

# NEUROLOGICAL SIGNS AND COGNITIVE IMPAIRMENTS IN SCHIZOPHRENIA

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## SUMMARY

Neurological signs and cognitive impairments are important features of schizophrenic illness. Their investigations may enhance the understanding of the nature and course of deficits associated with schizophrenia. The relationship between neurological signs and cognitive impairments has however not been adequately defined. Recent studies addressing the extent and longitudinal course of neurological signs and cognitive impairments in schizophrenia are reviewed, focusing on information that might clarify the potentially complex relationship between the two domains.

**Key words:** soft neurological signs, neuropsychology, schizophrenia

## INTRODUCTION

Among different lines of evidence suggesting that brain dysfunction underlies schizophrenia, subtle neurological signs and neuropsychological impairments have been consistently reported. Both of them (collectively referred to as neurocognitive impairments) involve quantitative assessment of patient responses to structured tasks. Neurocognitive assessment constitute important tools for understanding the nature of functional deficits associated with schizophrenia. Deficits in neurocognitive functions provide a level of analysis which bridges clinical observations (symptoms, functioning) and neurobiological findings (cerebral blood flow, brain structure).

In the developmental model of schizophrenia, genetic and early environmental events involved in cerebral development contribute to vulnerability factors which predispose an individual to the manifestation of a psychotic illness decades later. Candidate markers for such vulnerability factors include subtle neurological signs and cognitive dysfunction (Marcus et al 1985b; Kolakowska et al 1985; Woods et al 1991), as evidenced by the fact that abnormalities in both areas are detectable in children at high risk for schizophrenia (Rieder & Nichols, 1979; Marcus et al 1985b).

In the study of schizophrenia, neurological signs and cognitive performance have developed from conceptually separate approaches. The precise relationship between them (and their sub-components) remains poorly defined. As both neurological and cognitive domains are likely to be heterogeneous, they probably bear complex relationship with one another. Global correlation between the two domains therefore provides limited information concerning their relationship. It is necessary to study the sub-components within each domain and assess how they relate to one another. In addition, an important issue is whether these impairments run a progressively deteriorating course (dementia hypothesis), or whether they remain stable in time (static encephalopathy hypothesis).

## NEUROLOGICAL SIGNS IN SCHIZOPHRENIA

Various neurological signs have been described in schizophrenia (Rochford et al 1970; Mosher et al 1971; Walker & Green, 1982; Quitkin et al 1976). Though they are consistent with the view that schizophrenia is a brain disease, the full significance of these signs has not been elucidated. Among neurological signs that have been observed to be more prevalent in schizophrenia, the most intensely studied are the soft neurological signs (SNS).

Soft neurological signs refer to any neurological deviation, motor, sensory, or integrative, that does not localize the site of a putative central nervous system lesion (Quitkin et al 1976). SNS have originally been applied in the study of integrative motor and perceptual skills in development. They consist of two main domains: motor coordination and sensory integration. A large number of studies have consistently reported higher prevalence of SNS in schizophrenic samples (Heinrichs & Buchanan, 1988).

The detection of SNS in children at high risk for schizophrenia (Marcus et al 1985b) suggest that SNS may represent a trait marker for vulnerability to schizophrenia. Their quantity and nature appear to remain stable in childhood (Marcus et al 1985a). The presence of SNS in relatives of schizophrenic patients (Rieder & Nichols, 1979; Woods et al 1991; Kinney et al 1991) further suggests that the vulnerability is genetically determined.

It is important that SNS are not considered in isolation of other neurological signs. "Hard" neurological signs, extra-pyramidal signs and dyskinesia are frequently encountered in schizophrenia. Although some of these are related to anti-psychotic medication, it has been suggested that in some cases they may reflect cerebral dysfunction underlying the psychosis (Owens et al 1982). "Hard" signs such as the extensor plantar response can be present in schizophrenia (Rochford et al 1970; Woods et al 1991). Complex disorders of movement (such as

echopraxia, stereotypes etc.) traditionally referred to as "catatonic" (Lund et al 1991), may also be associated with SNS and extrapyramidal signs (EPS) (Manschreck et al 1982).

Despite the potential clinical significance of SNS, few standardized instruments have been developed and many studies adopted individually constructed instruments. Some of the published scales are either restricted to a subset of signs, or are too lengthy for routine clinical use. The Cambridge Neurological Inventory was developed with a view to provide a standardized schedule to enable further neurological assessment of psychiatric patients in routine clinical settings (Chen et al 1995).

