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Neurological soft signs and cognitive functions: Amongst euthymic bipolar I disorder cases, non-affected first degree relatives and healthy controls

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Abstract

Both neurological soft signs (NSS) and cognitive deficits are present among euthymic bipolar patients. NSS could be related to neurocognitive performance, but this is not explored thoroughly. Healthy relatives of patients may also suffer from similar deficits.

This study compared NSS and cognitive functions in euthymic Bipolar I Disorder (BPI) cases to their non-affected first degree relatives and healthy controls. We also investigated the association between NSS and cognitive functions in these three groups. NSS were assessed in three groups using Neurological Evaluation Scale-revised (NES-r). Eight cognitive domains were assessed in 31 euthymic BPI cases, their 30 non-affected first degree relatives and 30 healthy controls using Computerized Neurocognitive Battery (CNB). Euthymic BPI patients had significantly more NSS than non-affected first degree relatives on 5/7 tests (p -value ranges from 0.042 to $p = 0.0001$) and healthy controls on all tests (p -value from 0.042 to <0.0001). Non-affected first degree relatives and controls did not have any significant difference. BPI participants performed worse than their non-affected first degree relatives on one neurocognitive domain of CNB (spatial memory accuracy, $p = 0.03$) and healthy controls on four domains (spatial memory accuracy ($p = 0.04$), abstraction and mental flexibility efficiency ($p = 0.04$), spatial memory efficiency ($p = 0.04$), and emotion efficiency ($p = 0.04$). Non-affected relatives and healthy controls were similar on neurocognitive domains. Accuracy and efficiency indices of some specific cognitive domains were negatively associated with AV rating and tap copying NSS ratings.

Keywords

Bipolar disorder; Euthymic; Neurological soft signs; Cognition

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Conflicts of interest

The authors declare no conflicts of interest.

1. Introduction

Neurological soft signs (NSS) refer to subtle impairments in sensory integration, motor coordination and the sequencing of complex motor acts which cannot be precisely localized in the brain but an increased prevalence may suggest an underlying neurodevelopmental brain injury (Buchanan and Heinrichs, 1989; Griffiths et al., 1998). These signs possibly reflect role of genetic factors (Niethammer et al., 2000). Studies have reported the presence of NSS as commonly in Bipolar disorder as in schizophrenia (Nasrallah et al., 1983; Gureje, 1988; Dimitri Valente et al., 2012). About 9.5% and 14% of an affective disorder group were impaired on motor and sensory testing respectively compared to controls (Manschreck and Ames, 1984). Boks et al. (2004) reviewed 17 studies on first episode psychosis, bipolar patients and healthy controls comparing NSS and reported the conclusions as tentative mentioning small sample size of studies. Tobar and Hazem (2008) compared first degree relative of bipolar I disorder with normal controls and demonstrated significant difference on a subset of sensory integration tests (namely graphesthesia and rhythm-tapping).

Deficits in cognitive functioning among bipolar patients have been described as measures of illness progression or severity (Zubieta et al., 2001). Among remitted patients with bipolar I disorder (BPI) poorer performance has been reported on a range of cognitive tests, with deficits especially evident on tests of executive function, attention and memory (Malhi et al., 2007; Burdick et al., 2010). Euthymic BPI Chinese patients demonstrated marked cognitive impairments which correlated with illness parameters (Eric et al., 2013). Definite cognitive impairment and different patterns of cognitive style were reported in euthymic patients remitted from recent manic or depressive episode (Fakhry et al., 2013). Indian researchers have reported impairment of executive functions but not memory among first-degree relatives of patients with BPI (Goswami et al., 2006). Others have mentioned impairment in executive functioning and vigilance in first degree relatives of bipolar disorder (Trivedi et al., 2008; Pattanayak et al., 2012).

NSS and cognitive dysfunction in remitted state of bipolar disorder may represent trait deficits. A 6 year longitudinal study confirmed cognitive deficits in patients with bipolar disorder suggesting that these deficits persist even in the euthymic state of the disorder (Mora et al., 2013). The only Indian study correlating NSS with executive functions in euthymic bipolar disorder patients reported significant correlation (Goswami et al., 2006).

