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Research Paper

Neurological soft signs (NSS) and cognitive impairment in chronic schizophrenia

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ABSTRACT

Recent studies indicate that neurological soft signs (NSS) in schizophrenia are associated with generalized cognitive impairments rather than changes in specific neuropsychological domains. However, the majority of studies solely included first-episode patients or patients with a remitting course and did not consider age, course, education or severity of global cognitive deficits as potential confounding variables. Therefore, we examined NSS with respect to cognitive deficits in chronic schizophrenia, i.e. patients who are particularly vulnerable to both, NSS and cognitive impairments.

Eighty patients with chronic schizophrenia (43.36 ± 15a) and 60 healthy controls (47.52 ± 14.8a) matched for age, sex and years of education were examined on the Heidelberg NSS scale and a broad neuropsychological battery including short term, working, logical and autobiographic memory (AM), theory of mind (ToM), psychomotor speed and cognitive flexibility.

When contrasted with the controls, patients showed significantly higher NSS scores and impairments in all neuropsychological domains but short-term memory. NSS were significantly associated with all neuropsychological domains considered but short-term memory and semantic AM. Except for episodic AM (which was significantly correlated with NSS in patients only) these correlations applied to both groups and were confirmed when age, years of education and severity of global cognitive deficits (Mini Mental State Examination) were controlled for.

Results demonstrate that NSS reflect a rather wide range of cognitive impairments in schizophrenia, which also involves episodic AM and ToM. These associations were not accounted for by age, education or severity of global cognitive deficits and facilitate the clinical usage of NSS as a screening instrument.

1. Introduction

Neurological soft signs (NSS) or subtle motor and sensory deficits are frequently found in a wide range of psychiatric conditions, in particular schizophrenia (for review see: Bombin et al., 2005; Chan et al., 2010; Heuser, 2011; Schröder et al., 1992). NSS vary in the clinical course with severity of the condition as demonstrated by decreasing scores with remission of psychopathological symptoms (for review see: Bachmann et al., 2014; Bachmann and Schröder, 2018). Hence, one may hypothesize that NSS reflect acuity and severity of schizophrenia rather than specific dysfunctions.

In patients with chronic schizophrenia NSS scores were found to be significantly associated with neuropsychological impairments (overview see Table 1), which are one of the core features of the disorder (Bora and Pantelis, 2016; Fioravanti et al., 2012; Herold, 2011; Herold et al., 2017). In our table we solely cited studies focusing on patients with chronic schizophrenia with > 40 years of age and a duration of illness of > 20 years. These rigorous selection criteria were applied to especially focus on older patients with a chronic course of the disorder. According to the given literature (King et al., 1991; Owens and Johnstone, 1980) NSS seem to be associated with general cognitive functioning in this patient group. This was also the case when neuropsychological functions were assessed in detail (Chan and Chen, 2004b; Liddle et al., 1993): NSS showed correlations with verbal and visual memory, short term and working memory as well as executive functions and general intelligence. However, some studies focused only on selected cognitive domains such as executive functions or attention (Chan and Chen, 2004a; Sewell et al., 2010; Smith et al., 1999).

In a seminal paper Quitkin et al. (1976) examined 350 patients from 6 diagnostic groups. However, this study was not cited in Table 1, since it did not include patients older than 50 years. Results show negative correlations between the total number of soft signs and IQ scores.

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Table 1
Overview of studies showing NSS-cognition correlates in old-age patients with chronic schizophrenia.

Author/year	N	Diagnostic group	Duration of illness, years (M, SD)	Age, years (M, SD)	Neuropsychological tests	Evaluation of NSS	Results
Chan and Chen (2004a)	90	Chronic schizophrenic Patients (DSM-IV) 74 male	22.2 (9.7)	46.5 (9.7)	Short form of the WAIS-III, CPT, SART, Monotone Counting Test	Cambridge Neurological Inventory (CNI, Chen et al., 1995)	"*When the group was further divided into two subgroups by taking the lower and upper quartiles of their blink rate, patients at the upper quartiles exhibited significantly more disinhibition signs than those at the lower quartiles. There was also a trend for those patients at the upper quartiles to commit more error in a sustained attention task.*" "*Intense blinkers demonstrated significantly more disinhibition soft signs and commission error of the SART than the rare blinkers.*"
Chan and Chen (2004b)	51	Chronic schizophrenic inpatients (DSM-IV) 47 male	21.3 (9.5)	44 (9.58)	SART, SET, HSC, short-form of the WAIS-III, logical memory and visual reproduction tests of the WMS-III	Cambridge Neurological Inventory (CNI, Chen et al., 1995)	"*Significant relationships were found between executive function factors and neurological signs after adjustment for the confounding effects of age, education, illness duration, and medication.*"
King et al. (1991)	16	Chronic schizophrenic inpatients (DSM-III) 10 male	21.41 (10.64) Range: 5.3–41.2 years	44.4 (12.2) Range: 30–68 years	Withers and Hinton series of tests of the sensorium	Mirror movements, speech, right/left confusion, finger-to-thumb opposition, mirror movements, pronation-supination, foot tapping, face-hand test graphesthesia, hopping	"*NSS correlated positively with both positive and negative symptoms and cognitive impairment but not with cerebral ventricular size on CT. Patients with neurodysfunction had more positive and negative psychopathology, cognitive impairment and TD than those without*".
Liddle et al. (1993)	51	Chronic schizophrenic Patients (DSM-III) 33 male	27.8 Range 9–43 years	51.3 Range 31–65 years	WMS: logical memory, memory for designs tests, digit span; Corsi blocks FAS verbal fluency test, Stroop tests, modified card sorting test, TMT-A/B, graded naming test	Finger-to-thumb opposition, pronation-supination, fist/opposition of finger and thumb to create a ring, fist/edge/palm test, clenching and opening fist while performing the opposite movement with the other hand, graphesthesia, stereognosis, bilateral stimulation, articulation	"*Cortical sign total is significantly correlated with impairment in virtually all aspects of cognitive function assessed. The strongest correlation is with impaired performance in the graded naming test.*"
Owens and Johnstone (1980)	52	Drug-free patients (continuously hospitalized for one year or more)	–	With NSS: 68 (N = 27) Without NSS: 72.8 (N = 25)	Withers and Hinton series of tests of the sensorium	Movement disorders involving gait, face, upper limbs, trunk, lower limbs	"*There were very significant relationships between negative features of schizophrenia, cognitive functioning, neuro logical variables and behavioural performance*"
Sewell et al. (2010)	93	Male schizophrenic (N = 72) or schizoaffective (N = 21) patients (DSM-III-R)	Age at first hospitalization 22.5 (5.8)	41.2 (9.4)	WCST, Digit Symbol Substitution Task, Slosson Intelligence Test	Neurological Evaluation Scale (NES, Buchanan and Heinrichs, 1989)	"*Four factors explained 73% of the variance and had distinct clinical and neuropsychological correlates. Factor 1 reflected deficits involved with memory and sensory integration, and was associated with lower PANSS positive and higher AIMS scores. Factor 2 reflected impairments in motor control, and was associated with lower intelligence, more cognitive deficits, and deficit-syndrome schizophrenia. Factor 3 was related to lower intelligence and more perseverative errors on the WCST. Factor 4 was related to increasing age, more extrapyramidal symptoms, more perseverative errors, and worse scores on the DSST.*"

