CNS Spectrums

www.cambridge.org/cns

Neurological soft signs and schizophrenia

Eva-Maria Tsapakis[1,2], Calypso A. Mitkani[3*] and Konstantinos N. Fountoulakis[2]

[1]Agios Charalampos Mental Health Clinic, Heraklion, Greece, [2]Department of Psychiatry, School of Medicine, Faculty of Health Sciences, Aristotle University of Thessaloniki, Thessaloniki, Greece and [3]Department of Neurology, Agios Pavlos General Hospital of Thessaloniki, Kalamaria, Greece

Review

Cite this article: Tsapakis E-M, Mitkani CA, and Fountoulakis KN (2023). Neurological soft signs and schizophrenia. *CNS Spectrums* **28**(6), 657–661.
https://doi.org/10.1017/S1092852923001189

Received: 02 January 2023
Accepted: 07 February 2023

Keywords:
Schizophrenia; neurological soft signs; NSS; neurocognition; endophenotype

Author for correspondence:
*Calypso A. Mitkani, MD
Email: m.calypso11@gmail.com

Abstract

Neurological soft signs (NSS) are likely to represent abnormal neurodevelopment and aberration in neural maturation and connectivity. They may not be unique to schizophrenia, but they appear to be a trait characteristic in psychosis and therefore could serve as an objective measure for the assessment of serious psychiatric disorder in the prodromal phase, at onset, and along the course of the disease. Evidence so far proposes that NSS are independent of antipsychotic treatment and therefore constitute a trait symptom, independent of the illness stage and medication. Somatomotor and somatosensory regions, spatial orientation, and visual processing areas, cerebellum, and basal ganglia are implicated as possible structural substrates of NSS. Several studies have examined the relationship between NSS and schizophrenia positive, negative symptoms and deficit syndrome; however, results have been so far ambiguous. Neurocognitive symptoms have been moderately related to NSS suggesting that neurocognitive deficits may contribute to the construct of NSS. Regardless of the fact that NSS are not unique to schizophrenia but extend across to the schizotypy continuum, they may help identify individuals at risk of developing schizophrenia later in life.

Introduction

Schizophrenia is a rather complex and heterogeneous disorder and its etiology has been a constant cause for debate for decades.[1] According to the neurodevelopmental hypothesis, schizophrenia may involve several pathological processes that begin before the brain approaches its adult anatomical state in adolescence, and are caused by both genetic and environmental factors.[2, 3] The neurodevelopmental hypothesis has gained a lot of support from genetic, imaging, and epidemiological studies.[4] Neurological soft signs (NSS) are likely to represent abnormal neurodevelopment,[5] and aberration in neural maturation and connectivity.[6] The pathophysiology of NSS seems to be related to frontoparietal and cerebellar network dysfunction[7] but a clear neurodysfunctional basis and underlying circuits that are involved are still under investigation.[8, 9] Their presence in children who later develop schizophrenia provides further support for a neurodevelopmental etiology of schizophrenia.[10] NSS are subtle neurological abnormalities in sensory integration, motor coordination, and sequencing of complex motor acts.[11] A meta-analysis investigated the prevalence of NSS in patients with schizophrenia.[12] The authors reviewed 33 studies and found that on average, a substantial 73% of patients with schizophrenia performed outside the range of healthy controls on NSS measures. Theleritis and colleagues[13] investigated the association between NSS and schizotypal personality disorder in 169 Greek Army conscripts and found that NSS were more prominent in the high schizotypy group. Furthermore, Chrobak and colleagues[14] recruited 30 patients with borderline disorder, 30 patients with schizophrenia, and 28 controls to investigate whether NSS could discriminate one condition from another. Data analysis showed that although both conditions scored higher in NSS than healthy controls they did not differ from each other. Similar results derived from earlier studies, Zhao et al.[15] found that although NSS scores could discriminate patients with schizophrenia and bipolar disorder from patients with major depression and healthy control, they failed to differentiate from each other. Additionally, a recent meta-analysis[16] revealed that both disorders share the existence of NSS. Bipolar disorder is characterized by a substantial rise in NSS, which is not as prominent as in schizophrenia. These findings suggest that NSS may not be unique to schizophrenia; however, they appear to be a trait characteristic in psychosis and therefore could serve as an objective measure for the assessment of serious psychiatric disorder in the prodromal phase, at onset and along the course of the disease.[17]

Method of assessment

The clinical role of soft neurological signs in many neuropsychiatric disorders has led to the development of several instruments that vary in both context and psychometric properties. The

binary scoring of some scales may rule out important information during the assessment and the different domains of NSS being measured could end in different results across studies.

