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Determinants of neurological dysfunction in first episode schizophrenia

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ABSTRACT

Background. Although it is well recognized that individuals with schizophrenia display evidence of subtle neurological impairment, its aetiopathological and clinical significance continues to be unclear.

Methods. Patients presenting with a first episode of schizophrenia or schizophreniform psychosis (DSM-IV criteria) were examined using two previously validated neurological examinations. The majority ($N = 35$) were examined prior to their 'first ever' dose of neuroleptic while the remaining patients ($N = 21$) had been medicated for less than one month. The manner in which neurological functioning is influenced by symptomatology and handedness was ascertained.

Results. The majority of patients who were examined neuroleptic-naive displayed evidence of neurodysfunction. A combination of relative hand preference and symptomatology explained a significant proportion of the variance in neurological functioning. Mixed handedness among adults at the time of first presentation with schizophrenia was associated with more severe neurological impairment and a history of poorer scholastic attainment and pre-morbid social adjustment.

Conclusions. Neurological soft signs are an intrinsic part of schizophrenia rather than a direct consequence of treatment. Early developmental processes are associated with the level of subsequent neurological impairment in first episode schizophrenia. However, symptomatology appears to have an influence on the apparent severity of neurological impairment.

INTRODUCTION

The term 'neurological soft signs' (NSS) refers to subtle impairments in sensory integration, motor coordination and the sequencing of complex motor acts (Heinrichs & Buchanan, 1988), which are viewed to be indicative of non-specific brain damage (Kennard, 1960). Several studies demonstrate that individuals with schizophrenia have more NSS compared to non-psychiatric control subjects (Cox & Ludwig, 1979; Buchanan & Heinrichs, 1989; Rossi *et al.* 1990). Although neuroleptics may affect neurological functioning (Woods *et al.* 1986). Heinrichs & Buchanan (1988) concluded that the higher prevalence of NSS found among patients with schizophrenia compared with normal control subjects is not simply a consequence of medication. However, some (King *et al.* 1991; Flashman *et al.* 1996), but not all (Kolakowska *et al.* 1985; Schroder *et al.* 1992) studies have reported a correlation between medication-induced neurological side effects and NSS in populations with chronic schizophrenia. Consequently, the most feasible method of clarifying if neurodysfunction is inherent to schizophrenia or merely a medication epiphenomenon is to assess first-episode patients before they commence neuroleptics. This methodology was used in the current study in an attempt to replicate recent findings (Sanders *et al.* 1994; Gupta *et al.* 1995) that NSS are present in neuroleptic-naive, first-episode cases of schizophrenia.

The aetiopathological and clinical significance

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of NSS are unclear. Family (Marcus *et al*. 1985; Rossi *et al*. 1990) and high-risk (Erlenmeyer-Kimmling *et al*. 1982; McNeil *et al*. 1993) studies indicate that these neurological abnormalities may antedate the onset of the illness. Other investigators have demonstrated a relationship between NSS and different dimensions of symptomatology (King *et al*. 1991; Schroder *et al*. 1992; Wong *et al*. 1997). Comparisons across these studies are hampered by a wide variability in the instruments used to evaluate neurological functioning. Consequently, we used two previously validated examinations to clarify whether neurological impairment in schizophrenia is predominantly influenced by the patient's mental state at the time of assessment or by factors antedating the onset of illness.

Although a genetic basis for handedness has been postulated (Annett, 1985), recent studies suggest that obstetric complications may influence hand dominance (Saigal *et al*. 1992; O'Callaghan *et al*. 1993; Powls *et al*. 1996) and the development of schizophrenia (O'Callaghan *et al*. 1992; Kendell *et al*. 1996). Furthermore, pre-schizophrenic children prospectively evaluated in the UK National Child Development Study were more likely to be mixed-handed at age 7 compared to their peers who did not later develop the illness (Crow *et al*. 1996). Consequently, we hypothesized that relative hand dominance is a variable that reflects events antedating illness onset. This hypothesis was tested by assessing the relationship between mixed-handedness, educational attainment and pre-morbid social adjustment in a series of adults presenting with their first episode of schizophrenia. To-date, some of the variability in the findings regarding mixed-handedness and schizophrenia appears to relate to differences between studies in the methods used to classify and assess hand dominance (Satz & Green, 1999). Therefore, we applied two sets of criteria for mixed-handedness to the findings of an examination in which patients demonstrated their hand-preference for a variety of common activities.

