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3D laser surface imaging and geometric morphometrics resolve frontonasal dysmorphology in schizophrenia

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Abstract

Background: Though a role for early developmental disturbance(s) in schizophrenia is postulated, it has proved difficult to identify 'hard', biological evidence. The brain and face emerge in embryological intimacy, such that in neurodevelopmental disorders, brain dysmorphogenesis is accompanied by facial dysmorphogenesis.

Methods: 3D laser surface imaging was used to capture the facial surface of patients and controls in 37 male and 32 female patients who satisfied DSM-IV criteria for schizophrenia in comparison with 58 male and 34 female control subjects. Surface images were analysed using geometric morphometrics and 3D visualisations to identify domains of facial shape that distinguish patients from controls.

Results: Both male and particularly female patients evidenced significant facial dysmorphology. There was narrowing and reduction of the mid/lower face and frontonasal prominences, including reduced width and posterior displacement of the mouth, lips and chin; increased width of the upper face, mandible and skull base, with lateral displacement of the cheeks, eyes and orbits, and anterior displacement of the superior margins of the orbits.

Conclusions: The frontonasal prominence, which enjoys the most intimate embryological relationship with the anterior brain and also orchestrates aspects of development in maxillary and mandibular domains, evidences a characteristic topography of dysmorphogenesis in schizophrenia.

Introduction

While much theorising posits an important role for early developmental disturbance(s) in the origins of schizophrenia (Waddington et al 1999a; Lewis and Lieberman 2000; Thaker and Carpenter 2001; Freedman 2003; McGrath et al 2003; Rapoport et al 2005), the biological basis of this process is poorly understood. The majority of evidence is epidemiological and has identified a number of adversities operating over intrauterine life to be associated with increased risk in offspring (Murray et al 2003; Brown 2006). However, both temporal resolution and biological evidence for resultant developmental perturbation are limited.

Well recognised structural brain pathology in schizophrenia on neuroimaging and in postmortem studies, in the absence of neuropathological evidence for any neurodegenerative process as currently conceptualised (Harrison 1999; Waddington et al 1999a; Lewis and Lieberman 2000; Thaker and Carpenter 2001; Freedman 2003), constitutes only indirect biological evidence for developmental disturbance(s). Some neuropathological findings indicate abnormalities of neuronal cytoarchitecture that implicate a dysplastic process (Waddington et al 1999a; Harrison 1999; Benes 2000; Arnold and Rioux 2001), but these are of uncertain developmental origin. This fundamental research front would be advanced by an index of early developmental disturbance that could be accessed directly in living patients and would inform incisively on the nature of the underlying developmental abnormality.

Minor physical anomalies are slight anatomical malformations of body regions that share the ectodermal origins of the brain; their presence indicates adverse events acting

over the first or second trimester and they occur to excess in most disorders of early neurodevelopmental origin (Waddington et al 1999a,b; Waldrop 1968; Smith 1988). Thus, though found reliably to be over-represented in schizophrenia (Lane et al 1996; McNeil et al 2000), minor physical anomalies constitute a non-specific, qualitative indicator of early biological adversity.

Over early fetal life, the anterior brain and face evolve in embryological intimacy (Waddington et al 1999b; DeMyer et al 1964; Diewert and Lozanoff 1993a,b; Diewert et al 1993; Schneider et al 2001; Marcucio et al 2005). This unity is responsible for facial dysmorphogenesis in disorders of early brain development (Kjaer 1995), ranging from major chromosomal abnormalities such as Down's syndrome (Allanson et al 1993) to less readily recognisable conditions such as velocardiofacial syndrome (Murphy and Owen 2001). In a complementary manner, individuals with facial dysmorphogenesis such as cleft lip/palate have been reported to show abnormalities of brain structure (Nopoulos et al 2002a) in association with cognitive deficits (Nopoulos et al 2002b). Anthropometric techniques have indicated subtle facial dysmorphology also in schizophrenia. We (Lane et al 1997) and others (McGrath et al 2002; Donovan-Lepore et al 2006) have noted altered proportions along the midline together with abnormalities of the eyes and widening of the skull base.

Because the developmental biology of facial morphogenesis is considerably better understood than is brain morphogenesis, resolution of the topography of facial dysmorphogenesis in schizophrenia may lead to increased understanding of brain dysmorphogenesis. As facial development is an intrinsically 3D process, anthropometrics [i.e. distances between anatomical landmarks] fails to access fundamental, geometric aspects of this process. As an interim approach, we have recently elaborated facial

dysmorphology in patients with schizophrenia using limited 3D configurations reconstructed from linear measurements (Hennessy et al 2004). However, 3D digitisation technologies now allow facial surfaces to be recorded in their entirety and landmark coordinates obtained (Hennessy et al 2002, 2005; Hammond et al 2004); in a complementary manner, geometric morphometrics, which analyses 3D landmark coordinates directly, provides the basis for relating shape to other biological variables both statistically and visually (Hennessy et al 2005; O'Higgins and Jones 1998; Dryden and Mardia 1998). We have recently applied portable, hand-held 3D laser surface imaging to specify statistically and anatomically the nature of sexual dimorphism in human facial morphogenesis (Hennessy et al 2002) and the relation of facial shape to cognitive function (Hennessy et al 2005, 2006). However, such studies involve a conventional approach based on selected anatomical landmarks which renders much of the facial surface uninformative.