(*continued on next page*)

Table 1 (*continued*)

Author/year	N	Diagnostic group	Duration of illness, years (M, SD)	Age, years (M, SD)	Neuropsychological tests	Evaluation of NSS	Results
Smith et al. (1999)	45	Chronic schizophrenic or schizoaffective patients (DSM-III-R) Subgrouped into chronic nonresponders (NR) or relative responders (RR)	25 chronic nonresponders (NR): 25.1 (7.9) 20 relative responders (RR) 15.4 (9.7)	43.8 (8.7) 39.4 (11.0)	Modified WCST, verbal fluency, digit-span (WAIS-R), graphomotor test (adapted from Dementia Rating Scale), TMT-A/B	Modified Neurological Evaluation Scale (NES, Buchanan and Heinrichs, 1989)	*"NSS total and component scores were negatively correlated with verbal fluency scores and NSS total and Motor Sequencing scores were moderately positively correlated with WCS total errors and perseverative errors, and with Trails A (…) When the NR and RR patients were examined separately, the negative correlation between NSS total score and verbal fluency was maintained, but the positive correlations between NSS scores and WCS variables were present only in the RR patients. Except for the negative correlation with verbal fluency, NSS sensory integration task scores were not significantly correlated with neuropsychological test scores."*

CPT - continuous performance test; HSC - Hayling sentence completion test; SART - sustained attention to response task; SET - six elements test; TMT-A/B - trail making test, part A/part B; WAIS-III/R - Wechsler adult intelligence scale-III/revised; WMS - Wechsler memory scale; WCST - Wisconsin card sorting test.

Barnes et al. (1995) solely considered primitive reflexes in a sample of 48 patients with schizophrenia (mean age: 51 ± 10 years) which were not found to be significantly correlated with current IQ or estimated IQ decline from premorbid to current level. Another study (Poole et al., 1999) found motor dyscoordination (i.e. inaccurate, dysfluent motor sequencing) not to be significantly related to semantic processing, intelligence, or symptoms in 26 patients with schizophrenia (mean age: 40 ± 10 years). In a large genetic study which involved 471 patients aged 18 to 60 years, Chen et al. (2001) reported a trend association between the genotype 102T/102C and better verbal fluency performance and less motor coordination NSS.

Especially the older studies could not rely on standardized instruments for NSS assessments (King et al., 1991; Liddle et al., 1993; Owens and Johnstone, 1980; Quitkin et al., 1976); others used the NES scale, which, besides NSS in a strict sense, also includes memory tasks (Buchanan and Heinrichs, 1989). According to the results of a meta-analysis (Chan et al., 2010) cognitive variables and NSS share about 10% of their variance, thus indicating that these parameters "reflect associated, but distinct, aspects of neurobehavioral function in schizophrenia". The respective studies included patients in all stages of the disease from first manifestation to chronic schizophrenia. While these studies confirmed the importance of NSS and their association with neurocognitive impairments in schizophrenia, confounding effects due to the heterogeneity of the patients' samples under investigation or the instruments for the assessment of NSS and cognition cannot be excluded.

We therefore sought to analyze NSS and cognitive impairment in a large sample of patients with chronic schizophrenia and in healthy controls. We solely included patients with chronic schizophrenia to reduce the potential impact of different clinical courses of the disorder (i.e. chronic vs. remitting) and thereby circumstances of life. Since NSS may be ameliorated by cognitive reserve (Urbanowitsch et al., 2015) years of school education, i.e. its established proxy, was considered as a covariate. Similarly, age (Herold et al., 2017) and severity of global cognitive deficits (King et al., 1991; Owens and Johnstone, 1980) had to be considered. To address the wide range of associations hypothesized between NSS levels and cognitive impairment we used a broad test battery, which also included domains rather scarcely investigated like theory of mind (ToM) and autobiographic memory (AM).

We expected NSS scores to be associated with a broad range of neuropsychological impairments from memory, psychomotor speed and cognitive flexibility to ToM even if age, years of education, and severity of global cognitive deficits were considered as covariates.

2. Methods

2.1. Subjects

80 patients with subchronic[1] (n = 14) or chronic[2] (n = 66) schizophrenia (N = 76) or schizoaffective disorder (N = 4) according to DSM-III/DSM-IV criteria (American Psychiatric Association, 1987, 2000) from three psychiatric long-term units (n = 36) and a mental state hospital (n = 44) were included. 60 healthy participants matched for age, years of education and sex were selected as control group (Table 2). Age at disease onset was determined on basis of the patients' history and case notes. None of the participants had a lifetime history of neurological or severe systemic illness, head injury or substance dependence. Along with this, patients with late onset schizophrenia as defined by an age of onset > 40 years were excluded (Schmid et al.,

[1] "The time from the beginning of the illness, during which the individual began to show signs of the illness (including prodromal, active, and residual phases) more or less continuously, is less than two years but at least six months." (DSM-III, p.192)

[2] "Same as above, but greater than two years" (DSM-III, p.192)

Table 2
Demographic characteristics of patients and healthy controls.

	Patients (n = 80)	Healthy controls (n = 60)	Main effects, F-values$_{[df]}$/χ^2-values, effect size η^2/φ
Sex m/f, N	50/30	33/27	χ^2 = 0.799; p = 0.371; φ = 0.076
Male, %	(62.5)	(55.0)	
Age, years	43.36 (15.00)	47.52 (14.80)	$F_{[1, 138]}$ = 2.660; p = 0.105; η^2 = 0.019
Education, years	12.66 (2.84)	13.52 (2.31)	$F_{[1, 138]}$ = 3.629; p = 0.059; η^2 = 0.026

Data are means (standard deviations), unless otherwise indicated.

2011), just as patients with pronounced extrapyramidal symptoms were.

The investigations were approved by the ethics committee of the Medical Faculty of Heidelberg University and written informed consent was obtained from all participants after the procedures of the study had been fully explained in accordance with the Declaration of Helsinki.

2.2. Clinical assessments

Psychopathological symptoms were rated on the Brief Psychiatric Rating Scale (BPRS, Overall and Gorham, 1962), the Scales for the Assessment of Positive and Negative Symptoms (SAPS and SANS, Andreasen, 1984a, 1984b) and – to especially address apathetic symptoms – the Apathy Evaluation Scale (AES, Lueken et al., 2006).

2.3. NSS and neuropsychological testing

NSS were rated on the Heidelberg scale (Schröder et al., 1992; Schröder et al., 1993), which comprises 16 items on five factors (motor coordination, sensory integration, complex motor tasks, right/left and spatial orientation and hard signs). Ratings are protocolled on a 0–3 point scale (no/slight/moderate/marked abnormality). The psychometric properties of the Heidelberg scale are well established (Bachmann et al., 2005; Schröder et al., 1992).

