Neurological soft signs in first-episode schizophrenia: State- and trait-related relationships to psychopathology, cognition and antipsychotic medication effects

Robin Emsley [a,*], Bonginkosi Chiliza [a], Laila Asmal [a], Sanja Kilian [a], M. Riaan Olivier [a], Lebogang Phahladira [a], Akinsola Ojagbemi [b], Freda Scheffler [a], Jonathan Carr [c], Martin Kidd [d], Paola Dazzan [e]

[a] Department of Psychiatry, Faculty of Medicine and Health Sciences, Stellenbosch University, Tygerberg Campus, Cape Town, South Africa
[b] Department of Psychiatry, University of Ibadan, Nigeria
[c] Division of Neurology, Faculty of Medicine and Health Sciences, Stellenbosch University, Tygerberg Campus, Cape Town, South Africa
[d] Centre for Statistical Consultation, Stellenbosch University, South Africa
[e] Psychosis Studies Department, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK

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ABSTRACT

Background: Neurological soft signs (NSS) are proposed to represent both state- and trait-related features of schizophrenia.
Method: We assessed the course of NSS with the Neurological Evaluation Scale (NES) over 12 months of standardised treatment in 126 patients with first-episode schizophrenia, schizophreniform or schizoaffective disorder, and evaluated their state- and trait-related associations with psychopathology, functionality, cognition and antipsychotic treatment. We considered change scores from baseline to be state-related and endpoint scores to be trait-related.
Results: Significant effects for time were recorded for all NSS domains. For state-related change-scores greater improvements in sensory integration were predicted by more improvement in working memory ($p = 0.01$); greater improvements in motor sequencing scores were predicted by more improvement in working memory ($p = 0.005$) and functionality ($p = 0.005$); and greater improvements in NES Total score were predicted by more improvement in disorganised symptoms ($p = 0.02$). There were more substantial associations between trait-related endpoint scores than for state-related change scores. For endpoint scores lower composite cognitive score predicted poorer sensory integration ($p = 0.001$); higher Parkinsonism score predicted poorer motor co-ordination ($p = 0.0001$); lower composite cognitive score ($p = 0.001$) and higher Parkinsonism score ($p = 0.005$) predicted poorer motor sequencing; higher Parkinsonism score ($p = 0.0001$) and disorganised symptoms ($p = 0.04$), and lower composite cognitive score ($p = 0.0007$) predicted higher NES total score.
Conclusions: NSS improved with treatment, but were weakly associated with improvements in psychopathology. Studies investigating NSS as trait-markers should ensure that patients have been optimally treated at the time of testing, and should take possible effects of extrapyramidal symptoms into account.

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1. Introduction

Neurological soft signs (NSS) are a well-established component of the symptom expression of schizophrenia spectrum disorders (Chan et al., 2010). As such, they have been proposed as an endophenotype for these conditions (Chan and Gottesman, 2008). NSS are present at the time of the first psychotic episode (Dazzan and Murray, 2002), and prior to first initiation of antipsychotic treatment (Gupta et al., 1995; Peralta et al., 2011). NSS are not static over time, although findings are inconsistent. While several studies reported that NSS remain stable, or worsen over the course of the illness (Madsen et al., 1999; Smith et al., 1999; Chen et al., 2000; Chen et al., 2005) a recent meta-analysis reported that 14 of 17 longitudinal studies found reductions in NSS in parallel with symptom improvement (Bachmann et al., 2014). NSS improvements were greater in patients achieving remission (Bachmann et al., 2014), and worsened in patients not attaining remission (Prikryl et al., 2012). However, even in patients achieving remission, some NSS persisted. This has led to the proposal that NSS represent both state- and trait-related features of the illness (Bachmann et al., 2014). Which NSS are state or trait markers is not clear (Cuesta et al., 2012). Many previous studies are limited by

methodological shortcomings including small samples, chronic samples, varying degrees of antipsychotic exposure, different follow-up durations and non-standardisation of treatments (Chan et al., 2015). Another critical consideration is timing of baseline assessments (Bachmann et al., 2014). For assessing state-related NSS, baseline assessments should be conducted during the acute psychosis, before treatment. Similarly, trait-related NSS should be investigated after optimal treatment-response.

We conducted a study addressing several of the methodological inconsistencies. Firstly, we selected first-episode patients to avoid the effects of disease chronicity. Secondly, by selecting treatment-naïve or minimally treated patients we minimised contaminating effects of prior medication. This also allowed us to accurately document treatment-emergent extrapyramidal symptoms (EPS) and their relationship to NSS. Thirdly, by treating patients with a single antipsychotic and according to a fixed protocol, we avoided differential effects of various antipsychotics. Fourth, we used a low-dosing strategy to minimise medication effects on NSS. Finally, using a depot antipsychotic formulation eliminated the confounding effect of non-adherence which may be substantial, given the very high rates of non-adherence reported in the early stages of illness (Coldham et al., 2002). Our aim was to investigate the course of NSS over the first 12 months of standardised treatment and to assess how both state- and trait-related NSS are related to other symptoms, functionality, cognition, antipsychotic dose and emergent EPS.

