Minor Physical Anomalies in Schizophrenia

by Michael Foster Green, Paul Satz, Donna J. Galer, Steven Ganzell, and Fereidoon Kharabi

Abstract

This study was conducted to investigate the value of using physical anomalies (PAs) to evaluate early prenatal injury in schizophrenia. PAs are minor abnormalities in development of the head, hands, and feet that are presumably associated with insult during the first trimester. Sixty-seven schizophrenic inpatients and 88 normal controls were evaluated for PAs. The schizophrenic patients showed significantly more anomalies than the controls. The difference remained significant even when patients were compared to controls of low socioeconomic status. Both male and female patients showed a high incidence of mouth abnormalities, and female patients showed a high incidence of abnormalities in head circumference. Patients with early age of onset (≤ 18 years) had more physical anomalies than did later onset patients. This relationship was most noticeable for males. Physical anomalies were not associated with deficits on measures of vigilance, selective attention, or orientation.

Several converging lines of evidence point to a neurodevelopmental disorder in a subgroup of schizophrenic patients (Murray and Lewis 1987). For example, a number of studies have now reported an increase in obstetric complications (OCs) in schizophrenia (see reviews by McNeil and Kaj 1978; Parnas et al. 1982). Research on OCs in schizophrenia has generally focused on deviations from expected events at or around the time of birth (e.g., low birth weight and unusual length of labor) as opposed to the early prenatal period (McNeil and Kaj 1978). However, the role of pregnancy complications (instead of birth complications) has also been emphasized in neurodevelopmental disabilities (Taylor et al. 1985; Soothill et al. 1987).

Are OCs in schizophrenia associated with later signs of central nervous system (CNS) damage? Several studies have found a relationship between a history of OCs and ventricular enlargement on computed tomography (CT) (Schulsinger et al. 1984; Pearlson et al. 1985; DeLisi et al. 1986; Turner et al. 1986). This relationship is not limited to schizophrenic patients; ventricular enlargement and cerebral atrophy are also seen in nonpsychiatric individuals who suffered OCs (Reveley et al. 1984; DeVries et al. 1985).

In a review of this literature, Lewis et al. (1987) concluded that nongenetic causal factors are relatively important in a subgroup of schizophrenic patients. They contrast these “sporadic” patients (who could be characterized by a history of OCs and ventricular enlargement on CT) to a familial or genetic type of schizophrenia. Additional evidence for the association of OCs and CT abnormalities with nongenetic factors comes from studies which have reported that ventricular enlargement in schizophrenia is largely confined to patients without a family history of schizophrenia (Reveley et al. 1984; Turner et al. 1986; Romani et al. 1987). However, some studies have not found such a relationship (Nasrallah et al. 1983; Pearlson et al. 1985).

Although Lewis et al. (1987) provide a provocative formulation, any comprehensive theory of neurodevelopmental factors in schizophrenia would have to explain why a subgroup of schizophrenic patients with OCs and ventricular enlargement on CT is not also characterized by abnormalities on other measures of neurodevelopment (e.g., IQ, neurological signs, neuropsychological tests) and why this subgroup is not also characterized by a history of OCs and ventricular enlargement on CT.

Reprint requests should be sent to Dr. M.F. Green, UCLA Research Center, Box A, Camarillo, CA 93011.
schizophrenia also needs to take into account the possibility that neurodevelopmental abnormalities (e.g., OCs) could serve as stressors or triggers for individuals who are at genetic risk for the disorder.

A limitation of using OCs as a measure of early neurodevelopmental abnormality is that ratings depend on the memory of the parents (usually the mother). The problems with this are obvious: certain medical information might not be passed on to the mother, and information that is available to the mother might become distorted or forgotten over the two or three decades before being contacted by a researcher.

Measuring minor physical anomalies provides a means to bypass the reliability problems inherent in OC reports. Minor physical anomalies (PAs) are slight defects of the head, hair, eyes, ears, mouth, hands, and feet. These abnormalities are thought to be associated with injury or atypical development during the first trimester (Waldrop et al. 1968), presumably because this period is the most critical for the development of the ectodermal derivatives such as the epidermis, hair, ears, nose, and eyes (Langman 1963). PAs can be measured with a brief examination (about 5 min) using the Waldrop Scale (Waldrop et al. 1968).

