Neurological signs at the first psychotic episode as correlates of long-term outcome: results from the AESOP-10 study

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Abstract

Minor neurological signs are subtle deficits in sensory integration, motor coordination and sequencing of complex motor acts, present in excess in the early stages of psychosis. Still, it remains unclear whether at least some of these signs represent trait or state markers for psychosis, and whether they are markers of long-term disease outcome of clinical utility.

We examined the relationship between neurological function at illness onset assessed with the Neurological Evaluation Scale, and subsequent illness course in 233 patients from AESOP-10, a 10-year follow up study of a population-based cohort of individuals recruited at the time of their first episode of psychosis in the UK. In 56 of these patients we also explored changes in neurological function over time. We included a group of 172 individuals without psychosis as controls.

After ten years, 147 (63%) patients had developed a Non-Remitting course of illness, and 86 (37%) a Remitting course. Already at first presentation, patients who developed a Non-Remitting course had significantly more Primary, Motor Coordination, and Total signs than both Remitting patients and healthy controls. While Motor Coordination signs did not change over time, rates of Primary, Sensory Integration and Total signs increased, independently of illness course type.

These findings suggest that motor coordination problems could be a useful early, quick and easily detectable marker of subsequent clinical outcome. With other motor abnormalities, a measure of motor incoordination could contribute to the identification of the most vulnerable individuals, who could benefit from targeted and more assertive treatment approaches.

INTRODUCTION

Minor neurological signs are subtle deficits in sensory integration, motor coordination and sequencing of complex motor acts present in excess in the early stages of affective and non-affective psychoses, and even in drug-naïve patients[1]. Still, it remains unclear whether these signs represent trait or state markers of psychosis, and whether they are markers of long-term disease outcome of clinical utility.

Minor neurological signs are already present at illness onset with moderate to large effect sizes of impairment in patients and first-degree relatives with no psychosis[2], and may even precede the onset of psychosis, suggesting that they have a neurodevelopmental origin. As such, they may represent illness traits and endophenotypes[3, 4]. This is further supported by evidence that although often described as "soft", these signs have consistent brain morphometric and functional correlates, including the pre- and postcentral gyri, premotor and frontal gyri, inferior parietal lobule, temporal gyri and insula, thalamus and basal ganglia, and cerebellum[5-10]. Crucially, recent studies have also shown that sensorimotor dysfunction, proposed to be a primary domain of psychosis, is associated with aberrant connectivity of sensorimotor areas[11], iron loadings in the left accumbens[12], and volumes of medulla oblongata and pons[13]. Furthermore, multimodal imaging data have shown that gray matter volume alterations co-occur with aberrant brain activity in cortical and cerebellar systems subserving sensorimotor dynamics and psychomotor organization, pointing to a defined pathophysiological substrate for sensorimotor dysfunctions and contributing to their definition as potential biomarkers for psychosis[14].

Still, whether neurological signs, and sensorimotor dysfunction in particular at illness onset are a marker of long-term clinical and functional psychosis outcome remains to be established. Only two studies have explored their ability to predict outcome ten years after illness onset, but neither evaluated their stability over time[15, 16]. In these, Cuesta and colleagues[15] found that signs scores six months after onset predicted poorer psychosocial functioning, while White and colleagues[16] found that signs at onset just predicted service dependency, and only in patients with schizophrenia or schizoaffective disorder they predicted functional outcome.

More studies have evaluated neurological signs in relation to shorter term outcomes, with some also exploring their trajectories, with inconsistent results, possibly due to inclusion of small and heterogeneous clinical samples, and use of different neurological scales and outcome criteria. The study with the longest follow up evaluated neurological signs trajectories over 5 years in 17 first episode psychosis patients, finding that while total neurological signs did not change, baseline primitive reflexes predicted subsequent poorer functional outcome[17]. Other, shorter longitudinal studies also found no change in signs over time in first episode patients, although they reported higher rates in association with more negative symptoms[18, 19], higher antipsychotic dose[20], or improvement in psychopathology[21]. In contrast, others found an increase in signs, for example in patients with a non-remitting illness over two[20] and five years[22]. Finally, several have also described a decrease in signs after illness onset, with a meta-analysis reporting that fourteen out of seventeen studies observed a decrease in signs over time, in parallel with symptomatic remission[23]. This was replicated recently in a large study of 349 patients, where a reduction in signs over one year correlated with an improvement in psychopathology and functioning, and rates at baseline predicted lack of treatment response[24]. Of note, several studies reported that such reductions are more evident for sensorimotor signs[21, 25], in association with better clinical outcomes at one year[25] and six months[26], and even in children and adolescents with early onset psychosis[27].