Woods scale

The Woods scale comprises 79 items which rate from 0 (absent) to 3 (severe). It also includes coverage of possible etiology that is divided into three categories: medication induced, result of a neurological/psychiatric disorder, or unknown causes.[18] There is no reported information of test–retest reliability to assess internal reliability.

Heidelberger scale

Developed by Schroder et al.[19] the scale comprises 17 items that rate from 0 (absent) to 4 (marked abnormality). The authors reported internal reliability of 0.88 and conducted a factor analysis that revealed five items (motor coordination and complex motor tasks, right/left and spatial orientation, integrative functions, and hard signs).

Neurological evaluation scale

The Neurological Evaluation Scale was developed by Buchanan and Heinrichs[20] to assess neurological impairment specifically for schizophrenia. The battery consists of 26 items that score from 0 (absent) to 2 (extreme), has 4 subscales that measure sensory integration; motor coordination; Sequencing of complex motor acts subscale and "others" that include symptoms such as short-term memory and gaze impersistence. Compton and colleagues[21] conducted an exploratory factor analysis that aimed to identify any latent variables in NES in a sample of 110 individuals that included schizophrenia patients, their relatives, and non-psychiatric controls. Analysis showed that the factors revealed were consistent with the original conceptually-derived subscales suggesting that the total NES score may be more useful when comparing results across studies. Further support for the utility of the NES in studies of neurological deficits in schizophrenia derives from a study by Sewell et al.[22] The authors found that the subscales of NES reflect the intrinsic organization of neurological symptoms as they appear in schizophrenia disorder.

Condensed neurological examination

Condensed Neurological Examination consists of 26 items seven of which are bilateral. The scores of the scale fall from 0 to 1 for unilateral items and 0 to 2 for bilateral, and it has a good interrater reliability of 0.76.[23]

Cambridge neurological inventory

The Cambridge Neurological Inventory comprises 87 items that include not only soft neurological signs but also some extrapyramidal symptoms, catatonia, and tardive dyskinesia.[24] It covers 3 soft neurological signs: motor coordination; sensory integration and disinhibition. Responses rate from 0 (normal) to 2 (grossly abnormal).

Modified quantified neurological scale

The scale in total has 98 items of which 48 measure NSS. Items score from normal (0) to abnormal (2). The scale has a good interrater reliability but lacks test–retest reliability.[25]

Brief motor scale

The brief motor scale was developed to assess the motor impairment domain of NSS in schizophrenia and other psychiatric disorders. It consists of 10 items and factor analysis has identified two factors: motor coordination and motor sequencing. The scale and the subscales showed high internal consistency and test–retest reliability.[26]