The neuropsychological test battery included the Mini Mental State Examination (MMSE) as cognitive screening instrument to assess global cognitive deficits (Folstein et al., 1975), verbal and AM, short-term and working memory, psychomotor speed, cognitive flexibility and ToM by applying the subtests Logical Memory I (immediate recall) and II (delayed recall) from the Wechsler Memory Scale-Revised (WMS-R, Härting et al., 2000), a semi-structured AM inventory (Fast et al., 2006; Fast et al., 2007), the digit span forward and backward tasks from the WMS-R (Härting et al., 2000), the Trail Making Test version A and B (TMT, Reitan, 1992), the Reading Mind in the Eyes test (RMIE, Baron-Cohen et al., 2001; Bölte, 2005) and a ToM-test consisting of a picture sequencing task and a questionnaire (Brüne, 2005). In consideration of the age of the younger subjects, the assessment of AM was restricted to memories from the first three lifetime periods. A detailed description of the AM interview is given in former publications of our group (Herold et al., 2013, 2015).

2.4. Statistical analyses

All statistical analyses were performed using SPSS version 23 (IBM SPSS Statistics). Group differences concerning the variables “age” and “years of education” were investigated by analysis of variance (univariate ANOVA), or chi^2 test (variable “sex”). Paired samples t-test was used to compare SAPS and SANS global scores. When group differences of NSS and neuropsychological test results were analyzed, multivariate analyses of covariance (MANCOVA) with age as covariate were calculated.

Pearson correlation coefficients were performed to evaluate the relationships between NSS scores and CPZ equivalents, age, years of education or MMSE scores as well as between the variables of cognitive performance and years of education or age to identify potential confounding variables.

To assess the associations between NSS scores and the neuropsychological domains considered, Pearson correlation coefficients were calculated while controlling for age. Subsequently, these analyses were repeated with years of education, age/years of education and age/years of education/MMSE as covariates. Subsequently, the Bonferroni correction was applied.

3. Results

3.1. Clinical characteristics

The patients' clinical characteristics are given in Table 3. Negative symptoms were predominating in our patient group as revealed by a comparison of SAPS (5.77 ± 4.59) and SANS (7.92 ± 5.43) global scores (T = −2.77, df = 78, p = 0.007). All but 2 patients were under neuroleptic treatment according to their psychiatrist's choice.

3.2. NSS and cognition – group comparisons

As to be expected, patients showed significantly higher NSS scores than healthy controls ($F_{[6130]}$ = 14,570; p < 0.001; η^2 = 0.402); this difference was significant for the total score as well as the five subscales (Table 4). No significant correlations between NSS scores and CPZ equivalents arose (p > 0.15).

When compared to healthy controls, patients demonstrated significant impairments in all neuropsychological domains but short-term memory (Table 5).

Table 3
Clinical characteristics of the patients.

	Patients (n = 80)
Medication, mg CPZ equivalents	718.15 (691.43)
Antipsychotic medication: AT, AT + T, T, no medication, N (%)	45/27/6/2 (56.3/33.8/7.5/2.5)
Additional antidepressive medication, N (%)	30 (37.5)
Additional benzodiazepines, N (%)	7 (8.8)
Illness duration, years	19.54 (14.76)
Age at illness onset, years	23.65 (6.71)
Hospitalized, N (%)	36 (45.0)
SAPS, sum score	16.10 (14.12)
SANS, sum score	24.78 (18.07)
BPRS, sum score	38.60 (9.17)
BPRS – anxiety/depression	10.53 (4.86)
BPRS – anergia	9.72 (4.62)
BPRS – thought disturbance	8.81 (3.80)
BPRS – activity	4.70 (2.23)
BPRS – hostility/suspiciousness	4.84 (2.61)
AES, sum score	27.05 (12.15)

Data are means (standard deviations), unless otherwise indicated.
AES apathy evaluation scale; *AT* atypical antipsychotics; *AT + T* atypical and typical antipsychotics; *BPRS* brief psychiatric rating scale; *CPZ* chlorpromazine; *SANS* scale for the assessment of negative symptoms; *SAPS* scale for the assessment of positive symptoms; *T* typical antipsychotics.

Table 4
Results of group comparisons on NSS scores.

	Patients	Healthy controls	Main effects, F-values$_{[df]}$, effect size η^2
NSS total score	17.96 (13.94)	4.40 (3.44)	$F_{[1, 135]} = 81.793$; $\boldsymbol{p < 0.001}$; $\eta^2 = 0.377$
Motor coordination	7.00 (6.15)	1.73 (1.73)	$F_{[1, 135]} = 59.487$; $\boldsymbol{p < 0.001}$; $\eta^2 = 0.306$
Sensory integration	2.71 (2.23)	0.85 (1.13)	$F_{[1, 135]} = 58.916$; $\boldsymbol{p < 0.001}$; $\eta^2 = 0.304$
Complex motor tasks	3.05 (2.61)	1.08 (1.21)	$F_{[1, 135]} = 37.516$; $\boldsymbol{p < 0.001}$; $\eta^2 = 0.217$
Right/left and spatial orientation	3.56 (3.62)	0.37 (0.78)	$F_{[1, 135]} = 61.034$; $\boldsymbol{p < 0.001}$; $\eta^2 = 0.311$
Hard signs	1.73 (2.04)	0.38 (0.83)	$F_{[1, 135]} = 26.770$; $\boldsymbol{p < 0.001}$; $\eta^2 = 0.165$

Data are means (standard deviations).

3.3. NSS and cognition – correlations

As summarized in Table 6, NSS total scores were significantly correlated with performance on logical memory, digit span backward and TMT A and B ($p \leq 0.003$). In the control group a similar pattern of significant correlations between NSS scores and neuropsychological parameters arose with NSS total scores being significantly correlated to logical memory, digit span backward, TMT A and B ($p < 0.05$).

With respect to AM, solely the quality of autobiographic episodes recalled (specificity and details scores), but not semantic memory, was significantly correlated with NSS total scores and the subscales "motor coordination", "complex motor tasks" and "right/left/spatial orientation" in the patient group ($p < 0.02$). In the controls no significant associations between NSS and AM arose.

ToM total scores and the subscores "questions" and "order" were significantly associated with NSS total scores and all subscales ($p < 0.03$) except for "hard signs" in the patients. In the control group ToM total scores and the respective subscores correlated significantly to NSS total scores and the subscales "complex motor tasks" and "right/left/spatial orientation" ($p \leq 0.05$). The RMIE test scores were significantly correlated with NSS total scores and the subscales "motor coordination", "complex motor tasks" and "right/left/spatial orientation" ($p \leq 0.002$) in the patient but not in the control group.

After Bonferroni correction (α: 0.05/78 = 0.00064) the correlations between NSS and logical memory I and II, TMT A and B, ToM (total and questions, RMIE) remained significant in the patient group, while in the control group only the correlations between NSS and TMT A and B and ToM (total and questions) were confirmed.

These results were replicated when years of education and both, age and years of education were partialled out, since age and years of education were significantly correlated with variables of NSS and cognition (NSS total score and education: $r = -0.208$, $p = 0.014$; NSS total score and age: $r = 0.316$, $p \leq 0.001$; cognitive performance and education $-0.44 < r < 0.48$, $p \leq 0.005$, cognitive performance and age $-0.37 < r < 0.42$, $0.001 \leq p < 0.16$). In a next step MMSE scores were additionally entered as covariate in the calculation of correlations between NSS scores and cognition due to significant negative associations between MMSE and NSS scores ($-0.38 > r > -0.60$, $p < 0.001$). The correlations between NSS scores and cognitive impairments were confirmed when age, years of education and MMSE were partialled out as covariates.

