Discriminating Value of Total Minor Physical Anomaly Score on the Waldrop Physical Anomaly Scale Between Schizophrenia Patients and Normal Control Subjects

by Stefan T. Sivkov and Valentin H. Akabaliev

Abstract

Minor physical anomalies (MPAs) are slight structural aberrations that are believed to be associated with abnormal neurodevelopment. Studies of schizophrenia patients show that these patients score higher in MPAs than normal controls. The present study attempted to assess the potential value of MPAs as a classifying test in the status schizophrenia patient versus normal control. Seventy-six schizophrenia patients and 82 normal controls were assessed for MPAs using the Waldrop Physical Anomaly Scale, and specificity, sensitivity, and predictive value of the total MPA score were determined. A significantly higher percentage of schizophrenia patients than normal controls had high numbers of MPAs. Total MPA scores higher than 4 showed the most balanced set of sensitivity (76.3%), specificity (72.0%), and positive (71.6%) and negative (76.6%) predictive values for schizophrenia and were the cutoff scores that optimally discriminate schizophrenia patients from normal controls. Schizophrenia patients showed a higher percentage of subjects with prominent MPA scores. The results are consistent with the hypothesis that MPAs might reflect extragenetic stressful events and present total MPA score as a reliable index in distinguishing between schizophrenia patients and normal controls.

Keywords: Schizophrenia, minor physical anomalies, Waldrop scale, sensitivity, specificity. 


Current perspectives on schizophrenia as a neurodevelopmental disorder propose that unspecified early prenatal events might be the antecedents of the development of the disease in later periods of life (Weinberger 1987, 1995; Waddington 1993; Done et al. 1994; Murray 1994). The neurodevelopmental hypothesis is supported by several pieces of evidence, including increased incidence of obstetric complications in schizophrenia patients; presence of minor physical anomalies (MPAs); presence of neurological, cognitive, and behavioral dysfunction long before the disease onset; a course and outcome of the illness itself that is incompatible in most cases with a degenerative illness; stability of brain structural measures over time; and absence of postmortem evidence of neurodegeneration (Marenco and Weinberger 2000). Recent structural and functional imaging studies of schizophrenia patients indicate that the brain derangement is already present in the patients when they experience the first episode of the disease (DeLisi et al. 1991; Waddington 1993; McGrath et al. 1995). Given the large range of possible neurodevelopmental derangements that might be implicated in disease pathogenesis, the main neurodevelopmental hypotheses for schizophrenia set forth in the last 10 years are relatively restricted to the assumption of an early, static, and long-latency defect (Woods 1998).

One possibly important clue to developmental abnormality is the presence of MPAs. These slight defects of head, eyes, ears, mouth, hands, and feet represent mild errors of morphogenesis that have early prenatal (first or early second trimester) origin. Positive correlations between MPAs and congenital cognitive and behavioral deviations have been shown in numerous studies (Gualtieri et al. 1982; Krouse and Kauffman 1982; Lohr and Flynn 1993; McGrath et al. 1995). MPAs have major informational value for diagnostic, prognostic, and epidemiologic purposes. They provide an important clue to specific malformation diagnosis, brain pathology, and timing of the adversity (Nyhan 1990; Sperber 1992, cited by Lane et al. 1997; Ismail et al. 1998). The studies comparing MPAs in schizophrenia patients and normal controls have shown an excess of MPAs in schizophrenia patients (Lohr and Flynn 1993; Green et al. 1994; O’Callaghan et al. 1995; Ismail et al. 1998; Gourion et al. 2001), provid-
ing considerable support for a neurodevelopmental model in this disorder.

As part of a larger effort to investigate the neurodevelopmental hypothesis of schizophrenia, the present study focused on the potential value of exploring MPAs in schizophrenia samples and attempted to determine the value of the total MPA score in distinguishing schizophrenia patients from normal controls.

Material and Methods

Subjects. The subjects for this study were 76 schizophrenia inpatients (43 males, 33 females) consecutively admitted to the Clinic of Psychiatry in Plovdiv. Their mean age was 31.47 years (standard deviation [SD] = 9.53, range 16–56), mean duration of illness 6.86 years (SD = 6.09, range 1–27), and mean number of hospitalizations 4.22 (SD = 4.08, range 1–19). The patients satisfied DSM–IV criteria for a diagnosis of schizophrenia (APA 1994) on the basis of case records review and a semistructured interview (by V.H.A., the study psychiatrist) based on a checklist of items from DSM–IV and information obtained from relatives in order to enhance the validity of the diagnosis. Potential subjects were excluded if they had a history of drug or alcohol abuse, identifiable neurological disorder (seizure disorder, head injury, multiple sclerosis, etc.), or any signs of mental retardation or somatic disorder with neurological components.