The role of antipsychotic medication in neurological soft signs

Chiliza and colleagues[27] conducted a 12-month longitudinal study with a sample of 84 patients with first-episode schizophrenia to assess predictors of non-response to first-line antipsychotic treatment. Non-responders comprised the 12% of the sample who at baseline had more prominent disorganized symptoms, poorer social and occupational functioning, and more prominent NSS. At the endpoint, non-responders had elevated symptomatology, poorer quality of life, and greater cognitive impairments compared to the rest of the study population. The strongest predictors of non-response were prominent NSS at baseline. On the other hand, the potential role of antipsychotic therapy in NSS prevalence in schizophrenia is not fully clear. Antipsychotic treatment often causes the esmergence of extrapyramidal symptoms and/or tardive dyskinesia that appear to be more prominent with first-generation neuroleptic medication.[28,29] These motor symptoms may be either erroneously rated as neurological signs or influence the motor characteristics of NSS. Compton et al.[30] aimed to explore the relationship between tardive dyskinesia and catatonic symptomatology with NSS and symptomatology in 47 patients with the first episode of schizophrenia. Results showed that abnormal movements were associated with age and positive symptoms but there was no relationship with NSS, negative symptom severity, or neurocognition. On the other hand, Peralta and colleagues[31] found that motor coordination was significantly correlated to parkinsonism, dyskinesia, and catatonia but not akathisia. Motor sequencing was associated with parkinsonism and dyskinesia and release signs were related to parkinsonism only. Sensory integration did not correlate to any spontaneous movement disorder. Deficit disorder was independently related to motor sequencing, release signs, and parkinsonism. Emsley and colleagues[32] found that motor sequencing was a strong predictor of persistent dyskinesia at 24 months. Methodological differences in examining NSS may account for any inconsistency in research findings. Whether NSS, extrapyramidal symptoms, and tardive dyskinesia are distinct dimensions of schizophrenia or related ones, may depend on several factors, such as the role of striatal dopamine D2 receptor[33]or shared underlying neurobiological mechanisms. According to the evidence so far, NSS are independent of antipsychotic treatment and therefore constitute a trait symptom, independent of the illness stage and medication.[9,34-37] Finally, better-designed studies that include test–retest measures conducted with antipsychotic-naive patients or patients treated with second-generation neuroleptics, are needed.

https://doi.org/10.1017/S1092852923001189 Published online by Cambridge University Press

Imaging studies

Early back in 1998, Andreasen and colleagues,[38] proposed that a scattered disturbance in the cortico-cerebellar-thalamic-cortical circuit, seen in patients with schizophrenia, could explain the diversity of schizophrenic symptoms and the existence of NSS. Neurological signs have long been considered soft because of the absence of specific localized brain regions. Zhao and colleagues,[15] conducted a meta-analysis of 53 brain imaging studies to examine that hypothesis. Data revealed that NSS were associated with atrophy of the precentral gyrus, the cerebellum, the inferior frontal gyrus, and the thalamus. The findings provided further support for the "cerebello-thalamo-prefrontal" brain network model of schizophrenia and related psychotic disorders. However, to date, is not yet fully understood how NSS, map exactly on the cerebral motor circuit and how they might relate to other movement disorders seen in schizophrenia, since only a limited set of neuroimaging results exists.[39] The neuronal correlates of movement sequencing were investigated in 24 healthy controls and 24 schizophrenia patients using psychophysiological interaction (PPI) and the Granger causality modeling (GCM).[40] Results showed that movement sequencing in schizophrenia is related to aberrant frontoparietal network connectivity with cortical inhibition deficit and abnormal reliance on previous network activity. NSS were examined using the Heidelberg Scale during a whole brain high-resolution magnetic resonance imaging at 3 Tesla in 28 patients with recent-onset schizophrenia. Data showed that cortical thickness changes were associated with higher scores in NSS. Hirjak and colleagues[41] investigated the cerebellar correlates of NSS using the Spatially Unbiased Infratentorial (SUIT) toolbox and found that schizophrenia patients when compared to healthy controls differed in cerebellar volumes. Participants with schizophrenia exhibited significantly smaller cerebellar volumes in both hemispheres than controls, and NSS were associated with white matter but not with grey matter. Another study,[6] showed a statistically significant association of NSS with changes in the white matter of important motor pathways. According to a new systematic review[7] somatomotor and somatosensory regions, spatial orientation, and visual processing areas, cerebellum, and basal ganglia are implicated as possible structural substrates of NSS.

