

Minor Physical Anomalies and Quantitative Measures of the Head and Face in Patients With Psychosis

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Background: The aim of this study was to examine minor physical anomalies and quantitative measures of the head and face in patients with psychosis vs healthy controls.

Methods: Based on a comprehensive prevalence study of psychosis, we recruited 310 individuals with psychosis and 303 controls. From this sample, we matched 180 case-control pairs for age and sex. Individual minor physical anomalies and quantitative measures related to head size and facial height and depth were compared within the matched pairs. Based on all subjects, we examined the specificity of the findings by comparing craniofacial summary scores in patients with nonaffective or affective psychosis and controls.

Results: The odds of having a psychotic disorder were increased in those with wider skull bases (odds ratio [OR], 1.40; 95% confidence interval [CI], 1.02-1.17), smaller lower-facial heights (glabella to subnasal) (OR, 0.57; 95%

CI, 0.44-0.75), protruding ears (OR, 1.72; 95% CI, 1.05-2.82), and shorter (OR, 2.29; 95% CI, 1.37-3.82) and wider (OR, 2.28; 95% CI, 1.43-3.65) palates. Compared with controls, those with psychotic disorder had skulls that were more brachycephalic. These differences were found to distinguish patients with nonaffective and affective psychoses from controls.

Conclusions: Several of the features that differentiate patients from controls relate to the development of the neuro-basicranial complex and the adjacent temporal and frontal lobes. Future research should examine both the temporal lobe and the middle cranial fossa to reconcile our anthropomorphic findings and the literature showing smaller temporal lobes in patients with schizophrenia. Closer attention to the skull base may provide clues to the nature and timing of altered brain development in patients with psychosis.

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MINOR PHYSICAL anomalies (MPAs) are subtle variations in soft tissue, cartilaginous, and bony structures that are the result of an uncertain mix of genetic and environmental factors operating prenatally. Studies have examined MPAs in various disorders in order to provide clues about the nature and timing of risk factors for the disorder. There is now robust evidence that patients with schizophrenia have more MPAs compared with controls.¹⁻⁸ In particular, studies have suggested that MPAs involving the head and face best discriminate patients with schizophrenia from controls.^{9,10} Lane et al³ made an important contribution to the field when they included quantitative anthropomorphic measures in their study of 174 patients with schizophrenia and 80 controls. They reported an overall elongation of the middle and lower face, widening of the skull base, and a concentration

of MPAs involving the eyes, ears, and mouth in the patient group.

We examined craniofacial measurements in a large epidemiologically derived sample of patients with psychosis and used this sample to explore issues related to diagnostic specificity. The primary aim of this study was to examine the prevalence of selected MPAs and quantitative measures of the head and face in patients with psychosis vs healthy controls. Based on the literature,³ we predicted that patients with psychosis would have a pattern of craniofacial abnormalities characterized by wider skull bases and shorter lower-facial heights. We also predicted that the patients with psychosis would have more qualitative abnormalities involving the eyes, ears, and palate compared with controls. The secondary aim of the study was to explore the specificity of the pattern of craniofacial abnormalities in patients with nonaffective or affective psychosis and controls. Based on the literature,⁴ we

