Review Article

Potential Endophenotype for Schizophrenia: Neurological Soft Signs

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Abstract

Introduction: Neurological soft signs (NSS) are suggested as a candidate endophenotype for schizophrenia. This article aims to review relevant literature and discuss the role of NSS in understanding schizophrenia. Methods: This is an update on a review article published in 2003. Articles from 2003 onwards were specifically reviewed and discussed with relevance to the role of NSS as endophenotype for schizophrenia. Results: Consistent data suggest an excess of NSS in schizophrenic patients. NSS appear to be related to schizophrenic symptoms, in particular negative symptoms and disorganisation. Information on NSS and demographic correlates is scarce, and the confounding effects between age, education and intelligence on NSS constitute an important gap in current knowledge. Longitudinal data suggest NSS as both a trait and state variable in the course of disease. NSS are not specific with regard to diagnosis, although there are claims that individual sub-components may be more specific. The weight of evidence raises question on the specificity of NSS for schizophrenia. Conclusions: The usefulness and feasibility of NSS as a specific endophenotype target for schizophrenia is unclear. However, NSS remain an important feature and symptom correlate of schizophrenia. Future research should focus on delineating the effects of NSS from those of confounding demographic variables, and the stability of NSS over the course of illness to elucidate its role in schizophrenia.

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Background

The past decades have witnessed many research endeavours to understand neurological soft signs (NSS) in schizophrenia and its related disorders. These efforts mainly focused on the relationship between NSS and patients' clinical and cognitive features, demographic characteristics, and intelligence, as reviewed by Chen et al in 2003.[1] Recent discussions are suggesting NSS as one of the candidate endophenotypes in schizophrenia.[2-5] However, NSS are also observed in other psychiatric disorders, including personality and mood disorders.[6-8] In this paper, we reviewed our current knowledge on NSS and their correlates in schizophrenic patients. In relation to the ongoing debate on NSS as an endophenotype target, we will consider in particular whether NSS are a trait or state manifestation, and examine findings on its specificity to schizophrenic disorders.

Neurological soft signs are non-localising neurological abnormalities that can be elicited when an individual performs certain simple tasks. An example would be finger-thumb tapping, in which the subject is required to tap the tip of his/her thumb against the rest of the fingers in a consecutive manner repeatedly. Developmentally, young children tend to have difficulties with these signs, which normally resolve with maturation.[9] A decreased ability to manage such manoeuvres is observed in certain clinical populations, in whom NSS may persist or re-emerge.[10]

It is established that NSS are an area of abnormality in schizophrenia and related disorders. An excess in NSS has been demonstrated in first-episode medication-naïve schizophrenic patients,[9,11-21] thus medication side effects cannot completely account for it. Some authors have linked NSS with a history of obstetrics complications.[22,23] Existing data also suggest some heritability: compared with controls and patients, an intermediate prevalence of NSS has been found in healthy monozygotic co-twins[23,24] and first-degree relatives of schizophrenic patients.[4,25-27] Increased NSS is also found in at-risk populations, including individuals who score high on schizotypy.[28] Nevertheless, it is also known that genetic risk only partly determines NSS. For

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example, as noted in a twin-pair study, no difference in NSS was observed between the non-schizophrenic co-twins from monozygotic and dizygotic discordant pairs.[29]

Measuring NSS

Among the available instruments for assessing NSS, more widely used ones include the Neurological Evaluation Scale (NES),[30] the Heidelberg scale,[31] and the Cambridge Neurological Inventory (CNI).[32] More recently, there are attempts to devise instruments that measure specific aspects of NSS, such as the Brief Motor Scale (BMS).[33] Differences in the instruments adopted affect study findings and their interpretations. A very brief summary of the common instruments is given below. A more detailed review of these instruments can be found in the literature (e.g., see Bombin et al[34]).

The NES is a 26-item structured instrument. It allows ratings between 0 and 2, results of which can be interpreted along 3 domains of motor coordination, sequencing of complex motor acts, and integrative sensory function. The Heidelberg scale is a 17-item instrument, rated on a 4-point scale ranging from absent to marked abnormality, along 5 domains of motor coordination, integrative functions, complex motor tasks, right/left and spatial orientation, and hard signs. The CNI covers 3 soft signs domains, including motor coordination, sensory integration, and disinhibition. A rating of 0 indicates no abnormalities; 0.5, 1 and 2 indicate equivocal, abnormal and grossly abnormal responses, respectively. The BMS specifically assesses movements and motor skills in patients with schizophrenia and other psychiatric disorders.[33]

While the use of these instruments in clinical settings has been established, some methodological issues remain. For example, the compression of graded presentations into binary scoring (absence/presence) in some scales may mean that important information being lost in the assessment. Arbitrary quantification may be necessary should the presentation falls intermediately between 2 graded scoring (e.g., mild and severe). On the other hand, with different NSS domains assessed using different scales, results obtained may be difficult to compare across studies.[33]