The question of whether neurological signs progress with illness duration has not been directly addressed. Kolakowska et al. (1985) failed to find a difference in the number of neurological signs between three schizophrenic patient groups with different duration of illness (less than five years, five to nine years, and more than ten years). In a study of 98 patients and 50 controls, Buchanan and Heinrichs (1989) found no correlation between age and neurological signs. The relationship with the duration of illness was however not reported. In their review, Heinrich and Buchanan (1988) reported that the relationship between age and neurological signs was unclear. Merriam et al. (1990) in a study of neurological signs in 28 schizophrenic patients also did not detect a significant correlation with duration of illness, though the power of the study was limited by the small sample size. In a recent study involving more than 200 schizophrenic patients in Hong Kong, an increase in total neurological signs with age was found, however there was also a corresponding increase in the normal control subjects. The interaction between group and age was not significant. There was no significant relationship between neurological signs and duration of illness. In addition there was no relationship between the score in various subgroups of neurological signs and illness duration, apart from a trend of increased motor coordination signs in patients with more than 25 years of illness (Chen et al 1996a).

The precise relationship between SNS and structural brain abnormality has not yet been clearly defined. Although soft signs are traditionally regarded as having less localizing value compared to conventional 'hard' neurological signs, with increasing understanding of structure-function relationship in the brain, some regional specificity has been argued on theoretical grounds (Heinrichs & Buchanan, 1988). However, the relationship between an individual sign and a cerebral location is still expected to be complex, with a one-to-one mapping being extremely unlikely. More globally, lateral ventricular enlargement on computerized tomography (CT) has been reported to correlate with the presence of SNS, although there have also been negative findings (Kolakowska et al 1985; King et al 1991). A more specific association between a particular subgroup of signs (motor co-ordination) and size of basal ganglia on CT scan has been reported (Schroder et al 1992). A recent study using functional magnetic resonance imaging has identified decreased activation of the supplementary motor cortex (as well as the sensorimotor

cortex) with a reversed lateralization effect as a possible neurophysiological basis for motor coordination soft signs (Schroder et al 1995).

## COGNITIVE IMPAIRMENTS IN SCHIZOPHRENIA

Impaired cognitive performance has often been described in schizophrenia. Impairments that has been addressed included those of individual psychological modules, e.g. attention, memory, language, as well as executive functions (McKenna, 1994). A full account is beyond the scope of the current review. In summary, it is likely that there is a generalized cognitive impairment in schizophrenic patients (Braff et al 1991). It is more subject to contest whether specific impairments can be detected in addition to this generalized impairment (McKenna, 1994). Studies comparing differential deficits in different cognitive modules have suggested differential impairment in functions related to specific cortical regions such as the prefrontal cortex (Goldberg & Weinberger, 1988; Liddle & Morris, 1991; Shallice et al 1991) and the medial temporal cortex (Gruzelier et al 1988; Saykin et al 1991; McKenna et al 1990; Chen, 1994).

There is evidence to suggest that subtle intellectual impairments may be present many years before the onset of overt psychosis. Indeed, it is clear that significant neuropsychological impairment is already present at the first presentation of illness (Bilder et al 1992) though there has been some debate over whether cognitive impairment subsequently runs a deteriorating course. Such a progressive course would suggest a degenerative process, whereas an absence of progression would suggest a static process which occurs around (or prior to) the onset of the psychosis, but remains stable thereafter.

Progression in cognitive impairment in schizophrenia have been systematically studied over the last few decades (Klonoff et al 1970; Schwartzman & Douglas, 1962; Smith, 1964). These studies were conducted however before standardized diagnostic criteria was widely used. There has been few recent longitudinal studies and those conducted tend to suffer from small numbers, high drop-out rates and relatively short follow-up periods. Waddington et al (1990) followed 51 relatively older patients for five years (mean age 57 years) and found no overall decline on a 10-item global cognitive rating. Among cross-sectional studies, Goldstein and Zubin (1990) compared younger and older schizophrenic patients on their performance in the Halstead-Reiten Battery and found no significant difference in the rate of cognitive decline compared with those of controls. Bilder et al (1992) compared 33 first-episode schizophrenic patients with 34 chronic patients in their WAIS-R performance and reported evidence for the progression in cognitive deficit. Similarly Heaton et al (1994) compared neuropsychological deficits in 85 younger, and 35 older early-onset patients, as well as 22 late-onset patients and concluded that deficits were no more marked in patients with longer duration of illness. In a cross-sectional study comparing 74 patients in different age ranges, Goldberg et al (1993) and Hyde et al (1994) reported

no evidence of cognitive decline using an extensive neuropsychological battery. They made the point that cross-sectional studies remain important in the study of progression in cognitive impairment over long time spans, though the inclusion of a control group in future studies would enable an estimation of the effect due to normal aging (1993). In our cross-sectional study of neuropsychological performance in schizophrenic patients compared with controls, we found that illness duration did not affect performance in the WCST, verbal intelligence, attention, verbal fluency. In contrast there were deterioration in memory functions both for verbal and visual domains (Chen et al 1996b).