PARTICIPANTS AND METHODS

Individuals with psychosis were drawn from 1 of the 4 catchment areas in the recent Australian national prevalence study of psychosis (Queensland segment of the National Survey of Mental Health and Wellbeing: Study on Low-Prevalence [Psychotic] Disorders).^{11,12} Within an area of southeast Queensland (eligible population, 581 332), we undertook a 1-month census at a wide range of sites to identify persons aged 18 to 64 years who were in contact with mental health services in the area and who met the screening criteria for psychotic disorders. During the census month (June 1997), a total of 2180 individuals were screened for symptoms of psychosis using the Psychosis Screen.¹¹ This instrument, derived from psychosis screening items of the Composite International Diagnostic Interview¹³ and the Psychosis Screening Instrument Questionnaire,¹⁴ is a 6-item screen inquiring about the occurrence of specific psychotic symptoms currently or at any time in the past. The screen includes an item for raters to record their judgments about whether psychotic symptoms are present. Of the 2180 individuals screened, 1513 were screen positive. Over an 18-month period, we approached a random selection of the screen positive individuals to recruit 310 patients with psychosis for participation in the present study. Concerning the representativeness of the final 310 subjects, there were no significant differences in age ($t_{1511} = -1.31$; $P = .20$) or sex ($\chi^2_1 = 1.7$; $P = .19$) between this group and the remaining 1203 screen positive individuals. The healthy control subjects were drawn from the same catchment area via advertisements in local newspapers. All subjects included in this study provided written, informed consent, and the study was approved by the Wolston Park Hospital Institutional Ethics Committee, Wacol, Australia.

DIAGNOSTIC ASSESSMENT

Assessments were carried out in the subjects' homes or in community health clinics. Both patients and controls were assessed with the Diagnostic Interview for Psychosis,¹¹ which is a modified version of the Schedules for Clinical Assessment in Neuropsychiatry.¹⁵ The raters (clinical psychologists and experienced research nurses) attended national training programs on the use of the Diagnostic Interview for Psychosis and participated in interrater reliability exercises as part of the national study (agreement on diagnosis weighted $\kappa = 0.60$; $P < .01$). Controls' status or patients' diagnoses were confirmed with the Operational Criteria for Psychosis, a 90-item checklist linked to a computer diagnostic algorithm.¹⁶ The *DSM-III-R* diagnoses¹⁷ were divided into nonaffective psychosis (schizophrenia, schizophreniform psychosis, delusional disorder, and atypical psychosis) and affective psychosis (bipolar disorder and mania with psychosis, depression with psychotic features, and schizoaffective psychosis).

CRANIOFACIAL MEASURES AND MPAs

Symmetrical features were recorded for both right and left sides. If right-left differences were detected for the facial depths, we report the larger of the 2 sides. The qualitative items and the variants scored in this study included hair whorls (position, number, and direction), epicanthus, supraorbital ridge, ears (low-set, protrusion, hypoplasia, earlobe attachment, asymmetry, and helix width), and mouth (palate height and shape, palate ridges, and bifid tongue). For each qualitative item, the most prevalent variant in the control group was allocated a weight of "0," and all other variants were allocated "1" (**Table 1**). These weights were used to generate a total score from the sum of all qualitative items (MPA total score range, 0-24).

Continued on next page

predicted that patients with nonaffective and affective psychoses would have more dysmorphogenesis than controls.

RESULTS

The overall study included 310 individuals with psychosis and 303 controls. There were no significant group differences between cases and controls on age (mean [SD], 40.09 [11.93] and 40.60 [13.01], respectively; $t_{611} = 0.51$; $P = .61$) or sex (men/women, 185/125 and 159/144, respectively; $\chi^2_1 = 3.2$; $P = .07$). From these subjects, we extracted a maximum of 180 patients with psychosis matched with 180 controls; 109 of the pairs were female, and 71 were male. The mean (SD) age of these matched cases was 41.6 (12.3) years, whereas the mean for controls was 42.0 (13.1) years. The majority of the matched cases had *DSM-III-R* schizophrenia ($n = 130$), and other nonaffective psychotic disorders included delusional disorder ($n = 5$) and atypical psychosis ($n = 5$). The remaining 40 patients had affective psychoses (depression with psychosis, $n = 9$; bipolar disorder, $n = 21$; and schizoaffective disorder, $n = 10$).

Based on the matched pairs, the following variables were associated with significantly increased odds

of having a psychotic condition: having 2 or more hair whorls, ear protrusion, U-shaped palate, and a short, broad palate (Table 1). Patients with psychotic disorders tended to have smaller lower-facial heights (mean group differences, 0.32-0.52 cm), larger skull base width (mean group difference, 0.15 cm), and larger lower-facial depths (mean group differences, 0.21-0.44 cm) (**Table 2**).