Despite the advantages of measuring PAs as an indication of prenatal insult, we know of only four studies (one unpublished) that have used PAs with schizophrenic patients (Goldfarb and Botstein 1967; Gualtieri et al. 1982; Guy et al. 1983; Green et al. 1987).

Goldfarb and Botstein (1967) (cited in Guy et al. 1983) reported that schizophrenic children had more PAs than normal controls and nonpsychotic behavior-disordered children. A large proportion of the schizophrenic children (24 percent) had an anomaly score of 5 or more, compared to only 0.5 percent of the control group. Because the study is unpublished, however, we are unable to comment on the methodology used.

Gualtieri et al. (1982) used a subset of items from the Waldrop Scale to compare rates of minor physical anomalies in adult schizophrenic patients, alcoholics, and normal controls. Several items were excluded from analysis because the raters were unable to reach acceptable levels of reliability. In addition, other items were excluded because they were not scored for black subjects (e.g., hair characteristics). The authors reported higher rates of PAs in the schizophrenic group than in normal controls. However, the normal control group had a surprisingly high rate of PAs: the mean number of anomalies was 2.6, and 12.6 percent of the sample showed 5 or more anomalies. Such high rates in the normal controls raise questions about the validity of the anomaly rating. One partial explanation for the excessive rates could be that the author used external normative data (which may have been scored differently) for some of the items (e.g., U.S. Army norms for head size). No descriptive or performance variables were considered in this study.

Guy et al. (1983) administered the Waldrop Scale to 40 adult Caucasian schizophrenic males. They reported a higher incidence of PAs in the schizophrenic patients compared to unpublished norms (Waldrop 1979, cited in Guy et al. 1983). The Waldrop Scale can be scored in a variety of ways—hence, the reported difference between normal and schizophrenic patients could reflect differences in scoring criteria. PAs were associated with poorer premorbid adjustment, but not associated with age of onset, Wechsler Adult Intelligence Scale (WAIS; Wechsler 1955) Vocabulary score, neuropsychological impairment, or chronicity.

A preliminary report (Green et al. 1987) using a subset of the current sample found that the incidence of physical anomalies was associated with age of onset. Patients with early age of onset (before or equal to 18 years) had significantly more physical anomalies than patients with later onset. We speculated that the presence of physical anomalies reflected an early fetal insult which left the individual at risk for early-onset schizophrenia. This study did not use a control group, so the difference between schizophrenic subjects and normal controls was not considered.

In summary, only four reports to our knowledge have compared the incidence of PAs in schizophrenic patients and normal controls. Despite differences in methodology, all studies showed positive results.

The general goal of the current study was to investigate the potential value of exploring physical anomalies in schizophrenic samples. First, we wanted to establish norms for the Waldrop Scale. One limitation of both the studies of Guy et al. (1983) and Gualtieri et al. (1982) is the absence of reasonable normative data. In fact, we know of no published adult norms for the Waldrop Scale.

Second, we wanted to compare the types of physical anomalies shown by schizophrenic patients to those shown by normal controls. We were particularly curious about abnormalities in head circumference in light of the finding that schizophrenic males may have smaller head size compared with normal
controls (Andreasen et al. 1986).

Third, on the basis of our preliminary report, the present study was designed to test the relationship between physical anomalies and age of onset of schizophrenia. If supported, the finding suggests that early fetal insult places an individual at risk for early-onset schizophrenia.

Last, we tested the hypothesis that PAs are associated with cognitive deficits. Unlike the study of Guy et al. (1983) (where relatively global measures were used), the present study used specific measures of vigilance, selective attention, and orientation.