Mood and cognition share dynamic relationships with both state and trait dependent components. Because of their relatively static nature, study of the trait characteristics of cognition and neurological signs may provide insights into the etiopathogenesis of mood disorders (Trivedi, 2006).

Most studies, that have been examined, used individual domains, while the underlying neurocognitive systems are inherently complex and interrelated. The relationship between NSS and neurocognitive performance in euthymic bipolar disorder patients in comparison with their first degree non-affected relatives has not been studied to date, to the best of our knowledge. The present study was conducted to fill this lacuna.

2. Methodology

2.1. Study population

This cross-sectional study was conducted at the Department of Psychiatry, PGIMER, Dr. Ram Manohar Lohia Hospital, New Delhi, India. Ethical permissions were taken in accordance with the Indian Council of Medical Guidelines for human research from the Institutional Ethics Committee. A consecutive, consenting sample of 18–60 years old BPI participants (euthymic for one month, and on steady dose of medications for previous 3 months) and their non-affected first degree relatives closest to their age, were recruited. Thirty consenting healthy controls (age range 18–60 years) were also recruited from comparable communities or friends of the patients (relatives were excluded). Participants suffering from any DSM-IV-TR Axis I or II disorder (except BPI disorder in patient group), neurological disorders or substance dependence were excluded.

2.2. Hypotheses

1. Cognitive functions are impaired more in euthymic BPI patients than non-affected first degree relatives and matched healthy controls.
2. Neurological soft signs are present more in euthymic BPI patients followed by their non-affected first degree relative and healthy controls.
3. Neurological soft signs are associated with cognitive impairment.

2.3. Assessment instruments

2.3.1. Young mania rating scale (YMRS)—It is one of the most frequently utilized rating scales to assess manic symptoms. The scale has 11 items and is based on the patient's subjective report of his or her clinical condition over the previous 48 h (Young et al., 1978). A score of <12 is generally accepted to be within the normal range (or in clinical remission).

2.3.2. Hamilton depression rating scale (HAM-D)—It is a multiple choice questionnaire that clinicians may use to rate the severity of a patient's major depression (Hamilton, 1960). It consisted of 17 questions contributing to a total score. Each question has between 3 and 5 possible responses which increase in severity. A score of less than 7 is considered to be within normal range.

2.3.3. Diagnostic Interview of Genetic Studies (DIGS) – Hindi version—It is a structured interview schedule to record information regarding a subject's functioning and psychopathology with primary emphasis on information relevant to the study of the affective disorders and schizophrenia. The Hindi version has been validated in Indian population (Deshpande et al., 1998).

2.3.4. Simpson Angus scale (SAS)—It is a 10-item widely used instrument to assess extrapyramidal symptoms in clinical practice (Simpson and Angus, 1970). Rated for severity on a 0–4 scale, items focus on rigidity rather than bradykinesia, and do not assess subjective rigidity or slowness.

2.3.5. Barnes akathisia rating scale (BARS)—The scale measures motor phenomena as well as systematically probe subjective aspects of akathisia, including the amount of discomfort and distress that might be reasonably attributed to the condition (Barnes, 1989).

2.3.6. Abnormal involuntary movement scale (AIMS)—This 12-item instrument assesses abnormal involuntary movements associated with antipsychotic drugs, such as tardive dystonia and chronic akathisia, as well as ‘spontaneous’ motor disturbance related to the illness itself (Guy, 1976).

2.3.7. Neurological Evaluation Scale-revised (NES-r)—A revised version of NES was administered (Sanders et al., 1998). This has 13 items with consistent inter rater reliability. NSS were scored as per the evaluation procedure by Buchanan and Heinrichs (1989) on four broad domains – sensory integration (audiovisual integration and graphesthesia), sequencing of complex motor acts (fist-ring, fist-palm and tap-copying tests), response inhibition (go-no-go test) and motor coordination (rapid alternating movement test).

