TITLE:

Motor abnormalities and cognitive impairment in First-Episode Psychosis patients, their unaffected siblings and healthy controls

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ABSTRACT

Motor abnormalities (MAs) may be already evidenced long before the beginning of illness and are highly prevalent in psychosis. However, the extent to which the whole range of MAs are related to cognitive impairment in psychosis remains understudied.

This study aimed to examine comparatively the relationships between the whole range of motor abnormalities and cognitive impairments in the first-episode of psychosis (FEP), their unaffected siblings and healthy control subjects.

Fifty FEP patients, 21 of their healthy siblings and 24 age- and sex matched healthy controls were included. Motor assessment included catatonic, extrapyramidal and neurological soft signs (NSS) by means of standardized instruments. An exhaustive neuropsychological battery was also performed to extract the 7 cognitive dimensions of MATRICS initiative.

Higher scores on NSS but not on extrapyramidal and catatonic signs showed significant associations with worse cognitive performance in the three study groups. However, the pattern of associations regarding specific cognitive functions was different among the three groups. Moreover, extrapyramidal signs showed significant associations with cognitive impairment only in FEP patients but not in their unaffected siblings and healthy controls. Catatonic signs did not show any significant association with cognitive functioning in the three study groups.

These findings add evidence to the associations between motor abnormalities, particularly NSS and extrapyramidal signs, and cognitive impairment in first-episode psychosis patients. In addition, our results suggest that the specific pattern of associations between MAs and cognitive functioning is different in FEP patients from those of the unaffected siblings and healthy subjects.

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1. INTRODUCTION

Classic European psychiatric schools conferred different relevance to motor abnormalities (MAs) in nosological systems. The psychiatric tradition rooted in the writings of Kraepelin, Bleuler and Schneider did not consider motor abnormalities as core symptoms of psychosis (Jablensky, 2010). On the contrary, the tradition from the Wernicke, Kleist and Leonhard (WKL) school departed substantially from the referenced authors by giving prominence to MAs over other typical psychopathological symptoms of psychosis, such as delusions and hallucinations (Cuesta et al., 2015). Thus, WKL school emphasized clinical signs over symptoms in psychopathological assessment and define psychiatric entities based on signs, course and outcome, and family history (Peralta and Cuesta, 2017).

DSM-5 introduced catatonia as specifier for schizophrenia and other psychotic disorders, mood disorders and neurological and medical conditions causing mental disorders (APA, 2013). However, other MAs continue to be neglected in current classifications.

The motor domain comprises a wide number of abnormalities that are not restricted to catatonic phenomena but involves as well extrapyramidal signs, such as parkinsonism, akathisia and dystonia; abnormal movements, such as dyskinesia and coreic movements; and neurological soft signs (NSS) (Peralta and Cuesta, 2017; Walther and Strik, 2012). Moreover, certain MAs may be already evidenced long before the beginning of illness (Walker et al., 1994) and they are highly prevalent across psychotic disorders and other psychiatric and neurologic disorders (Peralta and Cuesta, 2017).

The vast majority of studies on MAs included one (usually focused on NSS) or two MAs domains, such as NSS and extrapyramidal signs (Whitty et al., 2009) or NSS and catatonic signs (Morrens et al., 2014) but very few comprising the whole range of MAs (Peralta et al., 2011; Peralta et al., 2014). In addition, there is comparatively much less research focused on the relationships between MAs and cognitive impairment in psychosis. The majority of these studies have been focused on NSS (Cuesta et al., 2002; Chan et al., 2010; Mellacqua et al., 2012). Few of them were focused on extrapyramidal signs (Cuesta et al., 2015; Fervaha et al., 2015); very few included

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catatonic signs (Docx et al., 2012); and none comprised the whole range of MAs and included first-episode psychosis patients and their first-degree relatives.

The present study has two aims. First, to examine comparatively the relationships between the whole range of motor abnormalities and cognitive impairments in the first-episode of psychosis (FEP). And second, to examine whether these associations are similar in FEP patients, their unaffected siblings and healthy control subjects.

2. METHODS

2.1. Subjects

50 patients admitted in our psychiatric unit hospital with a first-episode of psychosis, 21 of their healthy siblings and 24 age and sex matched healthy controls regarding patients gave written informed consent to participate in the study. FEP patients were included if they were between 17 and 45 years old and had no antecedents of lifetime substance abuse, neurologic or general medical illness or mental retardation DSM-5 diagnoses (APA, 2013). Siblings were invited to participate in the study. Siblings and controls were assessed by a trained psychologist for affective and psychotic disorders using the abbreviated version of the Comprehensive Assessment Symptoms and History (CASH) (Andreasen et al., 1992). The exclusion criteria for siblings were: current or past history of mental retardation of psychiatric, neurologic or general medical illness, including substance abuse. And an additional exclusion criterion (lack of first-degree relatives with psychosis) was applied only for control subjects.