The normal comparison group comprised 82 subjects (42 males, 40 females) with a mean age of 39.24 years (SD = 10.18, range 22–68). Their socioeconomic background was comparable to the patients’ Normality was defined as the absence of a major Axis I or Axis II disorder according to DSM–IV (APA 1994), based on an interview by the psychiatrist of the team (V.H.A.) and collateral information. The controls selected were mostly around or above the age of 40 years to minimize the cumulative risk of developing mental disorder in later life that could introduce a confound in the normal comparison group. Their exclusion criteria were similar to those applied to the patients. In addition, to better separate the control from the schizophrenia group, potential normal controls were excluded if they had a first degree relative with a history of a psychiatric disorder, a major affective disorder, or suicide.

To avoid a possible confound due to the lack of ethnic and racial references of MPA, both patients and normal controls were of Bulgarian origin. Individuals were excluded if their parental or grandparental ethnic group was other than Bulgarian.

The study was approved by the local ethics committee, and all subjects gave written informed consent to participate.

Assessment of MPAs. The subjects were examined with a slightly modified Waldrop Physical Anomaly Scale (Waldrop et al. 1968). It includes 19 morphological abnormalities from six body regions: head, eyes, ears, mouth, hands, and feet. Most of the abnormalities are scored qualitatively as present (1) or absent (0). The variables fine electric hair, head circumference, epicanthus, intercanthal distance, low-set ears, high/steepled palate, and third toe ≥ second are scored in a graded manner as 1 or 2, according to severity. The following modifications were made: the categories adherent earlobes and lower edges of the ears extend backward/upward (two grades of a single item in the original scale) were defined as separate items because of the high prevalence of the first and occasional finding of the second. The furrowed tongue was graded by scoring 1 randomly furrowed tongue (a normal variant) and scoring 2 transversely furrowed tongue (frequently observed in pathological conditions). In the original scale, both types are scored 1. To determine the variable low-set ears, we verified the ear canal position by the level of the ear canal on the head in relation to the midface, with the head of the subject placed in the Frankfurt horizontal line. Intercanthal distance abnormality was also determined in cases of hypotelorism. The intercanthal distance as well as the head circumference was scored 1 if they differed from the same-sex mean for normal controls by 1.5 to 2 SDs and as 2 if they differed by more than 2 SDs in both directions.

All examinations were performed by the same examiner (S.T.S., the study anatomist). Reliability studies were conducted using a second assessor (a medical technician in the Department of Anatomy, Histology and Embryology of the Medical University in Plovdiv) who was not otherwise involved in the study. She co-examined 30 schizophrenia patients (15 males, 15 females) and 20 normal controls (10 males, 10 females) of the current study groups. Except for one item, Cohen’s k for concordance between categorical/ordinal scores were all > 0.75 and intraclass correlation coefficients for continuous measures > 0.78. An acceptable level of reliability was not reached for curved fifth finger (k < 0.60), because of the lack of clear definition of its first and second grades and, hence, high subjectivity in their assessment. This necessitated another modification of the scale: curved fifth finger was scored as only present (1) or absent (0), while in the original scale its presence is weighted (1 or 2).

Statistical Analysis. The data were analyzed with SPSS 9.0 using descriptive statistics; independent Student t test: 2-tailed for comparing continuous data; $\chi^2$ test (in 2×2 table with Yates’ correction for continuity) or Fisher’s exact probability test; 2-tailed for comparing categorical data, multivariate analysis of variance (MANOVA). Sensitivity, specificity, and positive and negative predic-
tive values of total MPA score (MPA–T) for the status schizophrenia patients versus controls were calculated. Statistical significance was defined as \( p < 0.05 \).

Results

Comparison of MPA–T Between Schizophrenia Patients and Normal Controls. Schizophrenia patients showed significantly higher mean MPA–T than normal controls (4.95 vs. 2.66, \( p < 0.001 \)). In schizophrenia patients there was no case scored 0, MPA–T ranged from 1 to 11, the mode was 5 (29%), and 11.8 percent had MPA–T ≥ 8. In normal controls, MPA–T ranged from 0 to 7 and the mode was 3 (24.4%). Schizophrenia patients had a greater percentage of cases than controls for all MPA–T ≥ 4, while controls had a greater percentage than schizophrenia patients for all MPA–T ≤ 3. These differences in MPA–T distribution between the two groups were statistically significant (\( p < 0.001 \)).

