td>
<td>1</td>
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<tr>
<td>24. When he/she was 4 to 5 did he/she nod his/her head to mean &quot;yes&quot;?</td>
<td>0</td>
<td>1</td>
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<tr>
<td>25. When he/she was 4 to 5 did he/she shake his/her head to mean &quot;no&quot;?</td>
<td>0</td>
<td>1</td>
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<tr>
<td>Question</td>
<td>Yes</td>
<td>No</td>
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<td>------------------------------------------------------------------------</td>
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<tr>
<td>26. When he/she was 4 to 5 did he/she usually look at you directly in</td>
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<tr>
<td>the face when doing things with you or talking with you?</td>
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<td>27. When he/she was 4 to 5 did he/she smile back if someone smiled at</td>
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<tr>
<td>him/her?</td>
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<tr>
<td>28. When he/she was 4 to 5 did he/she ever show you things that</td>
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<tr>
<td>interest him/her to engage your attention?</td>
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<tr>
<td>29. When he/she was 4 to 5 did he/she ever offer to share things other</td>
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<td>1</td>
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<tr>
<td>than food with you?</td>
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<tr>
<td>30. When he/she was 4 to 5 did he/she ever seem to want you to join in</td>
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<td>1</td>
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<tr>
<td>his/her enjoyment of something?</td>
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<td>31. When he/she was 4 to 5 did he/she ever try to comfort you if you</td>
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<td>1</td>
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<tr>
<td>were sad or hurt?</td>
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<tr>
<td>32. Between the ages of 4 to 5 when he/she wanted something or</td>
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<td>1</td>
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<tr>
<td>wanted help, did he/she used to look at you and use gestures with</td>
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<tr>
<td>sounds or words to get your attention?</td>
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<tr>
<td>33. Between the ages of 4 to 5 did he/she show a normal range of</td>
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<tr>
<td>facial expression?</td>
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<tr>
<td>34. When he/she was 4 to 5 did he/she ever spontaneously join in and</td>
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<tr>
<td>try to copy actions in social games – such as The Mulberry Bush or</td>
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<tr>
<td>The Farmer’s in his Den?</td>
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<tr>
<td>35. When he/she was 4 to 5 did he/she play any pretend or make-believe</td>
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<td>1</td>
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<tr>
<td>games?</td>
<td></td>
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<tr>
<td>36. When he/she was 4 to 5 did he/she seem interested in other</td>
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<tr>
<td>children of approximately the same age whom he/she did not know?</td>
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<td>37. When he/she was 4 to 5 did he/she respond positively when another</td>
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<tr>
<td>child approached him/her?</td>
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<tr>
<td>38. When he/she was 4 to 5, if you came into a room and started</td>
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<tr>
<td>talking to him/her without calling his/her name, did he/she usually</td>
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<tr>
<td>look up and pay attention to you?</td>
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<tr>
<td>39. When he/she was 4 to 5 did he/she ever play imaginative games</td>
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<tr>
<td>with another child in such a way that you could tell they understood</td>
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<tr>
<td>what each other was pretending?</td>
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<tr>
<td>40. When he/she was 4 to 5 did he/she play co-operatively in games</td>
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<td>that need some form of joining in with a group of other children, such</td>
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<tr>
<td>as hide and seek or bull games?</td>
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</tbody>
</table>
1. What are the main difficulties (if any) as you see them?

2. In comparison with his/her peers how is the child at present in terms of;

<table>
<thead>
<tr>
<th></th>
<th>Well below average</th>
<th>Below average</th>
<th>Average</th>
<th>Above average</th>
<th>Well above average</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. General level of ability</td>
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<td>2. General level of attainment</td>
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<tr>
<td>3. Ability in reading</td>
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<td>4. Ability in writing</td>
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<td>5. Ability in maths</td>
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<tr>
<td>6. Ability in spelling</td>
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</tbody>
</table>

Is the child receiving any extra help and if so what does this entail?
4. Compared with his / her peers, how would you rate the child in terms of the level of the following?