The remaining analyses are based on the entire sample. Principal component analysis of the quantitative variables identified only 2 factors. The first factor (eigenvalue = 4.72; 42.9% of the variance) had substantial positive loading for every quantitative measure. This factor, henceforth referred to as the craniofacial size factor, is often identified in similar analyses²³ and usually represents general head size. The second factor (eigenvalue = 2.01; 18.3% of the variance) had positive loadings (0.50-0.73) for the 3 overlapping vertical midline glabella measurements and negative loadings for skull width (-0.47), skull length (-0.34), and head circumference (-0.30). Tragus to gnathion contributed a negative loading (-0.45), and the other variables contributed weaker loadings of -0.28 through 0.01. This factor, henceforth referred to as the craniofacial shape factor, identified a relationship between smaller lower facial

Head circumference was measured with a cloth tape measure wrapped around the glabella and the opisthocranium, with the tape firmly placed against the skull to minimize the influence of hair. All other quantitative measures were assessed with spreading calipers according to the landmarks defined by standard anthropomorphic guidelines.^{18,19} To optimize reliability, we selected measures with reliable landmarks, and, for the vertical midline facial distances, we measured larger overlapping distances rather than adjacent smaller distances.²⁰ Quantitative measurements were rounded to the nearest 0.5 cm. Apart from head width at the level of the skull base (tragus-tragus, henceforth referred to as "skull width") and maximum head length (glabella-opisthocranium, henceforth referred to as "skull length"), we measured 5 facial heights (superio-inferior dimensions: glabella-subnasal, glabella-stomion, glabella-gnathion, glabella-trichion, and gnathion-nasion) and 3 facial depths (anteroposterior dimensions: tragus-subnasal, tragus-gnathion, and tragus-trichion). The location of these points is displayed in the **Figure**.

The variables were assessed by 7 research assistants who participated in a standardized training program. Raters worked in pairs, with one rater undertaking the assessment or measurement while the other rater checked and recorded the measurements. Based on a panel of 8 subjects (healthy controls not included in the present study; 4 men and 4 women; age range, 21-55 years), the intraclass correlation coefficient for the quantitative variables ranged from 0.71 (tragus-trichion) to 0.93 (tragus-gnathion). The intraclass correlation coefficient for the MPA total score was 0.72.

DATA ANALYSIS

To best characterize the pattern of any potential dysmorphogenesis in patients with psychosis, we compared each

of the qualitative and quantitative items in carefully matched pairs (patients with psychosis vs controls). Ethnicity, age, and sex are known to be associated with anthropomorphic measures.²¹ To reduce the influence of ethnic variability in the matched pairs, we selected white subjects who were born (and who were offspring of parents born) in Australia, New Zealand, the United Kingdom, Europe, and North America. In addition, those subjects who were adopted or who were of Aboriginal/Torres Strait origin were excluded from the matched pairs. We used procedures within SAS statistical software (SAS Institute Inc, Cary, NC) to match as many patients with psychosis as possible with controls based on sex and age (± 5 years). When more than 1 control was available for matching to a case, the final match was randomly selected from the pool.

To optimize the power to detect subgroup differences, we included all subjects in the assessment of diagnostic specificity. Summary scores were generated from the individual qualitative and quantitative items to reduce the number of comparisons. Ratios related to "skull width divided by skull length" are often used to characterize skull shape as brachycephalic (wider, shorter skulls) and dolichocephalic (narrower, longer skulls).²² In this study, we examined the ratio of skull base width to the maximum skull length (henceforth referred to as width/length ratio). Principal component analysis was undertaken on all quantitative variables. The resultant components, the total MPA score, and the width/length ratio were examined in the secondary group comparisons. We examined 4 planned comparisons (all patients with psychosis vs controls, patients with nonaffective psychosis vs controls, patients with affective psychosis vs controls, and patients with nonaffective psychosis vs patients with affective psychosis) in the entire sample (corrected for age and sex). Statistical tests used an α level of .05, and tests were 2-tailed.

height and wider skull base width, larger skull length, and longer facial depth.