Discriminating Effect, Sensitivity, Specificity, and Predictive Value of MPA–T. The discriminating effect of MPA–T for schizophrenia patient versus normal control status was assessed by comparing the groups for each step of MPA hierarchical scoring. Schizophrenia patients showed a significantly greater percentage than normal controls for all MPA–T categories—except for MPA–T ≥ 1. For this and for MPA–T ≥ 9, the difference was close to statistical significance (\( p = 0.059 \) and \( p = 0.051 \), respectively). The highest values of statistical significance were found for MPA–T ≥ 4 (\( \chi^2 = 34.87 \)) and MPA–T ≥ 5 (\( \chi^2 = 30.78 \)), indicating that they were best at discriminating between schizophrenia patients and normal controls.

Sensitivity, specificity, and positive and negative predictive values of the different total anomaly scores were examined to evaluate MPA–T as a classifying test in the status schizophrenia patients versus controls (table 1). In our model, the test is the MPA–T and the tested condition is schizophrenia.

The sensitivity of a test is the percentage of individuals with the disease who are classified as having the disease. From table 1, it is evident that the higher the anomaly score, the lower the sensitivity for schizophrenia because fewer schizophrenia patients present with these higher values of MPA–T.

The specificity of a test is the percentage of individuals without the disease who are classified as not having the disease. With the increase of MPA–T, its specificity as a test for schizophrenia increases because the number of controls with higher MPA–T decreases rapidly.

The positive predictive value is the percentage of individuals with a positive test who have the disease. Consequently, the increase in MPA–T is associated with an increase in its positive predictive value for schizophrenia because the percentage of schizophrenia patients among the individuals with these higher values of MPA–T increases.

The negative predictive value is the percentage of individuals with a negative test who do not have the disease. Hence, with the increase of MPA–T values, its negative predictive value decreases because the percentage of controls among the individuals who do not have these higher values of MPA–T decreases.

These four test values trends (table 1) show that the cutoff scores that optimally discriminate schizophrenia patients from normal controls (having the most balanced sets of sensitivity, specificity, and positive and negative predictive values) are MPA–T ≥ 4 and MPA–T ≥ 5.

MPA–T ≥ 4 classifies as schizophrenia patients 58 of all 76 schizophrenia patients in the sample (sensitivity

<table>
<thead>
<tr>
<th>MPA–T</th>
<th>Schizophrenia (n = 76)</th>
<th>Controls (n = 82)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive predictive value (%)</th>
<th>Negative predictive value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPA–T ≥ 1</td>
<td>76</td>
<td>77</td>
<td>100.0</td>
<td>6.1</td>
<td>49.7</td>
<td>100.0</td>
</tr>
<tr>
<td>MPA–T ≥ 2</td>
<td>75</td>
<td>60</td>
<td>98.7</td>
<td>26.8</td>
<td>55.6</td>
<td>95.7</td>
</tr>
<tr>
<td>MPA–T ≥ 3</td>
<td>70</td>
<td>43</td>
<td>92.1</td>
<td>47.6</td>
<td>61.9</td>
<td>86.7</td>
</tr>
<tr>
<td>MPA–T ≥ 4</td>
<td>58</td>
<td>23</td>
<td>76.3</td>
<td>72.0</td>
<td>71.6</td>
<td>76.6</td>
</tr>
<tr>
<td>MPA–T ≥ 5</td>
<td>43</td>
<td>11</td>
<td>56.6</td>
<td>86.6</td>
<td>79.6</td>
<td>68.3</td>
</tr>
<tr>
<td>MPA–T ≥ 6</td>
<td>24</td>
<td>3</td>
<td>31.6</td>
<td>96.3</td>
<td>88.9</td>
<td>60.3</td>
</tr>
<tr>
<td>MPA–T ≥ 7</td>
<td>12</td>
<td>1</td>
<td>15.8</td>
<td>98.8</td>
<td>92.3</td>
<td>55.9</td>
</tr>
<tr>
<td>MPA–T ≥ 8</td>
<td>9</td>
<td></td>
<td>11.8</td>
<td>100.0</td>
<td>100.0</td>
<td>55.0</td>
</tr>
<tr>
<td>MPA–T ≥ 9</td>
<td>4</td>
<td></td>
<td>5.3</td>
<td>100.0</td>
<td>100.0</td>
<td>53.2</td>
</tr>
</tbody>
</table>

