Earlier Age of First Diagnosis in Schizophrenia Is Related to Impaired Motor Control

by Theo C. Manschreck, Brendan A. Maher, and Steven F. Candela

Abstract

We examined the control of motor behavior in relation to age of first diagnosis (AFD; an approximation of age of onset) in schizophrenia. We hypothesized that earlier AFD reflects increased vulnerability to the disorder, vulnerability that may be indexed by elevated levels of motor abnormality. AFD, symptom and demographic features, motor performance on a line drawing task, and the presence and severity of dyskinesia and extrapyramidal side effects were evaluated in 65 chronic schizophrenia subjects. More severely impaired motor control was significantly related to an earlier age of diagnosis. Potential confounds, including age, gender, education, length of illness, current medication dosage, symptom status, and motor side effects, did not appear to influence this relationship, although greater chronicity appeared to be independently related to more severely impaired motor control. In summary, the data are consistent with the hypothesis that an earlier AFD is associated with more pronounced motor impairment.

Keywords: Schizophrenia, motor control, age of onset, age of first diagnosis, motor abnormality.


Motor abnormalities, an early and intrinsic part of the natural history of schizophrenia, include a spectrum of voluntary and involuntary disturbances of gait, general movement, and intentional action (Manschreck 1986; King 1991; Wolff and O’Driscoll 1999). Many of these abnormalities are independent of the extrapyramidal side effects of antipsychotic medication (although medications are clearly implicated in some motor disturbances). For example, motor abnormalities can be detected premorbidly, and a frequent observation in high-risk studies has been that a significant number of individuals who are at risk for or who have developed a schizophrenic disorder have experienced motor symptoms or impairment of motor control, especially fine motor coordination, prior to the onset of psychosis (Fish and Albert 1963; Robins 1966; Watt 1974; Fish 1975; Hanson et al. 1976; Walker and Lewine 1990; Ismail et al. 1998; Rossi et al. 2000).

Among the early features of schizophrenic illness, subjective symptoms of motor impairment are frequent (Schneider 1959; Chapman 1966; Mellor 1970). Recent clinical and laboratory instrumentation studies have indicated the presence of parkinsonian features and other dyskinesias in both first break, neuroleptic-naïve subjects and more chronic, yet neuroleptic-naïve, schizophrenia subjects (Caligiuri et al. 1993; Fenton et al. 1997; Kopala et al. 1998; Fenton 2000).

Various forms of impaired motor functioning have been associated with impaired cognitive abilities (e.g., Manschreck 2003), and the severity of motor dysfunction may predict prognosis (e.g., Manschreck 1986), with greater motor impairment portending a more severe course of illness (e.g., Turner 1992) and poor treatment outcome (e.g., Poole et al. 1999). Motor abnormalities may thus be viewed as an index of severity in the disorder, and they may serve as markers of vulnerability to the disorder.

Relatedly, an earlier age of onset has also been conceptualized as a marker of greater severity (e.g., Lieberman et al. 1994), as it is commonly associated with poor prognosis and poor response to treatment (e.g., Perlick et al. 1992; Lieberman et al. 1994; Meltzer et al. 1997; Dernovsek and Tavear 1999), as well as more severe symptomatic and cognitive disturbance (e.g., Johnstone et al. 1989; Hoff et al. 1996). Given this convergent framework, it seems plausible to predict that earlier onset could also be associated with greater severity of impairment in motor control. Anecdotal observation in our laboratory, which has a long history of exploring motor impairment in schizophrenia, suggests that earlier onset cases do indeed suffer from more marked motor impairment.

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Direct evidence on this topic has been limited but encouraging. Hoff et al. (1996) found that age of onset in schizophrenia was positively associated with performance on measures of motor ability and speed. Additional work suggests that neurological soft signs, including general clumsiness, are more prevalent in earlier onset compared to later onset schizophrenia (Guez et al. 2000; Bjoerck et al. 2001). Other data have failed to demonstrate an excess of motor abnormalities in relation to earlier onset in schizophrenia (Rossi et al. 2000).