Taken together, these findings confirm the significance of neurological signs, and particularly of sensorimotor deficits as one of the core dimensions of psychosis[28]. Motor signs are easily quantifiable, and their potential link with illness outcomes makes them useful candidate markers for the prediction of long-term trajectories of psychosis course.

In this study, we examined the relationship between multiple domains of neurological function at psychosis onset and ten-year outcomes. We additionally examined change in signs during this time in a subset of these patients. To our knowledge, this is the first, large longitudinal study (n=233 patients) to examine neurological function at first episode of any psychosis across multiple functional domains, and over a long duration of illness. We hypothesised that higher motor neurological signs at onset, and their persistence over time would be associated with a non-remitting illness course over the first ten years of illness, reflective of their potential neurodevelopmental origin and of their role as early markers of long-term illness severity.

METHODS

This study was conducted as part of the AESOP-10 study (Aetiology and Ethnicity in Schizophrenia and Other Psychoses), a ten-year follow-up of a cohort of 557 patients, who consecutively presented to secondary mental health services in South East London, Nottingham and Bristol (United Kingdom) for the first episode of a functional psychotic illness (ICD-10 F10-19; F20-29 and F-30-39, psychotic coding)[29]. A detailed overview of the follow-up procedures in the AESOP-10 study has been published elsewhere[30, 31]. The study also recruited a group of 172 individuals without psychosis, aged 16 to 64 years, as a control group. All controls were screened for the presence of psychotic symptoms with the Psychosis Screening Questionnaire[32] and excluded if they rated positively. All participants gave written consent and ethical approval was granted by the local Ethical Committee.

Baseline assessment

At baseline, socio-demographic and clinical information were obtained for all subjects. Handedness was assessed with the Annett Hand Preference Questionnaire[33]. Premorbid Intelligence Quotient (IQ) was estimated with the National Adult Reading Test (NART)[34] and current full-scale IQ was assessed using a shortened form of revised Wechsler Adult Intelligence Scale (WAIS-R). For patients, diagnoses were made according to the International Classification of Disease (ICD)-10 Criteria[29] using the Schedules for Clinical Assessment in Neuropsychiatry[35], based on consensus meetings with senior clinicians. Age of illness onset was evaluated with the Personal and Psychiatric History Schedule (PPHS)[36], based on interviews with the patient, a close relative and clinical notes. Duration of untreated illness (DUP) was defined as the period in weeks from onset of psychotic phenomena to first contact with statutory mental health services. Duration of illness was then defined as the time between onset of symptoms and time of assessment. Antipsychotic type and dose (in chlorpromazine equivalents) were also recorded.

Follow-up assessment and illness course

Information on course of illness and symptom history were obtained retrospectively at follow up, using an extended version of the WHO Life Chart[37], based on case notes and clinical interview with patients and treating clinicians whenever possible. In interviews we used significant anchor dates to assist recall and, as appropriate, interviews were structured around key events, such as hospital admissions. The Schedules for Clinical Assessment in

Neuropsychiatry (SCAN)[35]criteria were used to establish absence or presence of psychotic symptoms over the follow-up period, consistent with WHO and other long-term outcome studies[38]. Following the Schizophrenia Working Group Remission criteria[39], we adopted a six-month period for establishing remission on the basis of absence of overt psychotic symptoms (operationalized as score of 2 or 3 on Rating Scale 2 in the SCAN; 0=absence, 1=symptom occurred, but fleeting, 2=symptom definitely present, 3=symptom present more or less continuously). From the WHO Life Chart, we used illness course type to classify patients into "Non-Remitting", those with a more severe course (in the Life Chart, those with a Continuous or Intermediate illness course, the former defined as having no periods of symptom remission greater than six months, and the latter as having at least one illness episode and one period of remission greater than six months) or "Remitting", those with a more benign course (in the Life Chart, those with an Episodic illness course, defined as having one or more periods of remission greater than six months, and no episode of psychosis, including the first one, lasting six months or more). Level of functioning was assessed using the Global Assessment of Functioning (GAF)[40] which rates psychological, social and occupational functioning. We recorded the number of weeks of treatment with antipsychotics from starting to stopping medications across the whole follow up, through face-to-face interviews and evaluation of patients' records. We also estimated the proportion of the time patients could be considered adherent to medications over the follow up using clinical notes and the WHO Life Chart.