Note.—MPA–T = total minor physical anomaly score.
76.3%) and as normal controls 59 of all 82 normal controls in the sample (specificity 72.0%). The same score assigns 58 schizophrenia patients to the group of 81 subjects who are positively tested and have an MPA-T ≥ 4 (positive predictive value 71.6%) and 59 normal controls to the total of 77 subjects who are negatively tested and scored less than 4 (negative predictive value 76.6%).

MPA-T ≥ 5 classifies as schizophrenia patients 43 of all 76 schizophrenia patients (sensitivity 56.6%) and as normal controls 71 of all 82 normal controls in the sample (specificity 86.6%). Forty-three schizophrenia patients are assigned to the group of 54 subjects who are positively tested and have an MPA-T ≥ 5 (positive predictive value 79.6%), while 71 normal controls are assigned to the total 104 subjects in the sample with MPA-T < 5 (negative predictive value 68.3%).

Thus, MPA-T ≥ 4 and ≥ 5 define the “border zone,” where schizophrenia patients begin to prevail sufficiently and definitely over normal controls, although some normal controls still present with these MPA-T values. It is notable that normal controls most frequently present with MPA scores 3 and below and rarely with scores higher than 6.

Outliers. MPA-T ≥ 6, which is 2 SDs above the mean MPA-T of the normal control group (mean = 2.66, SD = 1.57), was accepted as a cutoff point for highly stigmatized subjects (outliers). Of 76 schizophrenia patients, 24 (31.6%) had MPA-T ≥ 6, while of 82 normal controls, only 3 (3.7%) did (p < 0.05) (table 2). This indicates a considerably greater prevalence rate of highly stigmatized individuals in schizophrenia patients than in normal subjects.

The intragender comparison (table 3) shows that the percentage of outliers is significantly greater in male schizophrenia patients than in their same-sex controls (46.5% vs. 4.8%, p < 0.001). Female schizophrenia patients also have a greater percentage of highly stigmatized individuals than in same-sex normal controls (12.1% vs. 2.5%), but the difference is less prominent than in males and fails to reach statistical significance (p = 0.169), perhaps because of the small number of cases (4 vs. 1). This indicates a relatively greater increase in the prevalence of highly stigmatized individuals in male than in female schizophrenia patients compared to their same-sex controls.

In contrast to the nonsignificant gender differences in the control group (4.8% vs. 2.5%, Fisher exact test: 2-tailed, p > 0.05), males with schizophrenia show a significantly higher rate of outliers than do females with schizophrenia (46.5% vs. 12.1%, χ² = 8.69, p = 0.003). Among normal controls, the proportion of subjects with prominent MPAs tended to be slightly greater in males than in females, but this between-gender difference expanded definitively in schizophrenia patients.

To examine more exactly the gender effect on MPA in schizophrenia patients, the group × gender interaction was analyzed using MANOVA. In our MANOVA model, the independent classification variables were group status, gender, and group × gender interaction, while the set of multiple dependent variables was the 19 MPAs. The Pillai’s trace, which is the most powerful and robust statistics test for evaluating multivariate differences, revealed statistically significant group × gender interaction in this model (F = 1.69; p = 0.045). This suggests that there is a different effect of gender on the pattern of MPA increase in schizophrenia patients compared to controls. The univariate analyses indicate a statistically significant contribution to the group × gender interaction for intercanthal distance abnormality (F = 5.00, p = 0.027) and head circumference (F = 4.49, p = 0.036). Close to these but failing to reach statistical significance is curved fifth finger (clinodactyly) (F = 3.45, p = 0.065).

### Discussion

Like other investigators (Lohr and Flynn 1993; Green et al. 1994; O'Callaghan et al. 1995), we found more MPAs in schizophrenia patients than in controls. The mean MPA-T of the patient group is close to the score antici-

### Table 2. Comparison of outliers (MPA-T ≥ 6) between schizophrenia patients and normal controls

<table>
<thead>
<tr>
<th>MPA-T</th>
<th>Schizophrenia (n = 76)</th>
<th>Controls* (n = 82)</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>MPA-T &lt; 6</td>
<td>52</td>
<td>68.4</td>
<td>79</td>
</tr>
<tr>
<td>MPA-T ≥ 6</td>
<td>24</td>
<td>31.6</td>
<td>3</td>
</tr>
</tbody>
</table>

Note.—MPA-T = total minor physical anomaly score.