Onset, of course, is likely to be influenced by a number of factors, and earlier onset may arise in patients who do not exhibit motor impairment. Because of the heterogeneity of the disorder, we recognize that any proposed connection between specific features may apply to only a subgroup of schizophrenic disorders. Furthermore, the question of the definition of age of onset in schizophrenia is complex. The systematic detection of early signs of the disorder is most reliable in prospective high-risk studies. In studies of patient samples, the first documented date is often that at which the disorder was first diagnosed and treated (e.g., Rossi et al. 2000). In this article, we use the age of first diagnosis (AFD) as the index of onset, recognizing that it is necessarily an approximation to the age of onset of the pathology.

One methodological concern in the study of motor abnormalities lies in the subjective way they are usually evaluated. Most assessments of motor abnormalities rely on rating scales. Besides being dependent on the clinical training, experience, and judgment of the rater, rating scales lack the numeric range and sensitivity to detect subtle yet possibly meaningful abnormalities and relationships. Instrumental assessment of motor abnormalities is a significant advance over ratings and may help clarify the role of motor disturbance in the disorder (e.g., Caligiuri et al. 1991). Our laboratory has developed several quantitative measures. We chose for our study a simple line drawing task that provides an index of motor control, testing the accuracy, precision, and coordination of fine motor movement. It is described in detail below.

It is plausible that increased vulnerability to schizophrenia, reflected in a greater degree of motor abnormalities, is associated with earlier recognition and diagnosis of the manifest psychotic disorder. The development of a profile of measures that may detect high levels of vulnerability to schizophrenia has obvious potential value in the development of preventive interventions that might delay and/or mitigate the disorder. The present study, therefore, tests the hypothesis that adult schizophrenia subjects with poor motor control will have an earlier AFD than subjects with better motor performance. As male and female patients may differ on some of the variables involved, particularly onset (AFD), we examined our hypothesis with both a mixed sample of men and women, and separately within each sex.

Method

Participants. We studied 65 subjects diagnosed with schizophrenia according to DSM-III-R criteria (APA 1987). Participants came from two state hospitals. Potential subjects were approached to participate in studies of cognition (including memory, language, and motor abilities); those who agreed to the study procedures and were deemed competent to consent were included. Demographic characteristics did not differ between those inpatients who agreed to participate and those who did not.

Diagnostic conclusions were formed based on all available evidence, including a semistructured clinical interview (which included the 18-item Brief Psychiatric Rating Scale [BPRS; Overall and Gorham 1962]); diagnoses reflected a consensus among a staff psychologist, the research psychiatrist (T.C.M.), and the attending psychiatrist. All participants provided written informed consent. Participants were included in the present report if they completed the measure of motor control described below and if their records provided the date at which they were first diagnosed and treated for schizophrenia. Patients with developmental disorders, a significant head injury (defined by a loss of consciousness), significant medical or neurological disease, or current substance dependence were excluded from the study; such decisions were based on a thorough review of medical and psychiatric records.

Measures

Demographics. Demographic information was collected by chart review; daily neuroleptic dosage was recorded and converted into chlorpromazine equivalents. The hand used in writing was used to define handedness.

Symptom severity ratings. Psychopathology was measured with the 18-item BPRS (Overall and Gorham 1962). An additional 58 percent of the sample (38 subjects) was evaluated with the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen 1981) and the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen 1983). Total BPRS, total SANS, and total SAPS scores were used as variables in the analyses.

AFD and length of illness. Age was determined by obtaining a reliable date of birth from the psychiatric records. The date of first diagnosis was established by a review of the case record, confirmed where possible with key informants such as family members and other caregivers. The length of illness (LOI) was established by subtracting the AFD from the patient’s current age. Current age and AFD are necessarily confounded in LOI. In any sample of patients who have been hospitalized for some years, it is inevitable that those with the earliest AFD will also tend to have a longer LOI than those whose
diagnosis came at a later age. By definition, a group of patients matched for AFD and for current age (each of which are independent variables) are thereby matched on LOI. LOI is, therefore, most appropriately regarded as a derivative of AFD and current age rather than an orthogonal independent variable.