Neurological Signs

Neurological function was assessed at baseline and at follow up with the expanded and previously validated version of Neurological Evaluation Scale (NES)[41, 42]. For individuals with FEP, the first assessment of neurological abnormalities was performed as soon as possible after initial presentation. The expanded version of NES is a structured scale providing scores in four sub-scales reflecting different functional areas and demonstrating good construct validity[41, 43]: 1) Primary neurological dysfunction (dysfunction that can be identified by a standard neurological examination); 2) Sensory Integration dysfunction (dysfunction apparent in integration of sensory information); 3) Motor Coordination dysfunction (reflecting signs of motor incoordination); 4) Motor Sequencing dysfunction (reflecting the ability to perform complex motor sequences).

Scores for the items present in the original NES (included in the three subscales Sensory Integration, Motor Coordination and Motor Sequencing) were left unchanged (from 0=no abnormality to 2=marked impairment, except for the snout and suck reflexes, scored as either 0 or 2). The remaining items (in the Primary signs subscale), were scored as 0=no abnormality; 1=intermediate criterion; 2=clearly abnormal/marked impairment[42]. Minor neurological signs were rated by physicians blind to diagnosis reaching a good inter-rater reliability (r=0.87 to 0.96). Each sub-scale was analysed separately in order to provide a better representation of the different neurological dysfunction than the global score.

We evaluated extra-pyramidal symptoms with the Simpson-Angus Rating Scale[44], akathisia with the Barnes rating scale[45], and tardive dyskinesia with the Abnormal Involuntary Movement in Schizophrenia scale (AIMS)[46].

Statistical Analysis

Descriptive data are presented as individual values, mean ± standard deviation (SD). Sociodemographic and neurological signs differences between groups were compared using unpaired t-test, ANOVA, or chi-square test, as appropriate. We repeated these comparisons of neurological function using ANCOVA to account for potential confounders including age, sex, ethnicity, and IQ. To estimate changes in neurological signs over time, we performed a repeated measure ANOVA in individuals with both a baseline and a follow up assessment. Correlation analyses were used to investigate correlations between factors. A hierarchical linear regression was used to explore whether neurological signs at baseline predicted functioning at follow up, over and above employment status at baseline. All statistical tests were two-tailed. Statistical analyses were carried out using the Statistical Package for Social Sciences (SPSS) version 23.

RESULTS

For 233 patients who had a baseline neurological assessment there were also data on illness course. Of these, 147 (63%) fulfilled criteria for a Non-Remitting course of illness, and 86 (37%) for a Remitting course. Demographic and clinical characteristics of both patient groups and healthy controls are shown in Table 1. The Non-Remitting group included significantly more males than the Remitting and control groups. Both psychosis groups were slightly younger, less likely to be White British, and had a lower premorbid and full-scale IQ than controls. Non-Remitting patients also had a significantly lower premorbid and full-scale IQ than Remitting patients (Table 1). Finally, the Non-Remitting group included a higher proportion of individuals with a diagnosis of schizophrenia, had more positive and negative symptoms, and less hypomanic symptoms at baseline, and had significantly lower GAF-s and GAF-d scores at follow up than the Remitting group (Table 1).

[Table 1]

Approximately ten years later (mean 9.1 years, SD 2.1), we obtained a second neurological assessment in 56 patients. These individuals were similar to those who only had a baseline assessment in premorbid IQ (NART 99 vs 97 respectively) and illness course (Remitting 36% vs 37% respectively), but were slightly younger (28 years vs 32 years of age), less likely to be White British (48 vs 60%), more likely to be males (62% vs 52%) and to have a diagnosis of non-affective psychosis (62 vs 46%). Healthy controls were assessed only once at baseline.

Relationship between baseline neurological signs scores and illness course
At baseline, individuals who subsequently became Non-Remitting already showed significantly more neurological signs than both Remitting individuals and controls. The one-way ANOVA identified significant between-group differences for Primary signs (F=15.3; df=2; p<0.001), Motor Coordination (F=48.1; df=2, p<0.001), Motor Sequencing (F=5.4; df=2; p=0.005) and Total signs (F=27.1; df=2; p<0.001). The post-hoc analysis revealed that this was due to the Non-Remitting group showing higher scores than the Remitting group for Primary signs (p=0.030), Motor Coordination (p=0.001) and Total signs (p=0.001) than the Remitting group. Furthermore, the Non-Remitting group also showed higher scores than controls for Primary signs (p<0.001), Motor Coordination (p<0.001), Motor Sequencing

(p=0.003) and Total signs (p<0.001). In contrast, individuals who became Remitting had more signs than controls on Motor Coordination (p<0.001) and Total signs (p=0.020).

