Minor Physical Anomalies in Schizophrenia Patients, Bipolar Patients, and Their Siblings

by Michael Foster Green, Paul Satz, and Cynthia Christenson

Abstract

Minor physical anomalies (MPAs) are believed to reflect abnormalities in fetal neurodevelopment. Several studies have shown that schizophrenia patients have more MPAs than normal controls, but little is known about the meaning of this increased rate of MPAs. The current study first attempted to determine whether the increased MPAs are associated with schizophrenia in particular or with psychosis in general. Second, the study tested whether the patients’ siblings also show an increased rate of MPAs by assessing MPAs in schizophrenia patients, bipolar manic patients, the siblings from each group of patients, and normal controls. The schizophrenia patients had significantly more MPAs than normal controls and bipolar patients. The rate of MPAs in bipolar patients did not differ from normal controls. This pattern suggests that MPAs have some degree of specificity to schizophrenia. Both sibling groups had fewer MPAs than the patients, and this difference was significant for the comparison between schizophrenia patients and their siblings. When viewed within a vulnerability-stress model, the results are consistent with the theory that MPAs may reflect early, largely extra-genetic, stressful events.


Schizophrenia fits neither a medical model nor a psychological model particularly well. That is one reason some investigators have proposed that schizophrenia can be better viewed within a neurodevelopmental model (Weinberger 1987; Murray et al. 1992b). According to this model, schizophrenia results from an early (most likely prenatal) abnormality in neural development. This abnormality is latent (or partially latent in the case of patients with a poor premorbid history) until the affected region matures and is required to function optimally (Weinberger 1987). At this time, the more prominent symptoms of schizophrenia appear.

To empirically test the neurodevelopmental model with adult schizophrenia patients, investigators must surmount a methodologic obstacle: the prenatal or perinatal period of interest has occurred several decades earlier. This challenging situation has led to the development of some remarkably creative methodologies.

One approach has been to use natural events such as influenza epidemics to determine if events during a woman’s pregnancy can place her offspring at increased risk for schizophrenia. Mednick et al. (1988) considered a population from Helsinki that was exposed to a relatively brief, fairly widespread A2 influenza epidemic in 1957. Offspring who were in utero during the influenza epidemic were compared with controls born in the same hospitals during the same months of previous years. This study found that the offspring of mothers who were exposed to the influenza virus during the second trimester of pregnancy (but not the first or third trimester) were at increased risk for schizophrenia. The finding

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suggests that a virus may lead to neural disruption that has etiologic significance for schizophrenia. This finding has been replicated with other samples from Denmark (Barr et al. 1990) and England (O'Callaghan et al. 1991b), but not in samples from Scotland (Kendell and Kemp 1989) or the United States (Bowler and Torrey 1990).

The conclusions of these studies have received support from the field of neuropathology. Several neurohistologic studies have found that the brains of schizophrenia patients are characterized by abnormalities in cell orientation and cell placement that likely reflect disruption during the period of cell migration in the second trimester (e.g., Kovelman and Scheibel 1984; Conrad and Scheibel 1987).

Another study of early neurodevelopmental abnormalities used an "archival-observational" approach. Walker and Lewine (1990) obtained home movies from families who had an offspring with schizophrenia and at least one normal offspring. Untrained raters viewed segments of the home movies and were asked to identify the preschizophrenia child. The raters were able to detect the preschizophrenia child, even at early ages, at a rate significantly above chance. The raters' decisions were often based on abnormalities in fine and gross motor coordination.

An alternative approach to studying neurodevelopmental factors has been to look for markers of abnormalities in neurodevelopment in adult schizophrenia patients. These markers are usually physical characteristics that are measurable in adults and reveal abnormal neurodevelopmental processes that occurred before or shortly after birth. Such markers include atypical handedness (Green et al. 1989b), dermatoglyphic signs (Bracha et al. 1992), and MPAs (Gualtieri et al. 1982; Guy et al. 1983; Green et al. 1989a; O'Callaghan et al. 1991a).

