

Neurological soft signs in first-episode psychosis: a systematic review*

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Background Neurological soft signs (NSS) are minor neurological signs indicating non-specific cerebral dysfunction. Their presence has been documented extensively in schizophrenia but not during the first psychotic episode.

Aims To review studies that have specifically investigated NSS at the time of the first psychotic episode.

Method A review of studies investigating neurological function in first-episode psychosis, using a clinical examination.

Results Patients with first-episode psychosis show an excess of NSS, particularly in the areas of motor coordination and sequencing, sensory integration and in developmental reflexes. Furthermore, NSS may be associated with a specific laterality pattern.

Conclusions More studies on first-onset schizophrenia are needed, evaluating both sensory and motor neurological domains (scoring separately for the two sides of the body), integrating this knowledge with neuroimaging findings and clarifying the role of NSS as markers of cognitive dysfunction.

Declaration of interest None. Funding from the Stanley Foundation and the Medical Research Council (UK).

Neurological soft signs (NSS) are minor ('soft') neurological abnormalities in sensory and motor performance identified by clinical examination. They have been described in excess in patients with schizophrenia (Buchanan & Heinrichs, 1989). There is still a lack of consensus on the neurodysfunctional area underlying NSS; some authors suggest that NSS reflect a failure in the integration within or between sensory and motor systems (Griffiths *et al*, 1998), whereas others advocate deficits in neuronal circuits involving subcortical structures (e.g. basal ganglia, brain-stem and limbic system; Heinrichs & Buchanan, 1988). Although the presence of NSS has been documented extensively in schizophrenia as a whole, the same cannot be said for patients undergoing their first psychotic episode. This review will briefly describe the NSS that have been commonly reported in patients with schizophrenia, and then concentrate on studies that have specifically investigated NSS at the time of the first psychotic episode.

NEUROLOGICAL SIGNS REPORTED IN SCHIZOPHRENIA

The majority of investigations into patients with schizophrenia at various stages of chronicity have described an excess of neurological 'soft' abnormalities. The term 'soft' was originally used, as opposed to

'hard', to reflect the absence of any obvious localised pathological lesion underlying these signs (Tucker *et al*, 1974; Quitkin *et al*, 1976). This term has been employed, more recently, to indicate signs that do not reflect primary tract or nuclear pathology (Woods *et al*, 1986). Although the categorisation of neurological signs as 'soft' (e.g. frontal release and cerebellar signs) and the batteries used to measure them have varied, neurological abnormalities in schizophrenia seem to be localised to three main neurological domains: integrative sensory function; motor coordination; and motor sequencing (Table 1) (Buchanan & Heinrichs, 1989). Deficits in integrative sensory function (possibly resulting from a parietal dysfunction) are reflected in higher rates of bilateral extinction, impaired audio-visual integration, agraphaesthesia and astereognosis (Buchanan & Heinrichs, 1989; Griffiths *et al*, 1998). Deficits in motor coordination have been reported through tests of general coordination, intention tremor, finger-thumb opposition, balance and gait. Finally, poor performance in complex motor tasks (possibly resulting from a dysfunction of the frontal-basal ganglial circuitry) has been reported in tests that involve repetitive alternating hand positions, such as the fist-edge-palm, the fist-ring and the Ozeretski tests.

Abnormalities have also been reported in eye movements (pursuit and saccadic movements; Stevens, 1982) and developmental reflexes (Boks *et al*, 2000), particularly in signs of frontal release. Other abnormalities, such as those of primary sensory function, have been less often described.

NEUROLOGICAL SOFT SIGNS IN FIRST-EPISODE PSYCHOSIS

Investigating patients at the early stages of the illness has the following potential

Table 1 Functional areas frequently reported as abnormal in schizophrenia, and some of the tests that can elicit disturbances in these areas

Sensory integration	Motor coordination	Motor sequencing	Primitive reflexes
Audio-visual integration	Tandem walk	Fist-ring test	Gaze
Stereognosis	Rapid alternating movements	Fist-edge-palm test	Palmomental
Graphaesthesia	Finger-thumb opposition	Ozeretski test	Snout
Extinction	Finger-nose test		Grasp
Right-left confusion	Rhythm tapping		

*Presented in part at the European First Episode Schizophrenia Network Meeting, Whistler BC, Canada, 27 April 2001.

advantages: it can clarify whether NSS are part of a neurodysfunction that underlies schizophrenia rather than the consequence of degenerative processes; and it can elucidate whether or not they are simply a neuroleptic-induced epiphenomenon (i.e. a consequence of long-term pharmacological treatment).