The 4 planned group comparisons were undertaken on the entire sample, and each comparison was adjusted for age and sex. For all patients with psychosis vs controls, the psychosis group had significantly higher MPA total scores (mean [SD], 7.82 [3.05] for patients with psychosis and 7.26 [2.85] for controls; $F_{3,613}=4.87$; $P=.03$), comparable skull size, as indicated by the craniofacial size factor ($F_{3,561}=0.36$; $P=.55$), wider skulls and shorter lower thirds of the face, as indicated by the craniofacial shape factor ($F_{3,561}=38.37$; $P<.001$), and more brachycephalic skulls, as indicated by larger width/length ratios (mean [SD], 0.74 [0.04] for patients with psychosis and 0.73 [0.04] for controls; $F_{3,609}=17.72$; $P<.001$).

When patients with nonaffective psychosis were compared with controls, the nonaffective group had significantly higher MPA total scores (nonaffective group: mean [SD], 7.88 [3.06]; $F_{3,536}=4.50$; $P=.03$), comparable-sized skulls, as indicated by the craniofacial size factor ($F_{3,490}=0.36$; $P=.55$), wider skulls and shorter lower thirds of face, as indicated by the craniofacial shape factor ($F_{3,490}=30.91$; $P<.001$), and more brachycephalic skulls,

as indicated by larger width/length ratios (mean [SD], 0.74 [0.04]; $F_{3,532}=17.19$; $P<.001$).

The affective psychosis group did not differ from the controls on MPA total scores (affective group: mean [SD], 7.62 [3.04]; $F_{3,380}=1.53$; $P=.22$) or the craniofacial size factor ($F_{3,342}=.07$; $P=.79$). However, compared with controls, patients with affective psychosis had wider skulls and shorter lower thirds of the face, as indicated by the craniofacial shape factor ($F_{3,343}=11.42$; $P<.001$) and more brachycephalic skulls, as indicated by larger width/length ratios (affective group: mean [SD], 0.74 [0.03]; $F_{3,378}=3.66$; $P=.05$).

The final planned comparison examined patients with nonaffective vs affective psychosis. Compared with patients with affective psychosis, the patients with nonaffective psychosis did not differ on MPA total score ($F_{3,310}=0.07$; $P=.79$), craniofacial size factor ($F_{3,290}=0.12$; $P<.73$), craniofacial shape factor ($F_{3,290}=0.60$; $P=.44$), or width/length ratio ($F_{3,308}=0.89$; $P=.35$).

COMMENT

Overall, patients with psychosis had significantly more MPAs compared with controls. Patients had palates that were shorter

Table 1. Qualitative MPAs for 310 Patients With Psychosis, 303 Controls, and 180 Matched Pairs*

