Physical Manifestations of Neurodevelopmental Disruption: Are Minor Physical Anomalies Part of the Syndrome of Schizophrenia?

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The well-documented excess of minor physical anomalies (MPAs) among individuals with schizophrenia generally supports the neurodevelopmental model, which posits that both genetic and environmental factors contribute to structural and functional brain changes in the intrauterine and perinatal periods that predispose one to developing schizophrenia. This review synthesizes select areas of research findings on MPAs to address the question, Are MPAs part of the syndrome of schizophrenia? Although MPAs are not specific to schizophrenia, their presence in some patients indicates that aberrations in the development of the nervous system contribute to risk for the disorder. The broadly defined, heterogeneous MPA construct may be of limited value in further elucidating the specific pathophysiology of schizophrenia, though particular anomalies, such as those pertaining to nasal volumes, palatal abnormalities, or craniofacial morphology, may be informative. Given the availability of more sophisticated microarray technologies, and in light of recent findings on spontaneous mutations in patients with schizophrenia, it is possible that MPAs will prove to be useful in identifying etiologic subtypes and/or the loci of genetic risk factors. It remains to be determined whether MPAs—which, of course, are fixed markers present throughout childhood and adolescence well before the onset of the prodrome and psychosis—may have utility in terms of risk stratification for future preventive efforts. Taken together, research findings on MPAs indicate that these minor anomalies are indeed part of some schizophrenia syndromes, representing a stable systemic or physical set of manifestations of the underlying neurodevelopmental processes that lead to the illness.

Key words: minor physical anomalies/psychosis/schizophrenia

Introduction

The neurodevelopmental model of schizophrenia proposes that both genetic and environmental factors contribute to structural and functional brain changes in the intrauterine and perinatal periods, as well as in childhood and early adolescence.1–3 Therefore, these changes occur well before the onset of psychotic symptoms that typically first appear in late adolescence or young adulthood. The notion that early brain insults predispose to schizophrenia is supported by findings that some patients with the disorder exhibit morphologic evidence of subtle developmental abnormalities that presumably occurred during embryogenesis.4 The field of schizophrenia research has a rich history of investigating physical developmental anomalies as potential clues linked to the enigmatic development of the disorder and perhaps to the pathophysiology of its intriguing symptoms.

Minor physical anomalies (MPAs) are subtle signs of developmental abnormalities, primarily involving the craniofacial region and limbs, which are typically of little or no functional or cosmetic consequence.5–7 Thus, MPAs are fixed markers that presumably signify gestational developmental insults.8–11 However, many of these physical traits are partly genetically determined as well. MPAs involving the eyes, ears, mouth/palate/tongue, and limbs have been found consistently at a higher frequency in patients with schizophrenia than in healthy individuals.7–10,12–21 Thus, the finding that a diverse set of broadly defined MPAs are found in excess among individuals with schizophrenia is very well replicated. Further, the fact that these studies reveal quantitative and qualitative heterogeneity among patients in the manifestation of MPAs is consistent with the overwhelming evidence of etiologic, especially genetic, heterogeneity in schizophrenia.

Defining and Measuring MPAs

The Scope of the “MPAs” Construct

As noted above, MPAs are subtle morphologic signs that are of little or no consequence but which represent fixed markers of gestational developmental abnormality. The MPA concept emerged from the study of minor
anomalies in newborns, preschool children, and elementary school children, and their association with behavioral disturbances (eg, hyperactivity, impulsivity) in childhood. Over time, MPAs evolved into a construct of interest to schizophrenia researchers as well as those studying a variety of other neurodevelopmental and behavioral disorders, including but not limited to attentional disorders, autism, fetal alcohol syndrome, learning disabilities, and sensory impairments.

Some of the MPAs that commonly have been assessed by schizophrenia researchers are shown in Table 1. Qualitatively assessed morphologic anomalies include features such as confluent eyebrows, a flat occiput, hypertelorism, ear protrusion, low-set ears, palatal abnormalities, tongue furrows, a curved fifth digit, and a large gap between the first and second toes, to name just a few. Quantitatively measured MPAs include abnormalities in head and facial measurements, such as elongation of the lower facial region, reduced head circumference, and reduced mouth width. Several reports have provided tables that show frequencies/percentages of individual anomalies in patients compared with those found in control groups. Additionally, a recent meta-analysis provides summary effect sizes of MPA frequencies by anatomical region from many of these and other studies.

MPAs are often grouped on the basis of body region alone (as in Table 1), though other groupings may be more informative. Trixler et al suggested that minor malformations (abnormal qualitative defects of embryogenesis that arise during organogenesis) should be distinguished from phenogenetic variants (quantitative defects of final morphogenesis that arise after organogenesis and that are morphologically equivalent to normal anthropometric variants). Such a distinction may have utility because separation of features occurring before and after organogenesis (gestational days 1 to approximately 56) can aid in elucidating the temporal sequence of events that predispose to schizophrenia.