Neurological soft signs and symptomatology

Several studies have examined the relationship between NSS and schizophrenia positive, negative symptoms, and deficit syndrome; however, results have been so far ambiguous. Chan and colleagues[42] recruited 145 first-episode schizophrenia patients of whom 29 were diagnosed with prominent negative symptoms and followed the course of NSS over a period of 1 year. Results showed that patients with prominent negative symptoms exhibited significantly more NSS than patients without negative symptoms. However, the authors pointed out that the number of patients with persistent negative symptoms was so small that it was not feasible to make any meaningful statistical comparisons and interpretations. Hembram et al.[43] compared the NSS in 60 schizophrenia patients with and without first-rank symptoms (ie voices commenting and/or arguing, delusional perception, thought withdrawal, and made volition), 30 first-degree relatives, and 30 normal controls, matched for age, education, and handedness. Data analysis showed that first-degree relatives had significantly lower scores of NSS than schizophrenia patients, and NSS were highly correlated with negative but not with positive symptoms. The authors claimed their results provide further support for the theory that NSS as a trait marker of schizophrenia particularly in those without prominent positive symptoms. Albayrak and colleagues[44] recruited 24 patients with deficit disorder (ie primary and enduring negative symptoms), 42 individuals without deficit syndrome, and 30 healthy controls to examine the prevalence of NSS. The authors found that NSS were more prominent in the deficit group suggesting that they may represent a candidate as an endophenotype for schizophrenia. Similarly, Peralta and colleagues[31] examined the relationship between NSS, spontaneous movement disorders, and symptoms in 20 drug-naïve patients with deficit disorder who were compared to 82 schizophrenia patients without deficit symptoms. Results showed that patients with deficit syndrome revealed higher scores of neurological soft symptoms relative to the non-deficit group. A recent systematic review[45] revealed that patients with a higher burden of NSS, dyskinesias, or parkinsonism experienced poorer long-term functional outcomes.

Neurocognition and neurological soft signs

Neurocognitive symptoms (ie attention and information processing, processing speed, reasoning and problem-solving, social cognition, working memory, verbal and visual learning, and memory) have been moderately related to NSS suggesting that neurocognitive deficits may contribute to the construct of NSS[46] Indeed, Solanki et al.[47] found that the motor domain of NSS had a negative influence on working memory. Later studies have found stronger associations between neurocognition and NSS. Chan and colleagues[48] examined different domains of neurological signs in 157 patients with first-episode schizophrenia and their relationships with neurocognitive functions at baseline and at 6 months. Data showed a stable relationship between neurological signs and neurocognitive deficits over time pointing at potential causal dependencies as the measurement and structure of these relationships appeared to be stable over time. Some years later Feng and colleagues[49] correlated neurocognitive deficits in attention, speed of information processing, and social cognition with sensory integration in patients with schizophrenia and unaffected first-degree relatives, suggesting them as possible endophenotypes.

Neurological soft signs in schizophrenia: a possible endophenotype?

NSS have been proposed as an endophenotype candidate for schizophrenia. The criteria established for candidate endophenotypes are: association with illness in the population (higher prevalence rates of NSS in people with schizophrenia compared to the general population); heritability (how much can be attributed to the genetic variation), state independence (stability across the different stages of the illness), familial association (found in unaffected relatives at a higher rate than in the general population), co-segregation within families (occurs more frequently among the ill relatives of schizophrenia patients compared to healthy relatives).[50]

Xu and colleagues[51] investigated the heritability and familiality of NSS in 267 pairs of monozygotic twins, 124 pairs of dizygotic twins, and 75 pairs of patients with schizophrenia and their non-psychotic first-degree relatives. Data showed significant heritability and familiarity of NSS. In another study[52] which included 262 patients with schizophrenia, 243 healthy controls and 177 healthy first-degree relatives, NSS were more prominent in

https://doi.org/10.1017/S1092852923001189 Published online by Cambridge University Press