In considering patients with first-onset psychosis, it is important to note that some studies have included not just patients with schizophrenia but also those with other forms of psychosis. This over-inclusiveness is unavoidable as assessments are frequently performed at the very early stages of a psychotic presentation, when a diagnosis of definite schizophrenia may still be doubtful. Not including cases until they definitely qualify for a diagnosis of schizophrenia at a later stage would mean losing potential cases of schizophrenia from the initial sample. Therefore, for the purpose of this review, we will also include studies that have evaluated first-episode psychosis as a whole.

We decided to evaluate those studies that investigated neurological function in patients with first-episode psychosis using

a clinical examination that specifically reported on the neurological function of this group of patients. We performed a Medline literature search of the period between 1966 and 2001 using the following terms: PSYCHIATRY *and* NEURO*; SCHIZOPHRENIA *and* NEURO*; FIRST EPISODE *and* NEURO*; FIRST EPISODE *and* SOFT-SIGNS; SOFT-SIGNS and NSS. We also examined cross-references from the articles identified.

We identified nine studies, which are listed in Table 2.

First-episode studies of NSS can be divided into: (a) studies that have evaluated the prevalence of NSS among patients with first-episode psychosis only (i.e. without including a comparison group); (b) studies that have evaluated NSS in first-episode patients and compared them with healthy controls; (c) studies that have compared first-episode patients with subjects at high risk of developing psychosis; and finally, (d) studies that have evaluated NSS at first-episode and then at follow-up. Unfortunately, a variety of instruments have been used to evaluate neurological function, and not all studies have used a published,

validated instrument, often reporting on findings derived from a 'clinical neurological assessment', which makes comparison of the results difficult (Table 2).

The prevalence of NSS among first-episode psychosis patients

Studies that evaluated patients with first-episode psychosis have reported a high prevalence of NSS, the percentage of patients with NSS varying from 20% (The Scottish Schizophrenia Research Group, 1987) to 97.1% (Browne *et al*, 2000). The Scottish Schizophrenia Research Group (1987) used the Northwick Park Brief Neurological Assessment (Cunningham Owens & Johnstone, 1980); abnormalities were observed particularly in plantar responses and coordination (as well as weakness in lower limbs), diminished tone in lower limbs and increased ankle and knee jerks.

The study by Browne *et al* (2000) is noteworthy in that information was collected using two validated scales: the Neurological Evaluation Scale (NES; Buchanan & Heinrichs, 1989) and the Condensed Neurological Examination

Table 2 Studies included in this review, listed in alphabetical order

Reference	First-episode patients <i>n</i>	Diagnosis	Healthy controls <i>n</i>	High-risk subjects <i>n</i>	Evaluation scale
Browne <i>et al</i> , 2000	56	Schizophrenia/schizophreniform disorder	–	–	Neurological Evaluation Scale (Buchanan & Heinrichs, 1989) Condensed Neurological Examination (Rossi <i>et al</i> , 1990)
Carr <i>et al</i> , 2000	56	Psychosis	–	60	Neurological Evaluation Scale (Buchanan & Heinrichs, 1989)
Flyckt <i>et al</i> , 1999	21	Schizophrenia	55	–	Standard neurological examination
Johnstone <i>et al</i> , 1990	137	Schizophrenia	–	–	Neurological examination (adapted from Quitkin <i>et al</i> , 1976)
Lawrie <i>et al</i> , 2001	30	Schizophrenia	35	152	Neurological Evaluation Scale (Buchanan & Heinrichs, 1989)
Madsen <i>et al</i> , 1999	34 ¹	Schizophrenia	20	–	Standard neurological examination
Rubin <i>et al</i> , 1994	45	Schizophrenia/schizophreniform disorder	24	–	Standard neurological examination
Sanders <i>et al</i> , 1994	17	Schizophrenia/schizophreniform disorder	15	–	Neurological Evaluation Scale (Buchanan & Heinrichs, 1989)
The Scottish Schizophrenia Research Group, 1987	49	Schizophrenia	–	–	Northwick Park Brief Neurological Assessment (Cunningham Owens & Johnstone, 1980)