**Extrapyramidal side effects.** Extrapyramidal side effects (EPS) were assessed with the Simpson-Angus Rating Scale (Simpson and Angus 1970), and other dyskinesias were assessed with the Abnormal Involuntary Movement Scale (AIMS) (Guy 1976). Total scores from both these scales were examined; in addition, the AIMS provided three subscale scores: Orofacial, Extremities and Trunk, and Severity and Incapacitation.

**Motor control.** Motor control was assessed by the line drawing task developed by Maher (Maher 1993; Blyler et al. 1997; Maher and Manschreck 1998). In this task, participants are instructed to draw oblique straight lines from one bottom corner to the opposite upper corner of a 5.08-cm (2-in.) square. Four such squares are provided, two to be completed with the right hand and two with the left hand. For each hand, one of the squares is completed with a line drawn from left to right and the other from right to left. The completed line drawings are then optically scanned into a computer, after which each line is digitized into a series of xy coordinates. A simple linear regression is then fitted to each set of coordinates. The resulting root mean square error (RMS) is a measure of departure from linearity of the drawn line. The lower the RMS, the more accurately and precisely the line has been drawn. Overall accuracy or precision in performance is then calculated as the sum of the four RMS values; higher scores indicate poorer performance or more error.

We employed this measure because it provides a continuous ratio-scale (quantitative) measure of performance, it is brief, it is relatively unaffected by prior experience, and it does not depend upon clinical judgment (Maher and Manschreck 1998). This assessment has demonstrated adequate psychometric properties; these and additional details about the measure can be found in Blyler et al. (1997).

Overall motor control assessed with this measure has been reported to be significantly associated with the diagnosis of schizophrenia (Blyler et al. 1997), to be significantly associated with self-reported schizotypal symptoms in healthy young adult controls (Lenzenweger and Maher 2002), and to be impaired in first degree relatives of schizophrenia patients (Ballard 2000).

In a sample of 103 healthy normal participants with a mean age of 39.6 years (standard deviation [SD] 11.6) and a range of 19 to 66 years, the correlation between age and mean age of 39.6 years (standard deviation [SD] 11.6) and it does not depend upon clinical judgment (Maher and Manschreck 1998). This assessment has demonstrated adequate psychometric properties; these and additional details about the measure can be found in Blyler et al. (1997).

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In a sample of 103 healthy normal participants with a mean age of 39.6 years (standard deviation [SD] 11.6) and a range of 19 to 66 years, the correlation between age and RMS was $r = 0.15$ (nonsignificant) (Maher 1993). This correlation is comparable to the one reported in the patient sample in the present study (see Results); it therefore seems unlikely that the process of aging is a significant factor in performance on this task.

**Statistical Analysis.** First, simple linear regressions were examined comparing the performance measure from the line drawing task (RMS) with potential confounding variables, including age, education, LOI, medication dosage (in chlorpromazine equivalents), symptom status, AIMS, and EPS. Analysis of the data then focused on the relationship between AFD and motor control as measured by RMS. Linear regressions were computed for the sample as a whole and by gender. A priori hypotheses allowed the use of 1-tailed tests of significance for these analyses. Those “confounding” variables that significantly covaried with RMS were partialed out of the relationship between RMS and AFD. As RMS and AFD scores both follow a positively skewed distribution, we conducted parallel analyses with log transformations of RMS and AFD. Transformed variables had minimal effect on the correlation coefficients produced, and in general we present the results of analyses using untransformed variables.

Two-group comparisons were undertaken with either analysis of variance or chi-square techniques. Some correlations between variables were assessed with Pearson product moment correlations. A final set of post hoc analyses designed to investigate the independence of age, AFD, LOI, and RMS included a principal components factor analysis and a multiple linear regression.