<table>
<thead>
<tr>
<th>Issue</th>
<th>Major problem</th>
<th>Medium problem</th>
<th>Minor problem</th>
<th>No problem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leaving seat without permission</td>
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<tr>
<td>Fidgeting or squirming</td>
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<tr>
<td>Excessive &amp; inappropriate running</td>
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<tr>
<td>Excessively noisy in play</td>
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<tr>
<td>Excessive motor activity</td>
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<tr>
<td>Excessive &amp; inappropriate talking</td>
<td></td>
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<tr>
<td>Difficulty turn taking</td>
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<tr>
<td>Butting into others' conversations</td>
<td></td>
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<tr>
<td>Blurtling answers out of turn</td>
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<tr>
<td>Forgetfulness</td>
<td></td>
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<tr>
<td>Inability to listen to instructions</td>
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<tr>
<td>Inability to complete task</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Poor organisation</td>
<td></td>
<td></td>
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<tr>
<td>Careless errors in work</td>
<td></td>
<td></td>
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<tr>
<td>Easily distracted</td>
<td></td>
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<tr>
<td>Inability to sustain attention</td>
<td></td>
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<tr>
<td>Dislike of tasks requiring concentration</td>
<td></td>
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<tr>
<td>Losing things necessary for certain tasks – eg books</td>
<td></td>
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</tr>
</tbody>
</table>

5. How would you rate the following?

<table>
<thead>
<tr>
<th>Topic</th>
<th>Well below average</th>
<th>Below average</th>
<th>Average</th>
<th>Above average</th>
<th>Well above average</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Self esteem / confidence</td>
<td></td>
<td></td>
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<tr>
<td>2. Response to rules and discipline</td>
<td></td>
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<tr>
<td>3. Attendance record</td>
<td></td>
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</tr>
</tbody>
</table>

Additional Comments:
6. In terms of peer relationships, how would you rate the following on a scale of 0 to 10?

<table>
<thead>
<tr>
<th>Interest in other children</th>
<th>0</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>None at all</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response to other children's approaches</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Withdraws</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>Enjoys / Participates</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>None / isolated</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>Several close friends</td>
<td>0</td>
<td>10</td>
</tr>
</tbody>
</table>

Please comment on any additional concerns regarding the child’s ability to relate to others:

7. How would you describe the child’s emotional state?

8. What strategies have been tried with this child? What has worked?

9. Have you any additional concerns?

Please return this form to ________________________ at the following address:

or telephone: ________________________

Date form completed: ________________________
Signed: ________________________
Contact telephone: ________________________
Appendix 13
Conners’ Parent Rating Scale—Revised (S)
by C. Keith Conners, Ph.D.

Child’s ID: ___________________________ Gender: M F
Birthdate: / / Age: ______ School Grade: ______

Month Day Year

Parent’s ID: ___________________________ Today’s Date: / / 

Month Day Year

Instructions: Below are a number of common problems that children have. Please rate each item according to your child’s behavior in the last month. For each item, ask yourself, “How much of a problem has this been in the last month?”, and circle the best answer for each one. If none, not at all, seldom, or very infrequently, you would circle 0. If very much true, or it occurs very often or frequently, you would circle 3. You would circle 1 or 2 for ratings in between. Please respond to each item.

1. Inattentive, easily distracted .................................................. 0 1 2 3
2. Angry and resentful .................................................................. 0 1 2 3
3. Difficulty doing or completing homework ............................. 0 1 2 3
4. Is always “on the go” or acts as if driven by a motor ............... 0 1 2 3
5. Short attention span ............................................................... 0 1 2 3
6. Argues with adults ................................................................ 0 1 2 3
7. Fidgets with hands or feet or squirms in seat ......................... 0 1 2 3
8. Fails to complete assignments ............................................... 0 1 2 3
9. Hard to control in malls or while grocery shopping .............. 0 1 2 3
10. Messy or disorganized at home or school .............................. 0 1 2 3
11. Loses temper ....................................................................... 0 1 2 3
12. Needs close supervision to get through assignments ........... 0 1 2 3
13. Only attends if it is something he/she is very interested in ..... 0 1 2 3
14. Runs about or climbs excessively in situations where it is inappropriate ..
15. Distractibility or attention span a problem ......................... 0 1 2 3
16. Irritable ............................................................................. 0 1 2 3
17. Avoids, expresses reluctance about, or has difficulties engaging in tasks that require sustained mental effort (such as schoolwork or homework) ....
18. Restless in the “squirming” sense ........................................... 0 1 2 3
19. Gets distracted when given instructions to do something .......... 0 1 2 3
20. Actively defies or refuses to comply with adults’ requests ...... 0 1 2 3
21. Has trouble concentrating in class ........................................ 0 1 2 3
22. Has difficulty waiting in lines or awaiting turn in games or group situations
23. Leaves seat in classroom or in other situations in which remaining seated is expected ......................................................... 0 1 2 3
24. Deliberately does things that annoy other people .................. 0 1 2 3
25. Does not follow through on instructions and fails to finish schoolwork, chores or duties in the workplace (not due to oppositional behavior or failure to understand instructions) .......................... 0 1 2 3
26. Has difficulty playing or engaging in leisure activities quietly ................................................................. 0 1 2 3
27. Easily frustrated in efforts ...................................................... 0 1 2 3