1. This study evaluated 34 patients with schizophrenia and 29 patients with other psychiatric disorders at the time of their first admission, and 20 healthy controls. After 5 years, the authors re-investigated 18 patients with schizophrenia, 11 patients with other psychiatric disorders and 10 healthy controls.

(CNE; Rossi *et al*, 1990). The results of the two scales were correlated strongly; at least one NSS (defined as one NES item rated 2) was displayed by 97.1% of patients, with 63% showing at least two NSS (defined as 2 or more NES items rated 2).

The prevalence of NSS in patients with first-episode psychosis in comparison with healthy controls

The prevalence of NSS in healthy subjects has been reported to vary from 5% (Hertzog & Birch, 1968; Rochford *et al*, 1970) to more than 50% (Kennard, 1960; Cox & Ludwig, 1979), the proportion reported being mainly a function of the measure used. It is therefore advantageous to compare the rates of NSS in patients with first-episode psychosis with those of healthy controls, using identical assessment procedures.

Overall, there is a higher prevalence of NSS in first-episode patients compared with healthy controls. In particular, significantly higher total rates of NSS in patients with first-episode schizophrenia or schizophreniform disorder have been reported (Rubin *et al*, 1994; Gupta *et al*, 1995). Moreover, first-episode patients also show a worse performance in: each of the NES sub-scales (Sanders *et al*, 1994); facial expression (Flyckt *et al*, 1999); hypokinesia (Flyckt *et al*, 1999); hand tremor (Flyckt *et al*, 1999); neck tonus (Flyckt *et al*, 1999); and cerebellar signs (Rubin *et al*, 1994).

In the study by Flyckt *et al* (1999), patients with first-episode schizophrenia and patients with chronic schizophrenia were compared as a whole with healthy controls. The patient group reported significantly higher NSS scores than the controls, and although the absolute figures were not reported separately for chronic and first-episode patients, the authors commented that there were no differences between first-episode and chronic patients.

We can conclude that the rates of neurological signs in patients at their first-episode of psychosis are already higher than those of healthy controls. Furthermore, these rates are comparable with those described in studies of schizophrenia as a whole, which have reported an excess of NSS, particularly for motor coordination, in 59–92% of patients (Tucker *et al*, 1975). A higher consistency in rates could be achieved if the assessors were blind to

the subject's status, a task easier to achieve if patients with other psychiatric disorders represent the control group. Considering that NSS rates similar to those observed in schizophrenia have been reported in patients with personality disorder (Rochford *et al*, 1970), it seems important that subjects with schizophrenia are also compared with subjects affected by other putative neurodevelopmental disorders (e.g. obsessive-compulsive disorder, attention-deficit hyperactivity disorder).

The prevalence of NSS in patients with first-episode psychosis in comparison with high-risk subjects

Having established that an excess of NSS is already present in the early phases of psychosis, the next question is whether or not this excess pre-dates the onset of psychosis and thus could be a vulnerability marker for psychosis. Impairments of motor development and fine motor coordination have been observed in children from cohort studies who later go on to develop schizophrenia (Crow *et al*, 1995; Cannon *et al*, 1999). The presence of these abnormalities suggests that neurological dysfunction could reflect a neurodevelopmental abnormality that puts the individuals at risk of later schizophrenia.

Much attention has been devoted to asymptomatic subjects at high genetic risk of schizophrenia, with similar abnormalities having been reported (Rieder & Nichols, 1979; Fish *et al*, 1992; Marcus *et al*, 1993). In one study (Carr *et al*, 2000), subjects at first-episode psychosis were compared with high-risk asymptomatic individuals, and were reported as showing similar NSS rates. In another study, although first-episode patients showed more NSS than high-risk subjects, high-risk subjects had an excess of NSS compared with healthy controls, specifically for signs of sensory integration (Lawrie *et al*, 2001).