2. Methods

This longitudinal study assessed the outcome of patients with a first-episode of schizophrenia or related disorder treated with the lowest effective dose of flupenthixol decanoate according to a standard protocol over 12 months. Ethics approval was obtained from the Human Research Ethics Committee of Stellenbosch University Faculty of Medicine and Health Sciences.

2.1. Participants

Participants were recruited from hospitals and community clinics in Cape Town and vicinity. Written, informed consent was obtained from participants. Inclusion criteria were: men and women; aged 16–45 years; experiencing a first psychotic episode meeting Diagnostic and Statistical Manual of Mental Diseases, Fourth Edition, Text Revisions (DSM-IV TR) (American Psychiatric Association, 1994) criteria for schizophrenia, schizophreniform or schizo-affective disorder. Exclusion criteria were: lifetime exposure >4 weeks antipsychotic medication; previous treatment with a depot antipsychotic; mental retardation; overt current substance abuse; unstable general medical condition; history of head injury or epilepsy.

2.2. Treatment

Patients received oral flupenthixol 1–3 mg/day for 7 days, followed by flupenthixol decanoate injections 2-weekly for the study duration. Initiation dose was 10 mg 2-weekly, with 6-weekly increments of 10 mg 2-weekly IMI permitted, to a maximum of 30 mg 2-weekly IMI. Additional oral flupenthixol was permitted at the discretion of the investigator, as was lorazepam, anticholinergics, propranolol, antidepressants and medication for general medical conditions. No benzodiazepines, propranolol or anticholinergics were permitted in the 12 h prior to assessments.

2.3. Assessments

Assessments were conducted at baseline (prior to treatment), 6 and 12 months.

2.3.1. Neurological soft signs

NSS were assessed with the Neurological Evaluation Scale (NES) (Buchanan and Heinrichs, 1989). Thirteen of 26 items are assigned to three 'functionally meaningful' sub-scales reflecting dysfunction in sensory integration, motor coordination and motor sequencing, and NES total score (Buchanan and Heinrichs, 1989; Sanders et al., 2000). NES assessments were performed by three psychiatrists (BC, LA, LP) who underwent initial training (Inter-rater reliability >0.9) and participated in ongoing reliability assessments to ensure stability of rating over time.

2.3.2. Clinical evaluations

Patients were assessed with the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1994). Psychopathology was assessed with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). We used factor-analysis derived symptom domains for positive, negative and disorganised symptoms (Emsley et al., 2003). Functionality was assessed with the Social and Occupational Functioning Assessment Scale (SOFAS) (American Psychiatric Association, 1994), depressive symptoms with the Calgary Depression Rating Scale for Schizophrenia (CDSS) (Addington and Addington, 1993) and EPS with the Extrapyramidal Symptom Rating Scale (ESRS) (Chouinard and Margolese, 2005).

2.3.3. Cognitive evaluations

Cognitive performance was assessed by the MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) Cognitive Consensus Battery (MCCB), developed to measure cognitive functioning in schizophrenia. The MCCB measures seven cognitive domains (speed of processing; attention/vigilance; working memory; verbal learning; visual learning; reasoning and problem solving; and social cognition) and a composite score (Nuechterlein and Green, 2006). The MCCB was administered by trained psychologists.

2.4. State vs. trait assessments

NSS display both state and trait characteristics (Bachmann et al., 2014). We assumed that NES scores in the acute state represent both state and trait components, while those in clinically stable patients represent trait components, and the degree of change from the acute state to stable state would represent state components. Therefore, for state-related NSS we used change scores (endpoint-baseline score). (For ESRS change scores we subtracted the baseline score from the highest score at any time point.) For trait-related NSS we used endpoint scores, calculated by last observation carried forward.

2.5. Statistical analyses

All participants with completed baseline NES assessments were included in the analyses. We assessed the distribution of the data by inspection of histograms and normal probability plots. We employed linear mixed-effect models for continuous repeated measures (MMRM) to assess the changes in NSS subscale and total scores over time, with age, gender and previous antipsychotic exposure (yes/no) as covariates. Within analyses Fisher's Least Significant Difference (LSD) tests were used for post hoc multiple comparisons. We conducted Pearson correlational coefficient analyses to investigate both state (change scores) and trait-related (endpoint scores) associations between NSS and psychopathology, cognition and EPS. We used general regression models to further explore these correlations. NSS subscales and total score were dependent variables, covariates were age, gender and level of education and for the predictor variables we were guided by effect sizes >0.3 (moderate) in the correlational analyses. All tests were 2-tailed.