Research on craniofacial dysmorphology, based on quantitative measurements, rather than qualitative assessment, is described further below.

MPAs can be considered in the context of the totality of congenital anomalies; ie, on a spectrum from normal morphologic variants and dimorphisms based on sex and race to major congenital disorders. Waddington et al studied the relationship between congenital anomalies, excluding MPAs, and risk for schizophrenia in the Child Health and Development Study conducted with the Kaiser Permanente Medical Care Plan in Alameda County, California. They reported that the presence of a craniofacial/midline anomaly or early functional-neural impairment (eg, cleft palate, microcephaly, febrile convulsions, slow speech development) was associated with an increased risk of a schizophrenia-spectrum disorder (rate ratio: 2.18; 95% confidence interval: 1.11, 4.28). In a quantitative review and meta-analysis of obstetric complications and risk for schizophrenia, Cannon et al found that congenital malformations were associated with increased risk for schizophrenia. The pooled odds ratio estimate across the few pertinent studies was 2.35 (95% confidence interval: 1.21, 4.57), though...
most data in this area primarily come from the large Swedish cohort follow-up study of Dalman et al.30 These findings suggest that the broader spectrum of congenital malformations, which includes the diverse varieties of MPAs, is associated with risk for schizophrenia.

Aside from these traditionally defined MPAs and more substantial congenital anomalies, a number of markers of developmental abnormalities that are not usually included in the construct of MPAs have been studied as well. For example, dermatoglyphics (the epidermal ridge patterns that form on the fingerprints, palms, and soles during the late first and early second trimesters) are, like MPAs, subtle but permanent markers of the fetal environment that are also genetically influenced. Individuals with schizophrenia and people with high levels of schizotypy have been found to have lower total finger ridge count, more arch patterns, fewer whorl patterns, and greater ridge count fluctuating asymmetry compared with healthy controls.31–36 Unaffected individuals with a strong family history of schizophrenia have been shown to display an intermediate pattern of dermatoglyphic complexity (between patients and controls),37 though other studies have not found elevated rates of dermatoglyphic abnormalities in first-degree relatives (M. K. Gabalda and M.T.C., 2008, unpublished data).38 Some limited evidence suggests that particular dermatoglyphic features are associated with an earlier age of onset and a declining course of schizophrenia.39 Research on dermatoglyphics is relatively limited and complicated by methodological shortcomings, but mixed results also likely stem from different developmental responses to various developmental insults.

Another example of a developmental abnormality that has been studied as a marker of schizophrenia, but which lies outside the scope of the traditional MPA construct, is nailfold plexus visibility. A highly visible plexus has been shown to be more common among patients with schizophrenia compared with healthy controls.40–43 Curtis et al44 found that patients with schizophrenia with a highly visible plexus have greater oculomotor dysfunction, negative symptoms, symptom severity, chronic course, and neuropsychological dysfunction. Furthermore, nailfold plexus visibility appears to be at least moderately heritable.40,45

Other physical features have been studied in the context of schizophrenia, suggesting that MPAs, as measured by the most widely used instruments, represent only one heterogeneous subgroup of morphologic markers with both genetic and environmental determinants. It is possible that relying on a relatively small number of MPAs (typically only a few dozen are assessed, rather than hundreds) could underestimate the prevalence of morphological abnormalities and, more importantly, limit the possibility of detecting patterns of co-occurring abnormalities.46 Nonetheless, for the remainder of this review, MPAs will be considered as a heterogeneous group of subtle anomalies, which are nonetheless delimited (eg, excluding dermatoglyphics and nailfold plexus visibility) largely by virtue of the measurement instruments that have been developed.

The Measurement of MPAs

MPAs are not usually assessed for clinical purposes, though some minor anomalies may be observed incidentally during routine clinical interactions and physical examination. MPAs typically are recorded for research purposes using one of several structured rating scales, such as the one developed by Waldrop and Halverson,47 revised and adapted versions of the Waldrop Scale,13,16,17,48,49 and the more comprehensive instrument used by Lane et al.9 Qualitative items are usually scored as 0 (absent) or 1 (present). Quantitatively measured MPAs may be scored 0–3 to indicate measurements falling within a mean population range or within 1, 2, or 3 SDs above or below this mean range.13,48 A total MPA score is usually derived by summing all items, and some studies also report on several body regions (ie, subscale/regional scores for eyes, ears, mouth, hands, etc).

Research groups often assess inter-rater reliabilities using intraclass correlation coefficients and kappa statistics for continuous measurements and binary variables, respectively. However, an important limitation in nearly all studies conducted to date is the fact that assessors usually have not been blinded to participants’ group status when assessing MPAs (and could not feasibly have been blinded due to the behavioral impact of the symptoms of schizophrenia). This is obviously less of a limitation in studies that assess healthy family members of patients with schizophrenia and healthy controls without a family history of the disorder.