These findings suggest that neurological dysfunction observed in first-episode patients is at least in part related to the pathogenesis underlying the illness, and can be observed in association with an increased risk of the disorder, even before the onset of a full-blown psychotic illness (Lawrie *et al*, 2001). This is consonant with reports of neurological abnormalities not only in the relatives of patients with schizophrenia (Kinney *et al*, 1986; Griffiths *et al*,

1998; Niethammer *et al*, 2000), but also in the offspring of parents with schizophrenia (Fish & Hagin, 1973; Marcus *et al*, 1985). In these latter cases, the neurological abnormalities were similar to those described in adult patients: problems in coordination, motor dysfunction and sensory integration (Heinrichs & Buchanan, 1988).

The temporal stability of NSS following the first psychotic episode

If we accept the above evidence that NSS are already present at first onset and indeed in vulnerable asymptomatic high-risk individuals, the question of their temporal stability can only be addressed by follow-up studies.

The only study that we have identified that investigated NSS at both first onset and at follow-up is that of Madsen *et al* (1999). At the time of their first psychotic episode, patients showed a significantly higher total rate of neurological abnormalities than healthy controls. Five years later, the difference between patients with schizophrenia and healthy controls was increased, especially for frontal, corticospinal and temporo-parietal functions. By contrast, patients with other psychiatric disorders showed a reduction in the number of neurological abnormalities at follow-up, indicating that their neurological function improved with remission, although they still showed significantly higher rates of neurological abnormalities than healthy controls, mainly in frontal lobe functions. Thus, this study suggests a progression of neurological dysfunction comparable to that previously reported in chronic patients with schizophrenia (Torrey, 1980), although treatment effects could have contributed to this.

Thus NSS, particularly in motor coordination and in developmental reflexes, are already present in patients at very early stages of the illness. Furthermore, the neurological anomalies shown by patients undergoing their first episode of schizophrenia do not improve with time and may actually deteriorate. A similar neurological dysfunction is present even in high-risk subjects without psychosis. This is in accord with previous evidence that an impairment of motor development and fine motor coordination can predict schizophrenia-spectrum disorders in adulthood (Crow *et al*, 1995), and may be part of a genetically transmitted vulnerability to develop schizophrenia, as suggested by

studies on children at high genetic risk (Rieder & Nichols, 1979; Fish *et al*, 1992; Marcus *et al*, 1993).

NEUROLOGICAL SOFT SIGNS AND FAMILIARITY

Therefore, investigators have studied the relationship between NSS and genetic vulnerability to this illness. An excess of NSS (especially of integrative signs) has been reported in patients with a positive family history for schizophrenia, in comparison with those without such a history (Walker & Shaye, 1982; Griffiths *et al*, 1998), and indeed healthy relatives of patients with schizophrenia (Griffiths *et al*, 1998; Ismail *et al*, 1998; Niethammer *et al*, 2000).

The majority of the first-episode studies reviewed did not evaluate the relationship between neurological function and familiarity. Three studies (Flyckt *et al*, 1999; Madsen *et al*, 1999; Lawrie *et al*, 2001) evaluated family history or genetic loading and neurological function and reported no association between prevalence of NSS and family history. However, a relationship was reported between family history and a specific laterality pattern in psychomotor performance in one study (Flyckt *et al*, 1999), and family history and progression of neurological dysfunction in another (Madsen *et al*, 1999).

In the study by Madsen *et al* (1999), information was obtained on psychiatric disorders in the first- and second-degree relatives. Although there was no association between a positive family history of psychosis and NSS at first presentation, the patients with a history of psychotic disorder in first-degree relatives showed a significant neurological deterioration at follow-up.

The report of no association between positive family history and neurological dysfunction in these first-episode studies is in contrast with previous observation of a relationship between the two reported in patients at various illness stages. However, it is possible that, if a positive family history is associated with more progression in neurological dysfunction, studies of patients in more advanced stages of schizophrenia could have had more chances of identifying this association, less evident in the initial stages of the illness. It is, however, difficult to draw a conclusion from the few studies reported.