4. Discussion

The present study yielded the following findings: (i) NSS were significantly elevated in elderly patients with chronic schizophrenia who also showed significant neurocognitive impairments in almost every domain considered when contrasted to healthy controls, and (ii) significant associations between NSS scores and a wide range of neuropsychological parameters emerged in both, the patients and the control group.

The present study of patients with chronic schizophrenia, demonstrated significantly increased NSS scores in the patient group when compared to a control group carefully matched for age, education and sex. Despite methodological differences, increased NSS scores in "old" patients with chronic schizophrenia were also reported in previous studies (Table 1). This result confirmed and extended previous studies in young or middle-aged patients with schizophrenia, which yielded significant higher NSS scores than in age-adjusted controls, a finding, which was particularly pronounced in patients with a chronic course of the disorder (Schröder et al., 1992; Schröder et al., 1996) and could already be demonstrated one year after manifestation of the disease (Bachmann et al., 2005). Since the differences between patients and controls could be demonstrated in all age groups (Bombin et al., 2005; Chan et al., 2010), these findings also correspond to the hypothesis that NSS are not subject to age-related changes per se, as demonstrated in a population-based study (Urbanowitsch et al., 2015). Similarly, the neuropsychological impairments found in the patient group correspond to the results of a wealth of studies (for review see: Herold et al., 2017) as neuropsychological deficits are considered to be among the core features of schizophrenia.

In the patient group, increased NSS scores were significantly

Table 5
Results of group comparisons on neurocognition.

Cognitive domain	Tests	Patients	Healthy controls	Main effects, F-values$_{[df]}$, effect size η^2
Cognitive screening	Mini mental state examination	26.64 (3.61)	29.00 (1.06)	$F_{[1, 137]} = 31.744$; $\boldsymbol{p < 0.001}$; $\eta^2 = 0.188$
Verbal memory	Logical memory I	16.99 (9.15)	28.65 (6.24)	$F_{[1, 137]} = 86.948$; $\boldsymbol{p < 0.001}$; $\eta^2 = 0.388$
	Logical memory II	12.06 (8.57)	24.75 (7.13)	$F_{[1, 137]} = 103.263$; $\boldsymbol{p < 0.001}$; $\eta^2 = 0.430$
Short-term memory	Digit span forward	7.20 (2.03)	7.73 (1.70)	$F_{[1, 137]} = 3.736$; $\boldsymbol{p = 0.055}$; $\eta^2 = 0.027$
Working memory	Digit span backward	5.43 (2.09)	6.38 (1.77)	$F_{[1, 137]} = 11.991$; $\boldsymbol{p = 0.001}$; $\eta^2 = 0.080$
Psychomotor speed	Trail making test A	55.81 (45.46)	33.18 (14.15)	$F_{[1, 137]} = 25.422$; $\boldsymbol{p < 0.001}$; $\eta^2 = 0.157$
Cognitive flexibility	Trail making test B	146.91 (76.46)	73.27 (34.99)	$F_{[1, 137]} = 88.030$; $\boldsymbol{p < 0.001}$; $\eta^2 = 0.391$
Autobiographic memory	Autobiographic memory – semantic	12.90 (2.41)	13.80 (1.81)	$F_{[1, 133]} = 6.687$; $\boldsymbol{p = 0.011}$; $\eta^2 = 0.048$
	Autobiographic memory – episodic	12.09 (4.65)	15.23 (2.66)	$F_{[1, 133]} = 23.532$; $\boldsymbol{p < 0.001}$; $\eta^2 = 0.150$
	Autobiographic memory – episodic details	16.64 (10.36)	23.25 (7.19)	$F_{[1, 133]} = 19.214$; $\boldsymbol{p < 0.001}$; $\eta^2 = 0.126$
Theory of mind	Theory of mind – total	41.56 (13.35)	53.15 (7.90)	$F_{[1, 112]} = 50.211$; $\boldsymbol{p < 0.001}$; $\eta^2 = 0.310$
	Theory of mind – questions	17.43 (5.18)	21.80 (2.25)	$F_{[1, 112]} = 43.910$; $\boldsymbol{p < 0.001}$; $\eta^2 = 0.282$
	Theory of mind – order	12.08 (4.72)	15.63 (2.94)	$F_{[1, 112]} = 37.431$; $\boldsymbol{p < 0.001}$; $\eta^2 = 0.250$
	Reading mind in the eyes test	19.14 (5.36)	22.57 (3.95)	$F_{[1, 131]} = 26.104$; $\boldsymbol{p < 0.001}$; $\eta^2 = 0.166$

Data are means (standard deviations).

Table 6
Correlations between NSS and neuropsychological parameters, patient group/control group.

NSS/neuropsychology		NSS total score	Motor coordination	Sensory integration	Complex motor tasks	Right/left and spatial orientation	Hard signs
Logical memory I[a,d]	Patients	**−0.40**$^{***+}$	**−0.38*****	−0.20	**−0.45**$^{***+}$	**−0.35****	−0.12
	Controls	**−0.32***	−0.22	**−0.27***	−0.15	−0.14	−0.12
Logical memory II[a,d]	Patients	**−0.36*****	**−0.35****	−0.15	**−0.46**$^{***+}$	**−0.29***	−0.09
	Controls	**−0.28***	−0.20	**−0.26***	−0.22	−0.07	0.03
Digit span forward[a,d]	Patients	−0.19	−0.09	−0.05	**−0.30****	**−0.32****	0.04
	Controls	−0.13	−0.16	0.05	**0.27***	0.14	0.02
Digit span backward[a,d]	Patients	**−0.34****	**−0.36****	−0.13	**−0.38*****	**−0.30****	−0.06
	Controls	**−0.26***	**−0.35****	−0.08	−0.21	−0.02	0.12
Trail making test A[a,d]	Patients	**0.57**$^{***+}$	**0.45**$^{***+}$	0.18	**0.57**$^{***+}$	**0.60**$^{***+}$	**0.42**$^{***+}$
	Controls	**0.41*****	0.20	0.17	**0.29***	**0.54**$^{***+}$	−0.02
Trail making test B[a,d]	Patients	**0.40**$^{***+}$	**0.37*****	0.16	**0.41**$^{***+}$	**0.44**$^{***+}$	0.11
	Controls	**0.52**$^{***+}$	0.25	**0.29***	**0.42*****	**0.32***	0.19
Autobiographic memory semantic[a,e]	Patients	−0.07	−0.04	0.05	−0.06	−0.04	−0.16
	Controls	−0.09	0.10	−0.25	−0.07	−0.12	−0.00
Autobiographic memory episodic[a,e]	Patients	**−0.36****	**−0.33****	−0.13	**−0.38*****	**−0.37*****	−0.05
	Controls	0.02	0.00	−0.04	0.04	−0.06	0.13
Autobiographic memory episodic details[a,e]	Patients	**−0.28***	**−0.27***	−0.10	**−0.27***	**−0.35****	−0.04
	Controls	0.04	−0.02	−0.01	0.17	−0.05	0.04
Theory of mind - total[b,f]	Patients	**−0.54**$^{***+}$	**−0.50**$^{***+}$	**−0.36****	**−0.49**$^{***+}$	**−0.44*****	−0.16
	Controls	**−0.45*****	−0.15	−0.14	**−0.28***	**−0.62**$^{***+}$	−0.23
Theory of mind - questions[b,f]	Patients	**−0.59**$^{***+}$	**−0.56**$^{***+}$	**−0.40****	**−0.46**$^{***+}$	**−0.46**$^{***+}$	−0.24
	Controls	**−0.48**$^{***+}$	−0.25	−0.17	**−0.27***	**−0.47**$^{***+}$	**−0.31***
Theory of mind - order[b,f]	Patients	**−0.42*****	**−0.40****	**−0.29***	**−0.43*****	**−0.39****	0.03
	Controls	−0.26	−0.06	−0.12	−0.18	**−0.44*****	0.02
Reading mind in the eyes test[c,g]	Patients	**−0.40**$^{***+}$	**−0.35****	−0.09	**−0.45**$^{***+}$	**−0.43**$^{***+}$	−0.21
	Controls	−0.08	−0.07	−0.02	−0.08	−0.09	0.06