Further research to expand and refine the measurement of MPAs would be beneficial. Currently, comparisons across studies are difficult due to major variability in operationalizing and measuring MPAs, as well as differences in selection criteria for both patient and control groups. The most widely used scales—those based on the work of Waldrop and Halverson47—have poor inter-rater agreement; hence, they have not been blinded to participants’ group status when assessing MPAs (and could not feasibly have been blinded due to the behavioral impact of the symptoms of schizophrenia). This is obviously less of a limitation in studies that assess healthy family members of patients with schizophrenia and healthy controls without a family history of the disorder.

Prenatal Insults as an Origin of MPAs

A full understanding of the significance of MPAs in schizophrenia requires an examination of what is known about their origins, both environmental and genetic. The developmental timing of MPA formation limits their development, and MPAs are not usually assessed for clinical purposes, though some minor anomalies may be observed incidentally during routine clinical interactions and physical examination. MPAs typically are recorded for research purposes using one of several structured rating scales, such as the one developed by Waldrop and Halverson,47 revised and adapted versions of the Waldrop Scale,13,16,17,48,49 and the more comprehensive instrument used by Lane et al.9 Qualitative items are usually scored as 0 (absent) or 1 (present). Quantitatively measured MPAs may be scored 0–3 to indicate measurements falling within a mean population range or within 1, 2, or 3 SDs above or below this mean range.13,48 A total MPA score is usually derived by summing all items, and some studies also report on several body regions (ie, subscale/regional scores for eyes, ears, mouth, hands, etc).

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potential causes to prenatal and/or genetic/epigenetic factors that have the potential to disrupt fetal development. However, it should be noted that the timing of the insult likely substantially influences the nature and severity of the anomaly. Because all developmental processes are due to a complex interplay between maternal genes, the genotype of the embryo, and environmental influences, the etiology of MPAs is similarly complex. To date, the relative influences of prenatal events vs genetic factors are still under investigation.

The evidence for a link between prenatal events and MPAs comes from a variety of sources. In the general population, prenatal alcohol and drug exposure have been shown to be a significant predictor of MPAs in offspring, and serious alcohol use during pregnancy is linked with fetal alcohol syndrome, which has characteristic syndromic features such as wide-spaced eyes and flattened nose. Low birth weight, obstetrical complications, and other indicators of prenatal insult are also associated with elevated rates of MPAs.

Among individuals at risk for schizophrenia, there is also evidence of a link between prenatal complications and MPAs. In a twin study, pregnancy complications and MPAs were independently assessed in normal monozygotic (MZ) twin pairs and in twins discordant or concordant for schizophrenia. Complications occurring during early pregnancy were associated with a higher frequency of MPAs in the overall group, as well as the discordant twin pairs. Although no significant differences in anomaly rates were observed among the discordant, concordant, and normal twin pairs, the discordant ill twins showed a trend toward having more anomalies than their well co-twins. These results suggest that prenatal complications in early pregnancy are associated with greater MPAs and may be more pronounced in the affected twins of discordant MZ twin pairs.

**Genetics and the Origins of MPAs**

In considering the genetic determinants of MPAs, it is important to note the distinction between inherited genetic risk and acquired genetic risk. It is clear that risk for schizophrenia, like risk for many other physical and mental disorders, is partly, perhaps predominantly heritable. Data from family, twin, and adoption studies has provided strong support for a high heritability. At the same time, advances in molecular genetics have demonstrated the importance of non-heritable genetic risk factors. These entail mutations, as well as epigenetic processes that alter gene expression. Recent data indicate that both inherited and acquired genetic risk factors can give rise to both MPAs and schizophrenia.

**Findings From Studies Examining Family History**

In order to explore hereditary influences, some investigators have examined the relationship between family history of psychosis and MPAs in patients with schizophrenia, and the findings generally suggest a positive association. One study of MPAs in patients with schizophrenia revealed that MPA scores were associated with a family history of schizophrenia in a first-degree relative and with obstetric complications. A family history of schizophrenia was particularly associated with minor anomalies involving the mouth. In partial replication, a later report indicated that in male patients there was a positive correlation between MPAs and family history of a major psychiatric disorder, although MPAs were not linked with obstetric complications. These findings have been interpreted as indicating a potential overlap between the various genes that predispose to psychiatric illness and the genes that predispose to developmental instability and thus lead to MPAs (especially in males). In contrast, one research group examined MPAs in high-risk offspring of women with psychotic disorders and a comparison group of offspring of women with no history of psychosis, finding no difference in MPAs between the high-risk children and offspring of the control women.

**Findings From Studies Involving First-Degree Family Members**

Ismail et al found an association between schizophrenia patients’ MPA scores and their healthy siblings’ MPA scores. In contrast, Gourion et al found familiality for neurological soft signs but not for MPAs. Compton et al found that patients’ overall MPA scores and their respective relatives’ scores were significantly correlated, and correlations also were evident in 3 of 8 body regions, eyes, ears, and hands.