**Results**

**Demographics and Clinical Information.** Descriptive demographic and clinical features of the sample are presented in table 1. The average AFD in our sample was 20.9 years. AFD was modally distributed at age 18 and positively skewed, with a range from age 13 to age 40.

The sample included 38 males and 27 females (table 1). The female sample included a higher proportion of left-handedness by preference and showed trends toward being older, having more years of education, and having a longer LOI. AFD, medication dosage, and symptom scores did not significantly differ between the genders. Furthermore, motor side effects (EPS and AIMS assessment) were similar between the two genders (table 2).

**Motor Control.** The mean accuracy score on the line drawing task (RMS) in the sample as a whole was 7.0 (SD 2.6; range 3.5-15.7).

**Potential demographic and symptomatic confounds.** An examination of gender differences indicated no mean difference on RMS (males mean = 6.6 [SD 2.5; range 3.5-12.4]; females mean = 7.5 [SD 2.8; range 4.0-15.7]). Table 3 presents the simple linear regressions
Table 1. Demographic and clinical characteristics of the sample

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total sample (n = 65)</th>
<th>Male (n = 38)</th>
<th>Female (n = 27)</th>
<th>Difference$^1$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs), mean ± SD (range)</td>
<td>43.2 ± 10.3 (25–67)</td>
<td>41.5 ± 9.8 (25–62)</td>
<td>45.7 ± 10.8 (25–67)</td>
<td>p = 0.10</td>
</tr>
<tr>
<td>Education (yrs), mean ± SD (range)</td>
<td>11.2 ± 2.7 (5–18)</td>
<td>10.6 ± 2.6 (5–16)</td>
<td>11.9 ± 2.6 (8–18)</td>
<td>p = 0.06</td>
</tr>
<tr>
<td>Right/left hand preference (n)</td>
<td>56/9</td>
<td>37/1</td>
<td>19/8</td>
<td>p = 0.003</td>
</tr>
<tr>
<td>Age at first diagnosis (onset [yrs]), mean ± SD (range)</td>
<td>20.9 ± 5.1 (13–40)</td>
<td>21.2 ± 6.1 (13–40)</td>
<td>20.6 ± 3.3 (15–28)</td>
<td>p = 0.66</td>
</tr>
<tr>
<td>Length of illness (yrs), mean ± SD (range)</td>
<td>22.3 ± 10.3 (5–45)</td>
<td>20.4 ± 9.6 (5–44)</td>
<td>25.0 ± 10.9 (5–45)</td>
<td>p = 0.08</td>
</tr>
<tr>
<td>Current daily medication dose, mean ± SD (range)$^2$</td>
<td>811.2 ± 649.1 (0–3,000)</td>
<td>923.6 ± 709.0 (0–3,000)</td>
<td>655.6 ± 530.0 (0–2,000)</td>
<td>p = 0.11</td>
</tr>
<tr>
<td>Total psychopathology (BPRS), mean ± SD (range)</td>
<td>43.9 ± 12.8 (22–74)</td>
<td>42.5 ± 11.6 (26–67)</td>
<td>46.0 ± 14.4 (22–74)</td>
<td>p = 0.31</td>
</tr>
<tr>
<td>Total positive symptoms (SAPS), mean ± SD (range)$^3$</td>
<td>9.0 ± 3.1 (4–15)</td>
<td>8.6 ± 3.2 (4–15)</td>
<td>9.5 ± 3.1 (5–15)</td>
<td>p = 0.35</td>
</tr>
<tr>
<td>Total negative symptoms (SANS), mean ± SD (range)$^3$</td>
<td>13.5 ± 4.4 (2–22)</td>
<td>13.7 ± 5.3 (2–22)</td>
<td>13.3 ± 3.3 (8–19)</td>
<td>p = 0.83</td>
</tr>
</tbody>
</table>

Note.—BPRS = Brief Psychiatric Rating Scale; SANS = Scale for the Assessment of Negative Symptoms; SAPS = Scale for the Assessment of Positive Symptoms.