Patients: [a]df = 75, [b]df = 56, [c]df = 73.
Controls: [d]df = 57, [e]df = 53, [f]df = 51, [g]df = 53.
* $p \leq 0.05$.
** $p \leq 0.01$.
*** $p \leq 0.001$.
$^{+}$ Significant after Bonferroni correction.

correlated with various cognitive impairments ranging from different memory functions (logical and working memory), psychomotor speed, cognitive flexibility to AM and ToM. Except for AM performance, these correlations also applied to the control group and were confirmed after Bonferroni correction by large. These correlations do not appear to be accounted for by age, education or severity of global cognitive deficits since they were confirmed when the respective variables were partialled out. That NSS in chronic schizophrenia are associated with a wide range of neuropsychological impairments rather than specific changes in discrete domains is supported by a number of studies (for review see Table 1). Along with this, Chan et al. (2015) suggested that "*neurological signs capture more or less the same construct captured by conventional neurocognitive tests in patients with schizophrenia*". These significant associations of NSS scores with cognition performance facilitate the possibility to use NSS as a screening instrument for the assessment of neurocognitive impairments in patients with chronic schizophrenia. This may be of particular importance, as cognitive deficits have a high predictive value for everyday functioning in schizophrenia (Fett et al., 2011; Green et al., 2004; Shamsi et al., 2011), while human resources for neuropsychological examinations and the motivation and/or capacity of patients for such longer cognitive test procedures are often limited.

In addition, a noticeable number of reports focused exclusively on specific neuropsychological domains. In accordance with our results, significant relationships between NSS scores and verbal logical memory impairments (WMS, Arango et al., 1999; Chan and Chen, 2004b; Chan et al., 2009; Liddle et al., 1993), between NSS and impairments of psychomotor speed/cognitive flexibility (TMT-A/B, Arango et al., 1999; Braun et al., 1995; Cuesta et al., 1996; Flashman et al., 1996; Liddle et al., 1993; but see: Smith et al., 1999) were repeatedly described in chronic schizophrenia. With respect to the significant associations between NSS and cognitive flexibility as assessed on the TMT-B one may argue that the latter shares a psychomotor component with motor NSS. However, such a component is not involved when cognitive flexibility is assessed by using the WCST which was also found to be significantly correlated with NSS (Bersani et al., 2004; Braun et al., 1995; Jahn et al., 2006; Karr et al., 1996; Mohr et al., 1996; Smith et al., 1999). In addition, it has also been reported that NSS in patients with chronic schizophrenia are associated with ToM deficits (Romeo et al., 2014). However, significant associations between NSS and logical memory performance were not confirmed by Flashman et al. (1996), while Liddle et al. (1993) revealed significant correlations between NSS scores and corsi blocks (as a spatial analogue of digit span), but not digit span performance (WMS) (see also: Smith et al., 1999).

Even more so, a similar pattern of associations between NSS and cognitive performance emerged in the healthy control group investigated here; a finding which does not only apply to healthy subjects (e.g. Arabzadeh et al., 2014; Arango et al., 1999; Chan et al., 2011; Chen and Chan, 2003), but also to otherwise healthy first-degree relatives of patients with schizophrenia (Solanki et al., 2012). That NSS correspond to a rather global cognitive deficit is further supported by a recent investigation in patients with HIV associated neurocognitive disorder (HAND), which clearly involved an increase of NSS scores with more pronounced cognitive impairments (Toro et al., 2018). From this perspective, the present findings underline the transdiagnostic character of NSS.

Age has to be considered as a potential confounding variable since both, NSS and cognitive impairments in schizophrenia increase with age, as has been demonstrated in the present study, and two recent publications of our group (Herold et al., 2018; Herold et al., 2017). However, the associations found between NSS and cognitive performance were confirmed when age was partialled out as a covariate. With respect to neuroleptic side effects, significant associations between CPZ equivalents and NSS scores did not arose. Since the patients with

chronic schizophrenia investigated in our study had a mean duration of illness of 20 years, a detailed summary of all medication prescribed to the patients in the past was not feasible. As it was argued already by Heinrichs and Buchanan (1988) the notion that antipsychotic medication exerts a protective effect on NSS is widely supported by the results of longitudinal studies (Bachmann et al., 2014; Bachmann and Schröder, 2018). Moreover, NSS were also demonstrated in patients who did not receive any neuroleptic medication (Dazzan and Murray, 2002; Schröder and Heuser, 2008), as well as in first-degree relatives of patients with schizophrenia (Neelam et al., 2011) or in patients with HAND (Toro et al., 2018).

The significant inverse correlations between years of education and NSS scores/cognition deficits refer to a protective effect of this variable – generally used as a proxy for cognitive reserve – as it may ameliorate cognitive deficits by facilitating compensational mechanisms (Urbanowitsch et al., 2015). However, the associations between NSS and cognitive performance were confirmed when school education was partialled out. Even more so, the respective associations proofed to be independent of global cognitive deficits since they were confirmed when MMSE scores were entered as additional covariate.

This character of NSS as correlates of a wide range of neuropsychological impairments corresponds to the results of neuroimaging studies (Heuser et al., 2011; Kong et al., 2015; Thomann et al., 2008; for overview see: Zhao et al., 2014). The latter characterized NSS as a correlate of a wide range of structural cerebral changes, i.e. in the frontal cortices, thalamus and sensorimotor cortex, which are vice versa also involved in important neuropsychological deficits (Antonova et al., 2004; Crespo-Facorro et al., 2007a). Vast proportions of the frontal cortices involve aspects of imagery, planning, execution, monitoring and evaluation of motor acts (de la Vega et al., 2016; Miller and Cohen, 2001; Petrides, 2005). More specifically, thalamic changes may lead to both, increased NSS scores and impaired neurocognition (Andrews et al., 2006; Crespo-Facorro et al., 2007b; Hirjak et al., 2012; Thomann et al., 2008). In addition, changes in the sensorimotor cortex are associated with NSS and via mirror neurons with ToM (Heuser et al., 2011; Kong et al., 2015; McCormick et al., 2012; Pineda, 2008; Schröder et al., 1999; Thomann et al., 2008). Hence, NSS refer to a large variety of structural and functional brain alterations and therefore are associated to global cognitive limitations.