Prefrontal dysfunction has been postulated to be pivotal to the cognitive difficulties manifested in schizophrenia. Schizophrenic patients have been found to perform poorly on prefrontal function tasks (such as the Wisconsin Card Sorting Test and semantic fluency). Whether the prefrontal dysfunction is progressive is contentious. Set off against the negative findings of Hyde et al (1994) described above, Sweeney et al (1992) compared 27 first episode patients with 33 chronic patients and described poorer semantic fluency and Wisconsin Card Sorting Test performance in the chronic patients. Unfortunately in this study there was no attempt to control for the effect of age and it is difficult to ascertain to what extent the poorer performance was related to aging per se. In our study we did not find progressive deterioration in prefrontal functions in patients with increasing duration of illness (Chen et al 1996b).

## **RELATIONSHIP BETWEEN NEUROLOGICAL SIGNS AND COGNITIVE IMPAIRMENTS IN SCHIZOPHRENIA**

Although there has been few systematic study of the relationship between neurological signs and cognitive functions, a limited number of studies have reported, among other findings, global correlation between neurological signs and neuropsychological impairment in the same sample of schizophrenic patients. Owens and Johnstone (1980) found that there was a modest correlation between cognitive performance and neurological signs (mostly extrapyramidal signs) in 510 schizophrenic patients. However, in a further study involving 120 patients, the same group did not find significant correlation between neurological abnormality and cognitive performance (Johnstone et al 1981). In a small sample of 16 patients, King et al. (1991) reported a strong correlation between total neurological signs and cognitive ability (Spearman coefficient -0.818,  $p < 0.01$ ). In another study involving 37 patients, total score in neurological signs was also found to correlate with a global score in cognitive function (Kolakowska et al 1985). Liddle (1987) further observed that in 47 patients, total neurological signs score correlated with scores in a variety of cognitive tests. With a slightly different design, Merrian et al (1990) divided neurological signs into five groups (prefrontal, parietal, praxis, fine motor coordination, and nonlocalizing) and applied a vocabulary test and a visual

reproduction to the patients. They studied 28 patients and concluded that they could not detect correlation between different groups of signs and cognitive performance. In a more comprehensive study involving 176 patients, neuropsychological performance in patients with and without soft signs was compared. The presence of soft signs was found to be associated with poorer performance in tests entailing motor speed, but not in other areas in the neuropsychological battery (Flashman et al 1996). The study investigated soft signs as a global variable and did not address individual subgroups of soft signs. Taken together, while these studies suggest a potential relationship between neurological signs and neuropsychological impairment, the exact relationship remains unclear. Most of the studies reported so far employed a relatively small number of subjects. Often a single measure was derived from either neurological signs or cognitive performance, or both, potentially masking more specific relationship between smaller unit of analysis within these two domains. In addition, few of the studies considered the potential confounding effects of age and education level in patients. In our study, schizophrenic patients received assessments both of neurological signs and cognitive impairments, correlation analysis showed that SNS (motor coordination, sensory integration and disinhibition) but not other neurological signs were associated with impairments in cognitive functions. Subsequent path analysis revealed that motor coordination signs were specifically related to impairments in prefrontal functions while sensory integration signs were associated with more generalized cognitive impairments. Other groups of neurological signs were not related to cognitive function. We arrived at the conclusion that SNS are specifically related to cognitive impairments in schizophrenia. Subgroups of SNS are associated with specific profiles of cognitive impairments and may differ in underlying pathology: motor coordination signs may reflect prefrontal dysfunction while sensory integration signs indicate more generalized cognitive impairment (Chen et al. 1997).

## **CONCLUSIONS**

Neurological signs and cognitive impairments are both important manifestations of putative traits associated with schizophrenia. Each of the areas consists of sub-components which bear complex relationship with one another. Cross-sectional data so far have not detected significant changes in most areas of neurocognitive impairments with time. This implies that significant deterioration in neurocognitive functions probably occurs early around the onset of the illness and remain stable thereafter. Possible exceptions to this temporal stability are memory functions (both verbal and visuospatial) and to a lesser extent, possibly motor coordination. These areas deserved particular attention in future studies of the course of neurocognitive impairments.

Previous studies in neurocognitive function in schizophrenia have suggested a close relationship between the two domains. More specific characterization of this relationship has been difficult with some inconsistent results. This is partly a result of

the complexity of brain systems and the multiple levels of possible influence. Partly this could be related to the limitations in dealing with inherent heterogeneity in a situation where a small number of highly specialized observations are made in a relatively small number of patients. Studies employing a larger sample size and a greater number of assessment probes have better capability in addressing the relationship between these two domains. Our data suggests that the relationship between soft signs and neuropsychological performance is probably specific. Motor coordination signs are related to attention and verbal fluency (both of these are prefrontal cortical functions). Sensory integration signs are related to verbal performance. Longitudinal studies, with the addition of the temporal dimension, as well as elimination of variance due to inter-subject differences, are likely to be more powerful in delineating relationships between variables.

Future research in neurological signs should probably involve more detailed analysis of the nature of the motor coordination signs. Sensory integration signs probably yield information which overlaps with cognitive performance. In addition, since the results of cross-sectional study suggest the longitudinal stability of neurocognitive impairments in long term illness, it is important to employ a prospective study to describe the onset and early evolution of these impairments.

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