Neurological soft signs in schizophrenia – The past, the present and the future

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ABSTRACT

Clinical neurological abnormalities in patients with schizophrenia have been generally called “Neurological Soft Signs” (NSS). Studies have consistently shown increased NSS in patients with schizophrenia as compared to healthy persons. Early studies were limited by possible confounds of prior neuroleptic medications and illness chronicity. Studies in first episode never treated schizophrenia patients have addressed these confounds. The clinical significance of these findings and the correlation with cognitive dysmetria is the focus of the current review. Relevant literature was obtained using PUBMED and MEDLINE search (1980–2008) and a direct search of reference list of pertinent journal articles. In a 2003 study, neuroleptic-naive schizophrenia patients had significantly more NSS than controls. Patients who were more neurologically impaired had more negative symptoms. Higher NSS scores in treatment-naive schizophrenia patients and the absence of correlation between NSS and illness duration lends support to a neurodevelopmental pathogenesis for schizophrenia. The finding of incoordination and cerebellar signs in most studies also supports the “cognitive dysmetria” explanatory model for schizophrenia. A significant subgroup of patients with schizophrenia may have more neuropathological abnormalities, which predisposes them for a more severe and chronic course of illness. These patients may potentially be identified by clinical neurological examination, which might be very important for prognostication and evolving better methods of treatment for these patients. NSS, by themselves or as a composite index with other neurobiological parameters, hold potential as a candidate endophenotype for schizophrenia.

Key words: Cognitive dysmetria, endophenotype, neurological soft signs, schizophrenia

INTRODUCTION

More than a hundred years after Emil Kraepelin described dementia praecox or schizophrenia as we call it, the fundamental pathogenesis is still unclear. However, more and more research points toward the presence of organic brain pathology in first episode untreated schizophrenia. This makes the neurodevelopmental hypothesis of schizophrenia the primary etiological model at present.

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Cortical–Thalamic–Cerebellar–Cortical Circuit (CCTCC), causing a “cognitive dysmetria” which could explain the diversity of the disturbances in schizophrenia.[5-7]

Studies in this area can be divided into those investigating structural abnormalities and connections and clinical studies. Initial pathological studies and recent neuroimaging studies with increasing levels of refinement have convincingly demonstrated reduction of multiple brain areas in patients with schizophrenia, including the three key elements of the “cognitive dysmetria” model – the frontal lobe, thalamus, and the cerebellum.[8] This will be discussed further in the later part of this review.

Clinical neurological abnormalities like rigidity, gait imbalance, and tremors have been documented in patients with schizophrenia since the time of Kraepelin.[9] These Neurological Soft Signs (NSS) have been generally called “soft” neurological signs, in keeping with their reputed lack of specificity, validity, or localizing value.[10] However, recent research indicates that these “soft” signs may have some measure of neuroanatomical validity.

RECENT REVIEWS AND RATIONALE FOR THIS REVIEW

In a recent review of NSS research, Bombin et al.[11] observed that neurological signs occurred in the majority of patients with schizophrenia independently of demographic and most medication variables, and were strongly associated with negative symptoms and cognitive impairment. They also pointed out that there is evidence that the occurrence of these signs is under genetic control and that these signs may represent a trait feature of schizophrenia.

Another review by Chan and Gottesman[12] has evaluated the evidence for the utility of quantifiable NSS as a potential endophenotype for schizophrenia spectrum disorders. Endophenotypes are the crucial indicators to bridge the gap between the macroscopic level of clinical manifestations and the microscopic level of genomics and brain structures in understanding the etiology of a disorder. Target features are defined as “clinical or neurobiological characteristics that are expressions of the underlying predisposition to the illness”.[13] Neurological abnormalities have been considered as the “target features” that encompass the idea that genetic and non-genetic processes lead to maldevelopment in neurocognitive systems. Neural system abnormalities give rise to both soft signs and cognitive impairments. Chan and Gottesman provide substantial evidence to support the claims that NSS, motor coordination in particular, meet many of the criteria discussed above to evaluate the suitability of the presence of NSS as an endophenotype for schizophrenia.