[Table 2]

To ensure that differences in neurological function between groups were not influenced by age, gender, ethnicity or IQ (premorbid and current), we performed a two-way ANCOVA analysis using group membership, gender and ethnicity as fixed factors and age and IQ as covariates. This analysis showed that there was still a significant effect of group for Primary signs (F=10.4; df=2; p<0.001), Motor Coordination (F=27.7; df=2; p<0.001) and Total signs (F=14; df=2; p<0.001). The post hoc analysis confirmed that even when these factors were taken into account, the Non-Remitting group still had more Primary, Motor Coordination and Total neurological signs at baseline than both Remitting individuals (p=0.020, p=0.003 and p=0.002 respectively) and healthy controls (p<0.001). As there were more patients with a diagnosis of schizophrenia in the Non-Remitting group, we compared neurological signs between patients with schizophrenia, affective psychoses and other psychoses, and found no significant differences in mean scores between groups (all p>0.2). This suggests it is unlikely that the higher neurological signs in Non-Remitting patients were due to the higher proportion of patients with schizophrenia in this group.

Finally, we conducted an additional exploratory hierarchical regression analysis to examine neurological signs ability to also predict functional outcome (GAF-d scores), over and above baseline employment status (a proxy measure of baseline functioning). Employment status at baseline accounted for 15.1% (R^2=.151; p<0.001) of the variation in GAF score at follow up, and adding total neurological signs to the model increased variance to 17.7% (R^2=.177; delta R^2=.026, F=5.56, F change p=0.019), suggesting that neurological signs at presentation are also predictive of functional, and not only clinical outcomes.

Longitudinal changes in neurological signs over the first ten years of illness
The neurological signs scores for the 56 subjects who completed the two-time points neurological evaluations are presented in Table 3. Of these, 36 (64%) were classified as Non-Remitting, and 20 (36%) were classified as Remitting. To assess changes in neurological signs over the first ten years of illness, we performed a repeated measure analysis of variance with time as within-subject factor and group (Non-Remitting and Remitting) as between-

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subject factor. Both Non-Remitting and Remitting groups showed an increase in score over time for Primary (time effect F=8.5; df=1; p=0.005), Sensory Integration (time effect F=5.9; df=1; p=0.02) and Total signs (time effect F=7.9; df=1, p=0.007). No significant change over time was observed for Motor Coordination signs in the two groups (time effect F=0.07; df=1; p=0.1; time*group effect F=0.17; df=1; p=0.6). Interestingly, there was a non-significant increase in Motor Sequencing signs only in the Non-Remitting group (time*group effect F= 4.9, df= 1, p=0.031). There were no between-group or time differences in the course of Barnes, Simpson-Angus or AIMS mean scores.

[Table 3]

[Table 4]

Relationship with antipsychotic medications

We explored the potential role of antipsychotic medications in explaining neurological signs rates. We found no differences in the proportion of Non-Remitting and Remitting patients taking first or second generation antipsychotics, being drug-free or naïve at baseline, nor in antipsychotic dose (Table 1). Furthermore, there was no correlation between baseline antipsychotic dose and baseline neurological signs, nor between number of weeks on medications and neurological signs at follow up (Table 4). This suggests that between-group differences in baseline neurological signs and change in signs over time are unlikely to be related to antipsychotic exposure.

DISCUSSION

To the best of our knowledge, this is the first prospective study that has investigated the relationship between different domains of neurological signs at illness onset and long-term illness course and functional outcome, as well as change over the first ten years of illness, in a large sample of individuals with first-episode psychosis. Our main finding is that, at their first presentation to services, those patients who subsequently develop a more severe illness course (Non-Remitting) already show significantly more Primary, Motor Coordination, and Total signs than both those who follow a more favourable course (Remitting) and healthy controls, even when correcting for potential confounders such as cognitive ability. This suggests that certain domains of neurological impairment represent early markers of a more severe illness type. Our second main finding is that, independently of illness course type, impairments in Motor Coordination remain stable over time, and represent a trait-like feature of psychosis, while deficits in Primary, Sensory Integration and Total signs worsen, suggesting they reflect illness duration.

This study advances our previous findings that at first presentation, only Primary and Motor Coordination signs are specific to the presence of psychosis[47], showing that their higher rates at onset characterise those patients who develop a poorer illness course with worse functioning, possibly reflecting a more severe pathophysiological process. In addition, we find that Motor Coordination signs remain stable over time, likely representing illness traits. Indeed, this is consistent with reports from shorter follow ups that motor signs change little over one- two- three- and five-year and even across the lifespan in patients with schizophrenia[18, 48-50], that they predict poorer functional outcomes[51], and that distinct sensorimotor performance profiles may be even markers of risk for psychosis[52]. Motor coordination, with abnormal involuntary movements and catatonia could represent a sensorimotor dimension that cuts across psychopathology, and that has etiological and prognostic value as a psychosis endophenotype[28, 53]. As such, sensorimotor function became one of the Research Domain Criteria (RDoC) in 2019. As neurological soft signs reflect the integration of multiple rather than focal processes, they could well be considered abnormalities in any of the sensorimotor RDoC subconstructs, involving action planning, initiation, sensorimotor dynamics, execution or inhibition. The recognition of sensorimotor dysfunction could help the identification and stratification of patients based on an objective,

quantifiable measure that could inform clinical management and advance the investigation of the neurobiological correlates of psychoses subtypes.