METHOD

Subjects

Over a 24-month period, a detailed neurological, clinical and diagnostic assessment was carried out by either of two psychiatrists (S.B.; M.C.) on all patients presenting with a first episode of psychosis to the in- or out-patient departments of two psychiatric services. These assessments were carried out at Cluain Mhuire Family Centre (a catchment area service which provides psychiatric care for an urban population of approximately 165000) and St John of God Hospital (a private psychiatric facility that receives referrals from across Ireland). First episode of psychosis was defined as a first ever presentation to any psychiatric service with a psychotic episode. Patients who had commenced psychotropic medication prior to referral were included in the study provided they were being treated for a first psychotic episode and that their treatment had not commenced more than 30 days before assessment. All adolescents ($\geqslant$ 12 years of age) and adults presenting with delusions, hallucinations, thought disorder or a history of inappropriate/bizarre behaviour and who met these criteria were assessed. Results of these assessments were made available to the treating clinical team. However, treatment was not a controlled variable in this protocol and patients were treated using 'clinicians choice' medications and treatment programmes.

Evaluation of handedness and neurological soft signs

Handedness was rated using the Edinburgh Inventory (Oldfield, 1971), during which the patients were asked to perform 10 common activities. A laterality quotient (LQ) was computed using the following formula:

$$LQ = (R - L) \times 100/(R + L),$$

where R and L are the number of acts performed using the right and left hands respectively. Consequently, the LQ can range from $+100$ (a strong right hander) to -100 (a strong left hander).

Two alternative definitions of mixed-handedness were applied:

(1) Broad definition, if the LQ was less than $+100$ and greater than -100 (all individuals who were not strong right or left handers being classified as mixed-handed);

(2) Narrow definition, if the LQ was less than $+80$ and greater than -80 (individuals were classified as mixed-handed if there were two or more discrepancies in hand preference).

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Individuals who did not fulfil these criteria for mixed-handedness were classified as having a lateralized hand dominance.

After a routine examination of the peripheral and central nervous systems, we assessed each patient using two instruments designed to standardise the assessment of neurological impairment in schizophrenia. The Neurological Evaluation Scale (NES; Buchanan & Heinrichs, 1989) is a battery of 26 discrete items, of which 14 are tested bilaterally. Each item is scored using anchored ratings of 0 (normal), 1 (questionable or mildly abnormal) and 2 (abnormal) except for the snout and suck reflexes which are scored as either 0 or 2. The Condensed Neurological Examination (CNE; Rossi *et al.* 1990) consists of 19 items, of which seven are bilateral. Items are rated as absent or present (0, 1) or on ordinal scales having maxima between 2 and 6. Whenever possible, these examinations were performed prior to the introduction of the 'first-ever' dose of neuroleptic medication. During the neurological examinations patients were given a maximum of three explanations/demonstrations for each test; if they were unable to comply with the instructions given for any test, the entire examination was deferred until the patient was capable of following the instructions.

Clinical measures

We assessed symptomatology at the time of the neurological assessment using the Positive and Negative Syndrome Scale (PANSS) (Kay *et al.* 1987). Each patient underwent a Structured Clinical Interview for DSM (SCID) to ascertain a DSM-IV diagnosis (APA, 1995) when their clinical condition had stabilized. During this interview, we asked patients to detail their educational history and to date (to the nearest month) the onset of the first psychotic symptom experienced.

We then requested patients to consent to a parent, preferably mothers, being interviewed using the Premorbid Social Adjustment (PSA) scale (Foerster *et al.* 1991) which evaluates the patient's pre-morbid functioning over two discrete time periods; between 5 and 11 years (PSA 1) and from 12 to 16 years (PSA 2).

Inter-rater reliabilities

Investigators received prior training in the neurological examinations from a psychiatrist who had specific neurological training in the assessment of NSS (Lane *et al.* 1996). We assessed inter-rater reliabilities for the CNE, NES and PANSS by the concurrent examination of 10 patients with chronic schizophrenia. Intraclass correlation coefficients (ICCs) were in excess of 0·76 for all subscales and the total score of the NES, and 0·91 for the total score of the CNE. ICCs were 0·73 for the negative syndrome subscale and in excess of 0·84 for the remaining subscales and the total score of the PANSS. ICCs for the PSA 1 and PSA 2 were obtained by rating 10 maternal interviews and were in excess of 0·88.