However, the clinical significance of these findings and the correlation with cognitive dysmetria may merit closer attention. This is the focus of the current review. With this focus, relevant literature was obtained using the following methods: 1) An English language PUBMED and MEDLINE search (1980–2008) using the search terms “Neurological Soft Signs and Psychiatry” and “Neurological signs and Schizophrenia” and 2) a direct search of reference list of pertinent journal articles.

PREVALENCE

Early studies estimated the prevalence of NSS in patients with schizophrenia to be between 50% and 65%, compared with 5% in control groups.[14,15] However, many of these studies were limited by possible confounds of prior neuroleptic medications and illness chronicity. Early studies divided neurological dysfunction into “hard” and “soft” signs. The hard signs included pathological reflexes, cranial nerve abnormalities, motor weakness, unilateral sensory impairment and movement disorders, whereas the soft signs included agraphaesthesia, stimulus extinction and right left confusion.[16] Studies also compared neurological signs between patients with schizophrenia, bipolar disorder, alcohol and drug abuse, and healthy controls where the raters were blind to the diagnosis. It was found that patients with schizophrenia had more of these signs than the other patients as well as controls.[17]

A 2009 meta-analysis of NSS in schizophrenia which reviewed 33 studies in this area found that on average, 73% of patients with schizophrenia perform outside the range of healthy subjects on aggregate NSS measures.[18]

 Relatives of patients with schizophrenia have been found to have significantly greater neurological signs than healthy controls although lesser than patients, suggesting familial basis for these abnormalities.[19] A systematic review and meta-analysis published in 2009 used the Comprehensive Meta-Analysis software package to quantify group differences between schizophrenia patients, non-psychotic relatives of patients, and healthy controls. Quantification of NSS differences yielded a mean effect size of 0.81 for schizophrenia patients and their non-psychotic relatives, and 0.97 for non-psychotic relatives of schizophrenia patients and healthy controls. This study confirmed large group differences in NSS prevalence between patients with schizophrenia, non-psychotic relatives, and healthy controls.[20]

A major problem had been the inconsistent composition of neurological scales and subscales.[10,14] However, most recent studies have used the standardized version of the Neurological Evaluation Scale (NES).[21] the Cambridge Neurological Inventory (CNI),[22] or the Heidelberg Scale.[23] The NES, which has been used by the maximum number of studies, is a 30-item scale with ratings from 0 to 2 for each item, including Annett’s handedness questionnaire.
Motor Scale (BMS) is a recently developed scale which offers faster assessment with good sensitivity and specificity.[24] The recent upsurge of interest in the cerebellum has led to the use of separate scales for cerebellar signs, like the International Cooperative Ataxia Rating Scale (ICARS).[25]

**NSS AND ILLNESS VARIABLES**

There have been attempts to link NSS in schizophrenia to different illness variables as well as other abnormalities in patients and their family members. Kolakowska et al. found an association between the presence of NSS and a history of developmental abnormalities.[26] Other authors have found that neurological signs in a high-risk group of offspring of people with schizophrenia were stable through childhood and adolescence.

An attempt to differentiate responders (n=20) and nonresponders (n=25) with schizophrenia by NSS and neuropsychological tests showed that the NSS scores were the largest difference between the two groups. The component scores appeared to reflect deficits in both frontal and non-frontal areas. Higher NSS scores also significantly correlated with predominance of negative symptoms.[27]

Of the three symptom complexes of schizophrenia, disorganization has been found to be significantly related to NSS total score, sensory integration, and sequential complex movements. The deficit syndrome correlated with sensory integration. No correlation was found between positive symptoms and NSS or drug treatment.[28]

**CLINICAL STUDIES**

**Studies in neuroleptic-naive patients**

Many of the early studies included patients on medication and did not strictly screen out patients with alcohol abuse or dependence. This left some doubts as to the attribution of the neurological findings to possible medication or alcohol effects. Therefore, there was a need to examine patients who were antipsychotic-naive and free from alcohol use to establish the presence of these signs in such individuals. Recently, there has been a renewal of interest and many studies of NSS in first episode neuroleptic-naive schizophrenia have been published. One study with treatment-naive patients (n=26), patients on treatment (n=126) and healthy controls (n=117) found soft signs in 23% of the drug-naive patients and 46% of the medicated patients. Abnormal Involuntary Movements Scale (AIMS) scores and Simpson-Angus Extrapyramidal Symptoms Scale (SAEPS) scores correlated with soft signs in the patients.[29]