Methods

Subjects. The patients for this study were 67 (53 men, 14 women) Caucasian inpatients from Camarillo State Hospital. Each subject received a DSM-III (American Psychiatric Association 1980) diagnosis of schizophrenia based on an expanded version of the Present State Examination (Wing et al. 1974). The interviewers were trained to a percent agreement of at least 85 with the Diagnosis and Neuropsychology Unit of the Mental Health Clinical Research Center at the University of California at Los Angeles. Patients were excluded if they had a history of drug or alcohol abuse, an identifiable neurological disorder, any signs of mental retardation, or if they were over 55 years of age. The mean age was 31.6 (SD = 7.9), the average level of education was 11.1 (SD = 2.3) years, and the average number of hospitalizations was 8.0 (5.7). The 88 Caucasian normal controls (43 men, 45 women, mean age = 28.1 ± SD 9.4 years) were drawn from the Psychiatric Technician training program at the State hospital and from undergraduate psychology classes at a nearby university.

Physical Anomaly Scale. A modification of the Waldrop Scale (Waldrop et al. 1968) was used to measure physical anomalies. All subjects were taken to a private examination room for this 5-minute examination. The actual items are listed in table 1. Two modifications were made in the scale: subjects were given one PA point if their head circumference or intercanthal distance differed from the same-sexed mean for normals by more than 1.5 SD. In the original scale (used by Guy et al. 1983) subjects were given 1 point for a difference of 1–1.5 SD and 2 points for a difference greater than 2 SD. We measured head circumference by placing a tape measure just above the eyebrows and running it around the occipital protuberance.

Interrater reliability on the Waldrop Scale was established between our raters (Donna Gaier and Steven Ganzell) and Fereidoon Kharabi, who is board-certified in Psychiatry and Neurology and served as our standard. Reliability was calculated on independent examinations of a sample of 17 mentally retarded subjects, who were expected to show a large number of PAs (Soper, personal communication). The mean percent agreement was quite high: 93 percent when anomaly was present (according to Fereidoon Kharabi) and 97 percent when anomaly was absent. The mean correlation coefficient for measurement of head circumference was .95 and the mean correlation for measurement of intercanthal distance was .70.

Cognitive Measures. The information-processing measures included two versions of the Continuous Performance Test (CPT; Rosvold et al. 1956; Nuechterlein 1983), the Digit Span Distractibility Test (Oltmanns and Neale 1975), and the Camarillo Orientation Scale.

Both the 3–7 CPT and the degraded stimulus CPT are visual vigilance or sustained attention tasks. The numbers are presented one at a time for a duration of approximately 40 milliseconds and there is a 1-second interval between stimuli. The CPT was administered using an automated system in which a carousel slide projector and Ilex Synchro-Electronic Shutter presented the stimuli on a 12- × 12-inch rear projection screen. The carousel projector and shutter were controlled by a Radio Shack TRS–80 computer. The subjects were seated with their eyes 1 meter from the rear projection screen.

In the 3–7 CPT, the subject pressed a response button whenever the target sequence appeared. The target is a two-stimulus sequence: the number “3” followed by the number “7.” This test is the numerical version of the “A–X” CPT (Rosvold et al. 1956).

The degraded stimulus CPT was developed by Nuechterlein (1983) to provide a sensitive measure of sub-tle deficits in signal detection over sustained periods of visual monitoring that do not involve a short-term memory load. The stimuli were blurred to a standardized degree, and a pattern of pluses was placed on the rear projection screen. The subject responded whenever the number “0” appeared. This version of the CPT was designed to place a load on early encoding. Both versions of the CPT yield an overall d' (a measure of sensitivity) and a difference in d' between the first third and last two-thirds of the test.

The Digit Span Distractibility Test
Table 1. Waldrop Scale: Percentage of subjects with anomalies