2.3.8. Computerized neurocognitive battery (CNB)—This cognitive battery has ten cognitive domains of which eight performance domains were administered—abstraction and mental flexibility, attention, face memory, spatial memory, working memory, spatial ability, sensorimotor and emotion (Gur et al., 2001). We did not evaluate verbal domains as they are currently available only in English, and most of our subjects did not speak English. For each domain, three summary functions were calculated: (1) accuracy, which reflects the number of correct responses; (2) speed, which reflects the median reaction time for correct responses; and (3) efficiency, which reflects both accuracy and speed by the formula: $\text{accuracy}/\log(\text{speed})$ (Aliyu et al., 2006). CNB was administered in a quiet room, with minimal disturbance. Each test was preceded by a mock test to check the understanding and involvement of the subject. The battery was administered in a fixed order using clickable icons. The data was stored directly at University of Pennsylvania, USA and was downloaded in excel format. Mean and standard deviation were calculated.

2.4. Study design

The study was introduced to prospective BPI participants by their treating clinicians. Those who agreed to participate were referred to the first author who explained the study in detail and obtained oral consent from both patients and their relatives. Euthymic BPI patients, who had consenting first degree relatives, were assessed on YMRS and HAM-D to ascertain euthymic state. Written informed consent was obtained from participants with scores of less than 7 on HAM-D and 12 on YMRS. On these participants, DIGS was administered and diagnosis was confirmed in special reliability meetings with a board certified psychiatrist. SAS, BARS, AIMS were administered on all participants to rule out any extrapyramidal symptom which could mimic NSS or could interfere in cognitive performance. Finally, the assessment of NSS and neurocognitive functioning was performed using NES-r and CNB in all study participants. Euthymic BPI participants had not taken benzodiazepines or antihistamines during 8 h preceding cognitive assessments but had taken all other prescribed medications as usual.

2.5. Data analysis

Statistical analysis began with Univariate Analysis of Variance (ANOVA) and chi-square tests. ANOVA was followed by post hoc analyses applying Hochberg corrections for multiple comparisons.

Multivariate analysis of covariance (MANCOVA) was applied to evaluate the association between the NSS and neurocognitive performance. All cognitive domains were taken as dependent and NSS domains were taken as independent variables (separately for accuracy, speed and efficiency indices). Contrasts were computed to test difference among groups on CNB domains with different ratings on NSS. MANCOVA was used as the neurocognitive performance measures are correlated.

3. Results

A total of 54 euthymic bipolar patients who agreed orally to participate in the study were referred. YMRS and HAM-D were applied on these patients. Out of these three had a score of more than 7 on HAM D and six had a score of more than 12 on YMRS and were excluded to ascertain that all patients were euthymic at the time of the study. A total of 45 subjects fulfilling inclusion and exclusion criteria were asked for written consent. However, only 33 participants provided written consent while two withdrew during the assessment procedures. Thus 31 participants completed the study and were analyzed. A total of 39 non-affected first degree relatives were screened, out of which 30 participants who fulfilled the inclusion and exclusion criteria completed tests and were included for analysis. Similarly, 36 participants in the control group were recruited, but only 30 could be included for analysis. Thus, the total sample consisted of 91 participants in three groups (bipolar I $n = 31$; non-affected first degree relatives $n = 30$; healthy controls $n = 30$). SAS, BARS, AIMS were administered to all participants and extrapyramidal symptoms were assessed. Very few reported mild extrapyramidal symptoms.

As shown in Table 1, all three study groups were found to be similar (as expected) on gender, age and education. Majority of the participants in all groups were males. Mean age of onset of the disorder among patients was 25.32 ± 8.23 years; total duration of illness (sum of duration of episodes) was 38.19 ± 29.63 weeks. Mean Global Assessment of Functioning Score (GAF) at worst point of illness was 27.03 ± 5.6 . Forty eight percent of participants reported two episodes in the course of illness. Maximum of six episodes was reported by one participant only. Manic episodes were more frequent than depressive episodes.

3.1. Neurological soft signs

Results from the analysis of Neurological soft signs (NSS) are presented in Table 2. There was significant difference among three participating groups on sensory integration tests (AV integration $p = 0.018$; graphesthesia, $p = 0.001$); sequencing of complex motor acts (fist ring test, $p = 0.0005$; fist palm test, $p = 0.001$; tap copying test $p < 0.0001$); response inhibition (go-no-go-test $p < 0.0001$); motor coordination (rapid alternate movement test, $p = 0.003$). BPI participants had significantly more impaired soft signs than non-affected (healthy) first degree relatives on AV rating ($p = 0.042$), graphesthesia ($p = 0.30$), fist palm rating ($p =$