A study with 17 neuroleptic-naive patients with first break schizophrenia using the NES found significantly increased NSS in patients than healthy controls.[30] A review of studies examining NSS in first episode psychosis (FEP) revealed that patients showed an excess of NSS over healthy controls, particularly in motor coordination and sequencing, sensory integration and developmental reflexes.[31]

A recent study from our institute examined treatment-naive patients (n=25) and healthy controls (n=21) matched for age, sex, handedness and socioeconomic status. It found significantly more NSS in the patients along with other aberrant indicators of neurodevelopment like Minor Physical Anomalies (MPAs).[32]

**Studies in FEP and the course of NSS over time**

A 4-year follow-up study by Whitty et al. with 171 FEP cases showed that neurological function as measured by NES scores improved significantly over time. Patients whose neurological functioning deteriorated had a longer initial duration of untreated psychosis compared to those who evidenced improvement. At presentation and at 4-year follow-up, NSS were closely related to psychopathology.[33]

In another study, NSS were higher in the FEP group (n=39) than age- and gender-matched controls (n=22), both at baseline and after 14 months. NSS scores did not change in controls, but significantly decreased in patients. Patients who had a favorable course showed more reduction in NSS. Predictors of follow-up NSS scores were baseline NSS scores and compliance with treatment. The authors concluded that NSS may correspond to both genetic liability and the activity of the disease process and may be considered as potential predictors of outcome.[34]

A 3-year follow-up study investigating NSS in FEP (n=93) found that NSS were stable in the 3 years and that NSS were already elevated at the presentation of FEP in medication-naive subjects. The level of NSS was lower for patients with a shorter duration of untreated psychosis. A relationship between NSS and negative symptoms became apparent 1 year after the initial episode.[35]

Prikryl et al. recorded NSS at onset and at 1-year follow-up of 92 patients with FEP. At follow-up, overall severity of the NSS was significantly higher in non-remitters than in remitters. A significant reduction of NSS, with the exception of sensory integration, occurred in remitters.[36]

Mittal et al. treated 19 unmedicated male schizophrenia patients prospectively with haloperidol for 6 weeks. NSS at baseline were significantly associated with baseline positive and negative symptoms. NSS showed a strong trend toward improvement during 6 weeks of the prospective haloperidol trial. Hierarchical linear regression analyses indicated that more severe baseline NSS predicted poorer response to haloperidol treatment.[37]

Chen et al.[38] described a progressive increase over 3 years in these NSS in schizophrenia (n=43), mainly motor...
Cerebellar dysfunction in schizophrenia

Clinical descriptions of “cerebellar” abnormalities abound in the literature from the earliest descriptions of mental illness. A constellation of signs referable to the cerebellum or its connections with other brain areas has been described in patients with schizophrenia as part of the NSS. Saccadic eye movements and disturbed smooth pursuit eye movements have been well described. Saccadic Eye Movement (SEM) dysfunction (measured by instrumentation) was found in 54.6% of the patients with schizophrenia (18/33) as compared with only 6.7% (2/30) of healthy controls. Higher SEM dysfunction was associated with negative symptoms.

These dysfunctions have been ascribed to abnormalities in the anterior vermis of the cerebellum and the fastigial nucleus. Signs of cerebellar and cortical sensory dysfunction have been reported to be higher in patients with schizophrenia as well as their first-degree relatives compared to healthy controls.

Patients with schizophrenia were demonstrated to have facilitated eye blink conditioning compared to control subjects, suggesting an enhanced excitability in the cerebellum as part of a disrupted Cortical-Thalamic-Cerebellar-Cortical Circuit (CCTCC) in schizophrenia. Another study using ketamine in healthy subjects showed significant increase in the number of leading saccades and increased leading saccade ratios for more slowly moving targets. Ketamine has been known to cause abnormalities in eye tracking similar to those observed in patients with schizophrenia and their relatives.