NSS and Clinical Correlates

Tosato and Dazzan[35] had provided a more detailed review on NSS and symptom correlates in schizophrenia. A number of studies have found a positive relationship between NSS and schizophrenic symptoms.[4,36] In general, the association between NSS and negative symptoms is particularly robust.[4,8,36-41] However, the relationship with positive symptoms is less clear, with contrary findings reported.[42-44] Some authors found NSS correlated with disorganisation but not negative symptoms or hallucination/delusions.[45] It should also be cautioned that some studies have failed to find a relationship between symptoms and NSS.[1,21,46, 47]

NSS and Cognitive Correlates

Despite a few negative reports,[38,48] a substantial body of research has identified lower intelligence to be related to an excess of NSS in schizophrenic patients.[1,13,24,36,39,42,43,49] Chen et al[1] have critically reviewed the issue and noted that in children at high risk of developing schizophrenia, both lower intelligence and higher NSS are observed. The relationship, however, is also evident in conditions outside the schizophrenia spectrum, including children with learning disability and those who are neurologically impaired.[1]

Earlier studies have suggested an association between NSS and general cognitive impairments in schizophrenia,[15,42,50-53] although negative findings have also been reported.[38,54] Some suggested executive dysfunction in particular to be related to more severe NSS.[39,55] However, specific relationship between NSS and cognitive impairments remains poorly understood, as most studies considered single measures derived from a variety of cognitive tests, and confounding factors such as age, education, illness duration and general intelligence were seldom controlled for.

Attempts were thus made to delineate the relationship between individual cognitive tests and specific NSS domains. It should be emphasised that motor NSS were specifically associated with some cognitive impairments in schizophrenia. Flashman et al[48] found that timed motor speed (e.g., Purdue Pegboard task and part B of the trail-making test) correlated with motor coordination (e.g., finger tapping) in schizophrenic patients with NSS, where the effects of lifetime medication, extrapyramidal symptoms and abnormal involuntary movements were controlled for.[48] While NES motor subscale was related to verbal pairs subscale, NES sequencing of complex motor acts was associated with Stroop test and figural memory subscale of the Wechsler Memory Scale.[56] More recently, Sanders et al[57] have suggested that repetitive motor tasks are related to a number of cognitive functions except executive function, while cognitive/perceptual tasks are associated with memory and executive function. Finally, Das et al[58] showed an interesting association between cognitive changes and NSS. They found that schizophrenic patients with few or no NSS at baseline had greater improvements on verbal fluency, memory and psychomotor speed following atypical treatments for 6 months when compared with those with many NSS.

NSS and Demographic Correlates

In exploring NSS as a phenotypic expression of the complex disorder of schizophrenia, their possible relationship with demographic variables needs to be carefully elucidated. Some data are available on the

association with gender, ethnicity, age, and education level.

The majority of data do not support a gender effect on NSS.[1,13,39,42-44,52,59-61]

Few studies have investigated the effect of ethnicity on NSS. From available data, it was found that compared with Caucasians, NSS are more prevalent in African Americans.[30] Increased NSS is also found in Nigerians.[7] In a study comparing Asian and Caucasian patients, no major differences in NSS were found.[1]

The effect of patients' age at examination on NSS remains unclear. While data regarding older age and higher NSS are contradictory,[24,26,42,43,61,62] most of these studies were cross-sectional in design and not well placed to delineate factors that covary with age – for example, as mentioned above, illness duration is related to the patient's age. It has also been questioned whether inconsistencies across studies in patients' age range and approaches used to address potential confounders may explain for the discrepancy in findings.[1,13] More rigorous study designs and analyses are required to clarify the specific effect of age on NSS.

NSS and Structural Neuroimaging

Only a handful of NSS neuroimaging studies have been carried out in schizophrenia. In one study using computerised tomography (CT) in first-episode schizophrenic patients compared with normal controls, NSS correlated significantly with sulcal enlargement and reduced cerebral volume but not ventricular enlargement.[63] Keshavan et al[64] found a correlation between the cognitive/perceptual abnormalities factor and smaller volumes of the left heteromodal association cortex. In studies using magnetic resonance imaging (MRI), Bottmer et al[65] found that smaller cerebellar volumes in the right hemisphere is associated with NSS in remitted first-episode psychosis patients. A more recent study in chronic schizophrenic patients had confirmed Bottmer et al's finding, where cerebellar atrophy was particularly related to the NSS of rhythmic drumming, forefinger-right thumb opposition and forefinger-left thumb opposition tasks.[66] Ho et al[67] also found that in medication-naïve first-episode schizophrenic patients, those showing cerebellar neurological signs have smaller total cerebellar tissue volume than those without. On the other hand, a study using optimised voxel-based morphometry found that motor sequencing signs are negatively correlated with total and regional grey matter volume.[19]

Trait or State Marker: Longitudinal NSS Studies

Based on the above data, some researchers maintain that NSS may serve as a biological marker for schizophrenia and related disorders. It remains inconclusive whether NSS could be a trait or state marker, or both, for the disorders.