0.012), go no go ($p = 0.0001$) and rapid alternate movement test ($p = 0.042$). On comparing BPI participants with healthy controls, BPI participants were more impaired on all soft signs (AV integration, $p = 0.042$; graphesthesia, $p = 0.001$; fist ring test, $p = 0.0003$; fist palm test, $p = 0.001$; tap copying test, $p < 0.0001$; go no go test, $p = 0.0001$; and motor coordination rapid alternate movement test, $p = 0.003$). Non-affected first degree relatives were more impaired on fist ring test ($p = 0.045$) and tap copying test ($p = 0.05$). However after Hochberg correction, there was no significant difference between non-affected first degree relatives and healthy controls on any of the soft signs.

3.2. Cognition

Result from the analysis of univariate analysis of variance was carried out to compare the three groups on cognition. Euthymic BPI participants performed worse on various domains of neurocognitive battery as compared to the other two groups (Table 3). BPI participants performed worse than non-affected first degree relatives on accuracy index of spatial memory ($p = 0.03$). They were also more impaired than healthy controls on spatial memory accuracy ($p = 0.04$), spatial memory efficiency ($p = 0.04$), abstraction and mental flexibility efficiency ($p = 0.04$) and emotion efficiency ($p = 0.04$). However no significant difference was found when non-affected first degree relatives were compared with healthy controls.

3.3. Neurological soft signs and cognition

To examine the association between NSS and cognition multivariate analysis of variance, MANCOVA, was carried out taking age adjusted accuracy, speed and efficiency indices of CNB domains separately as dependent variables and NSS, and the three groups as independent variables using the total sample of 91 subjects. We note that three MANCOVA analyses were used separately for the three indices of CNB and differences in cognition domains between different NSS ratings were tested using contrasts analysis. Table 4 summarizes the significant results.

Abstraction and mental flexibility scores of participants with AV rating 0 were better than AV rating 2 ($p = 0.026$) and with AV rating 1 were better than AV rating 2 ($p = 0.003$). Working memory scores also were significantly higher for AV rating 0 than AV rating 2 ($p = 0.018$); AV rating 1 better than AV rating 2 ($p = 0.05$); sensorimotor scores were higher for participants with AV rating 0 than AV rating 1 ($p = 0.012$). Participants with Tap copying rating 0 had significantly higher scores on face memory than tap copying rating 1 ($p = 0.036$); and tap copying rating 2 ($p = 0.001$). On attention also tap copying rating 0 performed better than tap copying rating 2 ($p = 0.049$) while on working memory tap copying rating 0 performed better than tap copying rating 2 ($p = 0.01$).

Speed: there was no significant difference among different ratings of all soft sign tests on speed measures of all cognitive domains.

Efficiency: participants with Tap copying rating 0 performed better than tap copying rating 1 on abstraction and mental flexibility ($p = 0.037$), spatial memory ($p = 0.039$) and spatial ability ($p = 0.045$). Tap copying rating 0 was also better than tap copying rating 2 on abstraction and mental flexibility ($p = 0.021$), face memory ($p = 0.001$), working memory (p

= 0.004), emotion ($p = 0.016$). This proves our hypothesis that neurological soft signs are associated with cognitive functions.

4. Discussion

NSS and cognitive dysfunction in remitted state of bipolar disorder may represent trait deficits. This study aimed to compare and correlate NSS and cognitive functions in euthymic BPI cases with their non-affected first degree relatives and healthy controls.

The study groups were matched with respect to sex, age, and education. There were more males than females in all three groups. Previous studies at the same center also reported fewer female research participants (Bhatia et al., 2012). Majority of participants had completed high school; hence they were comparable on cognitive functions. Euthymic BPI participants were on steady dose of medications for last 3 months. However past studies on Bipolar disorder have shown no significant correlation between medications and NSS rating scores (Noroozian et al., 2009; Bourne et al., 2013).

In comparison to healthy controls, NSS scores among non-affected first degree relatives of BPI participants were higher only on – tap copying task and fist ring test of NSS (sequencing of complex motor acts) though this faded away with Hochberg correction. This may suggest the heritability of NSS. NSS may be a marker or endophenotype (Pardes et al., 1989; Tobar and Hazem, 2008). Non-affected first degree relatives of BPI cases, as compared to healthy controls, performed differently on NSS in all dimensions – sensory integration, motor coordination, response inhibition and sequencing of complex motor tasks suggesting heritability in other studies also (Tobar and Hazem, 2008). Thus NSS may be a trait marker which persists independent of the phase of illness as discussed by other studies also (Negash et al., 2004; Goswami et al., 2006).