The increasing availability of biological surface data has been accompanied by developments in 3D statistical analysis of surfaces which is now an important research front in morphometrics. In particular, an elegant method has recently been developed for interrogating the entire facial surface using thin plate splines to identify interpolated landmarks, i.e. pseudo-landmarks (Hutton et al 2003). However, while this substantial increase in detail over the facial surface indicated topographically distinct abnormalities of facial shape in developmental disorders such as velocardiofacial syndrome (Hammond et al 2004), statistical approaches to comparative analysis have been lacking. We have recently implemented an algorithm elaborated from this procedure to analyse, both statistically and visually, sexual dimorphism and its relationship to cognitive function in

normal subjects using interpolated landmarks over the entire facial surface (Hennessy et al 2005).

In this report we describe the application of 3D laser surface imaging and these geometric morphometric methods to investigate facial dysmorphology in patients with schizophrenia.

Methods and Materials

Subjects

Approval for this study protocol was obtained from the Research Ethics Committee of the North Eastern Health Board; all subjects gave written, informed consent to their participation in the study. Patients were drawn from attendees of Cavan-Monaghan Mental Health Service who were under the age of 65; each satisfied DSM-IV criteria (American Psychiatric Association 1994) for schizophrenia or schizoaffective disorder as described previously (Scully et al 2004; Baldwin et al 2005). Control subjects under the age of 65 were drawn from individual and community group volunteers in Cavan-Monaghan; on semi-structured interview with the same psychiatrist who assessed patients, those individuals giving a personal or family history of psychotic illness or suicide in a first degree relative were excluded. To ensure ethnic homogeneity, all subjects, their parents and grandparents originated from and were born in Ireland, Scotland, Wales or England; all were white. Subjects were questioned about any craniofacial trauma or surgery and individuals who reported such events were excluded. There were 37 male patients [age 46.5 (SD 12.4), range 23-64 years], 58 male controls

[age 42.7 (SD 9.7), range 23-64 years], 32 female patients [age 49.4 (SD 10.3), range 24-64 years] and 34 female controls [age 45.8 (SD 7.5), range 24-58 years].

3D Laser Surface Imaging

Facial surfaces were recorded using a portable, handheld Polhemus FastScan laser scanner (Hennessy et al 2002, 2005). A typical surface, consisting of ~80,000 points, is shown in **Figure 1**.

Pseudo-Landmark and Landmark-Based Approaches

To specify pseudo-landmarks [i.e. interpolated landmarks] over the whole facial surface, a smooth interpolation using thin plate splines was employed (Hutton et al 2003), as described recently in detail (Hennessy et al 2005). Briefly, a facial surface of low resolution is generated as a template and edited to remove surface points above the supraorbital ridge and below the inferior mandibular margin. Each high resolution surface is splined onto the template using as control points a set of 26 conventional landmarks; this consists of 24 landmarks described below together with an extra pair to improve the accuracy of the spline (see legend to **Figure 1**). Points of correspondence between each template vertex and the closest point on the surface are interpolated as pseudo-landmarks. Previous work (Hennessy et al 2005) has shown that results are largely insensitive to the number of pseudo-landmarks provided this is greater than approximately 300. Here, 1694 pseudo-landmarks distributed over the entire facial surface were selected to provide sufficient resolution for visualisation of facial features, particularly the mouth and frontonasal prominences (Hennessy et al 2005).

Twenty-four 3D conventional landmarks (Farkas 1994), were identified on these surfaces (see legend to **Figure 1**). They were located by the same investigator, blind to diagnostic category, with the aid of conventional vertical and horizontal profiles as described previously (Hennessy et al 2002). Error in location was minimised by landmarking each facial scan four times: twice using the original facial surface and twice with the facial surface mirrored, to avoid systematic asymmetric landmark placement, with the results averaged. A previous study using such data demonstrated intra-class correlation coefficients for interlandmark distances of 0.88 - 0.99 (Hennessy et al 2002).

Geometric Morphometrics

The *form* of an object is a combination of *shape* and *size*, such that a golf ball and a basketball have the same shape but different size, while a water-filled balloon retains a constant size when its shape is manipulated; surfaces thus record facial form. Facial shape and size were analysed separately by scaling the original landmark sets to unit size as measured by centroid size, which quantifies the dispersion of the configuration of the landmark set as the square root of the sum of squared Euclidean distances of landmarks from their centre (Dryden and Mardia 1998).

Covariance of facial shape with diagnostic category was analysed using geometric morphometrics, which allows shape covariance to be tested numerically and expressed visually. The analytical strategy for this work is based on that developed for the study of sexual dimorphism, as previously described in detail (Hennessy et al 2002, 2005); technical expositions (Rohlf 1999a,b) and summaries of geometric morphometrics for biological practitioners (O'Higgins 2000) are available. Sets of scaled landmark coordinates were aligned with a registration algorithm (Generalised Procrustes Analysis)

that has appropriate statistical properties. The transformed landmark residuals (i.e. differences from mean) approximate Procrustes tangent space coordinates and thus can be analysed statistically (O'Higgins and Jones 1998). Transformed landmark residuals were analysed by principal component [PC] analysis to compute the major elements in shape variability within the sample and PCs with eigenvalues greater than the mean value, a standard selection criterion (Mardia et al 1979), were selected for testing and modelling; this enables most of the shape variance to be captured in a modest number of PCs which is particularly advantageous for the pseudo-landmark sets, whose shape space has high dimensionality (Hammond et al 2004). Following testing for group difference, significant differences were modelled and visualised by regression techniques.