Research on the prevalence of MPAs in relatives of patients with schizophrenia has produced mixed results. Several studies report that relatives do not have a higher frequency of MPAs, with rates similar to those seen in healthy controls. Other studies suggest that relatives have elevated rates of MPAs, similar to findings in patients. In a study of 30 first-episode patients, 152 biological relatives of these patients, and 35 healthy subjects, MPAs and neurological soft signs were more common in both patients and their biological relatives than in healthy controls. Similarly, a study involving patients with schizophrenia and their siblings revealed a higher rate of MPAs in both groups, relative to controls. Interestingly, Griffiths et al reported that families with a single case of schizophrenia may manifest more MPAs than multiplex families, potentially suggesting that MPAs result from an insult during fetal development rather than from a genetic liability to schizophrenia. The fact that a higher prevalence of MPAs in first-degree relatives than in healthy controls without a family history of schizophrenia has been observed in some (though not all) of the studies involving family members could.
indicate that an external physical phenotype (ie, MPAs) in patients and their relatives may be more highly penetrant than the complex behavioral phenotype of schizophrenia.

Gourion et al conducted a series of investigations involving family members. In one study, they assessed neurological soft signs and MPAs in patients with schizophrenia, nonpsychotic parents of patients, and healthy subjects. Parents were further classified as “presumed carriers” of the genetic loading if they had a second relative with schizophrenia in their ascendants and/or collateral (first or second degree) or as “presumed non-carriers.” A discriminant function analysis based on neurological soft sign scores and MPA scores correctly classified 71% of nonpsychotic parents into presumed carriers or presumed noncarriers. The authors concluded that neurological impairments and MPAs are associated with the genetic risk for schizophrenia, even when the disease itself is absent. Yet, in another report, Gourion et al examined the intrafamilial similarities of neurological soft signs and MPAs in 18 probands with schizophrenia and their 36 nonpsychotic parents. A general linear model showed similarities within families for soft signs but not MPAs—indicating that there was no support for intrafamilial transmission of MPAs—leading the authors to suggest that MPAs could be more dependent on epigenetic influences.

In general, the results of research on MPAs in first-degree relatives, as well as that on family history of schizophrenia and MPAs in probands, provide only modest support for the notion that MPAs are influenced by the inherited liabilities that predispose to schizophrenia. Thus familial genetic risk for psychosis does not appear to clearly account for greater rates of MPAs in patients.

Findings From Twin Studies

Consistent with the findings reported by Gourion’s group, the limited data on heritability suggest that in normal populations, heritability of MPAs is negligible. Specifically, a study of MPAs in normal MZ and dizygotic twin children yielded no significant heritable component (E. A. Jenkins, 2008, unpublished thesis). However, the author also reported only moderate reliability for the measurement of MPAs, so these findings should be considered tentative. Nonetheless, the reported absence of significant concordance for MPAs in MZ twins does converge with growing evidence of epigenetic processes in fetal development.

Recent studies of twins discordant for birth weight have shed light on fetal neurodevelopmental processes. Riese examined MPA scores and developmental status in twin pairs that were concordant and discordant for weight. Because the early development of twins can be altered by prenatal factors that differentially influence co-twins, the 2 members of the pair are often discordant for birth weight. Riese found that discordant twin pairs (defined as having a $\geq 15\%$ difference in birth weight) had higher MPA scores and lower developmental status compared with nondiscordant pairs. Additionally, both the smaller and larger twin from the discordant group had greater MPAs and poorer developmental status compared with the concordant pairs. A higher number of MPAs in twins from birth weight discordant pairs suggests a common etiology for MPAs and discordant weight among twins. Among the potential causes of MZ co-twin discordance for birth weight are nonoptimal implantation site, asymmetric nutrition, placental lesions, fetomaternal transfusion, twin-to-twin transfusion, and mutations that affect only one member of the twin pair.

Findings Pertaining to Epigenetics and Specific Risk Alleles

It is of interest to note that other studies of MZ twins have revealed that birth weight differences are linked with subsequent behavioral disorders and academic achievement in the co-twins, with the smaller member of the twin pair showing greater problems. One source of these differences is assumed to be the effects of prenatal complications on gene expression. For example, it has been suggested that epigenetic factors, such as DNA methylation, may account for a proportion of MZ co-twin discordance in physical and behavioral characteristics. One research group assessed the methylation status of 2 sites in the promoter region of the catechol-O-methyltransferase (COMT) gene in MZ twin pairs that were discordant for birth weight but otherwise clinically unaffected. They found co-twin correlations in the degree of methylation, but there was considerable variation in the concordance of methylation levels among twin pairs. Some MZ pairs showed high methylation concordance, whereas others differed significantly in their methylation profiles. The researchers concluded that epigenetic variability may play a key role in the etiology of psychopathology and thus explain the incomplete phenotypic concordance observed in MZ twins.