LATERALITY AND CEREBRAL DOMINANCE

To date, research has not identified an unequivocal laterality pattern of neurological signs in schizophrenia in general (and by implication a lesion of a particular hemisphere). Some studies have reported a predominance of neurological abnormalities on the right side of the body (Torrey, 1980; Caligiuri & Lohr, 1994), but there are conflicting reports of higher scores for NSS on the left side of the body (Niethammer *et al*, 2000).

The first-onset study of Browne *et al* (2000) evaluated the relationship of mixed-handedness (measured with the Edinburgh Inventory; Oldfield, 1971) to NSS. In the Edinburgh Inventory, subjects are asked to perform 10 common activities and a laterality quotient is then calculated. The authors reported that narrowly defined mixed-handed subjects (two or more discrepancies in hand preference) performed worse on both the NES and the CNE examinations, in comparison with lateralised individuals. Although the number of mixed-handed subjects was small, this raises the possibility that individuals whose handedness is not lateralised have poorer motor coordination than those with a lateralised hand preference. This finding should be interpreted along with the reported excess of mixed-handedness in patients with psychosis, and especially with schizophrenia (Cannon *et al*, 1995; Malesu *et al*, 1996; Orr *et al*, 1999).

Mixed-handedness in schizophrenia has been postulated by Crow (1997) to reflect an abnormality of cerebral dominance. Possible relevant information comes from our preliminary report (Dazzan *et al*, 2001) of a worse neurological performance (especially for coordination and sequencing) on the left side of the body in a group of 145 subjects with first-episode psychosis. A common neurodevelopmental fault can underlie both the excess of mixed-handedness in schizophrenia and that of an abnormal neurological function (possibly lateralised to one side of the body), which was particularly marked in these subjects.

The study by Flyckt *et al* (1999) evaluated both patients with schizophrenia (some at first-episode and some in more advanced stages) and their parents. There were no differences in NSS between patients positive or negative for family history. However, probands and relatives

were also asked to perform the finger-tapping test, a test of psychomotor performance. A significant difference was observed in the laterality pattern of patients and parents who were family-history positive, compared with patients and parents who were family-history negative. More specifically, in this test, patients and parents who were family-history positive improved their performance with the preferred hand, whereas the family-history negative parents neither significantly improved nor decreased their performance with the preferred hand over time. Considering that the finger-tapping test can provide information on cerebral laterality (Gorynia & Uebelhack, 1992), and that an abnormal pattern of hemispheric asymmetry has been reported in families multiply affected by schizophrenia (Sharma *et al*, 1999), it is possible that the association between family history and a specific laterality pattern could reflect an inherited predisposition to this illness.

ROLE OF ANTIPSYCHOTIC MEDICATION IN NEUROLOGICAL PERFORMANCE

Could side-effects of antipsychotic medication in general, and tardive dyskinesia in particular, explain the excess of NSS in subjects with psychosis? No association between past and current neuroleptic exposure and presence of NSS has been found (Ismail *et al*, 1998). Indeed, most studies have failed to find any association between tardive dyskinesia and NSS (Wegner *et al*, 1985; King *et al*, 1991; Mohr *et al*, 1996). In an attempt to control for the possible contribution of neuroleptic medication to NSS, scales for extrapyramidal symptoms, akathisia and tardive dyskinesia have been used in studies of NSS; results have shown that these neurological abnormalities cannot be simply considered a medication effect (Griffiths *et al*, 1998).

However, more definitive information on the effect of antipsychotics on neurological function can be obtained by studying neuroleptic-naïve subjects who have never been exposed to pharmacological treatment, or subjects at their first psychotic episode, who have not been exposed to long-term pharmacological treatment.

Studies on neuroleptic-naïve first-episode patients consistently report higher

NSS rates in these subjects than in healthy controls. Madsen *et al* (1999) compared neuroleptic-naïve subjects with first-episode schizophrenia or schizophreniform disorder with healthy control subjects; neuroleptic-naïve patients showed significantly higher rates of neurological abnormalities than controls. Flyckt *et al* (1999) examined first-episode and chronic patients together. There were no differences in NSS between medicated and non-medicated subjects, except for facial expression. There was no correlation between NSS and either the daily dosage of medication or the length of treatment.