Data analysis

Neurological abnormalities are associated with drug and alcohol abuse (Woods *et al.* 1986; Keenan *et al.* 1996). Therefore, we excluded any individual who had a SCID diagnosis of alcohol or drug abuse/dependence in the month prior to neurological examination or who had a positive drug screen (urinalysis) at the time of assessment. Furthermore, patients with learning disability, a history of head injury/neurological disorder, a medical illness known to be associated with increased neurological abnormality or who were found to have localizing signs on the peripheral and central nervous system examination were also excluded. The remaining patients were dichotomized into groups of neuroleptic-naive (never previously received any neuroleptic medication) and neuroleptic-exposed (at least one dose of neuroleptic received prior to examination but treated for less than 30 days).

We used the results of the NES examination for neuroleptic-naive patients to ascertain baseline rates of neurodysfunction. Relationships between variables among the neuroleptic-naive group were analysed using Pearson correlation coefficients. Differences between groups were assessed using Student's t test, analysis of variance (ANOVA) or chi-square test where appropriate. Statistical tests were considered significant at a P value of 0·05 (two-tailed). We applied two separate stepwise multiple regression analyses to investigate the relationship between neurological functioning (dependent variables were the total scores of the CNE and NES) and the following variables: gender, duration of untreated psychosis, medication status, LQ, PANSS positive and negative syndrome scores.

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Developing a psychosis in early- to mid-adolescence usually interrupts an individual's education and seriously restricts the evaluation of pre-morbid functioning. Therefore, we confined the assessment of the relationship between mixed-handedness, educational attainment and pre-morbid social adjustment to those individuals who were aged $\geqslant$ 18 years at the time of presentation.

RESULTS

One hundred and forty-three patients with a first episode of psychosis were examined over the first 2 years of the assessment protocol. DSM-IV diagnoses included schizophrenia ($N = 55$), schizophreniform psychosis ($N = 33$), bipolar affective disorder with psychotic symptoms ($N = 19$), major depressive disorder with psychotic symptoms ($N = 11$), delusional disorder ($N = 13$), substance induced disorder ($N = 9$), psychosis due to a general medical condition ($N = 2$) and psychosis NOS ($N = 1$).

After the neurological examination, we excluded 22 patients with schizophrenia or schizophreniform psychosis from the analysis. These individuals had a history of one or more of the following; drug abuse/dependence in the past month or a positive drug screen at the time of examination ($N = 14$), alcohol abuse/dependence in the past month ($N = 9$) and a history of head injury/neurological illness ($N = 4$). All future discussion relates to the remaining 66 individuals with schizophrenia or schizophreniform psychosis. With the exception of two individuals (2·3%), these patients were of a similar ethnic (Caucasian) origin.

Thirty-five individuals (21 male, 14 female) were examined prior to the initiation of neuroleptics; 34 (97·1%) displayed at least one NSS (defined as one NES item rated 2) and 22 patients (63%) had a minimum of two NSS (2 or more NES items rated 2). There was a strong correlation ($r = 0{\cdot}73$, $P < 0{\cdot}001$) between the NES (mean 14·9, S.D. 7·4; median 14·5) and CNE (mean 7·6, S.D. 4·8; median 7·0) scores for these neuroleptic-naive individuals. The CNE score was significantly correlated with the LQ ($r = -0{\cdot}48$, $P < 0{\cdot}01$), PANSS total ($r = 0{\cdot}42$, $P < 0{\cdot}01$) and the PANSS positive syndrome ($r = 0{\cdot}50$, $P < 0{\cdot}01$) scores. Likewise, the NES score significantly correlated with the LQ ($r = -0{\cdot}33$, $P < 0{\cdot}05$), PANSS total ($r = 0{\cdot}57$, $P < 0{\cdot}001$) and PANSS positive syndrome ($r = 0{\cdot}46$, $P < 0{\cdot}01$) scores. The PANSS negative syndrome score was not significantly correlated with the CNE ($r = 0{\cdot}09$) or NES ($r = 0{\cdot}30$) scores.