On the CNB, statistically significant differences were present between the three study groups on several cognitive functions –spatial and working memory (accuracy and efficiency); spatial ability (speed); emotion and abstraction and mental flexibility (efficiency). Thus cognitive deficits may represent trait markers of underlying neurobiological dysfunction (Martinez-Aran et al., 2004; Clark et al., 2002). Education was comparable in all study groups not interfering in their CNB performance.

All the cognitive domains were found to be affected in BPI participants in our study. A recent meta-analysis also found generalized cognitive impairment rather any specific one in euthymic BPI patients (Eric et al., 2013). As hypothesized our study found that euthymic BPI patients were more cognitively deteriorated as compared to their non-affected first degree relatives and healthy controls. Poor performance was particularly found in memory tasks, abstraction and mental flexibility, sensorimotor and emotion, similar to others (Martinez-Aran et al., 2004; Thompson et al., 2005; Robinson et al., 2006; Mora et al., 2013). In contrast some studies failed to detect impaired executive function in people with bipolar disorder (Cavanagh et al., 2002; Clark et al., 2002). Effects of low power in both these studies and premorbid IQ could have led to different findings in these studies (Goswami et al., 2006).

BPI participants performed significantly worse on cognitive performance compared to both healthy relatives and controls, even in their euthymic state, similar to other studies (Trivedi et al., 2007; Bora et al., 2009; Eric et al., 2013). Contrary to some previous studies no significant deficit was found on attention among the three groups (Clark et al., 2002, 2005). Goswami et al. (2006) also reported deficits in executive functions and verbal memory but not in attention among BPI cases. To be assigned as a neuropsychological endophenotype for a disorder the deficit should be stated independent and present in non-affected first-degree relatives of probands (Glahn et al., 2004). Cognitive deficit was not shown in first degree relatives in this study.

There was no significant difference between non-affected first degree relatives and healthy controls on CNB domains. However, literature so far has been inconsistent on the type of cognitive tasks that are impaired in relatives, with some studies revealing deficits in executive functioning as well as response-inhibition (Antila et al., 2007; Zalla et al., 2004), while other studies suggest a deficit in response inhibition only (Frangou et al., 2005). A meta-analysis for 18 cognitive variables between relatives, patients and healthy controls reported mixed results (Bora et al., 2009).

Cognitive functioning is negatively associated with NSS scores. Participants with high cognitive domain scores have low rating on neurological soft signs suggesting they have no or few soft signs. While some NSS domains were significantly associated with certain cognitive domains, Goswami et al. (2006) reported correlation of NSS with cognition among euthymic BPI patients and healthy controls. In schizophrenia patients, while Arango et al. (1999) reported a relationship between NSS and general cognitive dysfunction (Flashman et al., 1996), specifically found on timed motor speed, and motor coordination. Das et al. (2004) have also found similar results in schizophrenia patients. Like schizophrenia neurological soft signs and neurocognitive deficits may have overlapping neural substrates (Chan et al., 2009).

Although cognitive impairment remained stable on average throughout the follow-up, it was found to have enduring negative effects on psychosocial functioning of BPI patients (Mora et al., 2013; Burdick et al., 2015). The development of specific cognitive remediation strategies is therefore a major hope for improving the quality of remission and functional outcome in this group of patients (Bellivier, 2012).

It is suggested that bipolarity may exist as a continuous trait or phenotype in nature (Johns and Van Os, 2001). Long-term premorbid studies of relatives at risk for bipolar disorder are important to study etiology as well as psychopathology of the disorder. This can help in planning prevention and intervention strategies. Studies have emphasized the need for early detection and treatment in order to avoid a full blown episode (Corcoran et al., 2005; Larsen et al., 2001).

4.1. Limitations

Although we tried our best to include equal number of males and females there were fewer female participants as compared to males. Due to cross sectional design we could not evaluate premorbid level of cognitive functioning and NSS.