Shape Analysis and Visualisation

These followed previously described procedures (Hennessy et al 2002, 2005). In outline, Goodall's F test, a well-established and powerful test of significance for shape difference between two groups (Rohlf 2000), was applied in its permutation version as this makes no assumptions about isotropic landmark variance and is applicable to landmark sets of arbitrary size. In addition, Hotelling's T^2 test, a parametric multivariate test of group difference, was applied to the selected PC scores. This test inversely weights factors by the inverse of their variance and can be considered a test of whether two groups can be distinguished, even if their differences are small. The tests were applied separately to male and female groups.

In order to model and localise significant group differences, logistic regression was carried out with diagnostic category, i.e. patient vs. control, as the dependent variable and PCs as independent variables to establish which PCs of shape contributed to shape

discrimination by diagnosis. A parsimonious regression model was produced using a forward stepwise procedure, with R^2 values calculated using the ordinary least squares method (Menard 2000). The model generates predicted values of the diagnosis variable in the range 0-1. Models were generated separately for male and female groups.

Parsimonious regression models were visualised by multivariate regression of significant shape PCs onto the predicted values for the diagnosis variable. The β coefficients of the model, which have the units of shape/diagnosis, were visualised by adding appropriately weighted eigenvectors to the Procrustes mean (O'Higgins 2000). This causes the coordinates of the Procrustes mean to be displaced and thus the mean face to be morphed along the patient-control discrimination axis. The morphing is displayed dynamically, with multiple views to visualise the anatomy underlying statistical shape change. The descriptions of morphings in subsequent sections uses the language of displacements to refer to coordinate movements with respect to the mean.

For the facial surface it is not feasible to view both the transformed surface and the mean surface and so the transformed surface is viewed dynamically with numerical information colour coded to aid understanding (Hennessy et al 2005): (a) change in surface vector area is coded as red [expanded] or blue [contracted]; (b) direction of displacement of surface is coded as red [angled outwards] or blue [angled inwards]; (c) length of displacement vector, in any direction, is coded as shades of red [darker shades code greater vector length].

For the 24 landmarks sets, the transformation can be viewed by displaying both the transformed landmark configuration and the mean. In order to test whether differences between schizophrenia and control groups depended on gender, the male and female

landmark data were pooled and Procrustes ANOVA (Klingenberg and McIntyre 1998) was applied.

Results

Facial Surface Analysis

Centroid size was slightly but significantly larger in female patients [2705.0 (SD 105.9) mm; +1.8%] than in female controls [2656.1 (SD 78.0) mm; $t = 2.14$, $p < .05$], but did not differ between male patients [2878.9 (SD 106.3) mm] and male controls [2878.1 (SD 87.2) mm; +0.03%, $p = .97$]. All subsequent analyses of shape are independent of centroid size.

Among females 12 PCs, describing 84.5% of the total shape variance, were selected. Both Goodall's test [$p < .005$] and Hotelling's test [$T^2 = 78.4$, $p < .001$] indicated overall facial shape in patients to differ from that in controls. The parsimonious patient-control discrimination model for females [$R^2 = 57.1\%$] consisted of six significant shape PCs: PC1: $\beta = 2979.6$, $SE\beta = 1020.3$, $p < .01$; PC2: $\beta = -3803.1$, $SE\beta = 1641.8$, $p < .05$; PC4: $\beta = 8853.0$, $SE\beta = 3050.5$, $p < .01$; PC7: $\beta = -7058.0$, $SE\beta = 3139.3$, $p < .05$; PC11: $\beta = -11378.5$, $SE\beta = 4581.7$, $p < .05$; PC12: $\beta = -10751.9$, $SE\beta = 4068.3$, $p < .01$. This model is visualised in **Figure 2**, where the mean female face is shown, together with the facial surface at positions along the patient-control discriminating axis which exaggerate the features of 'patientness' and 'controlness' by a factor of approximately 5 to render them visible. In **Figure 3**, the mean face is colour coded to highlight topographically those geometric features which distinguish female patients from female controls. **Figure 4,**

available online, depicts as a dynamic video sequence the transformation represented statically in **Figure 2**.

In overall terms, the female patient face is laterally broad and vertically short, with the medial facial features reduced in relative size and displaced posteriorly. Considered in more detail, the female patient face has the following features: the superior orbital margins are displaced anteriorly and inferiorly and the lateral margins are displaced laterally; the nose is shortened and displaced posteriorly, with the nasal bridge displaced inferiorly, the tip of the nose turned up and the alar base widened; the lips, mouth and chin are narrowed and displaced posteriorly and superiorly; the mandible is widened, particularly posteriorly; the cheeks are displaced outwards.

Among males 14 PCs, describing 85.0% of the total shape variance, were selected. While Goodall's test did not indicate a difference in overall facial shape between male patients and controls [$p = .51$], Hotelling's test was significant [$T^2 = 31.2$, $p = .04$]; the greater power of Hotelling's test is to be expected since it weights the later discriminating PCs [see below], which have small variance, by the inverse of their variance such that small differences in overall facial shape allow discrimination between male patients and controls. The parsimonious schizophrenia-control discrimination model for males [$R^2 = 13.7\%$] consisted of two significant shape PCs: PC11: $\beta = 4815.9$, $SE\beta = 2328.4$, $p < .01$; PC13: $\beta = 9238.4$, $SE\beta = 3094.3$, $p < .01$. This model is visualised in **Figure 2**, where the mean male face is shown, together with the facial surface at positions along the patient-control discriminating axis which exaggerate the features of 'patientness' and 'controlness' by a factor of approximately 5 to render them visible. In **Figure 3**, the mean face is colour coded to highlight topographically those geometric features which distinguish male patients from male controls.