first-degree relatives than controls and also in patients with early onset schizophrenia than in those with age of onset after 20 years. Chan and colleagues[42] investigated the effect size of NSS in 738 schizophrenia patients,155 unaffected first-degree relatives of schizophrenia patients, 256 individuals with schizotypal personality disorder (n = 256), 379 patients with other psychiatric disorders, and 1577 healthy individuals. Individuals along the schizophrenia continuum showed higher scores of NSS, compared to other psychiatric patients who had minimal NSS, as well as matched healthy controls. Tripathi et al.[53] compared the prevalence of NSS in 45 patients with schizophrenia, 45 patients with obsessive-compulsive disorder, and 45 matched healthy controls. Data showed that NSS, both as a total score and with individual domains, were significantly higher in the schizophrenia group compared to the other two. Ojagbemi and colleagues[54] conducted a longitudinal study to observe the prevalence of NSS in 84 first-episode patients at baseline, 3 months, and 12 months. Findings showed first that NSS were present in 96.4% of the sample and that from all NSS domains only motor sequencing was found stable across the course of the disease. The authors suggested that motor sequencing appeared to be a trait marker for schizophrenia. In their data, other NSS domains seemed to be associated with the symptomatic stages of schizophrenia. Neelam et al.[50] found a familial association in relation to the presence of NSS between schizophrenia patients and their first-degree relatives than controls; however, the prevalence of NSS was higher in the schizophrenia patients. Chan and colleagues[55] conducted a meta-analysis to determine the magnitude of difference in prevalence rates of NSS between two groups: first-degree non-psychotic relatives of schizophrenia patients and healthy controls and schizophrenia patients and their non-psychotic relatives. Findings showed that NSS was more prominent in individuals with schizophrenia and their relatives than controls. In another study, Chan et al.[56] examined the prevalence of NSS in 64 individuals with schizotypal traits and compared them to 51 controls. The authors found that individuals with schizotypal proneness personality demonstrated a significantly higher prevalence of soft signs than those without. Mechri and colleagues[57] examined the prevalence of NSS of 31 unaffected siblings of individuals with schizophrenia and 60 healthy controls matched according to age, gender, and school level. NSS were more prevalent in unaffected siblings than in controls, and motor coordination and integration abnormalities were found more prevalent in siblings with schizotypal dimensions. These results imply that NSS may be a trait characteristic, in line with the neurodevelopmental hypothesis.[9,52]

Conclusion

Empirical evidence favors the view that NSS have the potential of a possible endophenotype for schizophrenia. Their relationship with negative symptoms, the apparent lack of an association with positive symptomatology, and their presence in antipsychotic naive patients further support the hypothesis of NSS being a trait feature in schizophrenia. Regardless of the fact that NSS are not unique to schizophrenia but extend across to the schizotypy continuum, they may help identify individuals at risk of developing schizophrenia later in life. Finally, despite the fact that evidence so far has shown relative independence of NSS from neuroleptic treatment, their relationship with extrapyramidal symptoms and tardive dyskinesia is far from clear. Overlapping items among scales assessing neurological signs and those evaluating extrapyramidal symptoms and dyskinesia could produce mixed results across studies. There is clearly a need for the development of a new standardized assessment tool with specificity to schizophrenia.

Financial Support. This review received no specific grant from any funding agency, commercial or not-for-profit sectors.

Author Contributions. Conceptualization: E-M.T., K.N.F.; Investigation: E-M.T.; Supervision: E-M.T., K.N.F.; Writing—original draft: E-M.T., C.A.M., K.N.F.; Writing—review and editing: E-M.T., C.A.M., K.N.F.

Disclosures. The authors declare none.