<table>
<thead>
<tr>
<th></th>
<th>Normal Controls</th>
<th></th>
<th>Patients</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males (n = 43)</td>
<td>Females (n = 45)</td>
<td>Males (n = 53)</td>
<td>Females (n = 14)</td>
</tr>
<tr>
<td><strong>Head</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very fine hair</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Fine hair</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>—</td>
</tr>
<tr>
<td>2 or more hair whorls</td>
<td>—</td>
<td>—</td>
<td>2</td>
<td>—</td>
</tr>
<tr>
<td>Large circumference</td>
<td>9¹</td>
<td>7¹</td>
<td>6</td>
<td>36</td>
</tr>
<tr>
<td>Small circumference</td>
<td>—</td>
<td>2</td>
<td>6</td>
<td>21</td>
</tr>
<tr>
<td><strong>Eyes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deeply covered epicanthus</td>
<td>5</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Partly covered epicanthus</td>
<td>9</td>
<td>9</td>
<td>17</td>
<td>14</td>
</tr>
<tr>
<td>Large distance between ducts</td>
<td>5²</td>
<td>9²</td>
<td>4</td>
<td>—</td>
</tr>
<tr>
<td>Small distance between ducts</td>
<td>7</td>
<td>2</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td><strong>Ears</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low seated ears</td>
<td>—</td>
<td>—</td>
<td>2</td>
<td>—</td>
</tr>
<tr>
<td>Adherent earlobes</td>
<td>—</td>
<td>—</td>
<td>2</td>
<td>—</td>
</tr>
<tr>
<td>Malformed ears</td>
<td>—</td>
<td>—</td>
<td>2</td>
<td>14</td>
</tr>
<tr>
<td>Asymmetrical ears</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Soft &amp; pliable ears</td>
<td>—</td>
<td>—</td>
<td>6</td>
<td>—</td>
</tr>
<tr>
<td><strong>Mouth</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-steepled palate:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steeped</td>
<td>5</td>
<td>2</td>
<td>26</td>
<td>21</td>
</tr>
<tr>
<td>Flat &amp; narrow</td>
<td>5</td>
<td>—</td>
<td>13</td>
<td>21</td>
</tr>
<tr>
<td>Furrowed tongue</td>
<td>0</td>
<td>2</td>
<td>19</td>
<td>21</td>
</tr>
<tr>
<td>Tongue with smooth/rough spots</td>
<td>—</td>
<td>—</td>
<td>13</td>
<td>7</td>
</tr>
<tr>
<td><strong>Hands</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Curved 5th finger:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Markedly</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>7</td>
</tr>
<tr>
<td>Slightly</td>
<td>2</td>
<td>4</td>
<td>11</td>
<td>14</td>
</tr>
<tr>
<td>Single palmar crease</td>
<td>—</td>
<td>2</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td><strong>Feet</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Third toe:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Longer than 2nd</td>
<td>—</td>
<td>—</td>
<td>2</td>
<td>14</td>
</tr>
<tr>
<td>Equal to 2nd</td>
<td>—</td>
<td>11</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Webbed toes</td>
<td>—</td>
<td>4</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Gap between 1st and 2nd toes</td>
<td>16</td>
<td>2</td>
<td>21</td>
<td>7</td>
</tr>
</tbody>
</table>

¹Mean head circumference for males = 57.63 cm, SD = 2.16; for females = 55.03 cm, SD = 1.19.
²Mean distance between eye ducts for males = 3.07 cm, SD = 0.32; for females = 2.97 cm, SD = 0.32.
(Oltmanns and Neale 1975) consists of distraction and nondistraction conditions. In the nondistraction condition, subjects listened to a female voice reading a list of digits. In the distraction condition, the subjects heard a male voice reading distractor digits in between the target digits. Subjects were instructed to listen to the female voice and ignore the male voice. The two conditions were equated for mean and variance on a sample of 100 normal controls and cross-validated on a sample of 50 additional normal controls (Oltmanns and Neale 1975). The dependent measures for this test are the proportion correct for the nondistraction condition and the difference score for the nondistraction minus the distraction conditions.

The Camarillo Orientation Scale was developed for use with our patients at the State Hospital at Camarillo. Used to assess a variety of functions included in the term “orientation,” it contains seven subscales: biography, concentration, person, place, time, immediate memory, and spatial orientation. The biography, person, place, and time sections consist of questions often asked in a mental status examination (e.g., where are we; who is the governor; when were you born?). The concentration section requires the subject to list the days of the week backwards and to count backwards from 100 by 7’s. Immediate memory is assessed by the Digit Span from the WAIS.

We knew of no “ecological” method of assessing spatial orientation. For the Camarillo Orientation Scale, spatial orientation was assessed in the same outdoor corridor located near the center of the hospital grounds. Subjects all faced in the same direction and were asked to point toward four well-known locations (e.g., bank and canteen) that were out of view. The subjects held a compass in their hand, and each time they pointed to a location, the angle (in degrees) was recorded. Subjects received full credit if they were within 20 degrees of the correct angle and partial credit if they were between 20 and 40 degrees of the correct angle.