Browne *et al* (2000) reported that the rates of NSS did not differ significantly in neuroleptic-naïve or neuroleptic-treated patients, with 97.1% of neuroleptic-naïve subjects with psychosis showing at least one neurological sign. This rate is much higher than the rate reported from other studies (Gupta *et al*, 1995), and could have been related to differences in the sensitivity of the assessment and the scoring guidelines used. For example, in the study by Gupta *et al* (1995) the assessment did not include signs of frontal lobe dysfunction, which are considered the tests most likely to identify the motor disturbance present in schizophrenia (Manschreck *et al*, 1981). This is also supported by the findings of Cuesta *et al* (1996), who evaluated frontal signs through motor coordination and sequencing of complex motor tasks and reported rates of NSS in neuroleptic-naïve patients as high as those of Browne and colleagues.

Indirect evidence that NSS are not related to neuroleptic treatment also comes from the study of Lawrie *et al* (2001). They reported how the excess of sensory integration signs was similar in both first-episode patients and high-risk subjects, and significantly higher than in healthy controls, suggesting that NSS represent a neurodevelopmental risk factor for schizophrenia rather than being the consequence of having been exposed to neuroleptic treatment.

Surprisingly, some authors have proposed a hypothetical protective effect of antipsychotics on neurological dysfunction. For example, in the follow-up study by Madsen *et al* (1999), there was an increase in NSS in patients with schizophrenia 5 years after their first presentation; this increase was more marked in those patients who had been free of medication for the time of the entire

follow-up. Signs related to the corticospinal tract were over-represented. The authors reported how the neuroleptic load in non-responder patients was inversely related to change in total neurological abnormalities. It is also possible that the positive effect observed is related to the efficacy of antipsychotics on the clinical presentation.

Thus, first-episode studies demonstrate that the neurological dysfunction observed could not be interpreted as the consequence of neuroleptic medication, and one study suggests that antipsychotics may, directly or indirectly, improve the baseline neurological dysfunction. However, it is important that future studies addressing this issue include in their battery signs of frontal lobe dysfunction, because these best reflect the motor abnormalities typical of schizophrenia, rather than those related to neuroleptic use.

NEUROLOGICAL SOFT SIGNS AND DEMOGRAPHIC CHARACTERISTICS

Studies of patients at various stages of schizophrenia other than at first-episode have generally failed to report any consistent association between neurological abnormalities and socio-demographic characteristics of patients (Ismail *et al*, 1998). However, there have been isolated reports of NSS being increased especially in male patients with schizophrenia (Heinrichs & Buchanan, 1988), or more dependent on age and duration of illness (Lane *et al*, 1996; Blyler *et al*, 1997; Malla *et al*, 1997). When trying to disentangle whether these associations are part of the underlying aetiopathological process, or simply its epiphenomena, it is important to control for these variables.

The studies of patients with first-episode psychosis reviewed here reported no relationship between the presence of NSS and age (Sanders *et al*, 1994), but possible relationships have been reported with male gender (The Scottish Schizophrenia Research Group, 1987; Madsen *et al*, 1999), lower education (Rubin *et al*, 1994; Browne *et al*, 2000), and lower socio-occupational outcome (Johnstone *et al*, 1990).

Male patients were described as having a significant increase in the number of neurological abnormalities 5 years after

onset in a follow-up study by Madsen *et al* (1999). In this sample, males were also more likely to have been subjected to maternal obstetric complications and a non-remitting course of the illness. In the Scottish Schizophrenia Research Group's study (1987), most of the non-responders were males with neurological impairment. It is possible that the excess of neurological abnormalities in male patients, together with an increased risk of neurodevelopmental damage and of a generally more severe illness (Castle & Murray, 1991; Bullmore *et al*, 1995), is part of a greater vulnerability of the developing male brain to environmental insults (Murray, 1994).