Although there are no reported twin studies of the relation between MPAs and gene expression, there is one report that nonsyndromic clefts of the lip and/or palate, a relatively common anomaly, are linked with methylation discordance. It is possible, therefore, that MPAs are largely determined by variations in the expression of genes that govern fetal development. Placental differences may be one of the precipitants of differences in epigenetic processes.

Another source of discordance among MZ twins are de novo mutations that affect only one member of the twin pair. These mutations have been documented in a variety of MZ pairs discordant for various mental and other
disorders.\textsuperscript{70} Given the elevated rate of MPAs in disorders that result from \change{de novo mutations (eg, 22q deletion, Downs and Williams syndromes)}, it is possible that spontaneous mutations play a role in MPAs in schizophrenia. This would be expected to lower heritability estimates. As described below, recent evidence indicates that such mutations are common in schizophrenia.\textsuperscript{71}

To date, there is only one published report on the relation between a specific risk allele and MPAs in schizophrenia.\textsuperscript{72} The researchers focused on the COMT gene, which has been identified as a potential candidate gene for schizophrenia because of its role in dopamine metabolism. Also, COMT is located on chromosome 22q11.2, a region that has been implicated in both schizophrenia and velocardiofacial syndrome (VCFS), a disorder that is also associated with MPAs. Joo et al\textsuperscript{72} tested the hypothesis that patients with schizophrenia with MPAs represent a genotypic subgroup characterized by a disruption in neurodevelopment. Genotyping for the Val(158)-Met functional polymorphism in the COMT gene was conducted in 239 patients with schizophrenia and 248 normal controls. Although there were significantly more MPAs in the patients than controls, there were no significant group differences in allele or genotype frequency, nor was there an association between COMT genotype and the presence of a high number of MPAs among patients with schizophrenia.

\section*{MPAs as Risk Markers or Endophenotypes}

The foregoing evidence has been taken to suggest that MPAs represent a risk marker for schizophrenia.\textsuperscript{7,25} Can MPAs be thought of as an endophenotype, a measurable biological marker generally unseen by the unaided eye that is along the pathway between distal genotype and disease, which may be environmental, epigenetic, or multifactorial in origin? Gottesman and Gould\textsuperscript{73} provide criteria for endophenotypes, including (1) the marker is associated with illness in the population; (2) it is heritable; (3) it is primarily state independent (manifests in an individual whether or not illness is active); (4) within families, the marker and illness cosegregate; and (5) it is found in unaffected family members at a higher rate than in the general population. MPAs clearly meet the first and third of these criteria. Family studies suggest that the second, fourth, and fifth also may be met, though additional research involving first-degree family members is warranted.

\section*{Issues of Specificity in the Link Between MPAs and Schizophrenia}

A central, complex issue pertaining to the study of MPAs in schizophrenia is that of specificity. Two questions, which have yet to be firmly resolved, are briefly addressed here. (1) Are elevated rates of MPAs specific to schizophrenia as opposed to serious mental illnesses and developmental disorders more generally? (2) Are elevated rates of MPAs specific to any particular subtypes of schizophrenia, in terms of associations with certain types of signs/symptoms or illness features such as longitudinal course?

\textit{Specificity of MPAs for Schizophrenia Vs Serious Mental Illnesses and Developmental Disorders More Generally}

Elevated rates of MPAs are not specific to schizophrenia. As mentioned above, syndromes with both physical and behavioral characteristics that are environmentally induced (eg, fetal alcohol syndrome) and those that are genetically determined (eg, VCFS) are associated with both major and minor anomalies. Within the group of disorders commonly characterized as serious mental illnesses, MPAs appear to be more common in schizophrenia. That is, elevated rates of MPAs have not been observed consistently in samples of patients with affective disorders, including bipolar disorder and major depression. However, there has been very limited research on MPAs in the context of these disorders. Some findings indicate that patients with schizophrenia have significantly more MPAs than patients with bipolar disorder, suggesting that MPAs may have some degree of specificity to schizophrenia.\textsuperscript{27,60} Despite the fact that some conceptualizations place schizophrenia and bipolar disorder on a common disease continuum with shared etiological antecedents,\textsuperscript{74} However, as mentioned, it should be noted that bipolar disorder research does not have nearly the rich and lengthy history of studying MPAs as does the field of schizophrenia research. A small study examining the prevalence of MPAs among individuals with major depression did not find elevated rates of MPAs over healthy controls,\textsuperscript{75} though the very small literature has yielded mixed results.\textsuperscript{57,76} As discussed by Pine et al,\textsuperscript{20} inconsistent findings have been reported on the relationship between MPAs and disruptive and pervasive developmental disorders in childhood.