Taken together the present study supported our hypothesis that NSS are associated with a broad range of neurocognitive impairments in patients with chronic schizophrenia as well as healthy controls. With Chan et al. (2015) these findings underline the usability of NSS as a screening instrument for cognitive impairment. From a clinical perspective, these findings facilitate the use of NSS as a marker for severity of the disease and of poor prognosis (Bachmann et al., 2014; Bachmann and Schröder, 2018).

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Conflict of interest

All authors report no conflict of interest related to the current study.

CRediT authorship contribution statement

Christina J. Herold: Data curation, Formal analysis, Writing - original draft. **Céline Z. Duval:** Data curation, Validation. **Marc M. Lässer:** Data curation, Validation. **Johannes Schröder:** Methodology, Supervision, Validation, Writing - review & editing.

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References

American Psychiatric Association, 1987. Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised. APA, Washington, DC.
American Psychiatric Association, 2000. Diagnostic and Statistical Manual of Mental Disorders - DSM-IV-TR, 4th edition, Text Revision. APA, Washington, DC.
Andreasen, N.C., 1984a. Scale for the Assessment of Negative Symptoms (SANS). Department of Psychiatry, College of Medicine, University of Iowa, Iowa City.
Andreasen, N.C., 1984b. Scale for the Assessment of Positive Symptoms (SAPS). Department of Psychiatry, College of Medicine, University of Iowa, Iowa City.
Andrews, J., Wang, L., Csernansky, J.G., Gado, M.H., Barch, D.M., 2006. Abnormalities of thalamic activation and cognition in schizophrenia. Am. J. Psychiatry 163 (3), 463–469.
Antonova, E., Sharma, T., Morris, R., Kumari, V., 2004. The relationship between brain structure and neurocognition in schizophrenia: a selective review. Schizophr. Res. 70 (2), 117–145.
Arabzadeh, S., Amini, H., Tehrani-Doost, M., Sharifi, V., Noroozian, M., Rahiminejad, F., 2014. Correlation of neurological soft signs and neurocognitive performance in first episode psychosis. Psychiatry Res. 220 (1–2), 81–88.
Arango, C., Bartko, J.J., Gold, J.M., Buchanan, R.W., 1999. Prediction of neuropsychological performance by neurological signs in schizophrenia. Am. J. Psychiatry 156 (9), 1349–1357.
Bachmann, S., Schröder, J., 2018. Neurological soft signs in schizophrenia: an update on the state- versus trait-perspective. Front. Psych. 8 (272).
Bachmann, S., Bottmer, C., Schröder, J., 2005. Neurological soft signs in first-episode schizophrenia: a follow-up study. Am. J. Psychiatry 162 (12), 2337–2343.
Bachmann, S., Degen, C., Geider, F.J., Schröder, J., 2014. Neurological soft signs in the clinical course of schizophrenia: results of a meta-analysis. Front. Psych. 5, 185.
Barnes, T.R.E., Crichton, P., Nelson, H.E., Halstead, S., 1995. Primitive (developmental) reflexes, tardive dyskinesia and intellectual impairment in schizophrenia. Schizophr. Res. 16 (1), 47–52.
Baron-Cohen, S., Wheelwright, S., Hill, J., Raste, Y., Plumb, I., 2001. The "Reading the Mind in the Eyes" test revised version: a study with normal adults, and adults with Asperger syndrome or high-functioning autism. J. Child Psychol. Psychiatry 42 (2), 241–251.
Bersani, G., Clemente, R., Gherardelli, S., Pancheri, P., 2004. Deficit of executive functions in schizophrenia: relationship to neurological soft signs and psychopathology. Psychopathology 37, 118–123.
Bölte, S., 2005. Reading Mind in the Eyes Test für Erwachsene (dt. Bearbeitung) von S. Baron-Cohen. JW Goethe Universität Frankfurt am Main.
Bombin, I., Arango, C., Buchanan, R.W., 2005. Significance and meaning of neurological signs in schizophrenia: two decades later. Schizophr. Bull. 31 (4), 962–977.
Bora, E., Pantelis, C., 2016. Social cognition in schizophrenia in comparison to bipolar disorder: a meta-analysis. Schizophr. Res. 175 (1–3), 72–78.
Braun, C.M.J., Lapierre, D., Hodgins, S., Toupin, J., Léveillé, S., Constantineau, C., 1995. Neurological soft signs in schizophrenia: are they related to negative or positive symptoms, neuropsychological performance, and violence. Arch. Clin. Neuropsychol. 10 (6), 489–509.
Brüne, M., 2005. Emotion recognition, 'theory of mind', and social behavior in schizophrenia. Psychiatry Res. 133 (2–3), 135–147.
Buchanan, R.W., Heinrichs, D.W., 1989. The Neurological Evaluation Scale (NES): a structured instrument for the assessment of neurological signs in schizophrenia. Psychiatry Res. 27 (3), 335–350.
Chan, R.C.K., Chen, E.Y.H., 2004a. Blink rate does matter: a study of blink rate, sustained attention, and neurological signs in schizophrenia. J. Nerv. Ment. Dis. 192 (11), 781–783.
Chan, R.C.K., Chen, E.Y.H., 2004b. Executive dysfunctions and neurological manifestations in schizophrenia. Hong Kong J. Psychiatry 14 (3), 2–6.
Chan, R.C.K., Wang, Y., Wang, L., Chen, E.Y.H., Manschreck, T.C., Li, Z.-j., Yu, X., Gong, Q.-y., 2009. Neurological soft signs and their relationships to neurocognitive functions: a re-visit with the structural equation modeling design. PLoS One 4 (12), e8469.
Chan, R.C.K., Xu, T., Heinrichs, R.W., Yu, Y., Gong, Q., 2010. Neurological soft signs in schizophrenia: a meta-analysis. Schizophr. Bull. 36 (6), 1089–1104.
Chan, R.C., Xu, T., Li, H.J., Zhao, Q., Liu, H.H., Wang, Y., Yan, C., Cao, X.Y., Wang, Y.N., Shi, Y.F., Dazzan, P., 2011. Neurological abnormalities and neurocognitive functions in healthy elder people: a structural equation modeling analysis. Behav. Brain Funct. 7, 32.
Chan, R.C.K., Dai, S., Lui, S.S.Y., Ho, K.K.Y., Hung, K.S.Y., Wang, Y., Geng, F.-l., Li, Z., Cheung, E.F.C., 2015. Re-visiting the nature and relationships between neurological signs and neurocognitive functions in first-episode schizophrenia: an invariance model across time. Sci. Rep. 5 (11850).
Chen, E.Y.H., Chan, R.C.K., 2003. The Cambridge Neurological Inventory: clinical, demographic and ethnic correlates. Psychiatr. Ann. 33 (3), 202–210.
Chen, E.Y.H., Shapleske, J., Luque, R., McKenna, P.J., Hodges, J.R., Calloway, S.P.,