5. Conclusion

To conclude, the study suggests no conclusive evidence of neurocognitive deficits and neurological soft signs in first degree relatives of BPI patients. Neurological soft signs are negatively associated with cognitive functions; higher the cognitive functioning, lesser are the neurological soft signs.

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Table 1

Socio-demographic parameters of the sample.

Group/parameter	Euthymic BPI patients Mean $\pm$ SD N = 31	Healthy relatives Mean $\pm$ SD N = 30	Healthy controls Mean $\pm$ SD N = 30	F value/ χ^2	p-value
Age (in years)	35.10 $\pm$ (11.706)	32.47 $\pm$ (10.013)	28.57 $\pm$ 9.46	$F(2, 88) = 3.005$	0.055
Education status (total years completed)	10.81 $\pm$ (3.146)	11.17 $\pm$ 3.086	12.43 $\pm$ 3.85	$F(2, 87) = 1.608$	0.21
Gender male/female	22/9	21/9	21/9	$\chi^2 = 0.009$	0.99
Marital status married/unmarried	20/11	21/9	13/17	$\chi^2 = 4.943$	0.08
Living status with spouse/with parents	20/11	20/10	13/17	$\chi^2 = 2.241$	0.52

BPI, bipolar I disorder.

Table 2

Comparisons of NSS scores between three study groups.

Neurological soft signs	ANOVA				Euthymic BPI patients vs non-affected relatives	Euthymic BPI patients vs healthy controls	Non-affected relative vs healthy controls
	Mean rating score of NSS			<i>F</i> (2,88) (<i>p</i> value [#])	<i>p</i> -value (after Hochberg correction)	<i>p</i> -value (after Hochberg correction)	<i>p</i> -value (after Hochberg correction)
	BPI patients Mean ± SD	Relatives Mean ± SD	Healthy controls Mean ± SD				
Sensory integration							
Audio-visual integration	0.97 ± 0.83	0.47 ± 0.73	0.47 ± 0.77	4.18 (0.018)	0.042	0.042	1.000
Graphesthesia (right & left)	2.64 (1.27)	1.76 ± 1.38	1.36 ± 1.24	7.71 (0.001)	0.030	0.001	0.554
Sequencing of complex motor acts							
Fist ring test (right & left)	2.38 ± 1.11	1.80 ± 1.15	1.23 ± 1.04	8.31 (0.0005)	0.117	0.0003	0.142 *
Fist palm test	0.97 ± 0.98	0.37 ± 0.71	0.23 ± 0.62	7.46 (0.001)	0.012	0.001	0.886
Tap copying test	1.42 ± 0.84	0.93 ± 0.88	0.43 ± .67	11.36 (0.00004)	0.063	0.000022	0.059 *
Response inhibition							
Go-no-go-test	1.19 ± 0.83	0.43 ± 0.67	0.43 ± 0.56	11.93 (0.00003)	0.00018	0.00017	1.000
Motor coordination							
Rapid alternate movement test (right & left)	0.83 ± 1.34	0.24 ± 0.83	0.03 ± 0.18	6.24 (0.003)	0.042	0.003	0.771

Significant *p*-values are highlighted.

* Significant before Hochberg correction.

Table 3

Comparisons of cognitive domain scores between three study groups.