$^1$ Two-tailed difference between men and women.

$^2$ In chlorpromazine equivalents (mg).

$^3$ n = 38; male/female = 20/18.
coefficients between AFD and RMS are presented in table 6. Correlations are presented for the full sample (figure 1) when correlations were split by gender (correlation-by-RMS on the line drawing measure, and this pattern held when correlations were split by gender). Simpson-Angus scores were uniformly unrelated to total line drawing task are presented in table 5. AIMS and Simpson-Angus and AIMS scales and accuracy on the relationship was between overall motor control (RMS) and clinical and demographic confounds (these coefficients did not meaningfully change when split by gender). The only significant relationship was between overall motor control (RMS) and LOI, such that greater duration of illness was associated with poorer performance on the line drawing task. The intercorrelations between these potential confounds are presented in table 4 (again, these coefficients did not meaningfully change when split by gender). The simple linear regression analysis of motor variables and the other potential demographic and symptomatic confounds (these coefficients did not meaningfully change when split by gender). The only significant relationship was between overall motor control (RMS) and LOI, such that greater duration of illness was associated with poorer performance on the line drawing task. The intercorrelations between these potential confounds are presented in table 4 (again, these coefficients did not change meaningfully when split by gender).

**EPS.** The relationships between scores on the Simpson-Angus and AIMS scales and accuracy on the line drawing task are presented in table 5. AIMS and Simpson-Angus scores were uniformly unrelated to total RMS on the line drawing measure, and this pattern held when correlations were split by gender (correlation-by-gender analyses not shown).

**Motor control (RMS).** The simple linear regression coefficients between AFD and RMS are presented in table 6. Correlations are presented for the full sample (figure 1) and both male and female subjects separately. These correlations are also presented with the effects of age and LOI (singly) partialed out. In general, RMS was significantly associated with AFD in both males and females, with little effect from the confounds LOI or age. These results were uniformly stronger in male subjects. The parallel analyses with log(RMS) and log(AFD) produced a similar pattern of results, with negligible differences between coefficients using either the raw or the transformed scores.

**Interrrelations between age, AFD, LOI, and RMS.** With the interrelationships between age, AFD, and LOI, it is difficult to disentangle the independent effects of each on our motor measure (RMS). Given the high degree of colinearity between age and LOI (table 4) and the fact that one independent variable (LOI) is completely constructed from the other two (age and AFD), it is clear that a multiple linear regression of RMS versus each of these variables would be spurious and difficult to interpret.

Inspection of the simple relationships between age, AFD, and LOI (tables 3 and 4) suggests that age and LOI \( r = 0.86 \) represent a somewhat unitary factor, while AFD is more independent. To test this inference, which is based upon observation, a principal components factor analysis (orthotran/varimax rotation) including age, AFD, LOI, and RMS was conducted (table 7). The analysis further supported this interpretation by producing a two-factor solution, one factor primarily defined by large contributions from age and LOI and the other factor defined primarily by RMS and AFD, with a modest contribution from LOI. This implies that the critical control involves a simultaneous regression of two measures, each of which carries the highest loading on one or the other of the two orthogonal factors. This multiple linear regression was calculated with AFD and age as independent variables and RMS as the dependent variable. Consistent with the partial correlations presented earlier, the results of this regression \( \text{intercept} = 7.952; R^2 = 0.159; p = 0.004 \) indicate that both AFD (beta coefficient = -0.179; standard error (SE) = 0.06; \( t = 3.111; p = 0.003 \)) and age (beta coefficient = 0.062; SE = 0.03; \( t = 2.077; p = 0.04 \)) make independent contributions to the prediction of RMS.