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In Canada, 3770 Victoria Park Ave., Toronto, ON M2H 3M6, 1-800-268-0611, 1-416-492-2627, Fax 1-416-492-3343.
Profile for Males: Conners’ Parent Rating Scale–Revised (S)

<table>
<thead>
<tr>
<th>Child’s ID:</th>
<th>Gender: M F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birthdate:</td>
<td>Age:</td>
</tr>
<tr>
<td>Month</td>
<td>Day</td>
</tr>
<tr>
<td>Parent’s ID:</td>
<td>Today’s Date:</td>
</tr>
<tr>
<td>Month</td>
<td>Day</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>A. Oppositional</th>
<th>B. Cognitive Problems/ Impulsivity</th>
<th>C. Hyperactivity</th>
<th>D. Conners’ ADHD Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>T 1 2 3 4 5 1 2 3 4 5 1 2 3 4 5</td>
<td>T 6 7 8 9 10</td>
<td>T 11 12 13 14 15</td>
<td>T 16 17 18</td>
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<td>22</td>
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<td>24</td>
<td>25</td>
</tr>
</tbody>
</table>

Note:  
For age-groups:  
Column 1: ages 3 to 5  
Column 2: ages 6 to 8  
Column 3: ages 9 to 11  
Column 4: ages 12 to 14  
Column 5: ages 15 to 17  
Please see back of scoring sheet for Scale Descriptions  
Please see reverse for CPRS–R Female Profile
<table>
<thead>
<tr>
<th>I. Please list the sports your child most likes to take part in. For example: swimming, baseball, skating, skate boarding, bike riding, fishing, etc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ None</td>
</tr>
<tr>
<td>□ a.</td>
</tr>
<tr>
<td>□ b.</td>
</tr>
<tr>
<td>□ c.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>II. Please list your child's favorite hobbies, activities, and games, other than sports. For example: stamps, dolls, books, piano, crafts, cars, computers, singing, etc. (Do not include listening to radio or TV.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ None</td>
</tr>
<tr>
<td>□ a.</td>
</tr>
<tr>
<td>□ b.</td>
</tr>
<tr>
<td>□ c.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>III. Please list any organizations, clubs, teams, or groups your child belongs to.</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ None</td>
</tr>
<tr>
<td>□ a.</td>
</tr>
<tr>
<td>□ b.</td>
</tr>
<tr>
<td>□ c.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IV. Please list any jobs or chores your child has. For example: paper route, babysitting, making bed, working in store, etc. (Include both paid and unpaid jobs and chores.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ None</td>
</tr>
<tr>
<td>□ a.</td>
</tr>
<tr>
<td>□ b.</td>
</tr>
<tr>
<td>□ c.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Compared to others of the same age, how much time does he/she spend in each?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less Than Average</td>
</tr>
<tr>
<td>-------------------</td>
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<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Compared to others of the same age, how well does he/she do each one?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Below Average</td>
</tr>
<tr>
<td>---------------</td>
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</tbody>
</table>

Be sure to answer all items. Then see other side.
Please print. Be sure to answer all items.