MPA (Score)†	Total Sample		Matched Pairs OR (95% CI)‡
	Cases	Controls	
Hair whorls			
1 (0)	235	238	1
≥2 (1)	60	45	1.71 (1.00-2.94)§
Position of whorls			
Midline (0)	143	152	1
Right (1)	66	58	1.06 (0.55-2.01)
Left (1)	50	44	1.18 (0.53-2.64)
Mixed (1)	36	28	1.17 (0.54-2.52)
Direction of whorls			
Clockwise (0)	213	200	1
Counterclockwise (1)	33	28	1.70 (0.78-3.71)
Mixed (1)	49	52	1.17 (0.62-2.19)
Right epicanthus			
Not covered (0)	298	292	1
Covered	12	10	2.33 (0.60-9.02)
Partly covered (1)	10	9	...
Deeply covered (1)	2	1	...
Left epicanthus			
Not covered (0)	294	293	1
Covered	16	9	3.50 (0.73-16.85)
Partly covered (1)	14	8	...
Deeply covered (1)	2	1	...
Protruding supraorbital ridge			
Absent (0)	287	287	1
Present (1)	23	15	2.17 (0.82-5.70)
Palate roof shape			
U-shaped (0)	252	233	1
V-shaped (1)	40	49	0.41 (0.20-0.82)§
Palate vertical height			
High (0)	187	215	1
Short (1)	105	67	2.29 (1.37-3.82)§
Palate width			
Narrow (0)	123	158	1
Broad (1)	169	124	2.28 (1.43-3.65)§
Palate ridges			
<5 (0)	223	187	1
≥5 (1)	67	92	0.62 (0.38-1.01)
Bifid tongue			
Normal (0)	285	282	1
Bifid (1)	22	17	1.00 (0.40-2.52)
Low-set ears, right			
In-line (0)	245	246	1
Lower, <0.5 cm (1)	47	52	1.05 (0.58-1.88)
Lower, >0.5 cm (1)	17	3	...¶
Low-set ears, left			
In-line (0)	245	248	1
Lower, <0.5 cm (1)	46	51	1.10 (0.61-1.98)
Lower, >0.5 cm (1)	18	2	...¶

(continued)

and broader compared with controls. Patients also had ears that were more protruding compared with controls. Having 2 or more hair whorls was associated with increased odds of having a psychotic disorder. These findings are consistent with the literature.^{3,24} In contrast to many previous studies (see review⁸), we did not find that patients with psychosis had V-shaped palates. On the contrary, our patients had more U-shaped palates, a finding that is consistent with our other findings indicating that patients with psychosis tended to have wider, shorter palates. Post hoc analysis confirmed that the 89 individuals with V-shaped palates had significantly narrower, higher palates compared with those with

Table 1. Qualitative MPAs for 310 Patients With Psychosis, 303 Controls, and 180 Matched Pairs* (cont)

MPA (Score)†	Total Sample		Matched Pairs OR (95% CI)‡
	Cases	Controls	
Adherent earlobes, right			
Separate lobe (0)	171	176	1
Attached horizontal (1)	85	66	1.48 (0.87-2.51)
Attached oblique (1)	53	61	0.87 (0.41-1.82)
Adherent earlobes, left			
Separate lobe (0)	180	178	1
Attached horizontal (1)	82	63	1.48 (0.85-2.57)
Attached oblique (1)	47	62	0.80 (0.37-1.71)
Earlobe size, right			
Normal (0)	291	280	1
Hypoplastic (1)	18	23	0.79 (0.36-1.73)
Earlobe size, left			
Normal (0)	292	280	1
Hypoplastic (1)	17	23	0.71 (0.32-1.61)
Malformed ear, right			
Normal (0)	294	296	1
Malformed (1)	15	7	1.75 (0.51-5.98)
Malformed ear, left			
Normal (0)	296	299	1
Malformed (1)	13	4	2.67 (0.71-10.05)
Anterior helix shape, right			
Normal (0)	263	266	1
Widened (1)	46	37	1.21 (0.66-2.22)
Anterior helix shape, left			
Normal (0)	263	364	1
Widened (1)	46	39	1.19 (0.67-2.13)
Ear protrusion, right			
<10° (0)	118	157	1
11-30° (1)	145	112	1.72 (1.05-2.82)§
>30° (1)	46	34	2.14 (0.87-5.25)
Ear protrusion, left			
<10° (0)	114	151	1
11-30° (1)	140	125	1.70 (1.01-2.84)§
>30° (1)	55	27	2.43 (1.01-5.86)§
Symmetrical ears			
Symmetrical (0)	218	231	1
Asymmetrical (1)	91	71	1.05 (0.67-1.65)

*MPA indicates minor physical anomaly; OR, odds ratio; CI, confidence interval; and ellipses, not applicable.

†MPAs were weighted for the summary score as 1 or 0.

‡Mantel-Haenszel matched OR.