MPAs are minor abnormalities of the head, feet, hands, and face (e.g., high-steepled palate, large or small distance between tear ducts). MPAs and the central nervous system (CNS) both derive from the ectodermal layer. In addition, high rates of MPAs are associated with disorders that have known prenatal CNS involvement, such as Down's syndrome (Krouse and Kauffman 1982). Hence, MPAs are believed to reflect, albeit indirectly, CNS development.

The use of MPAs as a marker of abnormal neurodevelopment has clear advantages because it involves a brief examination, the assessments can be conducted reliably, and the exam requires minimal supplies—only a tape measure and a ruler. When used in research, MPAs have two major limitations. First, the exact timing of the neurodevelopmental events that are reflected by MPAs is not known, but they are believed to occur in the first and/or second trimester. Second, the assessment of MPAs requires an in-person examination, so it is not generally feasible for the raters to be blind to diagnosis when assessing symptomatic patients.

All studies that have compared MPAs in schizophrenia patients and normal controls have found an excess of MPAs in schizophrenia patients (Gualtieri et al. 1982; Guy et al. 1983; Green et al. 1989a). The increase in MPAs does not appear to be an artifact of socioeconomic status (Green et al. 1989a). Beyond this general conclusion, little else is known about the significance of MPAs in schizophrenia. A relationship between MPAs and age at onset of schizophrenia has been reported (Green et al. 1989a) but not replicated (O'Callaghan et al. 1991a). Likewise, there have been positive (O'Callaghan et al. 1991a) and negative (Green et al. 1989a) reports about the relationship between MPAs and cognitive functioning in schizophrenia.

Fundamental questions remain about the nature of MPAs in schizophrenia. For example, specificity issues have not been resolved. MPAs cannot be absolutely specific to schizophrenia because they also occur more frequently than normal in developmental disorders such as autism and learning disabilities (Gualtieri et al. 1982; Krouse and Kauffman 1982). However, if MPAs were relatively specific to schizophrenia among the psychotic disorders, it would suggest a larger role for neurodevelopmental factors in this illness. A recent study reported intermediate rates of MPAs in a mixed group of affective patients that were not significantly different from schizophrenia patients or normal controls (Lohr and Flynn 1993). Another fundamental question is whether MPAs reflect the genetic vulnerability to schizophrenia or the nongenetic events that place the individual at risk for schizophrenia.

To address the question of specificity among psychotic disorders, the current study assessed MPAs in bipolar (manic) inpatients, schizophrenia inpatients, and normal controls. A significantly higher rate of MPAs in the schizophrenia patients compared with the bipolar patients would be considered evidence of specificity. The bipolar inpatients were drawn from the
same units as the schizophrenia patients and have a rather severe illness; therefore, they present a reasonably strong test of specificity. The current study also addressed the question of the familiality of MPAs by assessing MPAs in schizophrenia patients and their full siblings. Siblings with significantly higher MPA scores than normal controls would support the notion that MPAs reflect part of the genetic vulnerability to schizophrenia. On the other hand, siblings with MPA rates lower than patients and comparable to normal controls would support the theory that MPAs reflect nongenetic events.

Methods

Subjects. Subjects included five groups: 63 schizophrenia inpatients, 33 siblings of schizophrenia patients, 26 bipolar inpatients, 9 siblings of bipolar patients, and 40 normal controls. Because certain aspects of MPAs cannot be scored with African-American (e.g., hair) and Asian (e.g., epicanthal fold) subjects, we selected only Caucasian subjects for this project. The demographic information for these subjects is listed in table 1.

Schizophrenia and bipolar subjects were drawn from the inpatient units of Camarillo State Hospital. The bipolar subjects had been admitted to the hospital for an episode of mania. All patients were diagnosed according to DSM-III-R (American Psychiatric Association 1987) criteria based on an expanded version of the Present State Examination (PSE; Wing et al. 1974). The PSE was supplemented with items from the Schedule for Affective Disorders and Schizophrenia (SADS; Endicott and Spitzer 1978) and the Structured Clinical Interview for DSM-III-R (SCID-P; Spitzer et al. 1990a). Interviewers were trained to a minimum kappa of 0.75 for key psychotic and affective symptoms compared with consensus rating of the Diagnosis and Psychopathology Unit of the UCLA Clinical Research Center for the Study of Schizophrenia. Potential subjects were excluded if they had a history of drug or alcohol dependence, evidence of an acquired neurologic disorder, any sign of mental retardation, history of seizure disorder, or were over 55 years of age.