Intercorrelations among the different scales on the Camarillo Orientation Scale ranged from $r = .31$ to $.74$. The overall mean correlation was $.48$.

**Results**

The mean physical anomaly score for the patients was $1.81$ (SD = 1.63) for the men and $2.57$ (1.40) for the women. For the normal controls, the mean anomaly scores were $.74$ (SD = $.82$) for men and $.62$ (SD = $.86$) for the women. These scores are approximately what we expected for an index of neurodevelopmental abnormality in a normal sample. Neither diagnostic group showed differences due to gender. When the men and women were combined, the difference between groups was highly significant ($1.97 \pm SD 1.6$ vs. $.68 \pm SD .84$) for the patients and normal controls, respectively; $t = 6.55$, $p < .001$). Of the 67 patients, 21 (31.3 percent) had a PA score of 3 or more, which was greater than 2 SD above the mean for normals. Among the normal controls, only 3 of 88 (3.4 percent) had a score of 3 or greater. The $\chi^2$ for the proportion of outliers by diagnostic group was highly significant ($\chi^2 = 22.56$, $p < .005$).

The percentage of subjects with each type of PA (separated according to gender and diagnosis) is listed in table 1. Male patients showed a high incidence of abnormalities of the mouth compared to the normal controls. Although the female patients also showed a high incidence of mouth abnormalities, the most impressive finding for women was the high incidence of deviations in head circumference. Thirty-five percent of the female patients had a large circumference, and 21 percent had a small circumference (outside 1.5 SD of same-sexed normal controls). Unfortunately, our sample of female patients was relatively small ($n = 14$); hence, interpretations should be made cautiously.

To test the relationship between age of onset and physical anomalies, a $\chi^2$ was calculated. Subjects were divided into early (18 or less) versus late (19 or greater) age of onset. We were unable to obtain reliable onset information on three of the patients. The groups did not differ in medication expressed in chlorpromazine equivalents ($1001 \pm SD 788$ vs. $1248 \pm SD 1142$ for early and late, respectively), total number of hospitalizations ($9.1 \pm SD 6.0$ vs. $6.6 \pm SD 5.3$), or years since initial hospitalization ($14.0 \pm SD 9.2$ vs. $10.8 \pm SD 5.5$). The two groups differed in current age ($28.3 \pm SD 8.4$ vs. $33.8 \pm SD 6.6$; $t = 2.7$, $p < .01$) and in years of education ($10.0 \pm SD 3.1$ vs. $11.9 \pm SD 1.4$; $t = 2.6$, $p < .02$) for the early and late groups, respectively.

Subjects who had an anomaly score of 3 or greater were considered to have prevalent anomalies. The $\chi^2$ for the entire sample was significant ($4.91$, $p < .05$) and indicated that the group with early onset had more subjects with prevalent anomalies (see table 2).

Although the number of female patients was too small for us to conduct separate analyses, we considered the effects of PAs and age
Table 2. Physical anomaly score—All patients

<table>
<thead>
<tr>
<th></th>
<th>&lt;3</th>
<th>&gt;3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early onset</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>Late onset</td>
<td>30</td>
<td>7</td>
</tr>
</tbody>
</table>

\[
x^2 = 4.912, p < .05.
\]

Table 3. Physical anomaly score—Male patients

<table>
<thead>
<tr>
<th></th>
<th>&lt;3</th>
<th>&gt;3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early onset</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>Late onset</td>
<td>25</td>
<td>3</td>
</tr>
</tbody>
</table>

\[
x^2 = 7.71, p < .01.
\]

of onset for the males alone. The resulting \(x^2 (7.71, p < .01)\) was markedly stronger than the original analysis (see table 3). Hence, the effect of age of onset on PAs is largely the result of our male sample.

Multiple regression analyses were performed to test the relationships among age of onset, physical anomalies, and the cognitive measures. The dependent measures included \(d'\) and the \(d'\) difference score for each version of the CPT, nondistraction score and the nondistraction-distraction difference score for the digit span test, and the totals of the seven subscales of the Camarillo Orientation Scale.