Deshmukh et al. compared clinical signs of cerebellar dysfunction in males with schizophrenia (n=34), alcohol dependence (n=15), and healthy controls (n=28). Patients with schizophrenia had impaired stance with eyes closed, dysdiadochokinesia and gait abnormalities as compared to controls, and more dysdiadochokinesia as compared to patients with alcohol dependence. The presence of dysdiadochokinesia suggested cerebellar dysfunction that is independent of the effects of alcohol. However, signs of gait disturbance and stance in patients may be common to patients with schizophrenia and alcohol dependence. In this context, any study in this area will have to control for the effects of alcohol.

There is a paucity of studies examining cerebellar signs in treatment-naive patients and, among the findings reported above, there is always a question as to whether they can be even partly ascribed to neuroleptic medication. Cerebellar signs had not been explicitly sought for by most investigators studying first episode and treatment-naive schizophrenia, and a standard instrument or rating scale for cerebellar signs had not been used in any of the studies.

In an attempt to address the above concerns, a recent study by our group examined 32 never-treated patients with schizophrenia (n=32) and age-, sex-, handedness-, and education-matched healthy controls (n=32) using comprehensive measures of NSS and cerebellar signs. None of the subjects had used alcohol, and none of the healthy controls had family history of psychosis in first-degree relatives. Subjects were evaluated for NSS using the modified NES. Cerebellar functioning was assessed with the International Cooperative Ataxia Rating Scale (ICARS) for pharmacological assessment of the cerebellar syndrome. The Abnormal Involuntary Movement Scale (AIMS) was used to rate any abnormal involuntary movements in subjects. The Simpson–Angus Extrapyramidal Side Effects Scale (SAEPS) – Short Version was used to measure extrapyramidal symptoms.

The study found that patients had significantly more NSS, cerebellar dysfunction, and extrapyramidal symptoms than controls. A stepwise multiple discriminant analysis identified two ICARS sub-scores to be significant (Kinetic sub-score and Dysarthria sub-score), which accounted for 78% classification. With the leave-one-out method of cross-validation, 75% could be correctly classified using these two variables. Soft signs scores did not correlate with positive symptoms or illness duration. Patients who had cerebellar dysfunction as indicated by ICARS scores had more negative symptoms. This could reflect a neurobehavioral link between the cerebellum and negative syndrome.

NSS and cognition

Motor coordination signs have been shown to be specifically associated with impairments in action and attention inhibition as well as with verbal performance and visual-spatial memory. Sensory integration signs were related...
to a wider range of neurocognitive functions in addition to executive functions and intellectual functioning.

More recent research indicates that there were significant regression relationships between NSS and different domains of neurocognitive functions (executive attention, verbal and visual memory) in a group of patients with schizophrenia and healthy volunteers. The authors speculate that NSS and conventional neurocognitive functions tests may capture very similar constructs or share common neural substrates.

Soft signs and neuropsychological deficits in patients with schizophrenia were found to be strongly associated even after medication, extrapyramidal symptoms, and involuntary movements were controlled for, in a study of 176 patients. The deficits were particularly in tasks that assess motor coordination and timed motor speed.

The question of whether NSS are specific to psychoses or simply an epiphenomenon of the lower general cognitive ability in psychosis was evaluated in a prospective cohort of all individuals presenting with psychoses over 2 years and in a control group from the general population. Higher rates of primary and motor coordination signs were not associated with lower cognitive ability and were found to be specific to the presence of psychosis.

IMAGING STUDIES

Initial CT studies using Ventricle Brain Ratio (VBR) reported that patients with schizophrenia had abnormally large ventricles. Other authors reported findings like reduced total brain volume, reduced total gray matter volume, temporal, parietal, and frontal neocortical reductions, basal ganglia abnormalities, and atrophy of the cerebellar vermis.

Rubin et al. (1994) examined patients with schizophrenia and controls along with computed tomography (CT) scan and regional Cerebral Blood Flow (rCBF). They found significantly more NSS in patients which could not be explained by medication effects. NSS were associated with smaller brain volumes.

Magnetic Resonance Imaging (MRI) studies in the last two decades have shown measurable reduction in gray matter volume in medial temporal lobe structures. A meta-analysis of studies of brain size confirmed a difference between patients with schizophrenia and normal controls in brain size and intracranial volume. Volumes of the parahippocampus, thalamus, and superior temporal gyri were also reduced in patients. Several studies have failed to find a correlation between the length of illness and degree of volumetric reduction, supporting a developmental etiology for these deficits rather than degenerative.