Neuroleptic-naive patients ($N = 35$) and those who had commenced medication ($N = 21$) did not differ significantly in terms of symptomatology or neurological functioning. However, there was a trend for the neuroleptic-naive group to have a longer duration of untreated psychosis (Table 1). Analysis of variance, controlling for the effect of duration of untreated psychosis, confirmed that there were no significant differences between these groups in terms of the CNE ($F = 2{\cdot}34$, $P = 0{\cdot}13$) and NES ($F = 0{\cdot}13$, $P = 0{\cdot}72$) scores. In a stepwise multiple regression, a significant proportion of the variance in the CNE score of the neuroleptic naive and treated patients (adjusted $R^2 = 20{\cdot}1\%$, $F = 9{\cdot}61$, $P = 0{\cdot}0002$) was explained by the LQ

Table 1. *Clinical and neurological comparison of neuroleptic-naive and neuroleptic-exposed patients*

	Naive ($N = 35$)		Exposed ($N = 31$)					
Characteristic	Mean	(S.D.)	Mean	(S.D.)	t	df	P	95% CI
Age (years)	26·4	(10·7)	24·6	(9·3)	0·75	64	0·45	(−3·09, 6·86)
Duration of untreated psychosis (months)	25·6	(44·6)	10·5	(12·9)	1·93	40	0·06	(−0·75, 31·1)
Total PANSS score	83·8	(16·6)	82·5	(17·1)	0·32	64	0·75	(−6·94, 9·63)
Positive syndrome*	23·1	(6·3)	23·4	(7·3)	−0·15	64	0·88	(−3·59, 3·10)
Negative syndrome*	19·7	(7·9)	17·9	(6·2)	1·04	64	0·30	(−1·68, 5·35)
Total CNE score	8·3	(5·6)	6·8	(3·6)	1·34	59	0·19	(−0·76, 3·83)
Total NES score	14·4	(7·8)	15·6	(6·9)	−0·63	64	0·53	(−4·80, 2·50)

* Syndrome scale scores on PANSS.

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Table 2. *Comparison between mixed-handed and lateralized individuals in symptomatology and neurological functioning using alternative definitions of mixed-handedness*

	Mixed-handed		Lateralized				
	Mean	(S.D.)	Mean	(S.D.)	*t*	df	*P*
Broad definition	($N = 22$)		($N = 44$)				
Total PANSS score	83·2	(15·7)	83·2	(17·3)	−0·01	64	0·99
Positive syndrome*	25·3	(6·6)	22·2	(6·6)	1·79	64	0·08
Negative syndrome*	17·6	(7·2)	19·5	(7·1)	−1·02	64	0·31
CNE score	8·4	(4·7)	7·2	(4·9)	−0·94	64	0·35
NES score	16·7	(7·7)	14·1	(7·1)	−1·34	64	0·18
Narrow definition	($N = 6$)		($N = 60$)				
PANSS score	81·3	(22·3)	83·4	(16·3)	0·28	64	0·77
Positive syndrome*	28·0	(6·3)	22·8	(6·6)	1·84	64	0·07
Negative syndrome*	16·3	(7·6)	19·2	(7·1)	−0·92	64	0·36
CNE score	13·2	(5·5)	7·1	(4·4)	−3·17	64	0·002
NES score	21·8	(9·9)	14·3	(6·8)	−2·48	64	0·02

* Syndrome scale scores on PANSS.

($t = -2{\cdot}69$, $P = 0{\cdot}009$) and the PANSS positive syndrome ($t = 3{\cdot}03$, $P = 0{\cdot}003$) scores. When the regression analysis was repeated using the NES score as the dependent variable, only the LQ ($t = -2{\cdot}78$, $P = 0{\cdot}007$) accounted for a significant amount of the variance in neurological impairment (adjusted $R^2 = 9{\cdot}4\%$, $F = 7{\cdot}72$, $P = 0{\cdot}007$). Medication status had no independent effect on neurological functioning in either regression analysis.

The relationship between mixed-handedness and neurological functioning is outlined in Table 2. Using a broad definition of mixed-handedness there were no significant differences between mixed-handed ($N = 22$) and lateralized ($N = 44$) individuals in terms of the total CNE and NES scores. However, when a narrow definition of mixed-handedness was applied, significant differences in neurological functioning between mixed-handed ($N = 6$) and lateralized ($N = 60$) individuals were found. There was a trend towards a significant difference in positive symptom severity between mixed-handed and lateralized individuals (Table 2). Analysis of variance, controlling for positive symptom severity, confirmed that individuals classified as mixed-handed (narrow definition) performed worse on both the NES ($F = 4{\cdot}31$, $P = 0{\cdot}04$) and CNE ($F = 4{\cdot}06$, $P = 0{\cdot}05$) examinations relative to lateralized individuals.

