Quantitative Measures of Craniofacial Dysmorphology in a Family Study of Schizophrenia and Bipolar Illness

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Several laboratories, including ours, have reported an overrepresentation of craniofacial (CF) anomalies in schizophrenia (SZ). How might this dysmorphology arise in a brain-based disorder? Because the brain and face derive from shared embryologic primordia and morphogenetic forces, maldevelopmental processes may result in both CF and brain dysmorphology. Our approach is 2-pronged. First, we have employed, for the first time in the study of psychiatric disorders, objective measures of CF morphology that utilize an extensive normative database, permitting computation of standardized scores for each subject. Second, we have rendered these findings biologically interpretable by adopting principles of embryology in the analysis of dysmorphology. Dependent measures in this investigation focused on derivatives of specific embryonic primordia and were contrasted among probands with psychotic disorders, their first-degree relatives, and normal controls (NC). Subject groups included patients with a diagnosis of SZ ($N = 39$) or bipolar (BP) disorder with psychotic features ($N = 32$), their clinically unaffected relatives ($N = 82$ and $N = 41$, respectively), and NC ($N = 95$) subjects. Anomalies involving derivatives of frontonasal and mandibular embryonic primordia showed a clear association with psychotic illness, as well as familial aggregation in relatives in both diagnostic groups. In contrast, one class of CF anomalies emerged *only* among SZ probands and their first-degree relatives: dysmorphology arising along the junction of the frontonasal and maxillary prominence derivatives, manifested as marked asymmetries. This class was not overrepresented among the BP patients nor among their relatives, indicating that this dysmorphology appears to be specific to SZ and not a generalized feature of psychosis. We discuss these findings in light of embryologic models that relate brain regions to specific CF areas.

Key words: anomalies/genetics/endophenotype/psychosis/embryology

Introduction

A number of laboratories have found dysmorphic features to be overrepresented in psychiatric disorders, including schizophrenia (SZ), with examples cited here.^{1–6} The features reported are typically minor physical anomalies (MPAs), of minimal medical or cosmetic concern, but which are manifested along a continuum of severity ranging in gradation from minor to major.⁷ It is worth noting that even minor anomalies in combination may be of major significance, revealing classes of altered morphogenesis or describing specific malformation syndromes.⁸

Psychiatric researchers originally relied on an MPA diagnostic inventory, the Waldrop and Halverson Scale,⁹ that assessed a small number of stigmata, including but not limited to craniofacial (CF) anomalies. However, many methodologic problems arose, including difficulties rendering diagnoses objective and reliable.¹⁰ Despite these limitations, the scale's composite score yielded significant group differences between psychiatric and control groups; yet it provided little in the way of meaningful biological interpretation. Much of the literature on anomalies in SZ has been based on these scores.^{3,6} More recently, digital imaging and morphometry have been employed to quantify CF variation.^{1,4,8,11,12,13}

We have attempted to overcome earlier methodologic limitations by adopting quantitative techniques that make the assessment of CF dysmorphology more objective and reliable. Dr Leslie Farkas, a dysmorphologist and plastic surgeon, developed these methods, adapting and expanding classical anthropometric measurement techniques to produce a comprehensive atlas of the head and face.¹² With the aid of these methods, Farkas and Deutsch created a protocol that allows assessment of CF anomalies on a graded continuum of severity.¹³

We are now able to utilize a recently developed, extensive electronic normative database, derived from the Farkas atlas, that permits the computation of standardized scores conditioned on demographics. Using these methods, specific anomalies are quantified on a within-subject basis, which we have applied here for the first time to the analysis of CF dysmorphology in the major psychoses.

Rather than focusing on isolated anomalies, which typically are of limited theoretical interest, we examined combinations of individual anomalies that reflect their embryological origins.⁸ These dysmorphology studies draw upon developmental neuroscience, specifically, the fact that the brain and face derive from common embryological primordia and are shaped by shared morphogenetic forces.¹⁴ Thus, a shared pathological process may result in not only CF but also brain dysmorphology. Patterns of CF anomalies may elucidate how neurodevelopment has gone awry, indicating specific classes of dysmorphogenesis. We apply these classes here to the study of SZ and bipolar (BP) affective disorder.