Physical anomaly score was not a significant predictor for any of the cognitive measures. The results were essentially the same whether the PA score was treated as a continuous variable or as a dichotomous variable (using a score of 3 as the cutoff). Age of onset was a significant predictor of only one dependent measure: the biographical section of the Camarillo Orientation Scale \((F = 5.95, p = .02)\). Earlier age of onset was associated with a better score on this subscale.

Discussion

PAs in Patients Versus Controls.

Physical anomalies were more prevalent in our sample of schizophrenic patients compared to normal controls. We found this effect with both mean PA score and number of outliers (score \(\geq 3\)).

The more common anomalies for the patients included abnormalities of the mouth and unusual head circumference (particularly for the women). Our sample of female patients was small, and any interpretation must be made with caution. Nevertheless, our finding was striking: 57 percent of the female patients had circumferences that differed by at least 1.5 SD from the female normal controls. Five of the female patients had an unusually large circumference, and three had small circumferences. A recent study by Andreasen et al. (1986) using magnetic resonance imaging (MRI) found that male (but not female) schizophrenic patients had significantly smaller cranial size compared to normal controls. Only 6 of 53 males in our sample received a PA score for head circumference, and these were evenly divided between those with large and small measurements (three each).

Stevens and Waldmon (1987) raised the possibility that the findings of Andreasen et al. (1986) might be an artifact of the high socioeconomic status of her normal controls. Could socioeconomic status also account for our observed differences in PA score between patients and normal controls? Although we did not rate our control subjects for socioeconomic status, about half of our control subjects (18 males and 22 females) were Psychiatric Technician trainees at the State hospital. These subjects would be rated a 4 on the Hollingshead 5-point scale of social position (Hollingshead 1957) and would not be expected to differ significantly from patients.

The trainees did not differ from the remainder of the normal controls (undergraduate students at a private university) on physical anomaly score (compared within gender and as a group). More important, the differences in physical anomaly score remained significant when patients were compared to trainees only: 1.97 (SD = 1.6) versus .72 (SD = .96), \(p < .001\)
for both genders; 1.81 (SD = 1.63) versus .89 (SD = .83), p < .02 for males; and 2.57 (SD = 1.4) versus .59 (SD = 1.05), p < .001, for female patients and normal controls, respectively. Hence, it appears unlikely that our findings are due to differences in socioeconomic status.

**PAs and Age of Onset.** Consistent with our preliminary report, early age of onset was associated with more prevalent physical anomalies. The effect of age of onset was particularly noticeable in our male sample. These data suggest that certain patients may have sustained prenatal injury that placed them at risk for early-onset schizophrenia.

The nature of this insult remains ambiguous. Instead of a single event, the injury could be the result of an abnormal neurodevelopmental process that occurs over an extended period of time. The presence of PAs might indicate that these patients could be considered "sporadic" patients (Lewis et al. 1987). Along with prevalent PAs, we might also expect to find a history of OCs, abnormal CT and MRI scans, and an absence of family history for schizophrenia. Lewis et al. (1987) might predict that these individuals were not at risk for schizophrenia before the insult occurred. Hence, this would be a nongenetic form of schizophrenia.

Conversely, it could be argued that the PAs reflect a common genetic vulnerability to abnormalities in neurodevelopment and development of schizophrenia. Both PA and schizophrenic symptoms might be part of a common "liability package." In this case, the neurodevelopmental abnormalities would not directly contribute to an individual's risk for schizophrenia. Prevalent PAs might indicate an especially strong liability that is associated with early onset, whereas the absence of PAs might indicate that the vulnerability is not as great and the onset is not as early.

A third alternative is that the PAs are nongenetic events that sometimes occur in an individual with a genetic predisposition to schizophrenia. The PAs in this case could represent an environmental stressor that burdens an already compromised CNS and contributes to the development of the illness. Such a burden might also increase the likelihood of an earlier onset when the PAs are particularly prominent.