We assessed the relationship between mixed-handedness, educational attainment and premorbid social adjustment among those individuals who were aged 18 years or over at the time of presentation ($N = 51$). Six of these adults were classified as mixed-handed using the narrow definition of mixed-handedness. There were significant differences in terms of number of years completed in education ($t = -3{\cdot}40$, 49 df, $P = 0{\cdot}001$) between these mixed-handed (mean 11·3, S.D. 1·5) and lateralized (mean 14·7, S.D. 2·3) adults. Likewise, mixed-handed adults were less likely to have completed second level education compared to those adults who were classified as having a lateralized hand preference ($\chi^2 = 6{\cdot}05$, 1 df, $P = 0{\cdot}01$).

We obtained consent for parental interviews from 41 of these adults; five of these individuals were classified as being mixed-handed using the narrow definition. Mixed-handed individuals (mean 16·2, S.D. 3·3) had significantly ($t = 3{\cdot}00$, 39 df, $P = 0{\cdot}005$) higher PSA 1 scores compared to those classified as having a lateralized hand preference (mean 10·7, S.D. 3·8). There was also a trend ($t = 1{\cdot}92$, 39 df, $P = 0{\cdot}06$) for mixed-handed individuals (mean 16·2, S.D. 3·9) to be judged by their parents as having poorer premorbid social adjustment between the ages of 12 and 16 (PSA 2) compared to lateralized individuals (mean 12·2, S.D. 4·3).

DISCUSSION

Research into the neurology of schizophrenia has been limited by the wide variation of items included as soft signs in previous studies and by the number of clinical factors that may affect neurological function. This study addressed

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these methodological considerations by using two previously validated instruments to assess neurological performance in first-episode patients and by excluding individuals with co-morbid conditions that are recognized to influence neurological functioning. The findings confirm the two previous reports that NSS are present in neuroleptic-naive individuals presenting with a first episode of schizophrenia.

Rate of neurodysfunction prior to treatment

We found that 97% of neuroleptic-naive individuals had at least one NSS. This rate is substantially higher than those reported by Gupta and colleagues (1995) in their study of 26 neuroleptic-naive patients who were examined for 13 soft signs (23%) and seven developmental reflexes (19%) using an assessment procedure derived from multiple sources. However, differences between studies in the reported rates of neurological impairment are related to differences in the comprehensiveness of the assessment procedure and to the sensitivity of the scoring guidelines used (Buchanan & Heinrichs, 1989). For example, items that preferentially evaluate frontal lobe dysfunction are considered the most likely tests to uncover motor disturbance in schizophrenia (Manschreck *et al.* 1981; Varga, 1988). It has been suggested that these signs 'might easily be missed if not carefully looked for' (Manschreck *et al.* 1982). The NES includes several items (for example, the 'Fist-Ring', 'Fist-Edge-Palm' and Ozeretski tests) that specifically address this issue. However, none of these items were included in the examination procedure used by Gupta and colleagues (1995). In contrast, Cuesta and colleagues (1996) reported that 97% of a young, neuroleptic-treated cohort had at least one frontal sign when examined using a battery that primarily assessed motor co-ordination and the sequencing of complex motor acts.

The total NES score was positively correlated with the PANSS positive syndrome score amongst neuroleptic-naive patients. Consequently, it is possible that the level of neurodysfunction found in this cohort may simply reflect attentional deficits secondary to untreated psychotic symptoms. If this was the case, one might expect that the NES score for this cohort would be higher than those reported in previous studies from treated populations. However, the mean NES score for this sample ($14{\cdot}9 \pm 7{\cdot}4$) is lower than the levels reported by Buchanan & Heinrichs (1989) for medicated, multi-episode patients with schizophrenia and schizoaffective disorder ($17{\cdot}42 \pm 7{\cdot}52$) but higher than the score for non-psychiatrically ill controls ($9{\cdot}66 \pm 4{\cdot}38$). Likewise, it is intermediate between the levels reported by Arango and colleagues (1999) for normal comparison subjects ($6{\cdot}77 \pm 3{\cdot}9$) and a neuroleptic-treated population with schizophrenia ($17{\cdot}65 \pm 8{\cdot}2$). This suggests that neurodysfunction (defined as the presence of one or more NSS on the NES examination) is a characteristic of most, if not all, patients with schizophrenia. However, it is unclear what percentage of control subjects would meet these specific criteria for neurodysfunction. Furthermore, the severity of neurological impairment evident at first presentation with schizophrenia is modest.