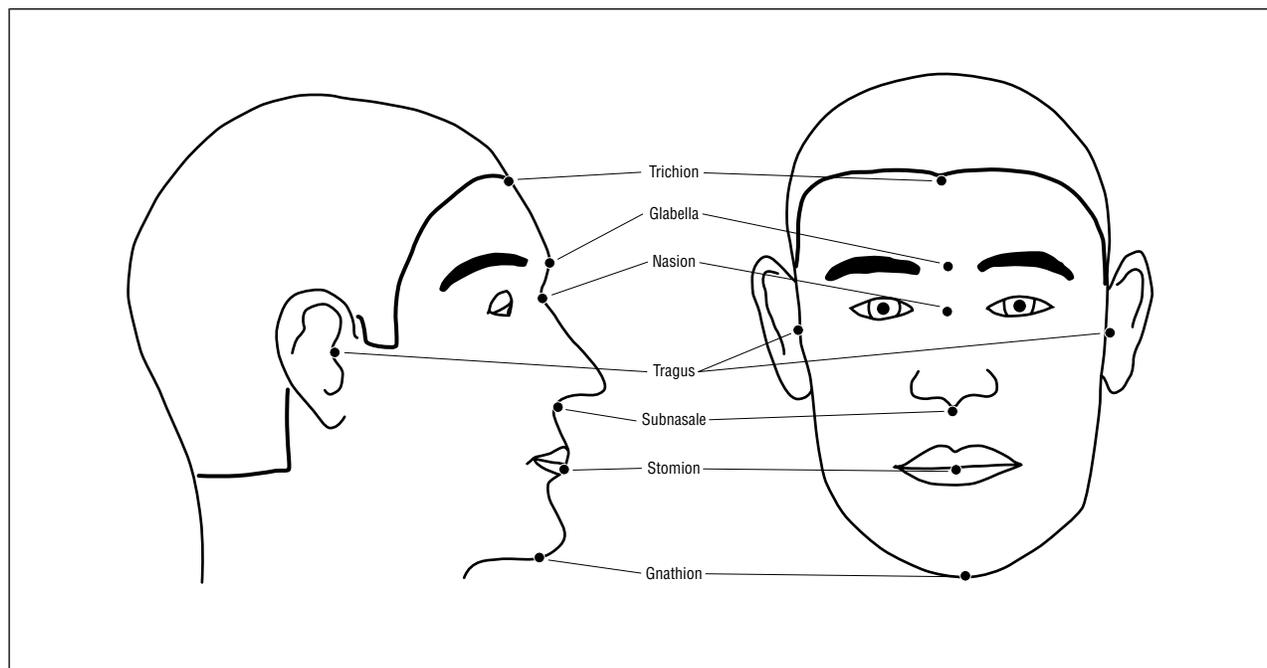
§Statistically significant group difference at $P < .05$.

||Counts for partly and deeply covered epicanthi were pooled for the matched-pair analysis.

¶Not found in matched pairs.

U-shaped palates (data not shown). Differences in the prevalence of particular MPAs in patients with psychosis between nations may provide clues to the differential role of ethnic and regionally specific environmental factors in the origin of these anomalies.

As a group, patients with psychosis had significantly wider skull bases and shorter lower facial heights. Measurements related to lower facial depth were also longer in the patient group. The differences identified in the matched-pair analyses were also identified in the comparisons based on the principal component analysis of the quantitative measures. The findings are in agreement with those of Lane et al.³ This relationship in craniofacial development (ie, the association between wider skull base and shorter lower facial heights) has also been



Landmarks used in quantitative craniofacial measurement. Skull length was measured from the glabella to the opisthocranium, which is a point in the occipital region that defines the most distant point from the glabella in the line of greatest head length.