The siblings of the schizophrenia and bipolar patients were invited to participate in this project if they lived within 80 miles of the UCLA-Camarillo Research Center and if they shared both biological parents with the proband. If more than one sibling was available, the one closest in age to the proband was invited to participate regardless of psychiatric or drug history. All siblings received the expanded PSE to assess Axis I disorders and the sections of the Structural Clinical Interview for DSM-III-R (SCID-II; Spitzer et al. 1990b) that probed for schizotypal, paranoid, and borderline personality disorder. These interviews identified those siblings who had a diagnosis in the schizophrenia spectrum. In four cases, data were collected from siblings, but the patient refused to participate.

The normal controls (n = 40) were drawn from the Psychiatric Technician Training Program at Camarillo State Hospital. Controls were given the same sections of the expanded PSE and SCID-II interviews as the siblings. The potential normal controls were excluded if they had a history of drug or alcohol dependence; showed evidence of an acquired neurologic disorder; had a history of a seizure disorder; met criteria for any of the three personality disorders that were probed; or had a history of any psychotic disorder, bipolar disorder, or more than one major depressive episode. In addition, to better separate the control group from the sibling group, potential normal controls were excluded if they had a first-degree relative with a history of a psychotic disorder.

Physical Anomaly Scale. All subjects received an approximately 5-minute examination for MPAs. As in Green et al. (1989a), a modified version of the Waldrop scale
was used to assess MPAs (Waldrop et al. 1968). The scale was modified for the head circumference and intercanthal distance by scoring one point if the measurements differed by more than 1.5 standard deviations (SDs) from the same-sex mean of the normal controls. The original scale was more liberal in scoring these items: subjects were given one point if they exceeded 1 SD and two points if they exceeded 2 SDs.

Interrater reliability was assessed with a sample of mentally retarded patients because such patients generally have prominent MPAs. Interrater reliability for total MPA score for all raters was greater than $r = 0.80$ (intraclass correlation coefficient).

**Results**

**Diagnostic Specificity.** The mean MPA scores are shown in figure 1. A series of comparisons with independent sample $t$ tests were conducted among the schizophrenia inpatients, manic patients, and normal controls. All levels of significance are reported for two-tailed tests. The mean score for the schizophrenia patients (1.95, SD 1.44) was significantly higher than the scores for the normal controls (0.95, SD 1.06, $p < 0.0001$) and bipolar patients (1.23, SD 1.03, $p < 0.01$). The MPA scores for bipolar patients and normal controls were not significantly different.

In addition to examining mean scores, it is helpful to consider the number of subjects in each group with prominent MPAs (i.e., the number of outliers). Prominent MPAs have been defined as scores of 3 or greater, which is 2 SDs above the mean for normal controls (Green et al. 1989a). The results are shown in table 2. Chi-square analyses indicated significant differences between schizophrenia patients and normal controls ($\chi^2 = 12.26, p < 0.001$), and the difference between schizophrenia and bipolar patients just failed to reach conventional levels of statistical significance ($\chi^2 = 3.40, p = 0.065$). The difference between bipolar patients and normal controls was not significant.

**Patient-Sibling Differences.** Initially, we considered the scores from all patients and all siblings, regardless of the psychiatric history of the siblings (see figure 1). The schizophrenia patients had significantly higher MPA scores than the sibling group ($p < 0.0001$).

The difference between bipolar patients and their siblings did not reach significance. Neither sibling group differed from normal controls; in fact, both sibling groups showed slightly fewer MPAs than normal controls.