Hymas, N.F.S., Dening, T.R., Berrios, G.E., 1995. The Cambridge Neurological Inventory: a clinical instrument for assessment of soft neurological signs in psychiatric patients. Psychiatry Res. 56 (2), 183–204.
Chen, R.Y.L., Sham, P., Chen, E.Y.H., Li, T., Cheung, E.F.C., Hui, T.C.K., Kwok, C.L., Lieh-Mak, F., Zhao, J.-H., Collier, D., Murray, R., 2001. No association between T102C polymorphism of serotonin-2A receptor gene and clinical phenotypes of Chinese schizophrenic patients. Psychiatry Res. 105 (3), 175–185.
Crespo-Facorro, B., Barbadillo, L., Pelayo-Teran, J.M., Rodriguez-Sanchez, J.M., 2007a. Neuropsychological functioning and brain structure in schizophrenia. Int. Rev. Psychiatry 19 (4), 325–336.
Crespo-Facorro, B., Roiz-Santianez, R., Pelayo-Teran, J.M., Rodriguez-Sanchez, J.M., Perez-Iglesias, R., Gonzalez-Blanch, C., Tordesillas-Gutierrez, D., Gonzalez-Mandly, A., Diez, C., Magnotta, V.A., Andreasen, N.C., Vazquez-Barquero, J.L., 2007b. Reduced thalamic volume in first-episode non-affective psychosis: correlations with clinical variables, symptomatology and cognitive functioning. NeuroImage 35 (4), 1613–1623.
Cuesta, M.J., Peralta, V., de Leon, J., 1996. Neurological frontal signs and neuropsychological deficits in schizophrenic patients. Schizophr. Res. 20 (1–2), 15–20.
Dazzan, P., Murray, R.M., 2002. Neurological soft signs in first-episode psychosis: a systematic review. Br. J. Psychiatry Suppl. 43, s50–s57.
de la Vega, A., Chang, L.J., Banich, M.T., Wager, T.D., Yarkoni, T., 2016. Large-scale meta-analysis of human medial frontal cortex reveals tripartite functional organization. J. Neurosci. 36 (24), 6553–6562.
Fast, K., Fujiwara, E., Markowitsch, H.J., 2006. Bielefelder Autobiographisches Gedächtnisinventar (BAGI). Swets & Zeitlinger, Lisse.
Fast, K., Fujiwara, E., Schröder, J., Markowitsch, H.J., 2007. Erweitertes Autobiographisches Gedächtnisinventar (E-AGI). Harcourt, Frankfurt.
Fett, A.-K.J., Viechtbauer, W., Dominguez, M.-d.-G., Penn, D.L., van Os, J., Krabbendam, L., 2011. The relationship between neurocognition and social cognition with functional outcomes in schizophrenia: a meta-analysis. Neurosci. Biobehav. Rev. 35 (3), 573–588.
Fioravanti, M., Bianchi, V., Cinti, M.E., 2012. Cognitive deficits in schizophrenia: an updated metanalysis of the scientific evidence. BMC Psychiatry 12 (64).
Flashman, L.A., Flaum, M., Gupta, S., Andreasen, N.C., 1996. Soft signs and neuropsychological performance in schizophrenia. Am. J. Psychiatry 153 (4), 526–532.
Folstein, M.F., Folstein, S.E., McHugh, P.R., 1975. “Mini-mental state”. A practical method for grading the cognitive state of patients for the clinician. J. Psychiatr. Res. 12 (3), 189–198.
Green, M.F., Kern, R.S., Heaton, R.K., 2004. Longitudinal studies of cognition and functional outcome in schizophrenia: implications for MATRICS. Schizophr. Res. 72 (1), 41–51.
Härting, C., Markowitsch, H.J., Neufeld, H., Calabrese, P.K.D., Kessler, J., 2000. Deutsche Adaptation der revidierten Fassung der Wechsler Memory Scale (WMS-R). Verlag Hans Huber, Bern.
Heinrichs, D.W., Buchanan, R.W., 1988. Significance and meaning of neurological signs in schizophrenia. Am. J. Psychiatry 145 (1), 11–18.
Herold, C.J., 2011. Zerebrale korrelate des autobiographischen gedächtnisses bei schizophrenen psychosen. In: Schröder, J., Brecht, F.G. (Eds.), Chronische Schizophrenien. Akademische Verlagsgesellschaft AKA GmbH, Heidelberg, pp. 85–105.
Herold, C.J., Lässer, M.M., Schmid, L.A., Seidl, U., Kong, L., Fellhauer, I., Thomann, P.A., Essig, M., Schröder, J., 2013. Hippocampal volume reduction and autobiographical memory deficits in chronic schizophrenia. Psychiatry Res. Neuroimaging 211 (3), 189–194.
Herold, C.J., Lässer, M.M., Schmid, L.A., Seidl, U., Kong, L., Fellhauer, I., Thomann, P.A., Essig, M., Schröder, J., 2015. Neuropsychology, autobiographical memory, and hippocampal volume in “younger” and “older” patients with chronic schizophrenia. Front. Psych. 6 (53).
Herold, C.J., Schmid, L.A., Lässer, M.M., Seidl, U., Schröder, J., 2017. Cognitive performance in patients with chronic schizophrenia across the lifespan. GeroPsych 30 (1), 35–44.
Herold, C.J., Lässer, M.M., Seidl, U.W., Hirjak, D., Thomann, P.A., Schröder, J., 2018. Neurological soft signs and psychopathology in chronic schizophrenia: a cross-sectional study in three age groups. Front. Psych. 9, 98.
Heuser, M., 2011. Strukturelle Hirnveränderungen bei Schizophrenen Psychosen in Assoziation mit Neurologischen Soft Signs und Klinischem Erscheinungsbild, Fakultät für Verhaltens- und Empirische Kulturwissenschaften (Thesis). University of Heidelberg.
Heuser, M., Thomann, P.A., Essig, M., Bachmann, S., Schröder, J., 2011. Neurological signs and morphological cerebral changes in schizophrenia: an analysis of NSS subscales in patients with first episode psychosis. Psychiatry Res. Neuroimaging 192 (2), 69–76.
Hirjak, D., Wolf, R.C., Stieltjes, B., Seidl, U., Schröder, J., Thomann, P.A., 2012. Neurological soft signs and subcortical brain morphology in recent onset schizophrenia. J. Psychiatr. Res. 46 (4), 533–539.
Jahn, T., Hubmann, W., Karr, M., Mohr, F., Schlenker, R., Heidenreich, T., Cohen, R., Schroder, J., 2006. Motoric neurological soft signs and psychopathological symptoms in schizophrenic psychoses. Psychiatry Res. 142 (2–3), 191–199.
Karr, M., Schröder, J., Tittel, A., 1996. Neurologische soft signs und neuropsychologische Störungen bei schizophrenen Psychosen. Nervenheilkunde 15, 326–331.
King, D.J., Wilson, A., Cooper, S.J., Waddington, J.L., 1991. The clinical correlates of neurological soft signs in chronic schizophrenia. Br. J. Psychiatry 158, 770–775.