Though discriminating dysmorphology in males is statistically significant, the shape difference is modest and hence greater caution is necessary in interpreting its visualisation. Therefore, male patient features are compared with those described above for female patients to examine whether a common topography is evident. In overall terms the male patient face is, like the female patient face, laterally broad and vertically short; similarly in the lower face the medial features are reduced in relative size and displaced posteriorly though in the midface the frontonasal process is not. Considered in more detail, dysmorphology in males compares with that in females as follows: in the upper face of male patients, the orbits are, as for females, displaced anteriorly and inferiorly but, unlike females, they are not widened; in the midface of male patients, the nose is broad and tipped downwards and thus is unlike females; in the lower face of male patients, the lips, mouth and chin are, as for females, narrowed and displaced posteriorly, though, unlike females, not superiorly; the lateral aspects of the mandible are wider, particularly posteriorly, as for females; the anterior regions of the cheeks are, as for females, displaced outwards but, unlike females, the posterior regions are displaced inwards.

In summary, careful inspection and comparison of the 3D visualisations reveals that the male patient discrimination model has a common topography with the female discrimination model in a majority of features. The main differences concern the nose and lateral cheeks.

Facial Landmark Analysis

The above ‘whole face’ surface analysis confers substantially increased anatomical resolution but depends on the generation of pseudo-landmarks, which are interpolated

and therefore not biologically homologous. Theoretically, this could be a concern if either the interpolation procedure could introduce spurious patient-control differences or if strong covariances between pseudo-landmarks, produced by the smooth interpolation, invalidated any of the analyses. There are no practical grounds for suspecting that either artefact would be introduced by the present procedures. Nevertheless, in order to confirm their reliability, these findings were compared with those obtained on applying a conventional landmark approach of low anatomical resolution.

Using the 24 biologically homologous landmarks depicted in **Figure 1**, there were no differences in centroid size between patients and controls of either gender; it is to be expected that these would be more detectable in the pseudo-landmark sets since they cover essentially the whole facial surface. For females 13 PCs, describing 87.5% of total shape variance, were selected. Both Goodall's test ($p < .01$) and Hotelling's test ($T^2 = 116.4$, $p < .001$) indicated overall facial shape to differ between female patients and controls. The parsimonious patient-control discrimination model for females [$R^2 = 65.4\%$] consisted of seven significant [$p < .05$] shape PCs. On visualisation, shown online in **Figure 5**, the main features that discriminate female patients from controls were: wider skull base (i.e. tragion to tragion distance); inner and outer canthii displaced laterally, anteriorly and superiorly; shorter and posterior displaced nose with lower nasion and wider alar base; narrower mouth; raised chin. For males 14 PCs, describing 85.8% of total shape variance, were selected. While both Goodall's test ($p = 0.69$) and Hotelling's test ($T^2 = 16.4$, $p = 0.46$) did not indicate overall facial shape to differ between male patients and controls, Procrustes ANOVA (Klingenberg and McIntyre 1998) for facial shape indicated a significant overall effects of diagnosis [$p < .001$] across males and females; additionally, an effect of gender [$p < .001$] and a gender × diagnosis interaction

[$p < .05$] indicated that patient-control differences in facial shape for males were less prominent than for females.

This landmark-based geometric analysis and visualisation is highly consistent with, though substantially less informative anatomically than, that deriving from the 'whole face' surface analysis described above. We have reported similar concordances between homologous landmark and more informative pseudo-landmark, 'whole face' approaches in relation to aspects of sexual dimorphism and associated differences in cognitive function (Hennessy et al 2002, 2005, 2006).

Discussion

In this study we capture, quantify and visualise, for the first time, subtle abnormalities of 3D morphology over the whole facial surface in schizophrenia.

Regarding facial size, a slight [1.8%] increase was found in female but not in male patients. Previous studies have involved linear evaluation of 'hat size' using a tape measure or derived from neuroimaging; while some have reported a slight reduction in cranial circumference, others have found either no difference or a slight enlargement (Bassett et al 1996; Ward et al 1996; Buckley et al 2002). It is not clear how these cranial measurements relate to 'true' facial size as determined on a 3D basis. The slight increase identified here derived primarily from widening of the posterior skull base, as considered further below.

Regarding facial shape, visualisations of the statistical models are best appreciated with dynamic 3D graphics and, for pseudo-landmark sets, colour coding (see supplementary material online). Significant patient-control differences can be

summarised as follows: overall widening and vertical shortening, including increased width of the skull base and upper face, with lateral displacement of the cheeks, eyes and orbits, and the superior margins of the orbits displaced anteriorly; narrowing and reduction of the mid/lower face and frontonasal prominences, including reduced width of the mouth, upper and lower lips and chin, which are displaced posteriorly; widening of the mandible. However, before these differences can be interpreted, methodological issues should be considered.