Neurological functioning and symptoms

The CNE and NES scores were correlated with total symptom severity in the neuroleptic-naive group. At the very least, this finding suggests that symptom severity may be an important confounding factor to be considered in studies comparing the severity of NSS between different psychotic disorders. Longitudinal studies are obviously required to clarify whether, or not, the degree of neurological impairment varies with fluctuations in symptomatology and neuroleptic treatment. However, the finding that NSS were related to the patients' clinical condition could be considered as support for the view expressed by Keshavan & Yeragani (1987) that these signs may have prognostic significance. Although there are contradictory findings in this regard (Kolakowska *et al.* 1985), some investigators (Torrey, 1980; Johnstone *et al.* 1990; Schroder *et al.* 1992) have reported a relationship between illness course and the extent of neurological impairment.

Neurological functioning and medication

Comparison of the neuroleptic-naive and exposed groups revealed no differences in symptomatology. This may be due to the fact that the neuroleptic-exposed group consisted of individuals who had received at least one dose of neuroleptic but had been prescribed medication for less than 30 days at the time of assessment. There were no significant differences between

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the groups in the CNE or NES scores. Likewise, the multiple regression analyses showed no independent effect of medication status on either measure of neurological functioning. This finding appears to support the conclusion of Heinrichs & Buchanan (1988) that 'medication does not alter neurological signs'. However, some cross-sectional studies in chronic schizophrenia (King *et al*. 1991; Flashman *et al*. 1996) indicate that patients with NSS had higher scores on the AIMS and Simpson–Angus scales compared to patients without neurological impairment. Consequently, longitudinal evaluations of cohorts prior to and subsequent to their initial treatment are required to clarify the effect of medication on neurological functioning in schizophrenia and to elucidate the potential confounding effects of symptomatology and side-effects.

Neurological functioning and handedness

Among the neuroleptic-naive cohort there was evidence of a relationship between neurological functioning and relative hand dominance. Likewise, the regression analyses confirmed that performance on both neurological examinations was independently influenced by the LQ. Furthermore, the small subgroup of individuals who fulfilled narrowly defined criteria for mixed-handedness had significantly more neurological impairment compared to individuals with a lateralized hand preference, even on controlling for the effect of positive symptom severity. One interpretation of these data is that individuals with a lateralized hand preference have better coordination compared with those whose handedness is not lateralized. However, recent research (Gabbard *et al*. 1993) indicates that hand preference does not have a significant influence on manual dexterity.

In this study, mixed-handed adults spent significantly less years in education, were more likely not to have completed second level education and were reported by their parents to have had a poorer pre-morbid social adjustment in pre- and early/mid-adolescence compared to those with a lateralized hand preference. If one considers the amount of time spent in education to be indicative of cognitive function, these findings appear to be at variance with the 'right shift' theory of handedness (Annett, 1985). This theory predicts that, in the general population, strong dextrals are at greatest risk of lower intellectual ability. Support for this theory comes from the finding that, when primary schoolchildren were stratified according to academic ability, there was a trend for educational test scores to decrease from left to right across a laterality continuum (Annett & Manning, 1989). However, this finding was primarily based on a measure of relative hand skill demonstrated by children between the ages of 5 and 11 years. These differences in study population and methodology limit the extent to which these findings can be compared. Furthermore, it is important to highlight that the amount of time spent in education is likely to be influenced by factors other than an individual's intelligence.

Data from this study provide evidence of a common thread that extends from mixed cerebral lateralization through poor scholastic attainment and impaired pre-morbid social adjustment to neurological dysfunction at the time of first presentation with schizophrenia. Low birth weight is associated with mixed-handedness in non-psychiatrically ill pre-adolescents (Powls *et al*. 1996) and the severity of neurological impairment in monozygous twins discordant for schizophrenia (Pollin *et al*. 1966). Furthermore, Gureje and colleagues (1994) reported that adults with schizophrenia who had a history of early brain injury were significantly more likely to display mixed cerebral laterality compared to individuals without early brain trauma. Therefore, the relationship between mixed-handedness in schizophrenia and factors of aetiological importance such as pre/perinatal environmental adversity and genetic risk requires further evaluation.

In conclusion, we found that NSS are evident in the majority of individuals presenting for the first time with schizophrenia before they ever receive neuroleptic medication. This suggests that neurological dysfunction is an intrinsic part of schizophrenia and not simply an epiphenomenon attributable to medication. However, we also found that an individual's psychiatric symptoms may influence their neurological functioning. Therefore, symptomatology may be an important confounding variable in comparing neurological functioning between populations with different psychiatric diagnoses. Finally, these data provide evidence for a developmental process that is initially reflected

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in mixed handedness and later in diminished scholastic performance, poor pre-morbid social adjustment and neurological dysfunction at presentation with schizophrenia.

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