In a recent study, Mednick et al. (1988) reported that viral infection during the second trimester of fetal development was associated with an increased risk for schizophrenia. Waldrop et al. (1968) and Guy et al. (1983) have both argued that PAs are associated with first trimester insult, although the evidence appears to be somewhat indirect (e.g., the first trimester is the critical period of differentiation for the ectoderm). Assuming that PAs are associated with first trimester insult, how do we incorporate the findings of Mednick et al.? Schizophrenia is often considered a heterogeneous disorder, and there are probably a variety of early neurodevelopmental problems that could increase one's risk for the disorder. Hence, PAs might reflect an insult that is different in type and timing from that associated with viral insult. Future research might consider the question of heterogeneity in schizophrenia from a prenatal perspective.

**PAs and Cognitive Functioning.** PA score did not predict cognitive functioning as measured by the information-processing tests and orientation scales. Age of onset was a predictor for only one of the orientation subscales. The presence of physical anomalies indicates that injury to the CNS took place prenatally. Why did we not see associated information-processing deficits? One possibility is that we were looking at the wrong tests. The ectodermal layer gives rise to the CNS as well as the physical structures assessed by the PA exam, and the critical periods of development for these components correspond with each other (Langman 1963). We reasoned that a test of neuromotor ability might be more sensitive to an insult during this period of development. As a post hoc analysis, we divided subjects into groups with high and low PA scores and compared their performance on the pin test. The pin test is a neuromotor task that requires the subject to place a pin through holes in a metal template as fast as possible. We administered the pin test to 43 subjects with PA scores less than 3, and 16 subjects with scores of 3 or more. This comparison revealed essentially no differences between the groups (44.9 ± SD 14.1 vs. 43.9 ± SD 11.3 for the low and high groups, respectively).

Guy et al. (1983) administered the WAIS Vocabulary subtest and calculated an impairment index based on three visual performance tests: the Memory for Designs Test (Graham and Kendall 1968), the Benton Visual Retention Test (Benton 1955), and the Trail-Making Test (Reitan 1958). There was no significant relationship between PAs and either the vocabulary score or the impairment index. Curiously, the zero-order correlations were in the opposite direction of what had been expected (r = .21 for vocabulary by
PA, and $r = -0.1$ for impairment index by PA).

Perhaps, the injury was so early that the cortex was able to reorganize, and as a result, cognitive sequelae were minimized. There are numerous examples from both the human and animal literature of dramatic recovery following early brain injury (see reviews by Spreen et al. 1984; DeVries et al. 1985). The puzzling aspect of this explanation is that the injury associated with PAs can still apparently influence the onset of the disorder.

The overall conclusion from this study is that PAs are an appropriate means for investigators to index prenatal injury. They can be measured reliably, they are more prevalent in schizophrenic patients than normal controls, and they appear to be associated with earlier age of onset. At this point, we are unable to find an association between PAs and our cognitive measures. To enhance our understanding of the significance of this measure, future studies are encouraged to test the relationship between PAs and such variables as OCs, MRI abnormalities, and family history of schizophrenia.

**References**

American Psychiatric Association. 


**Acknowledgments**

The authors express their gratitude to Keith H. Nuechterlein, Ph.D., for his kind support and careful consultation in the use of the information-processing measures. This work was supported in part by National Institute of Mental Health (NIMH) Research Grant MH-42344 to Dr. Green and by National Institute of Neurological and Communicative Disorders and Stroke 22074-01 to Dr. Satz. Diagnostic training and data analysis were supported by NIMH Clinical Research Center Grant MH-30911 (Robert P. Liberman, Principal Investigator). The data collection was made possible by the excellent cooperation of the staff and administration of Camarillo State Hospital.

**The Authors**

Michael Foster Green, Ph.D., is an Assistant Research Professor in the Department of Psychiatry and Biobehavioral Sciences; Paul Satz, Ph.D., is a Professor in the Department of Psychiatry and Biobehavioral Sciences; Donna J. Gaier, B.A., is a Staff Research Associate; Steven Ganzell, Ph.D., is a Postdoctoral Fellow in Neuropsychology; and Fereidoon Kharabi, M.D., is an Assistant Clinical Professor in Psychiatry at the University of California, Los Angeles.