V. 1. About how many close friends does your child have? (Do not include brothers & sisters)
- None  [ ]  1  [ ]  2 or 3  [ ]  4 or more  [ ]

V. 2. About how many times a week does your child do things with any friends outside of regular school hours? (Do not include brothers & sisters)
- Less than 1  [ ]  1 or 2  [ ]  3 or more  [ ]

VI. Compared to others of his/her age, how well does your child:
- Get along with his/her brothers & sisters? [ ] Worse [ ] Average [ ] Better
- Get along with other kids? [ ] Worse [ ] Average [ ] Better
- Behave with his/her parents? [ ] Worse [ ] Average [ ] Better
- Play and work alone? [ ] Worse [ ] Average [ ] Better
- Has no brothers or sisters  [ ]

VII. 1. Performance in academic subjects. [ ] Does not attend school because

Check a box for each subject that child takes
- a. Reading, English, or Language Arts
- b. History or Social Studies
- c. Arithmetic or Math
- d. Science
- e. Other academic subjects—examples: computer courses, foreign language, business. Do not include gym, shop, driver's ed., or other nonacademic subjects.
- f.
- g.
- h.
- i.
- j.
- k.
- l.
- m.
- n.
- o.
- p.
- q.
- r.
- s.
- t.
- u.
- v.
- w.
- x.
- y.
- z.

Falling [ ] Below Average [ ] Average [ ] Above Average [ ]

2. Does your child receive special education or remedial services or attend a special class or special school? [ ] Yes—kind of services, class, or school:

3. Has your child repeated any grades? [ ] No [ ] Yes—grades and reasons:

4. Has your child had any academic or other problems in school? [ ] No [ ] Yes—please describe:

Who had these problems? ____________________________
Has these problems ended? [ ] No [ ] Yes—when?

Does your child have any illness or disability (either physical or mental)? [ ] No [ ] Yes—please describe:

What concerns you most about your child?

Please describe the best things about your child.
Below is a list of items that describe children and youths. For each item that describes your child now or within the past 6 months, please circle the 2 if the item is very true or often true of your child. Circle the 1 if the item is somewhat or sometimes true of your child. If the item is not true of your child, circle the 0. Please answer all items as well as you can, even if some do not seem to apply to your child.