How do these CF primordia arise? They develop early on in the first trimester; by the 19th embryonic day, they have been sculpted into recognizable, discrete masses. These primordia are precursors (termed *Anlagen*) of fully differentiated facial features. The masses develop as a series of symmetric outgrowths (*prominences*) arising from the CF neural crest, and it is within these prominences that differentiation first takes place in the course of development. There are 3 primary outgrowths that differentiate into the mature face: the single median *frontonasal* and the paired *maxillary* and *mandibular* prominences. These prominences can be clearly delineated as they develop from the embryonic to the mature face, and it is straightforward to identify specific primordia from which individual CF anomalies derive (see figure 1).¹⁵ This figure illustrates the development of these primordia over time, with the frontonasal prominence derivatives in green, maxillary in pink, and mandibular in yellow.

In this study, we classified anomalies by their embryonic derivation. We included analysis of dysmorphology

along the junction of 2 of these Anlagen, the frontonasal and maxillary primordia. An independent study has found this region to be significantly associated with mid-sagittal brain dysmorphology in SZ (see “Discussion” below), consistent with embryologic fate maps.¹⁶

Methods

Subjects

The sample included probands who met DSM-III-R criteria for a lifetime diagnosis of SZ (*N* = 39) or BP disorder with psychotic features (*N* = 32), as well as a NC (*N* = 95) group. Additionally, we examined first-degree relatives (parents and siblings) of the SZ probands (RelSZ, *N* = 82) and first-degree relatives (parents and siblings) of the BP probands (RelBP, *N* = 41), who were also compared with the NC group.

All probands were outpatients and were recruited at least 6 months after being discharged from McLean Hospital. Relatives were recruited after receiving permission from the probands to contact family members. Control subjects were recruited through advertisements. Non-dysmorphology data on these and other subjects in the Psychology Research Laboratory database have been published elsewhere.^{17–19} Demographic and psychiatric characteristics of these groups are summarized in table 1.

Fig. 1. Development of embryonic primordia (Anlagen) at embryonic day 37, embryonic day 55, and postnatal month 6.

Table 1. Demographic and Psychiatric Characteristics of Schizophrenic (SZ) Probands, Their First-Degree Relatives (RelSZ), Normal Controls (NC), Bipolar (BP) Probands, and Their First-Degree Relatives (RelBP) (Mean/SD)

	SZ	RelSZ	NC	BP	RelBP
	<i>N</i> = 39	<i>N</i> = 82	<i>N</i> = 95	<i>N</i> = 32	<i>N</i> = 41
Age (y)	35.7/8.4	49.7/17.1	44.3/15.4	33.4/9.6	48.3/14.9
Gender	25 M, 14 F	32 M, 50 F	31 M, 64 F	16 M, 16 F	19 M, 22 F
SES (Hollingshead)	2.8/1.1	2.6/1.2	2.2/1.1	2.3/1.1	2.0/0.8
Education (y)	13.3/2.1	14.8/2.7	15.2/2.9	13.8/1.6	15.3/2.7
Estimated verbal IQ	97.2/11.2	107.8/16.1	106.4/12.1	110.2/13.1	111.5/15.0
BPRS	45.3/15.5	—	—	36.8/10.5	—
Duration of illness (y)	12.0/8.8	—	—	7.2/9.1	—

Note: BPRS, Brief Psychiatric Rating Scale; SES, socioeconomic status.

The probands in this study were outpatients. Lifetime Axis I diagnoses were based on the Structured Clinical Interview for DSM-III-R, patient version (SCID-P, version 1.0). The SCID-P was administered by experienced interviewers, and diagnoses were assigned by consensus among at least 4 senior clinicians based on the interview, family informant material, and a review of all hospital records. All interviewers and diagnosticians were blind to group membership and to the results of the dysmorphology examination. Written informed consent was obtained for all participants prior to the study.

The Brief Psychiatric Rating Scale was administered to probands. Socioeconomic status (SES) was based on the Hollingshead index,²⁰ with updated coding for current professions. Parental SES was used for probands' SES. Verbal IQ was estimated on the basis of the Vocabulary Subtest of the Wechsler Adult Intelligence Scale-Revised.²¹