### Table 2. Motor side effects (AIMS and Simpson-Angus scores), \( n = 65 \) (mean \( \pm \) SD [range])

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Total sample ( n = 65 )</th>
<th>Male ( n = 38 )</th>
<th>Female ( n = 27 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIMS Orofacial subscale</td>
<td>0.9 ( \pm ) 1.9 (0-9)</td>
<td>0.9 ( \pm ) 2.1 (0-9)</td>
<td>0.8 ( \pm ) 1.6 (0-6)</td>
</tr>
<tr>
<td>AIMS Extremities and Trunk subscale</td>
<td>0.4 ( \pm ) 1.3 (0-8)</td>
<td>0.5 ( \pm ) 1.6 (0-8)</td>
<td>0.2 ( \pm ) 0.6 (0-3)</td>
</tr>
<tr>
<td>AIMS Severity and Incapacitation subscale</td>
<td>0.4 ( \pm ) 0.9 (0-4)</td>
<td>0.4 ( \pm ) 0.9 (0-4)</td>
<td>0.4 ( \pm ) 0.9 (0-3)</td>
</tr>
<tr>
<td>Total AIMS score</td>
<td>1.7 ( \pm ) 3.7 (0-21)</td>
<td>1.9 ( \pm ) 4.2 (0-21)</td>
<td>1.3 ( \pm ) 2.9 (0-10)</td>
</tr>
<tr>
<td>Total Simpson-Angus score</td>
<td>2.3 ( \pm ) 3.5 (0-12)</td>
<td>2.1 ( \pm ) 3.2 (0-10)</td>
<td>2.4 ( \pm ) 4.0 (0-12)</td>
</tr>
</tbody>
</table>

**Note.**—AIMS = Abnormal Involuntary Movement Scale; SD = standard deviation.

1 All differences between males and females were nonsignificant.

### Table 3. Relationships (coefficients from simple linear regressions) between motor performance (total RMS) and clinical and demographic confounds, \( n = 65 \)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Relationship with motor performance (RMS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>0.18 ( ns )</td>
</tr>
<tr>
<td>Education (yrs)</td>
<td>-0.15 ( ns )</td>
</tr>
<tr>
<td>Length of illness (yrs)</td>
<td>0.39 ( p = 0.01 )</td>
</tr>
<tr>
<td>Current daily medication dose(^1)</td>
<td>-0.09 ( ns )</td>
</tr>
<tr>
<td>Total psychopathology (BPRS)</td>
<td>-0.11 ( ns )</td>
</tr>
<tr>
<td>Total positive symptoms (SAPS)(^2)</td>
<td>0.23 ( ns )</td>
</tr>
<tr>
<td>Total negative symptoms (SANS)(^2)</td>
<td>-0.02 ( ns )</td>
</tr>
</tbody>
</table>

**Note.**—BPRS = Brief Psychiatric Rating Scale; \( ns \) = nonsignificant; RMS = root mean square error; SANS = Scale for the Assessment of Negative Symptoms; SAPS = Scale for the Assessment of Positive Symptoms.

1 \( n = 38 \).

2 \( n = 38 \).

(standard beta coefficients) between the motor variables and the other potential demographic and symptomatic confounds (these coefficients did not meaningfully change when split by gender). The only significant relationship was between overall motor control (RMS) and LOI, such that greater duration of illness was associated with poorer performance on the line drawing task. The intercorrelations between these potential confounds are presented in table 4 (again, these coefficients did not change meaningfully when split by gender).
Table 4. Interrelationships among demographic and clinical variables (Pearson r's), n = 65

<table>
<thead>
<tr>
<th>Variable</th>
<th>Ed</th>
<th>AFD</th>
<th>LOI</th>
<th>Meds</th>
<th>BPRS</th>
<th>SANS¹</th>
<th>SAPS¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>-0.16</td>
<td>0.25*</td>
<td>0.86*</td>
<td>-0.12</td>
<td>0.03</td>
<td>-0.10</td>
<td>0.007</td>
</tr>
<tr>
<td>Education (yrs)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AFD (yrs)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.26*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LOI (yrs)</td>
<td></td>
<td></td>
<td></td>
<td>0.21</td>
<td></td>
<td>0.16</td>
<td>0.08</td>
</tr>
<tr>
<td>Medication²</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.01</td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>BPRS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.002</td>
<td></td>
<td>0.10</td>
</tr>
<tr>
<td>SANS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.39*</td>
</tr>
</tbody>
</table>

Note.—AFD = age at first diagnosis; BPRS = Brief Psychiatric Rating Scale; Ed = education; LOI = length of illness; SANS = Scale for the Assessment of Negative Symptoms; SAPS = Scale for the Assessment of Positive Symptoms.