Table 2. Quantitative Measures of the Head and Face for 310 Patients With Psychosis, 303 Controls, and 180 Matched Pairs*

	Total Sample, Mean (SD), cm		Matched Pairs	
	Cases	Controls	OR (95% CI)	Mean Difference, Control - Case, cm
Head circumference	57.4 (2.5)	57.2 (2.4)	0.99 (0.90-1.09)	0.03
Maximum skull length	19.8 (1.1)	19.7 (1.1)	0.93 (0.74-1.17)	0.06
Skull base width	14.7 (0.8)	14.3 (0.8)	1.40 (1.02-1.92)	-0.15†
Glabella to subnasal	7.4 (0.7)	7.8 (1.3)	0.57 (0.44-0.75)	0.52†
Glabella to stomion	9.3 (0.9)	9.7 (1.2)	0.63 (0.50-0.80)	0.43†
Glabella to gnathion	14.0 (1.1)	14.2 (1.4)	0.78 (0.64-0.95)	0.32†
Gnathion to trichion	18.9 (1.4)	18.7 (1.5)	0.98 (0.83-1.64)	0.03
Gnathion to nasion	12.2 (1.1)	12.0 (0.9)	1.23 (0.95-1.59)	-0.14
Tragus to subnasal	12.9 (0.7)	12.6 (0.8)	1.34 (1.01-1.77)	-0.44†
Tragus to gnathion	14.8 (1.0)	14.4 (1.1)	1.32 (1.03-1.68)	-0.21†
Tragus to trichion	14.1 (0.9)	14.0 (1.0)	1.01 (0.93-1.28)	-0.19

*OR indicates odds ratio; CI, confidence interval.

†Statistically significant at $P < .05$.

noted in research on the evolution of variation in human skull form.²⁵⁻²⁹ A major constraint believed to influence many aspects of craniofacial growth is the neuro-basiscranial complex.²⁹ The neuro-basiscranial complex is a highly integrated morphological unit that includes the basicranium (which derives from the chondrocranium and ossifies endochondrally) and the neurocranium (which ossifies intramembranously around the brain from the dura and related membranes).

The external pinna is not derived from the chondrocranium, but from cartilage derived from first brachial arch. The ears migrate cranially to reach their "normal" position by the second trimester.³⁰ Perturbations to the integrated development of the neuro-basiscranial complex and the external ear could result in protruding ears, as found in the patient group in this study.

Both the total MPA score and the quantitative measurements were normally distributed in both groups, and there was substantial overlap between cases and controls for these measurements. The group differences were not due to a subgroup of patients with very deviant measures, a finding similar to that reported for ventricular size in schizophrenia, as measured with structural neuroimaging.³¹ Both the total MPA score and the craniofacial measures operate as continuous graded risk factors for psychosis without a discernible critical threshold.

The results of the study confirm the findings of Lane et al³ and extend the findings by showing that patients with affective psychosis also differ significantly from controls on features related to the shape of the skull (ie, those with affective psychoses have wider, more brachycephalic skulls

and shortened lower thirds of the face). The nonaffective psychosis group (mainly patients with schizophrenia) had the highest MPA total scores, whereas the affective psychosis group's mean MPA total score fell midway between the nonaffective and control groups. Although these comparisons included 233 individuals with nonaffective psychosis, 77 individuals with affective psychosis, and 303 controls (a larger sample than that available in the matched-pair analysis), it lacked the power to confidently detect small differences between patients with affective psychosis and controls. For the craniofacial shape factor, both the affective and nonaffective psychosis groups were significantly different compared with the controls.