References

1. Gilmore JH. Understanding what causes schizophrenia: a developmental perspective. *Am J Psychiatry.* 2010;**167**(1):8–10.
2. Fatemi SH, Folsom TD. The neurodevelopmental hypothesis of schizophrenia, revisited. *Schizophr Bull.* 2009;**35**(3):528–548.
3. Jaaro-Peled H, Sawa A. Neurodevelopmental factors in schizophrenia. *Psychiatr Clin North Am.* 2020;**43**(2):263–274.
4. Rapoport JL, Giedd JN, Gogtay N. Neurodevelopmental model of schizophrenia: update 2012. *Mol Psychiatry.* 2012;**17**(12):1228–1238.
5. Mittal VA, Dean DJ, Bernard JA, et al. Neurological soft signs predict abnormal cerebellar-thalamic tract development and negative symptoms in adolescents at high risk for psychosis: a longitudinal perspective. *Schizophr Bull.* 2014;**40**(6):1204–1215.
6. Viher PV, Stegmayer K, Bracht T, et al. Neurological soft signs are associated with altered white matter in patients with schizophrenia. *Schizophr Bull.* 2022;**48**(1):220–230.
7. Samson GD, Lahti AC, Kraguljac NV. The neural substrates of neurological soft signs in schizophrenia: a systematic review. *Schizophrenia (Heidelb).* 2022;**8**(1):42.
8. Dazzan P, Murray RM. Neurological soft signs in first-episode psychosis: a systematic review. *Br J Psychiatry Suppl.* 2002;**43**:s50–s57.
9. Bachmann S, Schroder J. Neurological soft signs in schizophrenia: an update on the state- versus trait-perspective. *Front Psychiatry.* 2017;**8**:272.
10. Leask SJ, Done DJ, Crow TJ. Adult psychosis, common childhood infections and neurological soft signs in a national birth cohort. *Br J Psychiatry.* 2002;**181**:387–392.
11. Heinrichs DW, Buchanan RW. Significance and meaning of neurological signs in schizophrenia. *Am J Psychiatry.* 1988;**145**(1):11–18.
12. Chan RCK, Xu T, Heinrichs RW, Yu Y, Wang Y. Neurological soft signs in schizophrenia: a meta-analysis. *Schizophr Bull.* 2010;**36**(6):1089–1104.
13. Theleritis C, Vitoratou S, Smyrnis N, Evdokimidis I, Constantinidis T, Stefanis NC. Neurological soft signs and psychometrically identified schizotypy in a sample of young conscripts. *Psychiatry Res.* 2012;**198**(2):241–247.
14. Chrobak AA, Siwek GP, Siuda-Krzywicka K, et al. Neurological and cerebellar soft signs do not discriminate schizophrenia from bipolar disorder patients. *Prog Neuropsychopharmacol Biol Psychiatry.* 2016;**64**:96–101.
15. Zhao Q, Li Z, Huang J, Yan C, et al. Neurological soft signs are not "soft" in brain structure and functional networks: evidence from ALE meta-analysis. *Schizophr Bull.* 2014;**40**(3):626–641.
16. Bora E, Akgül Ö, Ceylan D, Özerdem A. Neurological soft signs in bipolar disorder in comparison to healthy controls and schizophrenia: a meta-analysis. *Eur Neuropsychopharmacol.* 2018;**28**(11):1185–1193.
17. Dimitri-Valente G, Rigucci S, Manfredi G, Girardi P, Ferracuti S. [Neurological soft signs: meaning and relevance along the course of psychiatric illness. an objective and rapid screening for psychosis?]. *Riv Psichiatr.* 2012;**47**(6):465–478.
18. Woods BT, Kinney DK, Yurgelun-Todd D. Neurologic abnormalities in schizophrenic patients and their families. I. Comparison of schizophrenic, bipolar, and substance abuse patients and normal controls. *Arch Gen Psychiatry.* 1986;**43**(7):657–663.

https://doi.org/10.1017/S1092852923001189 Published online by Cambridge University Press