The presence of a neurodevelopmental abnormality may also explain the reported association between lower educational achievement and higher rates of NSS in first-episode studies (Rubin *et al*, 1994). However, the evidence derived from the study by Browne *et al* (2000) is indirect. In fact, in their study a significant difference in years of education was present between mixed-handed and lateralised patients, with the mixed-handed patients having a significantly lower number of years of completed education. As mixed-handed patients showed more neurological abnormalities, the authors speculated that neurological abnormalities were also associated with lower years of education. These results should be interpreted cautiously; it is likely that patients with more severe forms of the disease, and with higher rates of neurological abnormalities, would have found it more difficult to continue their education.

Nevertheless, the above results are consonant with evidence of an association between IQ and neurological abnormalities, specifically between IQ and signs of sensory integration (Kennard, 1960; Mosher *et al*, 1971; Arango *et al*, 1999). It has been suggested that the concomitant presence of NSS and cognitive deficits in schizophrenia could reflect a diffuse, generalised brain disorder (Kolakowska *et al*, 1985; King *et al*, 1991; Flashman *et al*, 1996). The line between some NSS and selected neuropsychological tests is often difficult to draw: evaluating these together could provide comprehensive information on a range of regional neurological dysfunctions. Even just IQ, which has been extensively evaluated in previous studies, has not been frequently examined in first-episode studies on NSS.

NEUROLOGICAL SOFT SIGNS AND BRAIN STRUCTURAL ABNORMALITIES

Clarifying the relationship between brain structure and neurological dysfunction could point to the anatomical substrates of NSS present in schizophrenia. Unfortunately, only a few studies of chronic patients have examined this relationship. The presence of NSS has been associated with an enlargement of cerebral ventricles (Weinberger & Wyatt, 1982), and with smaller brain areas (DeMyer *et al*, 1988), whereas no correlation has been found between NSS and the calculated ratio between the width of the ventricles and the brain (Kolakowska *et al*, 1985).

Among first-episode studies, the only one that evaluated this relationship was the computerised tomography (CT) study by Rubin *et al* (1994). This study reported an association between NSS and shorter brain length and wider left Sylvian fissure, together with a tendency for patients with more neurological abnormalities to have smaller brain volume, more cerebrospinal fluid in the sulci and cisterna on the brain surface, increased width of the right Sylvian fissure and smaller temporal horn volume. As in previous studies (Kolakowska *et al*, 1985), there was no indication that NSS were associated with greater volume of lateral ventricles. The findings of this study suggest that neurological abnormalities could be associated with cortical rather than subcortical lesions. More studies with large samples, investigating the anatomical correlates of neurological signs specifically selected to explore regional function/dysfunction, are needed before firm conclusions can be drawn.

RELATIONSHIP BETWEEN NSS AND THE PSYCHOPATHOLOGY AND COURSE OF SCHIZOPHRENIA

Previous studies on patients at different stages of their illness have asked whether neurological abnormalities are associated with a specific symptom profile or course of the schizophrenic illness. Some studies have reported a relationship between NSS and different subtypes of schizophrenia, such as chronic *v.* acute schizophrenia (Torrey, 1980) and disorganised *v.* non-disorganised schizophrenia (Schroder *et al*, 1991). Neurological abnormalities have

also been associated with total number of psychiatric symptoms (Tucker & Silberfarb, 1978), thought disorder (Tucker *et al*, 1974, 1975; Manschreck *et al*, 1981, 1982), negative symptoms (Caligiuri & Lohr, 1994; Wong *et al*, 1997) and emotional stability (Quitkin *et al*, 1976). By contrast, other studies have found no association between NSS and positive symptoms (Kolakowska *et al*, 1985), or paranoid/non-paranoid schizophrenia (Manschreck & Ames, 1984).

Similar conflicting results have also characterised studies that evaluated the relationship between psychopathology and NSS in first-episode psychosis. For example, Browne *et al* (2000) described an association between NSS and total symptom severity and positive symptoms whereas others have reported no association with global measures of psychopathology (Sanders *et al*, 1994), or with positive and negative dimensions of schizophrenia (Flyckt *et al*, 1999). A possible reason for the inconsistency of these results lies in the different scale used to measure NSS. For example, Flyckt *et al* (1999) did not use a scale that included factors involving attention and initiative. As Browne *et al* (2000) suggested, the correlation between total NSS and positive symptoms may reflect attentional deficits secondary to untreated symptoms. Not only is the number of first-episode studies small, but some studies also lacked sufficient power to evaluate such associations.