We used 3D laser surface imaging of high resolution and accuracy together with powerful statistical tools for detecting and visualising shape differences (Hennessy et al 2005); this ensures precision in landmark localisation and anatomical visualisation of statistical models. Patients and controls were well matched, being drawn from the same rural region of substantive ethnic and socioeconomic homogeneity, as described previously (Baldwin et al 2005; Scully et al 2002); thus, ethnic and socioeconomic factors are unlikely to be prominent. Cavan-Monaghan Mental Health Service has pioneered in an Irish context the provision of home-based care for acute illness as an alternative to admission, together with outpatient clinics, day hospital and day centre services (Baldwin et al 2005; McCauley et al 2003); thus, nosocomial factors are unlikely to be operating.

Another factor to be considered is a putative effect on facial shape of either weight loss due to poor self care or weight gain associated with antipsychotic drug treatment (Anath et al 2004; Jin et al 2004; Wirshing 2004). Such a confound is unlikely for several reasons: (i) change in weight would be expected to effect primarily facial size, but this was altered minimally in females and not at all in males; (ii) differences in facial shape were topographically specific, with some regions expanded but others contracted, in a

manner inconsistent with any overall effect of weight; (iii) the 24 landmark analysis would be expected to be considerably less sensitive to any such confounding, yet this evidenced an overall effect of diagnosis congruent to, though less detailed than, analyses on a 'whole face' basis. To further exclude such an artefact, we analysed in females a subset of the face which excluded those maxillary and mandibular regions [i.e. 'cheeks and jowls'] whose shape might be expected to particularly reflect weight change; on excluding these regions, patient-control differences endured. As body mass index data were not available in this study, future studies should include this variable in analyses.

Recently, we have reported double dissociations between facial morphology and neuropsychological test performance in normal subjects: the shape of the anterior face covaried with spatial attention/visuomotor tracking in men but not women, and with verbal fluency in women but not men (Hennessy et al 2005, 2006); these findings complement evidence that men perform better than women on visuospatial tasks, while women perform better than men on verbal tasks (Caplan et al 1997; Gur et al 1999). Such relationships constitute strong evidence that the well established, intimate embryological relationship between facial and anterior brain morphogenesis extends to anterior brain function in adults, in a sex-specific manner. Furthermore, there were parallels between the characteristics of facial shape in schizophrenia, a disorder in which cognitive impairment is well recognised (Gold 2004; Bowie and Harvey 2005) and those associated with lower cognitive performance in normal subjects (Hennessy et al 2005, 2006): for females, the nose and mouth are smaller and narrower and the skull base is broader both in schizophrenia and in normal subjects with lower verbal performance; for males, the skull base is broader both in schizophrenia and in normal subjects with lower visuospatial performance.

There is considerably greater understanding of the molecular and cellular basis of craniofacial vis-à-vis cerebral development. Therefore, quantification and visualisation of facial dysmorphology, in its intrinsic 3-dimensionality on a 'whole face' basis in large numbers of patients, would *a priori* inform more strongly on the dysmorphogenic process(es) in schizophrenia than would examination of the brain itself. The trajectory of facial-cerebral morphogenesis, primarily a midline process, involves: (i) anterior brain growth with vertical growth and narrowing of the anterior mid-facial region, particularly the frontonasal prominence; (ii) primary palate formation; (iii) dissociation of cranial base width from anterior facial and cerebral changes; and (iv) the face growing forward more rapidly than is the brain (Waddington et al 1999a,b; Diewert and Lozanoff 1993a,b; Diewert et al 1993; Cohen et al 1993; Lieberman et al 2000a,b; Baldwin et al 2004).

More specifically, morphogenesis of the frontonasal prominence, forebrain and anterior midline cerebral regions are intimately regulated via epithelial-mesenchymal signalling interactions: the nascent forebrain, neuroepithelium, neural crest and facial ectoderm, from which the present surface analyses derive, function as a developmental unit in terms of 3D gene expression domains (Diewert and Lozanoff 1993a,b; Diewert et al 1993; Schneider et al 2001; Marcucio et al 2005; Kjaer 1995; Echevarria et al 2005; Tapadia et al 2005); posterior cerebral and craniofacial development are related less intimately and regulated by alternative mechanisms (Kjaer 1995; Brault et al 2001; Wilkie and Morriss-Kay 2001). Similarly, cranial base morphogenesis interacts intimately with neurocranial and craniofacial shape: cranial base dimensions influence rotation of the lower mid-face and hence frontonasal prominence; furthermore, the middle cranial fossa, which determines cranial base width, and the temporal lobes constitute an interactive developmental unit (Lieberman et al 2000a,b).

The ontogenic trajectory of facial morphogenesis is known to have multiple determinants which operate at diverse biological levels over varying phases of development. While recognising this diversity, the specific dysmorphogenic features encountered here implicate events acting particularly over a time-frame that has extreme limits of gestational weeks 6 through 19; more speculatively, they suggest within this time-frame a common denominator of weeks 9/10 through 14/15 of gestation (Waddington et al 1999a,b; Diewert and Lozanoff 1993a,b; Diewert et al 1993; Cohen et al 1993; Bayer and Altman 2005). Thereafter, the craniofacies continue to evolve, particularly in terms of overall growth, to attain adult form (Hennessy et al 2002, 2005; Enlow and Hans 1996).

Such a dysmorphogenic process would account for several aspects of structural brain pathology reported in adult schizophrenia (Wright et al 2000; Thaker and Carpenter 2001; Freedman 2003); this includes abnormalities of the forebrain, not just of the prefrontal and anterior cingulate cortex but also of temporal lobe structures which over early fetal life emerge in the forebrain before rotating to their final location, together with thalamic and other anterior midline structures (Waddington et al 1999a,b; Arnold and Rioux 2001; Diewert et al 1993; Mojsilovic and Zecevic 1991; Kostovic et al 1993; Arnold and Trojanowski 1996; Kier et al 1997). Facial morphology captured by MRI would allow the direct exploration of relationships between facial and cerebral dysmorphology in schizophrenia.