There is recent evidence of the caudate nucleus volume being reduced in neuroleptic-naive schizophrenia. Untreated patients with schizophrenia having spontaneous dyskinesia had a larger lentiform nucleus as compared to the controls. These findings suggest abnormalities in the basal ganglia of never-treated patients with schizophrenia, which correlates with parkinsonian signs and dyskinesia described in such patients.

The three key elements of the “cognitive dysmetria” model – the frontal lobe, thalamus, and the cerebellum – were found to be reduced in patients with schizophrenia in a structural MRI study using deformation-based morphometry. Positron emission tomography (PET) studies have shown a prefrontal–thalamic–cerebellar network that is activated when normal control subjects recall complex narrative material, but is dysfunctional in patients with schizophrenia when they perform the same task.

COMBINED STUDIES AND THE MODEL OF “COGNITIVE DYSMETRIA”

Recent studies attempt to correlate clinically measured NSS to imaging findings to establish a neuroanatomical basis for the signs. In a 2003 study, patients with neuroleptic-naive schizophrenia and non-schizophrenia psychoses were compared on total and factor scores for a reliable subset of NES items. The relationship between the neurological abnormalities and alterations in the relevant brain structures was assessed by MRI.

Factor scores for abnormalities in cognitively demanding and perceptual tasks were markedly higher in the schizophrenia group, relative to both comparison groups, and did not differ between the non-schizophrenia psychoses group and the healthy group. Higher scores for the cognitive/perceptual abnormalities factor were correlated with smaller volumes of the left heteromodal association cortex. This may indicate that cognitive/perceptual neurological signs may have a measure of diagnostic specificity. These abnormalities may reflect discrete neuroanatomical alterations in schizophrenia and may have a localizing value.

Dazzan et al. found that higher NSS were associated with a reduction of gray matter volume of the putamen, globus pallidus and thalamus. Sensory integration deficits were additionally associated with volume reduction in the cerebral cortex, including the precentral, superior and middle temporal and lingual gyri. The findings were independent of antipsychotic exposure. The authors conclude that they may represent a clinical sign of the perturbed cortical–subcortical connectivity that putatively underlies psychotic disorders.
In a 2008 study, patients with FEP on atypical neuroleptics were compared with age- and gender-matched healthy controls using optimized voxel-based morphometry (VBM). NSS were significantly associated with reduced gray or white matter densities in the pre- and post-central gyrus, pre-motor area, middle and inferior frontal gyri, cerebellum, caudate nucleus and thalamus. These associations did not apply for the control group. The conclusion from this study was that the pattern of cerebral changes associated with NSS clearly supports the model of “cognitive dysmetria” with a disrupted cortico–cerebellar–thalamic–cortical circuit in schizophrenia. Also, it indicates that NSS in patients and controls refer to different pathogenetic factors.

Two recent studies using the NES and optimized VBM analyses further illustrate this issue. In the first study, schizophrenia patients (n = 30) and age-, sex-, education- and handedness-matched healthy controls (n = 27) were studied. Logistic regression analysis showed that the Motor Sequencing Signs (MSS) sub-score was as a significant predictor of subject’s status. Prefrontal and temporal cortices, putamen and cerebellum had significant volume deficits in the schizophrenia group. VBM analysis showed MSS sub-score to have significant negative correlation with total and regional gray matter volumes (prefrontal, posterior cingulate, temporal cortices, putamen, and cerebellum) only in schizophrenia patients. Again, the cortical and cerebellar correlates of MSS seem to support the concept of “cognitive dysmetria” in schizophrenia.

The second study compared 30 unmedicated schizophrenia patients and 30 matched healthy controls. The modified NES and ICARS were used for neurological assessment. Patients had significantly more NSS and Cerebellar Soft Signs (CSS) than controls. There were significant gray matter volume deficits in the right and left cerebellum, right and left thalamus, and the right dorsolateral prefrontal cortex (DLPFC). There was a significant negative correlation between CSS scores and left cerebellar gray matter deficits. Higher negative symptom scores were associated with higher NSS/CSS (Venkatasubramanian et al., unpublished data). This finding of all three nodes of CCTCC being reduced in volume further supports the neurodevelopmental theory of “cognitive dysmetria” in schizophrenia. Also, there is a consistent finding of higher rate of CSS in those with a negative syndrome. CSS correlates inversely with left cerebellar volumes, and therefore may a better marker of CCTCC abnormalities than other soft signs.