In this regard, our group and others have shown that sensorimotor coordination deficits represent the expression of underlying cortical and subcortical brain alterations specifically associated with the pathophysiology of psychosis[6, 28]. Furthermore, while worse motor coordination has been linked with anterior cingulate-caudate aberrant connectivity, catatonia and dyskinesia have been associated with thalamocortical connectivity, suggesting sensorimotor abnormalities are linked to multiple pathophysiological mechanisms[54]. Finally, recent evidence that volume alterations co-occur with aberrant brain activity in cortical and cerebellar systems subserving sensory- and psychomotor organization adds to the concept of sensorimotor dysfunctions as potential biomarkers for psychosis[14]. As such, it is not surprising that motor coordination problems would be associated with more severe manifestations of the disease.

While there are no previous long-term studies that have investigated subgroups of neurological signs, our findings are consistent with the only two studies with a ten year follow up, which showed that total neurological signs predict poorer psychosocial functioning[15], particularly in patients with schizophrenia[16], and service dependency[16]. Similar evidence also comes from shorter and medium-term follow-ups of first episode psychosis patients. For example, a decrease in neurological signs over the first year of illness has been associated with better clinical[24, 25] and functional outcomes[24], and with less prominent negative symptoms, a potential indicator of illness severity[19]. Furthermore, higher baseline neurological signs at onset have also been found to predict lack of treatment response as early as six-weeks[55] and even one year after illness onset[15]. Finally, even when evaluated before illness onset, neurological signs in individuals at ultra-high risk of psychosis have been found to predict illness transition to the illness as well as the onset of severe negative symptoms twelve months later[4].

Another interesting finding in our study is that rates of sensory integrative signs at baseline do not differ between Non-Remitting and Remitting groups, nor from healthy controls. This advances our previous report of a similar sensory integration performance in patients with psychosis and controls, showing also that these signs are not markers of subsequent illness course, and that they increase over time in both patients groups, possibly reflecting ageing

rather than illness severity[47, 56]. Indeed, this may also be the case for Primary signs, which we found to also increase over time in both Remitting and Non-Remitting patients.

In contrast, only Motor Sequencing signs increased over time in patients with a Non-Remitting course. It is difficult to interpret this finding, which is consistent, at least in part, with reports that an increase or lack of change in function is present in patients with worse outcomes, and a reduction in those with a more episodic course[23, 57]. In fact, in the few studies that reported an overall increase in neurological impairment after a first psychotic episode, this increase was mostly seen in the subgroup of patients with a worse clinical course[20, 22, 58]. Taken together, these findings support the hypothesis that different sensorimotor signs represent a combination of trait- and state-like illness features.

Critical to the interpretation of neurological and particularly sensorimotor signs in psychosis is the evaluation of their relationship with antipsychotic use. Our findings however confirm previous reports from us and others[2, 47, 59] that sensorimotor abnormalities represent an intrinsic feature of psychoses and are not related to medications use[53]. Here we evaluated neurological signs at baseline, prior to long-term exposure to antipsychotics, and found no differences in the type or dose of antipsychotic in Non-Remitting and Remitting patients, nor any correlation between antipsychotic exposure and neurological performance at the ten year follow up. This makes our results even stronger, showing that differences in neurological performance between patients who develop different illness trajectories are unlikely to result from differences in antipsychotic treatment.

The present study has several strengths, particularly the large sample size with neurological function evaluated at baseline and the long follow up period. The evaluation of clinical outcome over a long period of time, with a standardised instrument allowed us to investigate neurological function as an early marker of poor long-term illness outcome. Although we could evaluate changes in neurological function only in a subset of patients, we provide here the first report of long-term changes that follow the first episode of psychosis. This should be evaluated in larger clinical populations, in parallel with other illness indicators. We cannot exclude the possibility of selection bias, as in longitudinal studies those patients more likely to be traced could be those with a more severe illness type and worse functional outcome. However, the sample with baseline neurological function and illness course data we included here was similar to the AESOP-10 core sample for age, sex, and illness course, and included

slightly less individuals with a diagnosis of schizophrenia[31]. While here we had more patients with schizophrenia in the Non-Remitting group, as in our previous report[47] we found no differences in neurological function across diagnostic groups, suggesting neurological signs are a marker of illness course rather than diagnosis. Finally, while psychotropic substances such as cannabis or amphetamines could also affect neurological function, the proportion of patients with lifetime cannabis or amphetamines use was similar in the Non-Remitting and Remitting group (34% vs 37% for amphetamines; and 88% vs 86% for cannabis, respectively), making it unlikely that substance use patterns could explain motor coordination signs differences between groups.