¹ n = 38.
² Current daily medication dose in milligrams of chlorpromazine equivalents.
* p < 0.05

Table 5. Relationships between motor performance (RMS) and motor side effects, n = 65

<table>
<thead>
<tr>
<th>Motor Side Effect</th>
<th>Correlation with motor performance (RMS)¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIMS Orofacial subscale</td>
<td>0.02</td>
</tr>
<tr>
<td>AIMS Extremities and Trunk subscale</td>
<td>0.04</td>
</tr>
<tr>
<td>AIMS Severity and Incapacitation subscale</td>
<td>0.06</td>
</tr>
<tr>
<td>AIMS total score</td>
<td>0.04</td>
</tr>
<tr>
<td>Simpson-Angus total score</td>
<td>-0.01</td>
</tr>
</tbody>
</table>

Note.—AIMS = Abnormal Involuntary Movement Scale; RMS = root mean square error.
¹ All correlations nonsignificant.

Discussion

Using quantitative measures of the accuracy or precision of motor performance, we found support for the hypothesis that impaired motor control is associated with AFD of schizophrenia: those with poorer performance on the motor task had been diagnosed at an earlier age. This was the case regardless of gender, although AFD was more strongly related to motor control among males than among females in our study. These results do not seem to be due to the effect of education, current medication dosage, current symptoms, or motor side effects.

In a cross-sectional study such as this, it is difficult to disentangle the effects of increasing age and LOI on motor control. Data from a group of healthy subjects suggested that age has minimal influence on RMS. Independently, age appeared to have no relationship to RMS in our patient sample, while a longer LOI was associated with increasing RMS. When age was included with AFD in a multiple linear regression against RMS, both variables independently contributed to the prediction of RMS. Given the nature of these relationships, we speculate that any relationship between age and RMS among our patients is driven primarily by the relationship between RMS and LOI, which is itself strongly correlated with age. Whether the detrimental effects of increasing LOI on motor control are due to the disease process, a synergistic interaction between the disease process and aging, or the effects of prolonged antipsychotic treatment cannot be easily determined, and none of those processes fundamentally changes the nature of the relationship between earlier AFD and poorer motor control. It is important that multiple attempts to statistically control for the effects of chronicity and age on the relationship between AFD and poor motor control indicate that the reported relationship between AFD and RMS is not an artifact.

The utility of the line drawing measure as an index of motor control in schizophrenia spectrum disorders is confirmed by another report in which the line drawing task was examined in relation to scores on schizotypy scales in a large sample of normal young adults (Lenzenweger and Maher 2002). Performance on this measure also differed between relatives of schizophrenia subjects and other unrelated normal controls (Ballard 2000). Of note, in neither case was LOI a possible factor, because psychotic disorder was not present. Similar findings have been reported in other examinations of motor abnormalities and onset among schizophrenia subjects (Hoff et al. 1996; Guez et al. 2000). The line drawing measure’s utility in our study is also consistent with our general hypothesis that in a subset of schizophrenia subjects, more marked motor impairment is related to an earlier diagnosis or onset of schizophrenia.