19. Schröder J, Niethammer R, Geider FJ, et al. Neurological soft signs in schizophrenia. *Schizophr Res.* 1991;**6**(1):25–30.
20. Buchanan RW, Heinrichs DW. The neurological evaluation scale (NES): a structured instrument for the assessment of neurological signs in schizophrenia. *Psychiatry Res.* 1989;**27**(3):335–350.
21. Compton MT, Bercu Z, Bollini A, Walker EF. Factor structure of the neurological evaluation scale in a predominantly African American sample of patients with schizophrenia, unaffected relatives, and non-psychiatric controls. *Schizophr Res.* 2006;**84**(2–3):365–377.
22. Sewell RA, Perry EB Jr, Karper LP, et al. Clinical significance of neurological soft signs in schizophrenia: factor analysis of the neurological evaluation scale. *Schizophr Res.* 2010;**124**(1–3):1–12.
23. Rossi A, De Cataldo S, Di Michele V, et al. Neurological soft signs in schizophrenia. *Br J Psychiatry.* 1990;**157**:735–739.
24. Chen EY, Shapleske J, Luque R, et al. The Cambridge neurological inventory: a clinical instrument for assessment of soft neurological signs in psychiatric patients. *Psychiatry Res.* 1995;**56**(2):183–204.
25. Convit A, Volavka J, Czobor P, de Asis J, Evangelista C. Effect of subtle neurological dysfunction on response to haloperidol treatment in schizophrenia. *Am J Psychiatry.* 1994;**151**(1):49–56.
26. Jahn T, Cohen R, Hubmann W, et al. The brief motor scale (BMS) for the assessment of motor soft signs in schizophrenic psychoses and other psychiatric disorders. *Psychiatry Res.* 2006;**142**(2–3):177–189.
27. Chiliza B, Asmal L, Kilian S, Phahladira L, Emsley R. Rate and predictors of non-response to first-line antipsychotic treatment in first-episode schizophrenia. *Hum Psychopharmacol.* 2015;**30**(3):173–182.
28. Peluso MJ, Lewis SW, Barnes TR, Jones PB. Extrapyramidal motor side-effects of first- and second-generation antipsychotic drugs. *Br J Psychiatry.* 2012;**200**(5):387–392.
29. Rummel-Kluge C, Komossa K, Schwarz S, et al. Second-generation antipsychotic drugs and extrapyramidal side effects: a systematic review and meta-analysis of head-to-head comparisons. *Schizophr Bull.* 2012;**38**(1):167–177.
30. Compton MT, Fantes F, Wan CR, Johnson S, Walker EF. Abnormal movements in first-episode, nonaffective psychosis: dyskinesias, stereotypies, and catatonic-like signs. *Psychiatry Res.* 2015;**226**(1):192–197.
31. Peralta V, Moreno-Izco L, Sanchez-Torres A, García de Jalón E, Campos MS, Cuesta MJ. Characterization of the deficit syndrome in drug-naive schizophrenia patients: the role of spontaneous movement disorders and neurological soft signs. *Schizophr Bull.* 2014;**40**(1):214–224.
32. Emsley R, Turner HJ, Oosthuizen PP, Carr J. Neurological abnormalities in first-episode schizophrenia: temporal stability and clinical and outcome correlates. *Schizophr Res.* 2005;**75**(1):35–44.
33. Corripio I, Ferreira A, Portella MJ, et al. The role of striatal dopamine D2 receptors in the occurrence of extrapyramidal side effects: iodine-123-iodobenzamide single photon emission computed tomography study. *Psychiatry Res.* 2012;**201**(1):73–77.
34. Fountoulakis KN, Panagiotidis P, Kimiskidis V, Nimatoudis I. 12-month stability of neurological soft signs in stabilized patients with schizophrenia. *Nord J Psychiatry.* 2019;**73**(7):451–461.
35. Fountoulakis KN, Panagiotidis P, Kimiskidis V, Nimatoudis I, Gonda X. Neurological soft signs in familial and sporadic schizophrenia. *Psychiatry Res.* 2019;**272**:222–229.
36. Prikryl R, Ceskova E, Kasparek T, Kucerova H. Neurological soft signs and their relationship to 1-year outcome in first-episode schizophrenia. *Eur Psychiatry.* 2007;**22**(8):499–504.
37. Chen EY, Hui CL, Chan RC, et al. A 3-year prospective study of neurological soft signs in first-episode schizophrenia. *Schizophr Res.* 2005;**75**(1):45–54.