In conclusion, we suggest that some neurological abnormalities, specifically motor coordination problems, could be a useful early, quick and easily detectable indicator of subsequent clinical outcome that could help stratify patients early in the illness, identifying those who might benefit from a particularly assertive treatment. From a therapeutic perspective, the presence of sensorimotor abnormalities could also inform the choice of antipsychotics, including consideration for clozapine as appropriate, given its possible beneficial effects on sensorimotor dysfunction, and favouring an approach focused not only on symptomatic improvement, but also on limiting sensorimotor abnormalities that may hamper social functioning in the community.

References

1.   Dazzan P, Murray RM. Neurological soft signs in first-episode psychosis: a systematic review. *Br J Psychiatry Suppl* Sep 2002;43:s50-57.
2.   Chan RC, 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* May 2010;34(6):889-896.
3.   Peralta V, de Jalon EG, Campos MS, Basterra V, Sanchez-Torres A, Cuesta MJ. Risk factors, pre-morbid functioning and episode correlates of neurological soft signs in drug-naive patients with schizophrenia-spectrum disorders. *Psychol Med* Jun 2011;41(6):1279-1289.
4.   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* Nov 2014;40(6):1204-1215.
5.   Ciufolini S, Ponteduro MF, Reis-Marques T, et al. Cortical thickness correlates of minor neurological signs in patients with first episode psychosis. *Schizophr Res* Oct 2018;200:104-111.
6.   Dazzan P, Morgan KD, Orr KG, et al. The structural brain correlates of neurological soft signs in AESOP first-episode psychoses study. *Brain* Jan 2004;127:143-153.
7.   Hirjak D, Wolf RC, Kubera KM, Stieltjes B, Thomann PA. Multiparametric mapping of neurological soft signs in healthy adults. *Brain Struct Funct* Apr 2016;221(3):1209-1221.
8.   Thomann PA, Wustenberg T, Santos VD, Bachmann S, Essig M, Schroder J. Neurological soft signs and brain morphology in first-episode schizophrenia. *Psychol Med* Mar 2009;39(3):371-379.
9.   Viher PV, Docx L, Van Hecke W, Parizel PM, Sabbe B, Federspiel A, Walther S, Morrens M. Aberrant fronto-striatal connectivity and fine motor function in schizophrenia. *Psychiatry Res Neuroimaging* Jun 30 2019;288:44-50.
10.   Zhao Q, Li Z, Huang J, et al. Neurological soft signs are not "soft" in brain structure and functional networks: evidence from ALE meta-analysis. *Schizophr Bull* May 2014;40(3):626-641.
11.   Kong L, Herold CJ, Cheung EFC, Chan RCK, Schroder J. Neurological Soft Signs and Brain Network Abnormalities in Schizophrenia. *Schizophr Bull* Apr 10 2020;46(3):562-571.
12.   Cuesta MJ, Lecumberri P, Moreno-Izco L, et al. Motor abnormalities and basal ganglia in first-episode psychosis (FEP). *Psychol Med* Mar 2 2020:1-12.
13.   Fritze S, Bertolino AL, Kubera KM, Topor CE, Schmitgen MM, Wolf RC, Hirjak D. Differential contributions of brainstem structures to neurological soft signs in first- and multiple-episode schizophrenia spectrum disorders. *Schizophr Res* Aug 2019;210:101-106.
14.   Hirjak D, Rashidi M, Fritze S, et al. Patterns of co-altered brain structure and function underlying neurological soft signs in schizophrenia spectrum disorders. *Hum Brain Mapp* Dec 1 2019;40(17):5029-5041.
15.   Cuesta MJ, Garcia de Jalon E, Campos MS, Moreno-Izco L, Lorente-Omenaca R, Sanchez-Torres AM, Peralta V. Motor abnormalities in first-episode psychosis patients and long-term psychosocial functioning. *Schizophr Res* Oct 2018;200:97-103.