Selection criteria included: (1) fluency in English (required for procedures other than assessment of dysmorphology), (2) no diagnosed organic brain disease, (3) no history of substance/alcohol abuse/dependence within the past 2 years, (4) no tardive dyskinesia, (5) no use of alcohol or other recreational drugs within 48 h prior to participation, (6) a minimum age of 18 years for probands, (7) Caucasian ethnicity (normative data are most extensive for this group), obtained by self-report, (8) no identified CF syndrome as determined by a medical geneticist (eg, Velo-cardio-facial syndrome [microdeletion of 22q11.2]), (9) no CF or oral-maxillofacial surgery that would affect quantitative measurements, and (10) estimated verbal IQ ≥ 80 . Probands with schizoaffective disorder were excluded from the study. Also excluded from the sample were those NC and first-degree RelSZ and RelBP who met DSM-III-R diagnostic criteria for a psychotic disorder (lifetime) or a nonpsychotic Axis I disorder (eg, BP manic disorder, severe major depression, major depression recurrent in partial remission). Additionally, subjects who met diagnostic criteria for schizoid, schizotypal, or paranoid personality disorder were excluded from the study. Controls were also excluded if they had a first-degree relative with a history of psychosis, psychiatric hospitalization, or suicide. Importantly, the exclusion criteria applied to the relatives and controls were symmetrical.

CF examinations were performed blind to diagnosis, family membership, and group. Examiners trained with Leslie G. Farkas, MD, DSc, who formalized anthropometric procedures and created the normative anthropometric database used in this study.¹³ An electronic version of these norms has been programmed as an interactive database (*FaceValue*; for information about obtaining this software, please contact C.K.D.).²²

Procedures

Anthropometric Examination. A brief description of measurement tools, positioning of the subject,

identification of measuring points (anthropometric landmarks), and methods of measurements is outlined below. Comprehensive methods are described in the Farkas CF atlas, *Anthropometry of the Head and Face*.^{12,13} The reliability of these measurements (inter-rater and test-retest correlation coefficients $>.90$) is summarized in the *Handbook of Anthropometry*.²² Examiners were trained by C.K.D. and established reliability prior to data collection, with subsequent monitoring for potential measurement drift.

Measurement Instruments. The examination uses standard anthropometry tools and instruments.¹² The locations of some anthropometric landmarks and measurements are influenced by the position of the head; standard or rest positions of the head are employed, depending on the requirements for each measurement. Some distance measurements and all inclinations are recorded with the subject's head in the Frankfort horizontal position. In this position, the line connecting the orbitale (or) and the porion (po) provides the reference for horizontal orientation.

Landmarks. These are illustrated in [supplementary figure A1](#) and are defined in [supplementary table A1](#).

A number of landmarks lie directly on the CF surface, and others are identified by their underlying bony structure. The landmarks used in this anthropometric examination include: vertex (v), glabella (g), opisthocranium (op), eurion (eu), frontotemporale (ft), zygion (zy), gonion (go), pogonion (pg), gnathion (gn), endocanthion (en), exocanthion (ex), palpebrale superius (ps), palpebrale inferius (pi), orbitale (or), orbitale superius (os), nasion (n), alare (al), alar curvature point (ac), pronasale (prn), subnasale (sn), subalare (sbal), highest point of the columella (c), maxillofrontale (mf), stomion (sto), cheilion (ch), labiale superius (ls), labiale inferius (li), sublabiale (sl), and tragon (t). These measures are based on linear distances and arcs between landmarks; proportions are derived from these distances and/or arcs; angles of inclination; and deviations among the landmarks.²²

Embryologically Derived Combinations of Anomalies

Our approach is to study combinations of anomalies that relate to specific developmental factors, including derivatives of embryologic primordia (see "Introduction" section). We specify 4 CF derivatives in this study: the frontonasal, maxillary, and mandibular prominences, and the interface of the frontal-maxillary Anlagen, for which multiple measurements are available within the anthropometric protocol ([supplementary figure A1](#), [supplementary table A2](#)).^{12,13}

We examined the interface of 2 of these Anlagen derivatives. In an earlier study, patients with SZ showed a marked degree of asymmetry arising along the frontonasal-maxillary

junction. This measure was also found to be significantly correlated with brain midline asymmetry, as predicted by embryologic fate maps (see “Discussion” section).¹⁶

Anlagen Derivatives. The anomalies delineated by derivatives of these embryonic primordia are listed in [supplementary table A2](#). To operationally define individual anomalies (deep nasal root, mandibular hypoplasia), we employed a $z \geq |1.5|$ cut-off point, a threshold commonly used to diagnose anomalies in anthropometric studies.¹³ The measurements in the anthropometric atlas typically follow a Gaussian distribution, as determined by the Shapiro-Wilk test. The frontonasal, maxillary, and mandibular prominence dependent measures are sums of anomalies by each region (Anlage), computed as continuously distributed variables. Sums of CF anomalies were computed for each prominence derivative on a continuous scale.