Additionally, such dysmorphogenesis along the anterior midline would be expected to disrupt neuroectodermal patterning and the critical repulsive and attractive guidance cues which, together with trophic and experiential factors, regulate neuronal connectivity (Chang et al 2000; Giger and Kolodkin 2001). This would accord with models of

neuronal network disconnectivity in schizophrenia, particularly in a fronto-striato-pallido-thalamo-cortical/temporal network (Bullmore et al 1998; Andreasen 2000; Waddington and Morgan 2001).

Anterior facial dysmorphogenesis identified here includes altered proportions along the midline. Thus, the present 'whole face' analysis elaborates a recent preliminary report of midline deviation in a small sample of primarily male schizophrenia patients, using a 3D camera and landmark-based analysis (Buckley et al 2005). Furthermore, within the present detailed resolution of the frontonasal prominence, the nose is reduced in relative length but not width; this elaborates a recent report of reduced posterior nasal volume in males with schizophrenia, using acoustic rhinometry (Moberg et al 2004). While we describe significant discriminating differences in overall facial shape in schizophrenia among males, these effects were more robust among females. It is self-revealing, as sustained by scientific evidence, that facial shape in normal females differs from that in normal males (Hennessy et al 2002; Enlow and Hans 1996). Thus, given sex differences in normal facial morphogenesis, it would be expected that a dysmorphogenic process in schizophrenia produces somewhat different, though overlapping, topographies of dysmorphology in males and females.

For example, the present data reveal that a particular aspect of nasal dysmorphogenesis in schizophrenia involves greater downward displacement of the tip of the nose in males than in females. Since confounding influences on nasal shape from ethnicity and trauma/surgery were eliminated by study inclusion and exclusion criteria, it may be relevant that the development of the tip of the nose derives from the earliest frontonasal prominence which enjoys the most intimate embryological relationship with the development of the anterior brain (Marcucio et al 2005; Tapadia et al 2005). Thus,

while patient-control differences in facial morphogenesis may appear more subtle in males than in females, facial dysmorphogenesis in male patients involves particularly the circumscribed nasal domain that relates most intimately to the forebrain; this may be more indicative of, and informative on, brain dysmorphogenesis.

Furthermore, the frontonasal prominence also contributes to development of the forehead, philtrum of upper lip and primary palate (Marcucio et al 2005; Tapadia et al 2005); the primary palate is a midline structure noted consistently to be dysmorphic in schizophrenia on inspection (Lane et al 1996; McNeil et al 2000; Lane et al 1997). In other domains of facial development: the lateral nasal prominences form the sides of the nose; the maxillary prominences contribute to the sides of the face and lips; and the mandibular prominences produce the lower jaw (Marcucio et al 2005; Tapadia et al 2005). Morphogenesis in each of these domains appears to be at least in part orchestrated by the frontonasal prominence (Marcucio et al 2005; Tapadia et al 2005) and each evidences a characteristic topography of dysmorphology in schizophrenia. This suggests that understanding the genetic and epigenetic regulation of midline morphogenesis involving the frontonasal prominence may inform importantly on early developmental perturbation in schizophrenia.

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FIGURE LEGENDS

Figure 1. Typical laser surface image showing the twenty-six 3D landmarks. Filled circles: the 24 landmarks used in landmark analysis; open circles with crosses: the 2 landmarks used, in addition to the 24 landmarks, to calculate the pseudolandmarks. Landmarks: a, soft tissue nasion; b, pronasale; c, sublabiale; d, pogonion; e/f, inner canthus; g/h, outer canthus; i/j, alar crest; k, subnasale; l/m, alare; n/o, columella breakpoint; p/q, christa philtrum; r, labiale superius; s, labiale inferius; t, stomion; u/v, cheilion; w/x, tragion; y/z, otobasion inferius.

Figure 2. Facial surface analysis. Procrustes mean shape is shown displaced equally in each direction along the patient - control discrimination axis, separately for females (top row) and males (bottom row). The displacement positions from mean facial shape (middle column) are exaggerated approximately five-fold. This is equivalent to the patient (left column) - control (right column) dimorphism exaggerated approximately ten-fold.

Figure 3. Facial surface analysis. Displacement vectors for each point on the surface are shown colour coded, separately for females (top row) and males (bottom row). Left column: change in surface area coded as red [expanded in schizophrenia relative to controls] or blue [contracted in schizophrenia relative to controls]; data are coded as 33% percentiles, with darker colours indicating upper percentiles. Centre column: change in angle of displacement vector to surface normal coded as red [angled outwards in schizophrenia relative to controls] or blue [angled inwards in schizophrenia relative to

controls]; darker colours code smaller angle to the normal, i.e. displacement vector more perpendicular to the surface. Right column: length of displacement vector, in any direction, coded as red; darker colour codes greater vector length, i.e. greater difference between schizophrenia and controls.

Supplementary material to made available online

Figure 4. Facial surface analysis. The transformation for females along the patient - control discrimination axis which is represented as static images in **Figure 2** is shown as a video sequence from three viewpoints.