Examinations of associations between MPAs and disease states are not limited to research on schizophrenia and other neurodevelopmental diseases. For example, Merks et al\textsuperscript{66} in the Netherlands recently reported on a study of 1073 patients with childhood cancer and 1007 comparison school children. Detailed physical examinations were directed at 683 morphological abnormalities. They found that pediatric patients with cancer show a significantly higher prevalence of morphological abnormalities compared with controls. The authors concluded that specific patterns of morphological abnormalities may reveal possible unrecognized tumor predisposition syndromes and perhaps even the identification of specific etiologic genes or genes functioning within the same developmental pathway. Thus, developmental
genes that play a role in body plan formation during embryonic and fetal development are also involved in the development of cancer and likely other disease states.

**Specificity of MPAs for Particular Symptoms, Subtypes, or Longitudinal Courses of Schizophrenia**

There is no consistent or convincing body of evidence that MPAs are markers of distinct illness features. Several studies report no consistent association between MPAs and positive or negative symptoms. Ismail et al reported that high rates of MPAs were not related to cognitive or neurological dysfunction or to premorbid history or other course features. At least one report suggests that MPAs may be more prevalent among patients with early-onset schizophrenia (<18 y) than those with an onset at ≥18 years of age. A small body of research suggests that MPA scores may be correlated with some brain imaging findings, such as brain and ventricular volumes, as reviewed by Dean et al. Recently, John et al reported that neuroleptic-naïve patients with recent-onset schizophrenia who had one or more MPAs had higher levels of positive, negative, and general psychopathology scores compared with those with no MPAs.

**Are Some MPAs More Informative Than Others?**

Although MPAs are usually measured as a broadly defined, heterogeneous subgroup of morphologic abnormalities, it is possible that some particular MPAs are more specific markers of schizophrenia than others. This would call into question the use of MPAs as a single construct (consisting of numerous different anomalies combined into a summary score) and indicate that some MPAs may be more informative singly (eg, palatal abnormalities). It has been clearly established that MPAs, assessed as a total score, are a reliable and powerful discriminator of cases vs controls, but more research is needed on specific MPAs.

MPAs of the craniofacial region may form concurrently with the in utero structural brain changes that ultimately are associated with schizophrenia. Trixler et al suggested that specific anomalies of the mouth and head may have more relevance to neurodevelopmental abnormalities than does the cumulative prevalence of MPAs. Similarly, Weinberg et al posited that information about which body regions are most susceptible to MPAs in the context of schizophrenia can provide clues to the temporal origins of the dysmorphology and its relationship to neurodevelopment.

It should be noted that one study involving 50 nonpsychiatric participants older than 60 years (mean ± SD: 79.9 ± 7.3 y) and 50 nonpsychiatric participants younger than 60 years (31.6 ± 8.3 y) found that select MPAs are influenced by advanced age, including absence of a trichion; presence of a short, broad palate; and ear protrusion. Whereas the former is obviously a consequence of age-related alopecia, the latter 2 were hypothesized to be related to dental changes with age, including loss or extraction of teeth or denture wearing, which could lead to overall changes in the shape of the face. Such findings suggest that the effect of age should be examined and controlled appropriately in future studies. On the other hand, many qualitative MPAs are unlikely to be influenced by age (eg, hypertelorism, adherent ear lobes, bifid uvula, curved fifth digit, café-au-lait spots), and age-related morphological traits should be distinguished from true MPAs deriving from fetal development.

Several studies recently have examined single morphologic features as specific markers of dysmorphogenesis. For example, male schizophrenia patients have been shown to have smaller posterior nasal volumes than both healthy male controls and male relatives and Kirkpatrick et al reported that patients with schizophrenia had significantly wider palates than controls. Gourion et al found that 3 specific items were independently predictive of patient vs comparison group status in a logistic regression model including data from 40 patients and 42 controls: facial asymmetry, cleft palate, and hair whorls. Akabaliev et al reported that a discriminant analysis including 6 specific MPAs (fine electric hair, presence of a large gap between the first and second toes, epicanthus, high/steeped palate, tongue with rough and smooth spots, and third toe equal in length or greater than second toe) correctly classified 79% of a sample of 68 patients and 69 healthy controls. Lane et al reported that 12 variables, all in the craniofacial region, made significant independent contributions to the prediction of patient vs control status, correctly classifying 88% of participants.

**Studies of Craniofacial Dysmorphology as a Subset of MPA Research**

Several studies have examined composites of quantitative facial measurements. Such studies are generally of 2 types, those reporting on differences in size (dimensions or facial measurement lengths) and those analyzing shape using 3-dimensional (3D) renderings and geometric morphometrics.