Frontonasal-Maxillary Junction. We previously identified a marked excess of CF asymmetries along the junction of the frontonasal and maxillary prominence derivatives among SZ patients and their first-degree relatives.¹⁶ These asymmetry scores are combinations along this junction and are derived from multiple anthropometric measurements, including those of the orbital architecture, eg, the inclination of the palpebral fissures and the apposition of the supraorbital to suborbital rims (see summary in [supplementary table A2](#)). Corresponding symmetries were not available for the interface of the maxillary and mandibular primordia.

Asymmetries were computed as the sum of left-right asymmetries at the frontonasal-maxillary interface ([figure 1](#)). The most superior aspect of this interface is at the orbits and its most inferior at the upper palate. Multiple measurements were represented along this interface. For the frontonasal-maxillary junction combination score, left-right asymmetries were summed across the orbital regions at the most superior aspect of this junction, which includes: the palpebral fissure inclinations (the line connecting the endocanthion and exocanthion); supra-orbital-suborbital rim inclinations (at their bony mid-points); nasal root depths (projective linear distance from the endocanthion to the selion, the bony “saddle point” of the nasal root at to the bony nasion); and the frontonasal-maxillary arcs spanning the distance between the

left and right tragi across the zygion through the subnasale. The [supplementary appendix](#) provides additional detail on anthropometric methodology.

Conditioning on Demographics. The operational definitions of individual anomalies are based on anthropometric measurements, computed as z -scores as detailed by Deutsch and Farkas¹³. The normative database in the Farkas atlas¹² (based on an N of 2326 individuals) permits computation of these standardized scores, conditioned on age, sex, and ethnicity.

Data Analysis

Subject groups and their relatives were contrasted in ANOVAs, in omnibus analyses followed by planned a posteriori comparisons, with individual contrasts made by t tests. The focus was on univariate procedures rather than multivariate methods that combine independent variables; the latter would require larger sample sizes and tests of interactions would have resulted in reduced statistical power. Moreover, the number of available anthropometric measurements within the various Anlagen classes varied greatly; for this reason, we did not directly compare the magnitude of combination anomaly variables.

We adjusted for multiple comparisons using the Benjamini-Hochberg (1995) adaptation of the Bonferroni technique,²³ which controls for the proportion of all discoveries that are false (the “FDR approach”). The critical P value varies as a function of the ordered size of the mean difference.

Results

The quantitative dysmorphology data are summarized in [tables 2](#) and [3](#), and the significance levels of group contrasts are outlined in [table 4](#). Significance levels have been adjusted for multiple comparisons as described above.

Anomalies Deriving From Specific Embryonic Primordia (Anlagen)

This analysis focused on anomalies deriving from the frontonasal, maxillary, and mandibular prominences (see [figure 1](#) and [table 2](#)). Both schizophrenic probands and their relatives had a significant excess of *frontonasal*

Table 2. Anomaly Derivatives of Embryonic Primordia (Combination Score, Mean/SD)

	SZ	RelSZ	NC	BP	RelBP
Anlagen derivative					
Frontonasal	2.09/1.52	1.81/1.90	1.08/1.20	2.27/2.16	2.58/2.03
Maxillary	0.05/0.23	0.10/0.30	0.06/0.24	0.12/0.34	0.23/0.43
Mandibular	0.39/0.50	0.37/0.49	0.19/0.40	0.41/0.50	0.44/0.50

Note: BP, bipolar disorder; NC, normal control; RelBP, first-degree relative bipolar proband; RelSZ, first-degree relative schizophrenic proband; SZ, schizophrenia.

Table 3. Frontonasal-Maxillary Junction Asymmetries (Combination Score, Mean/SD)

SZ	RelSZ	NC	BP	RelBP
11.49/7.89	9.20/3.97	6.69/3.14	8.20/4.82	6.62/2.95

Note: Abbreviations are explained in the footnote of table 2.

Table 4. Group Contrasts: Significance Tests With Correction for Multiple Comparisons^a

	SZ vs NC	RelSZ vs NC	BP vs NC	RelBP vs NC
Embryonic primordia derivative				
Frontonasal	.0002	.0144	.0199	.0003
Maxillary	.8193	.3891	.3429	.0257
Mandibular	.0144	.0128	.0146	.0026
Frontonasal-Maxillary junction	.0009	.0001	.1169	.9155

Note: Abbreviations are explained in the footnote of table 2.