When we consider the number of subjects in each group with prominent MPAs (table 2), the schizophrenia patients had more outliers than the siblings ($\chi^2 = 9.62, p = 0.002$). The difference between bipolar patients and their siblings did not reach significance.

Next, we considered pairings between patients and unaffected siblings. Among the schizophrenia patient-sibling pairs, we eliminated three pairs in which the siblings had a diagnosis in the schizophrenia spectrum (two with schizo-
Table 2. Number of subjects in each group with prominent minor physical anomalies (MPAs)

<table>
<thead>
<tr>
<th></th>
<th>Schizophrenia patients</th>
<th>Siblings of schizophrenia patients</th>
<th>Bipolar manic patients</th>
<th>Siblings of bipolar patients</th>
<th>Normal controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low MPAs</td>
<td>41</td>
<td>31</td>
<td>22</td>
<td>9</td>
<td>38</td>
</tr>
<tr>
<td>High MPAs</td>
<td>22</td>
<td>2</td>
<td>4</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>63</td>
<td>33</td>
<td>26</td>
<td>9</td>
<td>40</td>
</tr>
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</table>

Note.—Low MPA scores are defined as scores of < 3; high scores are > 3.

Phenotype and one with schizotypal personality disorder) and four pairs in which we had MPA exams on the sibling but the patient had refused to participate. The results are presented in figure 2. On the basis of paired \( t \) tests, the schizophrenia patients (2.03, SD 1.54) had significantly more MPAs than their unaffected siblings (0.96, SD 0.96, \( p = 0.002 \)) and the bipolar patients (1.11, SD 1.17) showed a trend for higher MPAs than their siblings (0.67, SD 0.71, \( p = 0.10 \)).

Perhaps neurodevelopmental abnormalities are familial but only in a subgroup of schizophrenia patients. If so, we might expect to see increased MPAs in the sibling only when the patient also has a high MPA score. First, we divided the siblings of the schizophrenia patients (including the three with spectrum diagnoses) into high (\( n = 11 \)) and low (\( n = 18 \)) groups depending on the MPA score of the patient. The scores for these two sibling groups were identical (mean = 1.0), suggesting that there was no increase of MPAs when we selected relatives of patients with prominent MPAs.

Last, we compared MPA scores for schizophrenia patients with and without a family history of a psychotic disorder in first-degree relatives. Neither the patients' reports nor the hospital charts were considered reliable sources of information on family history. Hence, the determination of family history of psychosis was based solely on interviews with the siblings, which limited the sample size for this analysis to those schizophrenia patients with siblings. We saw little difference in the MPA scores for the 6 patients with a family history compared with the scores for the 23 patients without a family history (2.0 vs. 1.9, respectively).

Discussion

The current study addressed two aspects of MPAs: specificity among psychoses and familiality. Regarding specificity among the psychoses, we found that schizophrenia patients showed an increase in MPAs compared with both normal controls and bipolar manic patients. The difference between schizophrenia patients and bipolar patients was significant for the mean MPA scores and just missed conventional levels of significance (\( p = 0.065 \)) for the number of outliers in each group. The results suggest some degree of specificity for MPAs to schizophrenia compared with another psychotic dis-
order, perhaps indicating that neurodevelopmental factors are more relevant to the etiology of schizophrenia. Although both clinical groups were State hospital inpatients, they were not entirely comparable on chronicity. However, such a confound might be largely unavoidable if neurodevelopmental factors are associated with earlier onset (Green et al. 1989a; Murray et al. 1992b).

Regarding the familiality of MPAs, we found that schizophrenia patients had significantly more MPAs than their siblings, and the siblings did not differ from normal controls. This pattern was true for mean MPA scores, as well as for the number in each group with prominent MPAs; it did not change when we selected only healthy siblings. A small group of siblings of bipolar patients showed the same pattern as the siblings of schizophrenia patients. The difference between bipolar patients and their siblings did not reach significance, perhaps due to the limited power of the analyses or perhaps because the bipolar patients did not have extremely high rates of MPAs to begin with.