NSS AS AN ENDOPHENOTYPE FOR SCHIZOPHRENIA

A number of studies have made a case for the viability of NSS as an endophenotype for schizophrenia, summarized by Chan and Gottesman in their 2008 review. The meta-analysis by Chan et al. published in 2009 also supports the argument that NSS are familial in nature, segregate with the illness, and may be valid and useful endophenotypes.

However, it has been pointed out that there are still several criteria that are not satisfied. In view of this, some authors have proposed a “composite endophenotype” by combining NSS with other markers of aberrant neurodevelopment like MPAs, neuropsychological deficits, and emotion recognition deficits in schizophrenia.

In a study published in 2003, patients with schizophrenia (n = 61), non-psychotic parents of these patients (n = 76) and healthy comparison subjects (n = 44) took part in a study comparing NSS and MPA in these groups. Parents were further classified as “presumed carriers” of the genetic loading (n = 26) if they had a first- or second-degree relative with schizophrenia or as “presumed non-carriers” (n = 50). Total NSS and MPA scores, adjusted for age and gender, were significantly related to group status. Presumed carriers showed higher motor coordination and integration sub-scores than presumed non-carriers. A discriminant function analysis based on total NSS and MPA scores correctly classified 71% of non-psychotic parents as presumed carriers or presumed non-carriers. Thus, neurological impairments and slight morphological anomalies seem to be associated with the genetic risk for schizophrenia, even when the disease itself is absent.

A 2008 study co-assessed MPAs and NSS in neuroleptic-naive recent-onset schizophrenia subjects (n = 40) in comparison to healthy control subjects (n = 30) to explore the predictive validity of this composite endophenotype. Schizophrenia subjects had significantly higher frequencies of MPAs and NSS than control subjects. MPA total scores were correlated with greater severity of illness, whereas NES scores did not show any relationship with clinical variables. Schizophrenia and control subjects were most accurately classified (82.9%) when MPAs and NSS were considered as a composite phenotype rather than independently.

Ongoing work on facial emotion recognition deficits in patients with schizophrenia suggests that there are significant differences between patients and healthy controls. This may add another dimension to the proposed composite endophenotype for schizophrenia.

SUMMARY AND CONCLUSIONS

In summary, there is significant evidence to suggest that NSS including cerebellar signs may form an intrinsic part of the syndrome of schizophrenia. This lends strength to the neurodevelopmental hypothesis for the etiopathogenesis of schizophrenia as well as the model of “cognitive dysmetria” to explain some of the features seen in this enigmatic disorder. Also, examination for cerebellar abnormalities in schizophrenia patients might help in objectively identifying...
those with potentially poorer prognosis. NSS can also be considered to be among the candidate neurological and cognitive endophenotypes for schizophrenia (albeit with some caveats). NSS and MPAs seem to be associated with the genetic risk for schizophrenia and could afford greater predictive validity when used as a composite endophenotype in genetic association studies.

Current limitations
Though the psychometric properties of some of the standardized rating scales are acceptable, they are potentially confounded by the significant influence of subjectivity. The development of a more scientific experimental paradigm is an important area of research priority; this can facilitate optimal quantification of NSS and possibly better neuroanatomical localization.

Future directions
• Standardized objective measurement of NSS needs to be implemented to increase the objectivity of the assessment.
• Clinically, agreement on cut-off scores which may indicate possible poorer prognosis can lead to early initiation of effective treatments in these patients.
• Ongoing advances in imaging techniques and kinesiology may help further clarify the underlying neural substrates between NSS and neurocognitive functioning.
• Combining standardized measurement of NSS with MPAs and other areas of dysfunction in schizophrenia like Facial Emotion Recognition Deficits (FERD) may help in improving specificity and also in the development of a viable endophenotype.

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