^aSignificant probabilities (2-tailed) prior to correction for multiplicity are italicized. Statistically significant probabilities after adjustment for multiple comparisons using the Benjamini-Hochberg false discovery rate method are both italicized and in boldface.

anomalies compared with controls (table 4). This was also the case for BP probands and their relatives.

Further, there were significant elevations of *mandibular* anomalies among both SZ and BP probands and their respective relatives (table 4). Compared with the percentage of frontonasal anomalies, mandibular dysmorphology was relatively infrequent, but it was significantly elevated above the baseline values in the NC group. In contrast, *maxillary* anomalies were not found to be excessive for any group contrast in the study.

Thus, there was an overrepresentation of frontonasal and mandibular anomalies associated with psychotic illness and a nonspecific familial aggregation of both kinds of anomalies in first-degree biological relatives of both patient groups.

Frontonasal-Maxillary Junction Asymmetries

There were excessive asymmetries along the *frontonasal-maxillary junction* in schizophrenic probands and in their relatives (tables 3 and 4). However, this pattern was not seen for BP probands or their relatives. Thus, there appears to be both *diagnostic specificity* for this finding as well as *specificity in the familial aggregation* of frontonasal-maxillary junction asymmetries. Excessive frontonasal-maxillary asymmetries appeared to be selectively associated with SZ or biological relatedness to a schizophrenic individual, but not with psychosis in general.

The effect size (ES) for this contrast between probands with SZ and NC was very large by Cohen's criterion (1988),²⁴ at $d = 0.80$, and the ES for the contrast between

relatives of the schizophrenic probands and NC was also substantial, at $d = 0.70$.

Independent Replication

The data presented here were collected in 2 stages of research that corresponded to 2 separate, consecutive National Institutes of Health funding periods. The statistical analyses presented here were performed on the combined data sets (tables 1–4). It is worth noting that the data sets derived from the 2 stages of research, when analyzed separately, yielded the same patterns of significant contrasts for the phenotypes presented when analyzed separately: (a) increased frontonasal and mandibular anomalies among schizophrenic probands and their relatives, as well as among BP probands and their relatives; (b) no effects for maxillary anomalies for any group contrast; and (c) elevated frontonasal-maxillary asymmetries among schizophrenic probands and their relatives, but not for BP probands and their relatives.

Discussion

Overview

In this study, we utilized a methodologically rigorous quantitative approach to the study of CF dysmorphology in the major psychoses. Each anomaly was assessed using reliable, objective anthropometric methods, and the resulting measurements were conditioned on demographics to compute standardized scores for each individual. Patterns of individual anomalies grouped by Anlagen derivatives were then contrasted among groups. These analyses identified dysmorphic phenotypes that were present not only among patients but also among their first-degree relatives.

Anomalies were localized to derivatives of the frontonasal and mandibular but not the maxillary Anlagen. Frontonasal and mandibular anomalies were overrepresented not only in schizophrenic patients but also in BP patients, and among clinically unaffected relatives of both patient groups. Overlapping CF phenotypes in SZ and BP disorder may reflect shared maldevelopmental processes. Previous reports in the literature have described frontonasal variation in SZ, taking the form of an altered conformation of the CF surface⁴ and of diminished nasal sinus volumes.¹¹ Hennessy and colleagues²⁵ also noted altered shape and size within the frontonasal region of BP disorder subjects.

How Might CF Dysmorphology Delineate Specific Brain Pathology?

Embryological fate-mapping studies have described how shared early embryonic regions generate both CF and brain derivatives.^{26–28} Using these fate maps one can employ patterns of CF dysmorphology to circumscribe specific areas of brain maldevelopment. Derivatives of

the frontonasal prominence, eg, correspond to 2 brain regions, the *anterior telencephalon* and *posterior diencephalon* (a topography determined by central nervous system unfolding during prenatal development).^{14,26} On a histologic scale, these regions might be considered broad expanses of brain tissue; at this stage of research, tests of CF-brain correspondences may be better suited to the scale of analysis used in structural magnetic resonance imaging (MRI) studies. However, the development of newer mammalian fate-mapping techniques holds promise for creating more detailed and resolute fate maps.