16. White C, Stirling J, Hopkins R, Morris J, Montague L, Tantam D, Lewis S. Predictors of 10-year outcome of first-episode psychosis. *Psychol Med* Sep 2009;39(9):1447-1456.

17. Behere RV. Dorsolateral prefrontal lobe volume and neurological soft signs as predictors of clinical social and functional outcome in schizophrenia: A longitudinal study. *Indian J Psychiatry* Apr 2013;55(2):111-116.

18. Chen EY, Hui CL, Chan RC, et al. A 3-year prospective study of neurological soft signs in first-episode schizophrenia. *Schizophr Res* Jun 1 2005;75(1):45-54.

19. Chan RC, Geng FL, Lui SS, et al. Course of neurological soft signs in first-episode schizophrenia: Relationship with negative symptoms and cognitive performances. *Sci Rep* Jun 08 2015;5:11053.

20. Boks MP, Selten JP, Leask S, Van den Bosch RJ. The 2-year stability of neurological soft signs after a first episode of non-affective psychosis. *Eur Psychiatry* Jul 2006;21(5):288-290.

21. Emsley R, Turner HJ, Oosthuizen PP, Carr J. Neurological abnormalities in first-episode schizophrenia: temporal stability and clinical and outcome correlates. *Schizophr Res* Jun 1 2005;75(1):35-44.

22. Madsen AL, Vorstrup S, Rubin P, Larsen JK, Hemmingsen R. Neurological abnormalities in schizophrenic patients: a prospective follow-up study 5 years after first admission. *Acta Psychiatr Scand* Aug 1999;100(2):119-125.

23. Bachmann S, Degen C, Geider FJ, Schroder J. Neurological soft signs in the clinical course of schizophrenia: results of a meta-analysis. *Front Psychiatry* 2014;5:185.

24. Lizano P, Dhaliwal K, Lutz O, Mothi SS, Miewald J, Montrose D, Keshavan M. Trajectory of neurological examination abnormalities in antipsychotic-naive first-episode psychosis population: a 1 year follow-up study. *Psychol Med* Aug 27 2019:1-9.

25. Bachmann S, Bottmer C, Schroder J. Neurological soft signs in first-episode schizophrenia: a follow-up study. *Am J Psychiatry* Dec 2005;162(12):2337-2343.

26. Whitty P, Clarke M, Browne S, et al. Prospective evaluation of neurological soft signs in first-episode schizophrenia in relation to psychopathology: state versus trait phenomena. *Psychol Med* Nov 2003;33(8):1479-1484.

27. Mayoral M, Bombin I, Castro-Fornieles J, et al. Longitudinal study of neurological soft signs in first-episode early-onset psychosis. *J Child Psychol Psychiatry* Mar 2012;53(3):323-331.

28. Bernard JA, Mittal VA. Updating the research domain criteria: the utility of a motor dimension. *Psychol Med* Oct 2015;45(13):2685-2689.

29. WHO. *The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines*. Geneva: World Health Organisation; 1992.

30. Dazzan P, Lappin JM, Heslin M, et al. Symptom remission at 12-weeks strongly predicts long-term recovery from the first episode of psychosis. *Psychol Med* Jul 31 2019:1-11.

31. Morgan C, Lappin J, Heslin M, et al. Reappraising the long-term course and outcome of psychotic disorders: the AESOP-10 study. *Psychol Med* Oct 2014;44(13):2713-2726.