38. Andreasen NC, Paradiso S, O'Leary DS. "Cognitive dysmetria" as an integrative theory of schizophrenia: a dysfunction in cortical-subcortical-cerebellar circuitry? *Schizophr Bull.* 1998;**24**(2):203–218.
39. Walther S. Psychomotor symptoms of schizophrenia map on the cerebral motor circuit. *Psychiatry Res.* 2015;**233**(3):293–298.
40. Zemankova P, Lungu O, Huttlova J, et al. Neuronal substrate and effective connectivity of abnormal movement sequencing in schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry.* 2016;**67**:1–9.
41. Hirjak D, Kubera KM, Wolf RC, et al. Local brain gyrification as a marker of neurological soft signs in schizophrenia. *Behav Brain Res.* 2015;**292**:19–25.
42. Chan RCK, Geng F-l, Lui SSY. et al. Course of neurological soft signs in first-episode schizophrenia: relationship with negative symptoms and cognitive performances. *Sci Rep.* 2015;**5**:11053.
43. Hembram M Simlai J, Chaudhury S, Biswas P. First rank symptoms and neurological soft signs in schizophrenia. *Psychiatry J.* 2014;**2014**:931014
44. Albayrak Y, Akyol ES, Beyazyüz M, Baykal S, Kuloglu M. Neurological soft signs might be endophenotype candidates for patients with deficit syndrome schizophrenia. *Neuropsychiatr Dis Treat.* 2015;**11**:2825–2831.
45. Pieters LE, Nadesalingam N, Walther S, van Harten PN. A systematic review of the prognostic value of motor abnormalities on clinical outcome in psychosis. *Neurosci Biobehav Rev.* 2022;**132**:691–705.
46. Chan RCK, Wang Y, Wang L, et al. Neurological soft signs and their relationships to neurocognitive functions: a re-visit with the structural equation modeling design. *PLoS One.* 2009;**4**(12):e8469.
47. Solanki RK, Swami MK, Singh P. An examination of relationship between neurological soft signs and neurocognition. *Asian J Psychiatr.* 2012;**5**(1):43–47.
48. Chan RCK, Dai S, Lui SSY, et al. Re-visiting the nature and relationships between neurological signs and neurocognitive functions in first-episode schizophrenia: an invariance model across time. *Sci Rep.* 2015;**5**:11850.
49. Feng Y, Wang Z, Lin G, Qian H, et al. Neurological soft signs and neurocognitive deficits in remitted patients with schizophrenia, their first-degree unaffected relatives, and healthy controls. *Eur Arch Psychiatry Clin Neurosci.* 2020;**270**(3):383–391.
50. Neelam K, Garg D, Marshall M. A systematic review and meta-analysis of neurological soft signs in relatives of people with schizophrenia. *BMC Psychiatry.* 2011;**11**:139.
51. Xu T, Wang Y, Li Z, et al. Heritability and familiality of neurological soft signs: evidence from healthy twins, patients with schizophrenia and non-psychotic first-degree relatives. *Psychol Med.* 2016;**46**(1):117–123.
52. Chen BY, Tsai IN, Lin JJ, et al. Risk model assessment in early-onset and adult-onset schizophrenia using neurological soft signs. *J Clin Med.* 2019;**8**(9):1443.
53. Tripathi R, Soni A, Tyagi A, Mehta S, Gupta S. Comparative study of neurological soft signs in patients with schizophrenia or obsessive-compulsive disorder, and healthy controls. *East Asian Arch Psychiatry.* 2015;**25**(2):64–72.
54. Ojagbemi A, Esan O, Emsley R, Gureje O. Motor sequencing abnormalities are the trait marking neurological soft signs of schizophrenia. *Neurosci Lett.* 2015;**600**:226–231.
55. Chan RCK, Xu T, Heinrichs RW, Yu Y, Gong QY. Neurological soft signs in non-psychotic first-degree relatives of patients with schizophrenia: a systematic review and meta-analysis. *Neurosci Biobehav Rev.* 2010;**34**(6):889–896.
56. Chan RCK, Wang Y, Zhao Q, et al. Neurological soft signs in individuals with schizotypal personality features. *Aust N Z J Psychiatry.* 2010;**44**(9):800–804.
57. Mechri A, Gassab L, Slama H, Gaha L, Saoud M, Krebs MO. Neurological soft signs and schizotypal dimensions in unaffected siblings of patients with schizophrenia. *Psychiatry Res.* 2010;**175**(1–2):22–26.