Initial evidence for NSS as a trait marker is drawn from findings that show an excess of NSS in schizophrenia independent of medication effects. These came from studies of NSS in first-episode medication-naïve patients[12,20,21,68] and studies that have controlled for conventional antipsychotic medications.[37,69] While these studies seem to indicate trait-like properties of NSS, longitudinal studies are required to confirm the stability of NSS over the course of illness. Results from several such studies are available for evaluation.

Longitudinal data supporting NSS as a trait marker include 2 studies involving chronic patients, which found a relatively stable NSS level throughout the illness course.[62,70] Similarly, in a small study involving first-episode functional non-affective psychosis patients, no significant change in the number of NSS was noted between baseline and 2-year follow-up assessments.[71] Another study involving a larger number of patients also suggested a stable course: Emsley et al[72] measured NSS in 66 drug-naïve first-episode schizophrenic patients, and found a stable pattern of NSS over a 1-year follow-up period.

Bombin et al[73] concluded that there is strong evidence to suggest NSS as a trait feature of schizophrenia. Nevertheless, there is also evidence to suggest that NSS vary across time as the illness evolves. In a 6-week follow-up study of first-episode patients who were medication-naïve at baseline, Scheffer[40] found that NSS are positively correlated with clinical symptom changes, and can be modified by treatment. Bachmann et al[74] studied the level of NSS in schizophrenic patients at presentation and 14 months after a first-episode illness and found a significant decrease at follow-up, although the level was still higher than that of normal population. This was confirmed in another longitudinal first-episode study with a longer follow-up period of 4 years.[8] A recent 2-year follow-up study in 24 early-onset psychosis patients and 30 healthy adolescent controls found a significant decrease in NSS in patients, which was correlated with their symptomatology.[16] Two longitudinal studies in first-episode schizophrenic patients have, on the other hand, shown an increase in NSS at 1-year and 5-year follow-ups.[14,75] Similar results have also been found in chronic schizophrenic patients at 3-year follow-up.[76] In at-risk adolescents with schizotypal symptoms, a 3-year follow-up study found that movement abnormalities significantly elevated over time, which were correlated with prodromal symptom measures across time points.[77] These findings all point to the sensitivity of NSS to changes in disease processes throughout the course of illness, suggesting their possible role as state marker for schizophrenia.

Diagnostic Specificity of NSS

The specificity of NSS for schizophrenia is central to the debate on their eligibility as an endophenotype target. As Keshavan et al have remarked, NSS are "soft" exactly because they are presumed to be diagnostically non-specific (in addition to neurologically non-localising).[64] As NSS are also observed in other conditions, researchers have been attempting to identify domains or items in NSS that can be used to distinguish patients with schizophrenia from those with other disorders.

Using factor analysis, Boks et al[2] have identified 5 NSS domains. In particular, they found that only the movement disorder domain can be used to discriminate mood disorders from first-episode schizophrenia.[2]

Despite tendency to consider NSS as an "endophenotype" for schizophrenia, the amount of evidence that undermines the specificity of NSS in schizophrenia also demands attention. Some studies suggested that NSS is shared by patients with other psychiatric disorders as well as the normal population.[7,8,78,79] For example, Gureje et al[7] found no difference in NSS between patients with schizophrenia and those with major affective disorders. The authors concluded that NSS may actually reflect the level of obstetric care in a community. Whitty et al[8] have similarly been unable to distinguish among the diagnostic groups in their study using NSS, which included schizophrenia, bipolar disorder, and other psychoses. Poyurovsky et al[79] compared patients with obsessive-compulsive disorders (OCD) and groups of schizophrenic patients with or without OCD. The authors noted that the groups scored similarly on the motor sequencing subscale, and concluded that NSS may have limited value as a putative endophenotype.[79]

Conclusions

Although current evidence has posed challenges and unanswered questions about the eligibility of NSS as an endophenotype of schizophrenia, their usefulness as a target feature should not be disregarded. As an area of abnormalities in schizophrenia, assessments of NSS have the advantage of allowing relatively objective ratings and ease of administration, which is valuable in clinical research in which assessment time is usually tight. As part of a comprehensive assessment of the schizophrenic patient, measurement of NSS is vital and in general well received by patients.

Future studies of NSS in schizophrenia should aim to delineate their role while controlling for age, education level and intelligence as important confounders. Longitudinal studies with longer follow-up period may help to elucidate the variability or stability of NSS during the course of illness, as well as the influence of medication and disease phase on NSS level. Quantitative instrumental measurements may also help to delineate the atomic processes underlying soft signs, and further reduction in their complexity should facilitate the identification of potential genotype. It is likely that NSS may emerge as a general endophenotype for a number of disorders rather than a specific endophenotype for schizophrenia.[80] Future studies will shed light on the potential role of NSS as a state or trait variable, while the two are not mutually exclusive.

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