Certain caveats must be mentioned. Our definition of AFD as an index of onset differs somewhat from the more generally used term "age of onset" but correctly reflects the actual measurement procedure most often used to establish age of onset. Similarly, medication or age may have contributed to the motor performance under exami-
Table 6. Correlations (standard beta coefficients) between age of first diagnosis and RMS (accuracy score), with and without potential confounds partialed out (n = 65)

<table>
<thead>
<tr>
<th></th>
<th>Full sample (n = 65)</th>
<th>Male (n = 38)</th>
<th>Female (n = 27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncorrected r</td>
<td>-0.36 (p = 0.002)</td>
<td>-0.41 (p = 0.005)</td>
<td>-0.29 (p = 0.07)</td>
</tr>
<tr>
<td>Age-corrected r</td>
<td>-0.43 (p = 0.0003)</td>
<td>-0.45 (p = 0.003)</td>
<td>-0.36 (p = 0.04)</td>
</tr>
<tr>
<td>LOI-corrected r</td>
<td>-0.29 (p = 0.01)</td>
<td>-0.34 (p = 0.02)</td>
<td>-0.25 (p = 0.11)</td>
</tr>
</tbody>
</table>

Note.—LOI = length of illness; RMS = root mean square error.

1 All p values 1-tailed.

Figure 1. AFD versus motor performance (RMS) in a sample of chronic schizophrenia patients, n = 65

Note.—AFD = age at first diagnosis; RMS = root mean square error.

nation. However, our statistical analysis did not support the notion that a medication effect influenced motor responses; statistical segregation of LOI and age from the effects under analysis indicated that these variables could not account for the findings.

The weaker relationship (i.e., smaller effect size) noted among female subjects may simply reflect a restriction of range, in that the range of AFD was twice as great for males as for females. Alternatively, the finding of a possible gender difference in the magnitude of the relationship between AFD and motor control could indicate that further investigation of this avenue would be worthwhile. Such a reduced relationship might reflect the effects of hypothesized hormonal protective factors.
or decreased vulnerability to the disorder among females.

On the basis of our data, we are inclined to argue that motor pathology is not simply an epiphenomenon or meaningless correlate of schizophrenia but an intrinsic part of the entire pathogenetic process. Much work from this laboratory and elsewhere has supported this view. There are several possible hypotheses about the basis for the relationships reported; motor pathology and other dimensions of the disorder may covary because of either topographical or functional overlap in the brain. For example, a dopamine-mediated disturbance in various brain areas may mediate the onset of psychosis and impaired motor performance. There is also the related possibility that impaired prefrontal function affects the attentional and programming processes involved in motor performance (poor motor control) and adaptive behavior (onset of psychosis).

As we have already mentioned, poorer motor control assessed with the line drawing measure was related to high scores on a schizotypy scale in a normal sample (Lenzenweger and Mahler 2002). Other work, much of it cited in the introduction to this report, has documented the existence of motor impairment during the childhood of individuals who later developed schizophrenia. For example, Fish and colleagues (Fish 1977, 1987; Fish et al. 1992) have shown that premorbid impairment of motor function is predictive of early-onset poor-prognosis schizophrenia. The premorbid existence of motor impairment suggests a fundamental relationship to the disease under investigation; still, it remains possible that the covariation between motor problems and pathology seen among premorbid samples represents the breakdown of a protective mechanism. It may also be that the damage producing the schizophrenic syndrome also disrupts a maturing motor system, so that the covariation is due to coincidental damage to motor areas and those more fundamentally related to the disease process. Our data do not suggest any age-based relationships between RMS and AFD and do not permit us to offer a maturational hypothesis.

To conclude, we report an association between more impaired motor control and earlier AFD. This association should be replicated in other schizophrenic samples. Further refinement of the definition of age of onset may help illuminate the meaning of this relationship. However, as with other ratings, there may be a methodological limit to the precision of this concept (e.g., Häfner et al. 1993). It may be useful to examine the relationship of these movement factors in the presence of schizotypy rather than psychotic features. Such work might also contribute to a better understanding of pathogenesis and would not be confounded by possible effects of medication or chronicity.

References


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**Acknowledgment**

We gratefully acknowledge the efforts of Laura Winzig, Scott Beaudette, and Deborah Redmond in the data collection component of this investigation. We are also indebted to the anonymous reviewers of this manuscript, who helped us strengthen both our analytical strategy and the presentation of this work.

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