Brain Regions Corresponding to Frontonasal Derivatives Implicated in SZ and BP Disorder

The *anterior telencephalon* generally corresponds to the frontal lobe regions, and these have been found to be abnormal with respect to volume and shape in many, but not all, studies of SZ.²⁹ Also, the *posterior diencephalon* includes as its principal structure the thalamus, which has also been reported to be smaller in volume in SZ than in controls in MRI studies.^{29,30} Although the literature on structural MRI findings in BP disorder is not as extensive as it is for SZ, there are multiple reports of abnormalities of the frontal lobes and thalamus.^{31,32}

Asymmetry of the Frontonasal-Maxillary Junction and Its Association With Specific Brain Maldevelopment

In the present study, the most diagnostically specific statistical effect was for asymmetry at the junction of the frontonasal and maxillary prominences in comparing probands with SZ and their relatives to contrasting groups. This CF region corresponds to the interface of the posterior diencephalon and the anterior mesencephalon.^{16,26} Embryology atlases classically display this interface in a lateral view as a line connecting the mamillary and pineal bodies; this line of demarcation passes through the posterior commissure, which is partly diencephalic and partly mesencephalic in origin.³³

Brain regions corresponding to the frontonasal-maxillary junction have been implicated in SZ. MRI studies in our laboratory found that the midline deviations that arise at the diencephalic-mesencephalic interface were significantly correlated with anterior-posterior midsagittal brain midline anomalies, as predicted from embryologic fate maps.¹⁶ Importantly, this brain midline deviation arose within the critical embryologic region, ie, at the interface of diencephalon and mesencephalon. Moreover, the quantitative measure of 3D midline skewing was positively correlated with CF frontonasal-maxillary junction asymmetry within subjects.

Rakic and colleagues have described a model of non-human primate fetal development that provides further independent validation for the correspondence between

these CF and brain regions.³⁴ Corroborating evidence for midsagittal brain deviation was also seen in an independent landmark-based morphometric analysis of first-episode SZ.³⁵ DeQuardo and colleagues assessed altered brain morphology in SZ as a geometric deformation of configurations observed among control subjects. Their results indicated marked structural abnormality at the diencephalic-mesencephalic interface.

The midsagittal deviation observed in SZ has not yet been studied in BP disorder to the authors' knowledge. Based on the brain-face model described above, one would predict that patients with BP disorder would not exhibit this brain midline deviation, because frontonasal-maxillary junction abnormalities were not observed in BP disorder.

Inclusion of Multiple Phenotypes in Genetic Analysis

The observation of parallel forms of dysmorphology both in probands with SZ and in their first-degree relatives raises the possibility that genetic factors might underlie CF and brain maldevelopment. Recent reports of associations between rare copy number variants and extremes in CF measures suggest that certain features of dysmorphology are correlated with genetic mutations. Examples include microdeletions and microduplications of 1q21.1³⁶ and of 16p11.2.³⁷ Environmental factors, such as mid-gestational prenatal nutritional deficiency and influenza virus, appear to be associated with the pathogenesis of SZ^{38,39} and might also play an etiologic role in CF and brain maldevelopment.

Certain dysmorphology measures in this study are statistically overrepresented among clinically unaffected relatives of psychotic probands—who are not themselves psychiatrically disordered. This dysmorphology may constitute elements of a broader phenotype for these clinical conditions.⁴⁰ The overrepresentation of specific dysmorphic features in relatives cannot be attributed to co-existing psychiatric disorders since only relatives without psychotic or nonpsychotic Axis I disorders and without SZ-related personality disorders were included in these analyses. Thus, the dysmorphology findings are unlikely to be epiphenomena of psychiatric illness, per se.

In summary, dysmorphology among schizophrenic and BP affective disordered probands was characterized by a marked overrepresentation of anomalies derived from the frontonasal and maxillary prominence derivatives. Additionally, schizophrenic probands exhibited marked asymmetries at the junction of the frontonasal and maxillary prominences. These were specific to SZ and not characteristic of psychosis in general. The patterns of dysmorphology observed for schizophrenic probands were also found among their clinically unaffected first-degree relatives. Findings of excessive dysmorphology in this subgroup of family members indicate that this trait meets the co-familiality criterion

for a SZ endophenotype and is not a consequence of SZ or its treatment.

Embryologically derived measures of dysmorphology in psychiatric disorders may provide insight into their underlying etiologies and developmental mechanisms. Moreover, based on fate map correspondences, patterns of anomalies within embryonic primordia may predict loci of brain maldevelopment, which can be evaluated in brain imaging studies.¹⁶

Supplementary Material

Supplementary material is available at <http://schizophreniabulletin.oxfordjournals.org>.

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