The schizophrenia group had a higher percentage of males than the sibling group. If males in general have higher MPA scores, the difference between patients and their siblings might be due to an artifact of gender. However, examination of the scores separated by gender revealed that males with schizophrenia (1.78, SD 1.39) showed a trend for lower MPA scores than females (2.57, SD 1.50), which cannot account for the difference between patients and their siblings. These results are surprisingly consistent with means from our previous study (1.81 for males, 2.57 for females; Green et al. 1989a). An intriguing side note is that the pattern for the schizophrenia patients is reversed from the normal control group, in which males had significantly higher MPA scores than females ($p = 0.016$). This reversal of patterns between the schizophrenia and normal control groups resulted in a highly significant group $\times$ gender interaction ($p = 0.005$). This interaction for gender may reflect a differential threshold for men and women, with women having a more benign illness. In addition, women are less likely to be involuntarily hospitalized because they are generally seen as less threatening than men. Hence, selecting patients from a State hospital could yield groups in which the women are more severely disturbed than the men (Walker and Lewine 1993). Perhaps female patients are less likely than males to require this degree of involuntary care without additional neurodevelopmental complications. On the other hand, the gender effects may reflect real gender differences in frequency of neurodevelopmental abnormalities. In a review of the literature on influenza and schizophrenia, Murray et al. (1992a) reported that the epidemiologic studies that have considered gender differences found a significant association between influenza exposure and risk for schizophrenia, Murray et al. (1992a) reported that the epidemiologic studies that have considered gender differences found a significant association between influenza exposure and risk for schizophrenia, Murray et al. (1992a) reported that the epidemiologic studies that have considered gender differences found a significant association between influenza exposure and risk for schizophrenia, Murray et al. (1992a) reported that the epidemiologic studies that have considered gender differences found a significant association between influenza exposure and risk for schizophrenia, Murray et al. (1992a) reported that the epidemiologic studies that have considered gender differences found a significant association between influenza exposure and risk for schizophrenia.

The findings from the siblings in our study could be viewed according to the familial-sporadic distinction (Murray et al. 1985; Lewis et al. 1987) in which neurodevelopmental abnormalities are seen as etiologically relevant for primarily nongenetic forms of schizophrenia. One prediction from this approach would be that patients without a family history (i.e., with a primarily nongenetic form of schizophrenia) would show a higher rate of MPAs. Contrary to this prediction, one previous study (O’Callaghan et al. 1991a) found higher rates of MPAs in patients with a positive family history. We found no evidence for differences in MPAs based on family history, but our power was low for this analysis.

Perhaps the data across studies are more consistent with a general vulnerability-stress model of schizophrenia (Zubin and Spring 1977; Mirsky and Duncan 1986) in which MPAs could be considered nongenetic stressors that interact with a genetic predisposition. In this model, the genetic predisposition would not necessarily be reflected in a positive family history, depending on protective factors and the degree of vulnerability.

The findings of this study are not consistent with the notion that MPAs reflect part of the genetic vulnerability for schizophrenia. For example, MPAs seem unlikely to fit a type of latent trait model that has been used successfully by Matthysse and colleagues (1986) to explain the association between schizophrenic symptoms and abnormalities in smooth-pursuit eye movements. Models in which the marker is believed to reflect a genetic predisposition for the disorder usually predict that the marker will be found more frequently in the first-degree relatives of the patient than in the general population.

It is worth noting that 65 percent of the schizophrenia patients did not have prominent MPAs, and 5 percent of our normal controls did. These distributions suggest that in the vast majority of individuals, this type of marker is not associated with schizophrenia.
Nonetheless, it appears that MPAs reflect a type of neurodevelopmental risk factor that can interact with other genetic and non-genetic factors to produce the symptoms of the illness.

Although assessment of MPAs offers a convenient way to bridge the gap between the time of data collection and the time of interest (prenatal and perinatal), this method offers only sketchy information regarding the specific time period (e.g., which month of development) involved. It seems worthwhile to combine multiple markers of abnormal neurodevelopment for which the timing is better known (e.g., dermatoglyphic markings).

References


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