32. Bebbington P, Nayani T. The Psychosis Screening Questionnaire. *Int J Methods Psychiatr Res* 1995;5:11-19.

33. Annett M. A classification of hand preference by association analysis. *Br J Psychol* 1970;61:303-321.

34. Nelson HW, JR. *National Adult Reading Test (Part II) Test Manual*. Windsor: NFER-NELSON; 1991.

35. WHO. *Schedules for Clinical Assessment in Neuropsychiatry (SCAN)-Version 2.0* Geneva: World Health Organisation; 1992.
36. WHO. *Personal and Psychiatric History Schedule*. Geneva: World Health Organisation; 1996.
37. Sartorius N, Gulbinat W, Harrison G, Laska E, Siegel C. Long-term follow-up of schizophrenia in 16 countries. A description of the International Study of Schizophrenia conducted by the World Health Organization. *Soc Psychiatry Psychiatr Epidemiol* Sep 1996;31(5):249-258.
38. Jablensky A, Sartorius N, Ernberg G, Anker M, Korten A, Cooper JE, Day R, Bertelsen A. Schizophrenia: manifestations, incidence and course in different cultures. A World Health Organization ten-country study. *Psychol Med Monogr Suppl* 1992;20:1-97.
39. Andreasen NC, Carpenter WT, Jr., Kane JM, Lasser RA, Marder SR, Weinberger DR. Remission in schizophrenia: proposed criteria and rationale for consensus. *Am J Psychiatry* Mar 2005;162(3):441-449.
40. APA. *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR)*. Washington, DC: American Psychiatric Association; 2000.
41. Buchanan RW, Heinrichs DW. The Neurological Evaluation Scale (NES): a structured instrument for the assessment of neurological signs in schizophrenia. *Psychiatry Res* Mar 1989;27(3):335-350.
42. Griffiths TD, Sigmundsson T, Takei N, Rowe D, Murray RM. Neurological abnormalities in familial and sporadic schizophrenia. *Brain* Feb 1998;121 (Pt 2):191-203.
43. Sanders CE, Field TM, Diego M, Kaplan M. The relationship of Internet use to depression and social isolation among adolescents. *Adolescence* Summer 2000;35(138):237-242.
44. Simpson GM, Angus JW. A rating scale for extrapyramidal side effects. *Acta Psychiatr Scand Suppl* 1970;212:11-19.
45. Barnes TR. A rating scale for drug-induced akathisia. *Br J Psychiatry* May 1989;154:672-676.
46. Health NIoM. In: Guy W, ed. *ECDEU: Assessment Manual for Psychopharmacology* Department of Health, Education and Welfare; 1976:534-537.
47. Dazzan P, Lloyd T, Morgan KD, et al. Neurological abnormalities and cognitive ability in first-episode psychosis. *Br J Psychiatry* Sep 2008;193(3):197-202.
48. Smith RC, Hussain MI, Chowdhury SA, Stearns A. Stability of neurological soft signs in chronically hospitalized schizophrenic patients. *J Neuropsychiatry Clin Neurosci* Winter 1999;11(1):91-96.
49. Emsley R, Chiliza B, Asmal L, et al. Neurological soft signs in first-episode schizophrenia: State- and trait-related relationships to psychopathology, cognition and antipsychotic medication effects. *Schizophr Res* Oct 2017;188:144-150.
50. Schroder J, Niethammer R, Geider FJ, Reitz C, Binkert M, Jauss M, Sauer H. Neurological soft signs in schizophrenia. *Schizophr Res* Dec 1991;6(1):25-30.
51. Walther S, Eisenhardt S, Bohlhalter S, Vanbellingen T, Muri R, Strik W, Stegmayer K. Gesture Performance in Schizophrenia Predicts Functional Outcome After 6 Months. *Schizophr Bull* Nov 2016;42(6):1326-1333.
52. Dean DJ, Walther S, Bernard JA, Mittal VA. Motor clusters reveal differences in risk for psychosis, cognitive functioning, and thalamocortical connectivity: evidence for vulnerability subtypes. *Clin Psychol Sci* Sep 1 2018;6(5):721-734.

53. Hirjak D, Thomann PA, Kubera KM, Wolf ND, Sambataro F, Wolf RC. Motor dysfunction within the schizophrenia-spectrum: A dimensional step towards an underappreciated domain. *Schizophr Res* Dec 2015;169(1-3):217-233.

54. Walther S, Stegmayer K, Federspiel A, Bohlhalter S, Wiest R, Viher PV. Aberrant Hyperconnectivity in the Motor System at Rest Is Linked to Motor Abnormalities in Schizophrenia Spectrum Disorders. *Schizophr Bull* Sep 1 2017;43(5):982-992.

55. Mittal VA, Hasenkamp W, Sanfilipo M, Wieland S, Angrist B, Rotrosen J, Duncan EJ. Relation of neurological soft signs to psychiatric symptoms in schizophrenia. *Schizophr Res* Aug 2007;94(1-3):37-44.

56. Mellacqua Z, Eyeson J, Orr KD, et al. Differential relationship between neurological and cognitive dysfunction in first episode psychosis patients and in healthy individuals. *Schizophr Res* Dec 2012;142(1-3):159-164.

57. Bachmann S, Schroder J. Neurological Soft Signs in Schizophrenia: An Update on the State- versus Trait-Perspective. *Front Psychiatry* 2017;8:272.

58. Prikryl R, Ceskova E, Tronerova S, Kasparek T, Kucerova HP, Ustohal L, Venclikova S, Vrzalova M. Dynamics of neurological soft signs and its relationship to clinical course in patients with first-episode schizophrenia. *Psychiatry Res* Dec 30 2012;200(2-3):67-72.

59. Chan RC, Xu T, Heinrichs RW, Yu Y, Wang Y. Neurological soft signs in schizophrenia: a meta-analysis. *Schizophr Bull* Nov 2010;36(6):1089-1104.