Regarding size of individual facial dimensions, various studies (which typically have used manual or digital calipers to measure distances between specific landmarks, such as the glabella, tragus, stomion, and gna-thion) have reported that patients with schizophrenia have abnormal head circumference, greater skull base width, greater nasion-stomion height, smaller biocular distance, smaller nasal width, smaller width of the mouth, and smaller cheilion-menton distance. Mcgrath et al evaluated facial measurements of 180 case-control pairs,
matched by age and gender. They found that patients had greater skull base width, greater tragus-subnasale depth, and greater tragus-gnathion depth than controls. In terms of facial heights, patients had smaller glabella-subnasale, glabella-stomion, and glabella-gnathion measures. Lane et al. assessed facial measurements in 174 patients and 80 matched controls, and patients were found to exhibit overall narrowing and elongation of the mid- and lower face. Compton et al. found that female patients had a greater midfacial depth (tragus-subnasale) compared with female controls, whereas male patients had lesser upper facial (trichion-glabella) and lower facial (subnasale-gnathion) heights compared with male controls.

Hennessy et al. compared craniofacial shape (rather than facial measurement lengths) by applying geometric morphometrics to 3D reconstructions derived from the data of Lane et al. Facial shapes were predictive of both gender and diagnostic group status, and there was a strong gender by diagnosis interaction. For both genders, patients exhibited a wider skull base, shortened upper midfacial height, and lengthened lower midfacial height compared with controls. Sex-specific asymmetries were noted; eg, male controls exhibited more directional asymmetry than male patients, whereas female patients exhibited more directional asymmetry than female controls. This group also is using 3D laser surface imaging and geometric morphometrics of craniofacial shape, as described in a recent publication. This methodology revealed that compared with controls, patients evidenced an overall widening and vertical shortening of the face, narrowing and reduction of the mid- and lower face, and widening of the mandible. Buckley et al. evaluated 65 anthropometrically derived landmarks using 3D facial images in 14 patients with schizophrenia and 11 controls and found an overall elongation of the face.

Studies involving facial measurements may be of particular interest given that the face and some regions of the brain develop in concert from the same ectodermal tissue. Other neurodevelopmental disorders, such as VCFS, Down syndrome, and fetal alcohol syndrome also involve malformations of facial features concurrent with brain development, but they are much less subtle than those observed in schizophrenia. For example, the characteristic facial features of VCFS include elongation of the face, prominent nose with narrow alar base and squared nasal root, retruded mandible with chin deficiency, and microcephaly. Ongoing research on the genetics of craniofacial development may shed light on the underlying genetic links between MPAs and schizophrenia; eg, human cranioskeletal development has been linked to fibroblast growth factor receptor (FGFR) genes, and therefore, allelic variations underlying FGFR genotypes represent potentially relevant loci, among many others.

**What Can Research on MPAs Tell Us About Schizophrenia?**

**MPAs Support the Neurodevelopmental Model of Schizophrenia**

The cumulative evidence from research on the origins and correlates of MPAs leads to the general conclusion that abnormalities in fetal neurodevelopment are implicated in the etiology of any disorder characterized by an elevation in the rate of MPAs. Thus, although MPAs are not specific to schizophrenia, they indicate that aberrations in the development of the nervous system contribute to risk for the disorder.

Waddington et al. proposed a more detailed model of the neurodevelopmental basis of schizophrenia, informed by the most commonly reported specific MPAs and craniofacial measures (eg, overall narrowing and elongation of the mid- and lower anterior facial region, heightening of the palate, reduced mouth width, and widening of the skull base). They suggested that schizophrenia is characterized by a shift toward more prominent narrowing and vertical elongation of the anterior midface during palate formation (around wk 9–15), which is associated with impairment in anterior cerebral development. Despite this level of detail, which is an important refinement of the more general neurodevelopmental model, further elucidation of the pathophysiology of schizophrenia through research on MPAs remains very challenging due to the heterogeneity of the MPA construct, in addition to the well-recognized heterogeneity of schizophrenia.

**MPAs May Be of Value in Further Elucidating the Pathophysiology of Schizophrenia**

Although the broadly defined, heterogeneous MPA construct is likely of limited value in further elucidating the pathophysiology of schizophrenia, investigations of more specific MPAs or groups of MPAs—especially those whose ontogenic timing and sequence have been refined—may inform understandings of the disorder beyond general support for the neurodevelopmental model.

Goodman et al. have proposed that the retinoid system may play a role in the emergence of both MPAs and brain abnormalities in schizophrenia. Disruption of retinoid signaling pathways in rodent models confirms their involvement in regulating synaptic plasticity and behavior. Furthermore, retinoid toxicity can result in craniofacial, limb, and digit abnormalities, as well as the dysgenesis of other organ systems. Retinoic acid receptors are present in the progenitor cells that lead to the formation of these regions, and retinoids modulate gene expression in these cells throughout embryonic and fetal development. Thus, Goodman and colleagues have proposed that alterations in retinoid function have implications for neurodevelopmental disorders that are...
characterized by MPAs, including schizophrenia. However, while involvement of the retinoid system in the etiology of schizophrenia is plausible, there is currently no evidence to support this assumption to the exclusion of others.