¹ χ² test (2 × 2 tables with Yates correction for continuity).
Table 3. Comparison of outliers (MPA–T ≥ 6) between schizophrenia patients and normal controls by gender

<table>
<thead>
<tr>
<th></th>
<th>Males (n = 85)</th>
<th></th>
<th>Females (n = 73)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Schizophrenia</td>
<td>Controls</td>
<td>Schizophrenia</td>
<td>Controls</td>
</tr>
<tr>
<td></td>
<td>(n = 43)</td>
<td>(n = 42)</td>
<td>(n = 33)</td>
<td>(n = 40)</td>
</tr>
<tr>
<td>MPA–T</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>MPA–T &lt; 6</td>
<td>23</td>
<td>53.5</td>
<td>40</td>
<td>95.2</td>
</tr>
<tr>
<td>MPA–T ≥ 6</td>
<td>20</td>
<td>46.5</td>
<td>2</td>
<td>4.8</td>
</tr>
</tbody>
</table>

Note.—MPA–T = total minor physical anomaly score.

1 $\chi^2$ test (2 × 2 tables with Yates correction for continuity).

2 Fisher's exact test; 2-tailed.

pacated on the basis of the results of previous studies (Ismail et al. 1998). When MPAs are regarded as imprints of early dysontogenetic processes (Ismail et al. 1998) that are not changed by the subsequent disease and its course, their overrepresentation in schizophrenia patients suggests a prenatal injury that probably increases the risk of diseases in later phases of life (O’Callaghan et al. 1991).

The present study addressed one aspect of MPAs: their ability to discriminate between schizophrenia patients and normal controls. The total anomaly score works well as a classifying test in the status schizophrenia patients versus normal subjects. The optimal cutoff MPA–T (score ≥ 4 and score ≥ 5) is very close to the median and mean scores in the patient group. Scores ≥ 4 have higher sensitivity and on the whole more evenly presented test parameters. Scores ≥ 5 have higher specificity and positive predictive value but lower sensitivity for schizophrenia. These scores yield sensitivity and specificity that are in the upper range of MPA rates in previous studies of schizophrenia patients (30%–75%) (cited by Ismail et al. 1998).

Significantly more schizophrenia patients than controls had MPA–T ≥ 6. It is worth noting that nearly 70 percent of the schizophrenia patients did not have prominent MPAs, and nearly 4 percent of the controls did. These distributions suggest that in the vast majority of individuals, this type of marker is not sensitive for schizophrenia. Regarding the gender effect on MPA stigmatization, males were notably more stigmatized with prominent MPAs than were females in the schizophrenia group. Nearly half of the male and only 12.1 percent of the female patients were classified as outliers. This greater stigmatization with MPAs suggests greater vulnerability of the males than females during prenatal development and denotes a significant group × gender interaction on MPAs. The data do not accord with the findings of Green et al. (1994), who found a trend to higher MPA scores in female than in male schizophrenia patients, while in their control group males had significantly higher MPA scores than females.

The overall conclusion from this study is that MPAs appear an appropriate means to discriminate between schizophrenia patients and normal controls and reflect a type of neurodevelopmental risk factor that can interact with other genetic and nongenetic factors to produce symptoms of illness, at least in a subpopulation of schizophrenia patients. In our model MPA scores ≥ 4 and 5 appear to be the most reliable index for discriminating between schizophrenia patients and normal controls.

Clearly, any specificity of such findings to schizophrenia can be determined only if comparable data involving other psychiatric diagnostic groups are available. Nonetheless, our data indicate the potential of this approach for clarifying further the nature of early events and resultant neurodevelopmental anomalies that appear to be involved in the subsequent emergence of this disorder.

Finally, some caveats regarding our study need to be considered. The major caveat is the problem of all studies based on samples of hospitalized patients: the evaluations are less blind because of the apparent presence of pathology in patients. A degree of blindness was achieved because of the inclusion of several diagnoses in our larger study design: schizophrenia, bipolar disorder I, and alcoholism. The examiner (S.T.S.) was unaware of the exact diagnosis of the patient. Although in some cases the patient’s diagnosis was clearly identifiable because of the current symptoms, this was the best we could do given the circumstances of our study.

References


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