Cognitive domains				ANOVA	Euthymic BPI patients vs non- affected relatives	Euthymic BPI patients vs healthy controls	Non- affected relative vs healthy controls
	Mean scores of cognitive domains			F value (p value)	p-value (after Hochberg correction)	p-value (after Hochberg correction)	p-value (after Hochberg correction)
	BPI patients Mean ± SD	Non-affected relatives Mean ± SD	Healthy controls Mean ± SD				
Accuracy							
Abstraction and mental flexibility	-1.110 ± 0.78	-0.984 ± 0.72	-0.638 ± 0.87	2.857 (0.063)	0.90	0.07	0.27
Attention	-0.144 ± 0.75	-0.280 ± 1.09	-0.066 ± 0.87	0.387 (0.68)	0.92	0.98	0.77
Face memory	-0.133 ± 1.04	-0.111 ± 1.04	0.277 ± 1.24	1.299 (0.28)	1.00	0.39	0.45
Spatial memory	-0.503 ± 0.82	0.125 ± 0.88	0.105 ± 1.09	4.427 (0.01)	0.03	0.04	1.00
Working memory	-0.789 ± 1.06	-0.335 ± 0.76	-0.290 ± 1.06	2.451 (0.09)	0.21	0.14	1.00
Spatial ability	-0.162 ± 0.72	-0.050 ± 0.55	-0.012 ± 0.68	0.400 (0.67)	0.89	0.77	0.99
Sensorimotor	0.429 ± 0.94	0.550 ± 0.41	0.668 ± 0.19	1.180 (0.31)	0.83	0.34	0.84
Emotion	-0.553 ± 0.68	-0.399 ± 0.77	-0.219 ± 0.81	1.502 (0.23)	0.81	0.24	0.74
Speed							
Abstraction and mental flexibility	-0.816 ± 0.98	-0.538 ± 0.95	-0.302 ± 0.72	2.55 (0.08)	0.54	0.08	0.67
Attention	-0.170 ± 1.27	0.208 ± 1.13	0.200 ± 0.65	1.152 (0.32)	0.45	0.49	1.00
Face memory	0.101 ± 1.12	-0.025 ± 1.30	0.237 ± 1.29	0.330 (0.72)	0.97	0.96	0.80
Spatial memory	0.264 ± 0.73	0.140 ± 0.74	0.438 ± 0.63	1.35 (0.26)	0.87	0.70	0.28
Working memory	-0.601 ± 1.45	-0.148 ± 1.12	-0.227 ± 1.26	1.07 (0.35)	0.44	0.59	0.99
Sensorimotor	0.636 ± 0.62	0.509 ± 0.86	0.771 ± 0.62	1.025 (0.36)	0.87	0.84	0.40
Emotion	0.344 ± 0.56	0.497 ± 0.75	0.584 ± 0.63	1.068 (0.35)	0.74	0.39	0.94
Efficiency							
Abstraction and mental flexibility	-1.308 ± 0.79	1.157 ± 0.76	-0.776 ± 0.92	3.353 (0.40)	0.86	0.04	0.22
Attention	-0.348 ± 1.16	-0.481 ± 1.59	-0.213 ± 1.33	0.261 (0.77)	0.98	0.98	0.85
Face memory	-0.082 ± 1.11	-0.072 ± 1.20	0.363 ± 1.28	1.353 (0.26)	1.00	0.38	0.42
Spatial memory	-0.461 ± 0.86	0.137 ± 0.95	0.196 ± 1.17	4.029 (0.021)	0.07	0.04	0.99
Working memory	-0.781 ± 1.06	-0.309 ± 0.67	-0.284 ± 0.99	2.785 (0.067)	0.15	0.11	1.00
Spatial ability	-0.693 ± 0.97	-0.538 ± 0.81	-0.486 ± 0.99	0.386 (0.68)	0.90	0.78	1.00
Sensorimotor	0.599 ± 0.81	0.582 ± 0.65	0.790 ± 0.43	0.946 (0.29)	1.00	0.59	0.53
Emotion	-0.573 ± 0.72	-0.236 ± 1.12	0.037 ± 0.96	3.191 (0.046)	0.43	0.04	0.61

Significant *p*-values are highlighted.

Table 4

Statistically significant differences of cognitive domain scores between NSS ratings.

Neurological soft signs	Accuracy index Cognitive domain	Contrast	p-value	Efficiency index Cognitive domain	Contrast	p-value
AV rating	Abstraction and mental flexibility	0 > 2	0.026			
	Abstraction and mental flexibility	1 > 2	0.003			
	Working memory	0 > 2	0.018			
	Sensorimotor	0 > 1	0.012			
	Working memory	1 > 2	0.05			
Tap copying rating	Face memory	0 > 1	0.036	Abstraction and mental flexibility	0 > 1	0.037
	Face memory	0 > 2	0.001	Abstraction and mental flexibility	0 > 2	0.021
	Attention	0 > 2	0.049	Face memory	0 > 2	0.001
	Working memory	0 > 2	0.010	Spatial memory	0 > 1	0.039
				Working memory	0 > 2	0.004
				Emotion	0 > 2	0.016
				Spatial ability	0 > 1	0.045
Go no go						

0, 1, 2 are ratings of NSS.