Altered expression of the genes that govern fetal neurodevelopment also can arise from de novo genetic mutations that result in deletions or duplications and can occur in coding regions or promoter and regulatory regions of genes. In fact, recent evidence from a genomic DNA scan of patients and controls indicates that this is indeed the case for patients with schizophrenia. That study revealed significantly more microdeletions and microduplications in patients compared with healthy controls, including the biological relatives of the patients. Moreover, the mutations were disproportionately found in genes related to the development of the nervous system. It is known that such mutations can give rise to neurodevelopmental abnormalities and broadly defined MPAs.

Given the availability of more sophisticated microarray technologies, and in light of recent findings on spontaneous mutations in patients with schizophrenia, it is possible that MPAs will prove to be useful in identifying etiologic subtypes. This possibility is suggested by recent findings on novel mutations in autistic children who manifest the “syndromic” subtype, which is accompanied by malformations or dysmorphic features (i.e., abnormal facial morphology). Researchers conducted array comparative genomic hybridization (array CGH) and identified 8 regions of copy number variations, with 7 of the 8 being de novo mutations that differed between these autistic children and normal controls.

Perhaps those with spontaneous mutations will have more MPAs or a unique profile of MPAs. Also, it seems likely that there is some specificity to the subset of genes that govern the development of various body regions, such as the craniofacial region vs the hands. It is possible that different genes, and therefore different mutations, are involved in MPAs in these body regions. Thus, the pattern of MPAs could hold information about the locus of the genetic anomaly.

MPAs Could Inform Future Risk Stratification Efforts

It may be possible that MPAs—which, of course, are fixed markers present throughout childhood and adolescence well before the onset of the prodrome and psychosis—may have utility in terms of risk stratification for future preventive efforts. The usefulness of specific MPAs, combinations of several MPAs, and composite MPA scores for risk stratification has yet to be clarified. It is possible that detailed MPA assessments, in conjunction with measures of other endophenotypes (in physical, neurocognitive, electrophysiologic, and neuroimaging domains) could provide composite endophenotypes that would enhance prediction of risk for schizophrenia and eventually sharpen the application of future preventive efforts. Along these same lines, research on the relation of MPAs with treatment response may shed light on strategies for targeting early pharmacologic interventions to enhance response.

Are MPAs Part of the Syndrome of Schizophrenia?

It seems clear that MPAs probably represent the complex interplay between maternal genes, the genotype of the embryo, and environmental influences during fetal development. Regarding genetic contributions, both heritable genetic risk and acquired genetic risk are likely at play in the formation of minor developmental anomalies. A plethora of research shows that MPAs are elevated in people with schizophrenia and likely in their first-degree family members, though more family studies are needed.

The current preponderance of research evidence suggests that MPAs are an inherent part of some syndromes of schizophrenia. This is consistent with the notion that schizophrenia is a neurodevelopmental disorder. MPAs are not specific to schizophrenia and do not show consistent associations with symptoms and longitudinal course of the illness. Nonetheless, MPAs may meet several or all of the criteria for an endophenotype, indicating that MPAs are closer to etiologic pathways of schizophrenia than are psychotic symptoms. In sum, findings pertaining to MPAs support the neurodevelopmental model of schizophrenia and may inform the field’s understanding of the neurodevelopment of the illness. Additional family studies—those measuring MPAs in patients, first-degree relatives, and controls—would benefit the field by providing better estimates of the prevalence of various MPAs in unaffected family members and estimates of heritability, which would inform considerations of MPAs as an endophenotype.

Conclusions

Research findings to date suggest that MPAs originate from both prenatal insults and genetic factors. However, the genetic mechanisms appear to be complex and may entail changes in gene expression and spontaneous mutations, as well as inherited genetic risk factors. In the current state of research, broadly defined MPAs confirm the developmental origins of schizophrenia (providing support for the neurodevelopmental model) but have not yet been useful in elucidating the pathophysiology of the illness. This is consistent with others’ suggestions that MPAs are nonspecific markers of generalized maldevelopment that may not necessarily arise from any of the genes for schizophrenia. It remains possible, however, that specific developmental anomalies (e.g., palatal abnormalities studied by Kirkpatrick et al or nasal volume...
abnormalities assessed by Turetsky et al (83), once tied to specific genes or developmental pathways, could inform the pathophysiology of neurodevelopmental disorders such as schizophrenia. It remains to be determined whether or not the assessment of MPAs would be valuable for efforts to stratify individuals at presumed risk for schizophrenia into higher risk and lower risk groups. If so, these fixed markers, which are inexpensively, non-invasively, and easily assessed, could allow for more precision in directing prevention-oriented efforts to those who are at particularly elevated risk based on composite indices of risk markers. Taken together, findings on MPAs in schizophrenia suggest that these minor anomalies are indeed part of some syndromes of schizophrenia, representing a stable systemic or physical set of manifestations of the underlying neurodevelopmental process that leads to the illness.

References


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