<table>
<thead>
<tr>
<th>0 = Not True (as far as you know)</th>
<th>1 = Somewhat or Sometimes True</th>
<th>2 = Very True or Often True</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 1 2 1. Acts too young for his/her age</td>
<td>0 1 2 32. Feels he/she has to be perfect</td>
<td></td>
</tr>
<tr>
<td>0 1 2 2. Drinks alcohol without parents approval (describe):</td>
<td>0 1 2 33. Feels or complains that no one loves him/her</td>
<td></td>
</tr>
<tr>
<td>0 1 2 3. Argues a lot</td>
<td>0 1 2 34. Feels others are out to get him/her</td>
<td></td>
</tr>
<tr>
<td>0 1 2 4. Fails to finish things he/she starts</td>
<td>0 1 2 35. Feels worthless or inferior</td>
<td></td>
</tr>
<tr>
<td>0 1 2 5. There is very little he/she enjoys</td>
<td>0 1 2 36. Gets hurt a lot, accident-prone</td>
<td></td>
</tr>
<tr>
<td>0 1 2 6. Bowel movements outside toilet</td>
<td>0 1 2 37. Gets in many fights</td>
<td></td>
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<tr>
<td>0 1 2 7. Bragging, boasting</td>
<td>0 1 2 38. Gets teased a lot</td>
<td></td>
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<tr>
<td>0 1 2 8. Can’t concentrate, can’t pay attention for long</td>
<td>0 1 2 39. Hangs around with others who get in trouble</td>
<td></td>
</tr>
<tr>
<td>0 1 2 9. Can’t get his/her mind off certain thoughts; obsessions (describe):</td>
<td>0 1 2 40. Hears sounds and things that aren’t there (describe):</td>
<td></td>
</tr>
<tr>
<td>0 1 2 10. Can’t sit still, restless, or hyperactive</td>
<td>0 1 2 41. Impulsive or acts without thinking</td>
<td></td>
</tr>
<tr>
<td>0 1 2 11. Clings to adults or too dependent</td>
<td>0 1 2 42. Would rather be alone than with others</td>
<td></td>
</tr>
<tr>
<td>0 1 2 12. Complains of loneliness</td>
<td>0 1 2 43. Lies or cheats</td>
<td></td>
</tr>
<tr>
<td>0 1 2 13. Confused or seems to be in a fog</td>
<td>0 1 2 44. Bites his nails</td>
<td></td>
</tr>
<tr>
<td>0 1 2 14. Cries a lot</td>
<td>0 1 2 45. Nervous, nightfright, or tense</td>
<td></td>
</tr>
<tr>
<td>0 1 2 15. Cruel to animals</td>
<td>0 1 2 46. Nervous movements or twitching (describe):</td>
<td></td>
</tr>
<tr>
<td>0 1 2 16. Cruelty, bullying, or meanness to others</td>
<td>0 1 2 47. Nightmares</td>
<td></td>
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<tr>
<td>0 1 2 17. Daydreams or gets lost in his/her thoughts</td>
<td>0 1 2 48. Not liked by other kids</td>
<td></td>
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<tr>
<td>0 1 2 18. Deliberately harms self or animals at home</td>
<td>0 1 2 49. Constipated, doesn’t move bowels</td>
<td></td>
</tr>
<tr>
<td>0 1 2 19. Demands a lot of attention</td>
<td>0 1 2 50. Too fearful or anxious</td>
<td></td>
</tr>
<tr>
<td>0 1 2 20. Destroys his/her things</td>
<td>0 1 2 51. Feels dizzy or lightheaded</td>
<td></td>
</tr>
<tr>
<td>0 1 2 21. Destroys things belonging to others or family or others</td>
<td>0 1 2 52. Feels too guilty</td>
<td></td>
</tr>
<tr>
<td>0 1 2 22. Dependent at home</td>
<td>0 1 2 53. Overeating</td>
<td></td>
</tr>
<tr>
<td>0 1 2 23. Disobedient at school</td>
<td>0 1 2 54. Overtired without good reason</td>
<td></td>
</tr>
<tr>
<td>0 1 2 24. Doesn’t do as asked</td>
<td>0 1 2 55. Overweight</td>
<td></td>
</tr>
<tr>
<td>0 1 2 25. Doesn’t get along with other kids</td>
<td>0 1 2 56. Physical problems without known medical cause:</td>
<td></td>
</tr>
<tr>
<td>0 1 2 26. Doesn’t seem to feel guilty after misbehaving</td>
<td>a. Aches or pains (not stomach or headaches)</td>
<td></td>
</tr>
<tr>
<td>0 1 2 27. Edibles</td>
<td>b. Headaches</td>
<td></td>
</tr>
<tr>
<td>0 1 2 28. Breaks rules at home, school, or elsewhere</td>
<td>c. Nausea, feels sick</td>
<td></td>
</tr>
<tr>
<td>0 1 2 29. Fears certain animals, situations, or places, other than school (describe):</td>
<td>d. Problems with eyes (not if corrected by glasses) (describe):</td>
<td></td>
</tr>
<tr>
<td>0 1 2 30. Fears going to school</td>
<td>e. Rashes or other skin problems</td>
<td></td>
</tr>
<tr>
<td>0 1 2 31. Fears he/she might think or do something bad</td>
<td>f. Stomachaches</td>
<td></td>
</tr>
</tbody>
</table>