The study has several limitations. The patients in this study were recruited during a prevalence study of psychosis. Thus, those with chronic, persisting types of illnesses would be overrepresented in this sample. No correction for multiple comparisons was made. Thus, some of the findings may have emerged by chance. The quantitative measures relied on spreading calipers that provided measurements only to the closest 0.5 cm. The measurements were taken externally on subjects, making it impossible to exclude the possibility that differential thicknesses of superficial soft tissues of the skull could have contributed to group differences. However, the pattern of findings identified in the skull base, facial height and depth, and palate width and height is consistent with patterns also identified in craniometric studies.²⁵

The findings of this study suggest a coherent pattern of alterations to the skull, facial bones, and palate in those with psychosis. Brachycephalic individuals tend to have wider skull bases, shorter lower facial heights, and longer facial depths. Dolichocephalic individuals tend to have narrower skull bases, longer lower facial heights, and shorter facial depths. This model may also relate to the findings about the palate detailed previously. The palate grows downward and forward from the anterior part of the skull base,²⁶ so that individuals with wider skull bases have a tendency to have shorter, broader palates.³⁰ From a developmental perspective, many features of the palate are influenced by the anterior cranial base.³² The wider skull base identified in patients with psychosis in this study is also consistent with the recent report of larger interorbital distance in patients with schizophrenia vs controls.³³

Recent research has shown that middle cranial fossa size and shape influence the relationship between skull base shape (eg, width) and facial measures (eg, midline facial heights). Because of its location in the base of the skull, the dimensions of the middle cranial fossa are intimately linked to the width of the skull. In addition, the midface (the ethmomaxillary complex) attaches and grows forward from the middle cranial fossa (via the posterior maxillary plane).^{25,29-32} Variations in the shape and size of the middle cranial fossa may have predictable quantitative effects on many of the measures that were found to differentiate those with psychoses from controls.

The middle cranial fossa cradles the anterior portion of the temporal lobe, an area of interest to schizophrenia research. Review articles and meta-analyses of regional brain volumes^{34,35} have consistently identified

a decrease in temporal lobe volumes in patients with schizophrenia vs controls. The shape and volume of the endocranial fossa is strongly correlated with the shape and volume of the adjacent neural structures.^{36,37} We speculate that the anthropomorphic differences found in the head and face in our patients with psychosis may be a consequence, in part, of features related to the development of the temporal lobe/middle cranial fossa complex.

High-resolution magnetic resonance neuroimaging may be able to assess both temporal lobe and middle cranial fossa shapes and volumes in the same individuals. One early computed tomographic study reported no difference in the volume of the middle cranial fossa in patients with schizophrenia vs controls.³⁸ Future research needs to reconcile our anthropomorphic findings of larger skull base with the magnetic resonance imaging finding of reduced temporal lobe volumes. As the brain involutes via normal aging mechanisms or disease processes, the skull continues to provide a "mold" that may reflect earlier peak brain size and shape. We speculate that psychosis may be associated with greater than normal temporal lobe size during development. This effect would influence middle cranial fossa size and, thus, lead to persisting skull changes (ie, wider skull bases and shorter lower third of the face heights). Sometime after peak brain size is achieved, perhaps the temporal lobes in psychosis undergo greater than normal involution, which leads to the magnetic resonance imaging findings of smaller temporal lobe volumes described above. Based on the ratio of brain matter to cerebrospinal fluid, Woods et al³⁹ have already reported changes in the frontal lobes and temporal lobes consistent with this hypothesis. The shape of the middle cranial fossae in patients with schizophrenia may provide important clues to the timing of brain changes reported in schizophrenia.^{40,41}

A clearer understanding of the linkages between MPAs and the risk of psychosis and a more detailed knowledge of how the developing brain interacts with the neuro-basiscranial complex may help discover novel candidate exposures and genes related to psychosis. Candidate exposures that can affect these structures also include prenatal viral exposures^{42,43} and obstetric complications.²⁴ General nutritional deficiencies⁴⁴ and low prenatal vitamin D, in particular,⁴⁵ have been proposed as risk-modifying factors for schizophrenia; these factors are known to affect craniofacial growth.^{30,46} Within the genetic domain, Waddington et al¹⁰ have suggested a range of candidate genes involved in craniofacial development. Informative craniofacial quantitative measures identified in this study and by Lane et al³ may serve as correlated phenotypes in genetic studies of psychosis.⁴⁷ Research on how the brain and the skull interact during development may provide fertile new leads in the understanding of psychosis.

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