Kong, L., Herold, C.J., Lässer, M.M., Schmid, L.A., Hirjak, D., Thomann, P.A., Essig, M., Schröder, J., 2015. Association of cortical thickness and neurological soft signs in patients with chronic schizophrenia and healthy controls. Neuropsychobiology 71 (4), 225–233.
Liddle, P.F., Haque, S., Morris, D.L., Barnes, T.R., 1993. Dyspraxia and agnosia in schizophrenia. Behav. Neurol. 6 (1), 49–54.
Lueken, U., Seidl, U., Schwarz, M., Völker, L., Naumann, D., Mattes, K., Schröder, J., Schweiger, E., 2006. Psychometric properties of a German version of the Apathy Evaluation Scale. Fortschr. Neurol. Psychiatr. 74 (12), 714–722.
McCormick, L.M., Brumm, M.C., Beadle, J.N., Paradiso, S., Yamada, T., Andreasen, N., 2012. Mirror neuron function, psychosis, and empathy in schizophrenia. Psychiatry Res. Neuroimaging 201 (3), 233–239.
Miller, E.K., Cohen, J.D., 2001. An integrative theory of prefrontal cortex function. Annu. Rev. Neurosci. 24, 167–202.
Mohr, F., Hubmann, W., Cohen, R., Bender, W., Haslacher, C., Honicke, S., Schlenker, R., Wahlheim, C., Werther, P., 1996. Neurological soft signs in schizophrenia: assessment and correlates. Eur. Arch. Psychiatry Clin. Neurosci. 246 (5), 240–248.
Neelam, K., Garg, D., Marshall, M., 2011. A systematic review and meta-analysis of neurological soft signs in relatives of people with schizophrenia. BMC Psychiatry 11.
Overall, J.E., Gorham, D.R., 1962. The brief psychiatric rating scale. Psychol. Rep. 10, 799–812.
Owens, D.G.C., Johnstone, E.C., 1980. The disabilities of chronic schizophrenia. Br. J. Psychiatry 136, 384–395.
Petrides, M., 2005. Lateral prefrontal cortex: architectonic and functional organization. Philos. Trans. R. Soc. Lond. B. Biol. Sci. 360 (1456), 781–795.
Pineda, J.A., 2008. Sensorimotor cortex as a critical component of an ‘extended’ mirror neuron system: does it solve the development, correspondence, and control problems in mirroring? Behav. Brain Funct. 4.
Poole, J.H., Ober, B.A., Shenaut, G.K., Vinogradov, S., 1999. Independent frontal-system deficits in schizophrenia: cognitive, clinical, and adaptive implications. Psychiatry Res. 85 (2), 161–176.
Quitkin, F., Rifkin, A., Klein, D.F., 1976. Neurologic soft signs in schizophrenia and character disorders: organicity in schizophrenia with premorbid a sociality and emotionally unstable character disorders. Arch. Gen. Psychiatry 33 (7), 845–853.
Reitan, C., 1992. The Trail Making Test: Manual for Administration and Scoring. The Reitan Neuropsychological Laboratory, Tucson.
Romeo, S., Chiandetti, A., Siracusano, A., Troisi, A., 2014. An exploratory study of the relationship between neurological soft signs and theory of mind deficits in schizophrenia. Psychiatry Res. 218 (1–2), 7–11.
Schmid, L.A., Lässer, M.M., Schröder, J., 2011. Symptomatik und kognition bei schizophrenie im alter. Fortschr. Neurol. Psychiatr. 79 (5), 267–276.
Schröder, J., Heuser, M., 2008. Neurological soft signs in first-episode schizophrenia. Dir. Psychiatr. 28 (19), 243–257.
Schröder, J., Niethammer, R., Geider, F.J., Reitz, C., Binkert, M., Jauss, M., Sauer, H., 1992. Neurological soft signs in schizophrenia. Schizophr. Res. 6 (1), 25–30.
Schröder, J., Richter, P., Geider, F.J., Niethammer, R., Binkert, M., Reitz, C., Sauer, H., 1993. Discrete motor and sensory disorders (neurologic soft signs) in the acute course of endogenous psychoses. Z. Klin. Psychol. Psychiatr. Psychother. 41 (2), 190–206.
Schröder, J., Tittel, A., Stockert, A., Karr, M., 1996. Memory deficits in subsyndromes of chronic schizophrenia. Schizophr. Res. 21 (1), 19–26.
Schröder, J., Essig, M., Baudendistel, K., Jahn, T., Gerdsen, I., Stockert, A., Schad, L.R., Knopp, M.V., 1999. Motor dysfunction and sensorimotor cortex activation changes in schizophrenia: a study with functional magnetic resonance imaging. NeuroImage 9 (1), 81–87.
Sewell, R.A., Perry, E.B., Karper, L.P., Bell, M.D., Lysaker, P., Goulet, J.L., Brenner, L., Erdos, J., D'Souza, D.C., Seibyl, J.P., Krystal, J.H., 2010. Clinical significance of neurological soft signs in schizophrenia: factor analysis of the Neurological Evaluation Scale. Schizophr. Res. 124 (1–3), 1–12.
Shamsi, S., Lau, A., Lencz, T., Burdick, K.E., DeRosse, P., Brenner, R., Lindenmayer, J.-P., Malhotra, A.K., 2011. Cognitive and symptomatic predictors of functional disability in schizophrenia. Schizophr. Res. 126 (1–3), 257–264.
Smith, R.C., Kadewari, R.P., Rosenberger, J.R., Bhattacharyya, A., 1999. Nonresponding schizophrenia: differentiation by neurological soft signs and neuropsychological tests. Schizophr. Bull. 25 (4), 813–825.
Solanki, R.K., Swami, M.K., Singh, P., 2012. An examination of relationship between neurological soft signs and neurocognition. Asian J. Psychiatr. 5 (1), 43–47.
Thomann, P.A., Wüstenberg, T., Santos, V.D., Bachmann, S., Essig, M., Schröder, J., 2008. Neurological soft signs and brain morphology in first-episode schizophrenia. Psychol. Med. 1–9.
Toro, P., Ceballos, M.E., Pesenti, J., Inostroza, M., Valenzuela, D., Henríquez, F., Forno, G., Herold, C., Schröder, J., Calderón, J., 2018. Neurological soft signs as a marker of cognitive impairment severity in people living with HIV. Psychiatry Res. 266, 138–142.
Urbanowitsch, N., Degen, C., Toro, P., Schröder, J., 2015. Neurological soft signs in aging, mild cognitive impairment, and Alzheimer's disease - the impact of cognitive decline and cognitive reserve. Front. Psych. 6 (12), 1–5.
Zhao, Q., Li, Z., Huang, J., Yan, C., Dazzan, P., Pantelis, C., Cheung, E.F., Lui, S.S., Chan, R.C., 2014. Neurological soft signs are not “soft” in brain structure and functional networks: evidence from ALE meta-analysis. Schizophr. Bull. 40 (3), 626–641.