Figure 5. 24 landmark analysis for females. Procrustes mean is shown as a dotted black line and its displacement along the patient - control discrimination axis is shown as a solid red line. The displacement position from mean facial shape in the direction of patient-ness is exaggerated approximately five-fold.

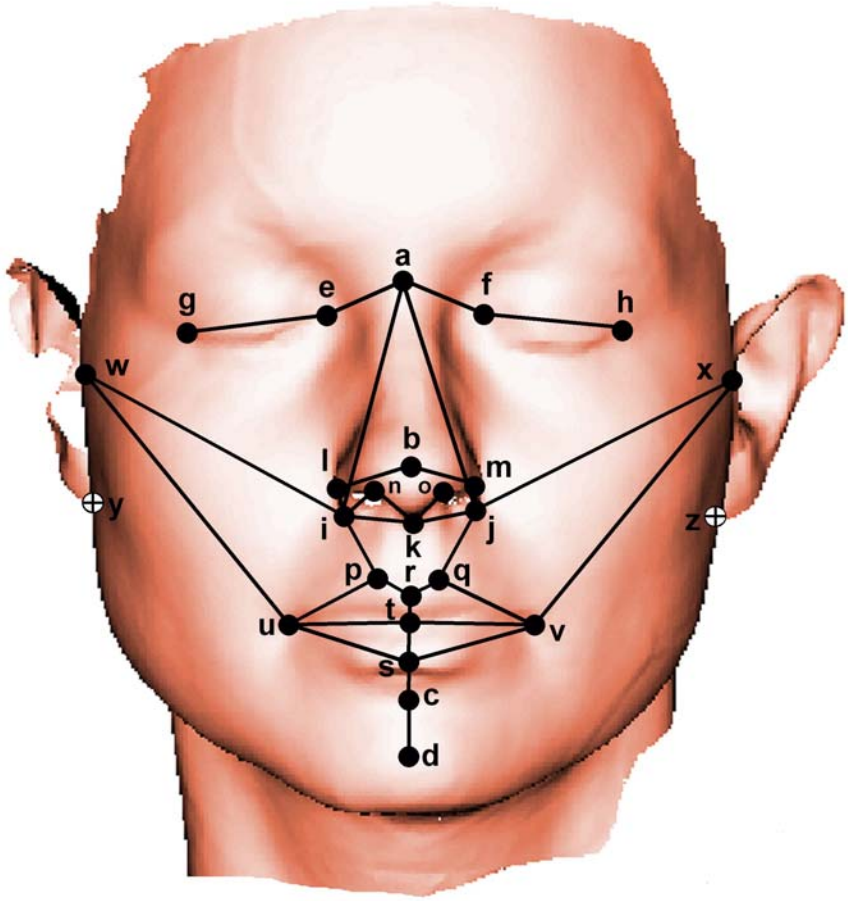

Fig 1

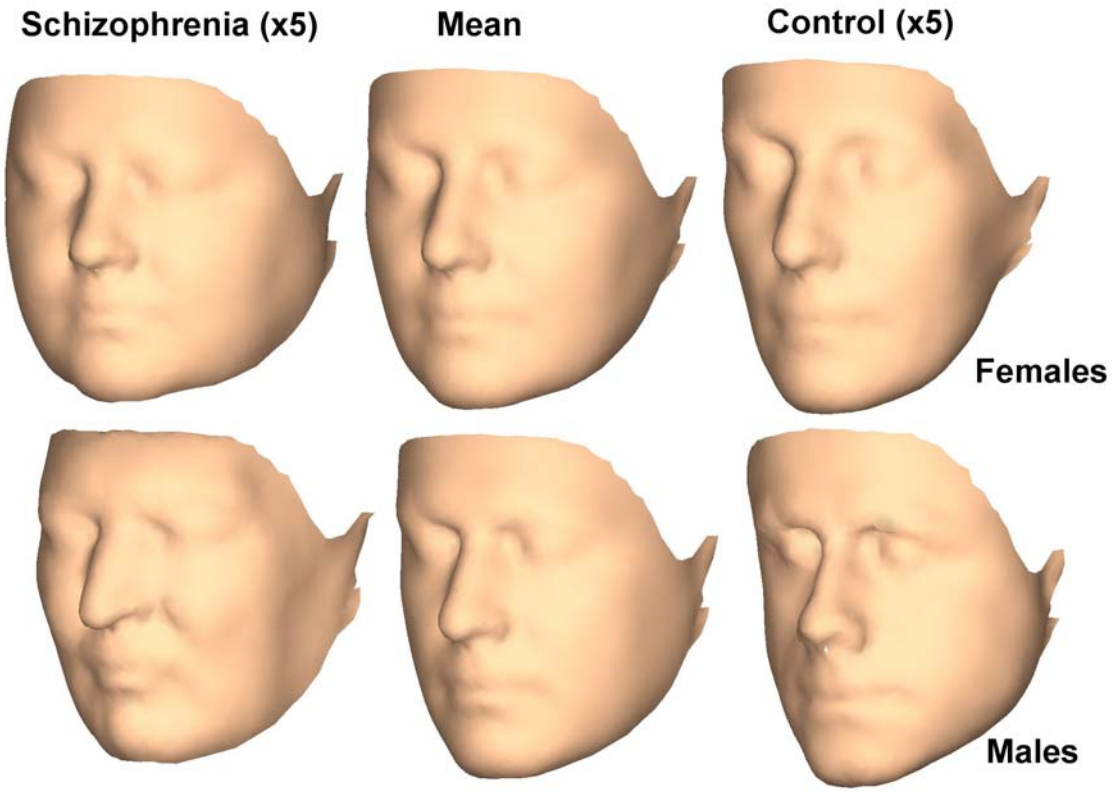

Fig 2

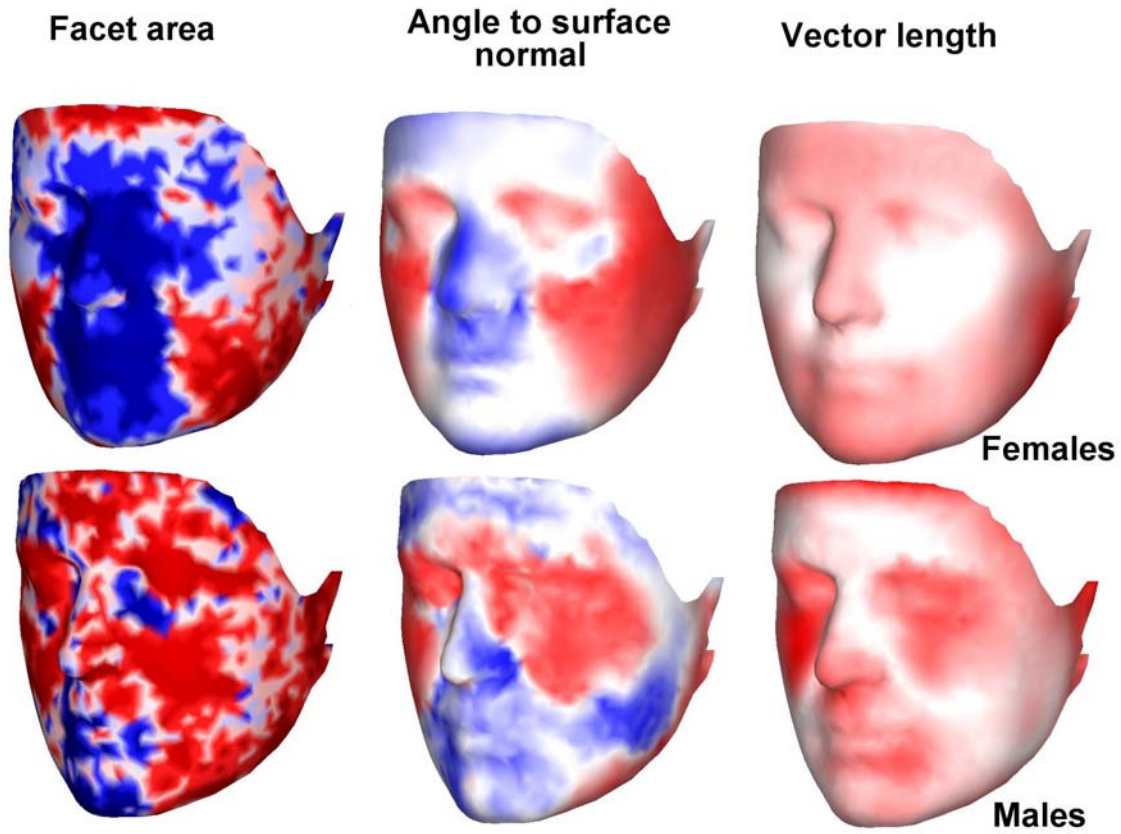
Facet area
Angle to surface normal
Vector length
Females
Males

Fig 3

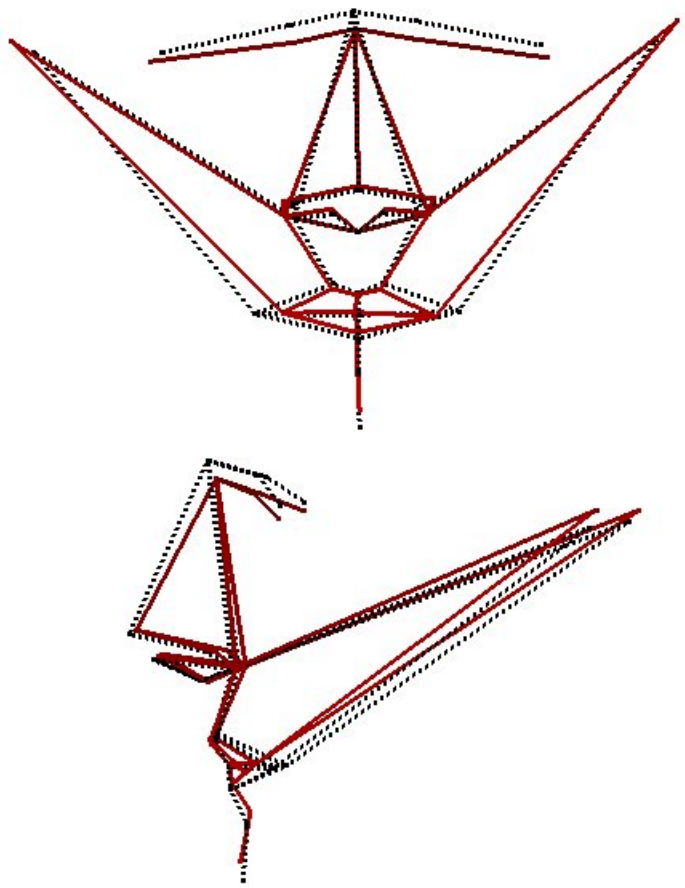

Fig 5