56. Physical problems without known medical cause:

a. Aches or pains (not stomach or headaches)
b. Headaches
c. Nausea, feels sick
d. Problems with eyes (not if corrected by glasses) (describe):
e. Rashes or other skin problems
f. Stomachaches
g. Vomiting, throwing up
h. Other (describe):
<table>
<thead>
<tr>
<th>Item</th>
<th>0 = Not True (as far as you know)</th>
<th>1 = Somewhat or Sometimes True</th>
<th>2 = Very True or Often True</th>
</tr>
</thead>
<tbody>
<tr>
<td>57.</td>
<td>Physically attacks people</td>
<td></td>
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<tr>
<td>58.</td>
<td>Picks nose, skin, or other parts of body (describe):</td>
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<tr>
<td>59.</td>
<td>Plays with own sex parts in public</td>
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<tr>
<td>60.</td>
<td>Plays with own sex parts too much</td>
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<tr>
<td>61.</td>
<td>Poor school work</td>
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<tr>
<td>62.</td>
<td>Poorly coordinated or clumsy</td>
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<tr>
<td>63.</td>
<td>Prefers being with older kids</td>
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<tr>
<td>64.</td>
<td>Prefers being with younger kids</td>
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<tr>
<td>65.</td>
<td>Refuses to talk</td>
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<td>66.</td>
<td>Repeats certain acts over and over; compulsions (describe):</td>
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<td>67.</td>
<td>Runs away from home</td>
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<td>68.</td>
<td>Screams a lot</td>
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<tr>
<td>69.</td>
<td>Secrecy, keeps things to self</td>
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<tr>
<td>70.</td>
<td>Sees things that aren't there (describe):</td>
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<tr>
<td>71.</td>
<td>Self-conscious or easily embarrassed</td>
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<td></td>
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<tr>
<td>72.</td>
<td>Sets fires</td>
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<tr>
<td>73.</td>
<td>Sexual problems (describe):</td>
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<td>74.</td>
<td>Showing off or clowning</td>
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<td>75.</td>
<td>Too shy or timid</td>
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<tr>
<td>76.</td>
<td>Sleeps less than most kids</td>
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<tr>
<td>77.</td>
<td>Sleeps more than most kids the day and/or night (describe):</td>
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<tr>
<td>78.</td>
<td>Inattentive or easily distracted</td>
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<td>79.</td>
<td>Speeches slowly (describe):</td>
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<td>80.</td>
<td>Stares blankly</td>
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<tr>
<td>81.</td>
<td>Stays at home</td>
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<td>82.</td>
<td>Stays outside the home</td>
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<tr>
<td>83.</td>
<td>Stores up too many things he/she doesn't need (describe):</td>
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</tbody>
</table>

**Please be sure you answered all items.**
Appendix 15
For each item, please mark the box for Not True, Somewhat True or Certainly True. It would help us if you answered all items as best you can even if you are not absolutely certain or the item seems daft! Please give your answers on the basis of the child’s behaviour over the last six months or this school year.

**Child’s Name**

**Date of Birth**

<table>
<thead>
<tr>
<th>Item</th>
<th>Not True</th>
<th>Somewhat True</th>
<th>Certainly True</th>
</tr>
</thead>
<tbody>
<tr>
<td>Considerate of other people’s feelings</td>
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<tr>
<td>Restless, overactive, cannot stay still for long</td>
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<tr>
<td>Often complains of headaches, stomach-aches or sickness</td>
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<tr>
<td>Shares readily with other children (treats, toys, pencils etc.)</td>
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<tr>
<td>Often has temper tantrums or hot tempers</td>
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<tr>
<td>Rather solitary, tends to play alone</td>
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<tr>
<td>Generally obedient, usually does what adults request</td>
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<tr>
<td>Many worries, often seems worried</td>
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<tr>
<td>Helpful if someone is hurt, upset or feeling ill</td>
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<tr>
<td>Constantly fidgeting or squirming</td>
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<tr>
<td>Has at least one good friend</td>
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<td>Often fights with other children or bullies them</td>
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<tr>
<td>Often unhappy, down-hearted or tearful</td>
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<tr>
<td>Generally liked by other children</td>
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<tr>
<td>Easily distracted, concentration wanders</td>
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<tr>
<td>Nervous or clingy in new situations, easily loses confidence</td>
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<tr>
<td>Kind to younger children</td>
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<td>Often lies or cheats</td>
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<tr>
<td>Picked on or bullied by other children</td>
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<tr>
<td>Often volunteers to help others (parents, teachers, other children)</td>
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<td>Thinks things out before acting</td>
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<td>Steals from home, school or elsewhere</td>
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<tr>
<td>Gets on better with adults than with other children</td>
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<tr>
<td>Many fears, easily scared</td>
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<tr>
<td>Sees tasks through to the end, good attention span</td>
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</tbody>
</table>

**Signature**

**Date**

Parent/Teacher/Other (please specify:)

*Thank you very much for your help*