The potential association between the presence of neurological signs and a more chronic and severe form of the illness has also been investigated by studies on patients at different stages of the illness. This has been supported by the association of NSS with young age at onset (Torrey, 1980), a more chronic course (Torrey, 1980), longer index hospitalisation (Rochford *et al*, 1970) and impaired premorbid functioning (Quitkin *et al*, 1976; Kolakowska *et al*, 1985). However, some of these findings have not been corroborated by other studies, in which no association was found with age at onset (Kolakowska *et al*, 1985), poor premorbid functioning (Torrey, 1980; Kolakowska *et al*, 1985), number of total hospitalisations in a 3-year follow-up (Tucker & Silberfarb, 1978) and lifetime hospitalisations (Mosher *et al*, 1971).

The majority of first-episode studies report no correlation between NSS and age at onset (Madsen *et al*, 1999), duration

of untreated psychosis (Madson *et al*, 1999; Browne *et al*, 2000), global assessment of functioning (Sanders *et al*, 1994), and occupational outcome (Johnstone *et al*, 1990). It is possible that factors such as occupational outcome and global assessment of functioning are worse in more advanced phases of the illness, and are therefore not associated with neurological dysfunction in the initial stages. However, two studies described an association between NSS and both poorer premorbid social adjustment (Browne *et al*, 2000) and number of in-patient days (Johnstone *et al*, 1990). These associations could be related to the fact that higher rates of signs are part of a more severe clinical picture, which could for example explain the longer time spent in hospital; it is also possible that this is reflected in longer pharmacological treatment, which could in turn give rise to more NSS.

In conclusion, the studies reviewed confirm that an excess of NSS is already evident in patients suffering their first-episode of schizophrenia or psychosis, and indeed in high-risk subjects without psychosis. Neurological performance appears to be worse in the areas of motor coordination and sequencing, in sensory integration and in developmental reflexes. These minor neurological anomalies are found particularly in males and in subjects with lower education, and possibly in those with a more severe clinical picture. The presence of neurological abnormalities cannot be explained away as a consequence of neuroleptic use, although higher NSS scores are observed in those first-episode subjects on neuroleptic treatment. For an optimal differentiation of the motor disturbance typical of schizophrenia from the side-effects of neuroleptic treatment, it is important that signs of frontal lobe dysfunction are included in the assessment.

First-episode studies also support an association between neurological signs and a specific pattern of laterality, as suggested by their particular excess in mixed-handed subjects, and by some preliminary reports of their lateralisation to one side of the body. This abnormal laterality pattern in psychomotor performance is more frequently accompanied by a positive family history of psychosis, and is present in relatives without psychosis that are positive for family history. It is possible that this could be related to the evidence that, as part of the genetic vulnerability to develop schizophrenia, the cerebral hemispheres develop less asymmetrically. These findings

support the notion that neurological signs mainly result from a genetic vulnerability rather than neurodegeneration, or the consequences of the illness (pharmacological treatment, institutionalisation). Future studies should therefore attempt to identify whether any NSS is specific and discriminative of schizophrenia, as opposed to other psychiatric disorders.

ACKNOWLEDGEMENTS

We thank Drs Ken G. Orr and Brian T. Toone for their useful comments on the manuscript. We are also grateful to the Stanley Foundation and Medical Research Council (UK) for financial support.

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CLINICAL IMPLICATIONS

■ A neurological dysfunction is already evident in patients having their first-episode of schizophrenia or psychosis, and is not the result of illness progression.

■ The presence of neurological abnormalities in schizophrenia cannot be explained away as a consequence of neuroleptic use.

■ The presence of a neurological dysfunction in schizophrenia may contribute to identifying subjects at risk of a poor prognosis, who may benefit from early intervention.

LIMITATIONS

■ The number of studies investigating neurological performance in first-episode psychosis is still small.

■ A variety of instruments have been used to evaluate neurological function, and this makes comparison of the results difficult.

■ The majority of first-episode psychosis studies did not investigate neurological performance separately for the two sides of the body, hampering the understanding of the role of lateralisation in neurological dysfunction.

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