Healthy controls were mainly recruited by public advertising and by word of mouth among staff of our hospital. This study was approved by the Ethics Committee of the Health Navarre System.

2.2. Diagnosis and psychopathological assessments

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The CASH (Andreasen et al., 1992) was used to evaluate patients and in its abbreviated form to discard any personal or familial psychiatric antecedent in healthy controls. Despite patients were initially referred with a diagnosis of 'acute psychotic episode', a final DSM-5 diagnosis was established by consensus using all available information 6 months after inclusion in the study by the two senior psychiatrists (MJC and VP). Positive, negative, disorganization, mania and depression scores were obtained from the CASH interview.

The antipsychotic doses at the time of the psychopathological assessment and the total exposure to antipsychotics during the episode were converted to chlorpromazine equivalents (Ho et al., 2011).

2.2.1. Motor Assessments

Scales for motor evaluation include the assessment of neurological soft signs (NSS) by means of the Neurological Evaluation Scale (NES) (Buchanan and Heinrichs, 1989). The NES scale provides a total score and 4 neurological subscales scores, namely: sensory integration, motor coordination, sequencing of complex motor acts, and 'other' soft signs ('other SS'). Extrapyramidal signs were evaluated by means of the Simpson-Angus Scale (SAS) (Simpson and Angus, 1970), and the Barnes Akathisia Rating Scale (BARS) (Barnes, 1989). And catatonic signs by means of the Bush-Francis Catatonia Rating Scale (BFCRS) (Bush et al., 1996).

Motor assessments were carried out by three psychiatrists (LMI, JLI and MR), who were specifically trained and achieved good interrater reliability scores before entering in the study.

2.2.2. Cognitive Assessments

Patients were evaluated through exhaustive neuropsychological battery in two or three sessions following the same order of presentation of tests. Neuropsychological assessments were carried by two neuropsychologists (AST and RLO). Both neuropsychologists achieved good interrater reliability and were blind to psychopathological examinations of patients.

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Neuropsychological tests with robust psychometric properties and adapted to Spanish were clustered to account for by the 7 cognitive functions of MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) Consensus Cognitive Battery (MCCB) (Nuechterlein et al., 2004; Nuechterlein et al., 2008). Speed of processing was assessed by means of symbol search and symbol coding subtests of the Wechsler Adult Intelligence Scale 3rd edition (WAIS-III) (Wechsler, 1999), and form A of the Trail Making Test (TMT-A) (Reitan and Wolfson, 1993). Attention was assessed by means of the Continuous Performance Test – Identical Pairs (CPT-IP Performance Test) (Cornblatt et al., 1988) included in MCCB battery (Nuechterlein and Green, 2006), the digit span forward subtest of the WAIS-III (Wechsler, 1999) and the spatial span forward subtest of the Wechsler Memory Scale 3rd edition (WMS-III) (Wechsler, 1998). A Spanish adapted test for assessing verbal learning similar to the California learning list test was used (Test Aprendizaje Verbal, España-Complutense. TAVEC) (Benedet and Alejandre, 1998). Visual memory was assessed by means of the Brief Visuospatial Memory Test Revised (BVMT-R) (Benedict, 1997) from the MATRICS battery (Nuechterlein and Green, 2006). Working Memory was assessed by means of the backwards digit span and letter-number sequencing subtests of the WAIS-III (Wechsler, 1999) , and the backwards spatial span subtest of the WMS-III (Wechsler, 1998). Executive function was assessed by means of the computerized version of the Wisconsin Card Sorting Test (WCST-64™ PAR Inc.) (Heaton, 1993) and form B of the Trail Making Test (TMT-B) (Reitan and Wolfson, 1993). Finally, social cognition was assessed by means of the Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT) included in the MCCB (Nuechterlein and Green, 2006). Premorbid intelligence was estimated by means of the Vocabulary test of the WAIS-III (Wechsler, 1999). A composite measure of global cognition score was obtained by averaging the 7 cognitive functions.

2.3. Statistical analyses

Total scores of the motor scales were used and additionally NES subscale scores were as well used. SAS and BFCRS scale were factorized with oblique rotation to extract main components resulting in two SAS factors (Hypokinesia and Rigidity) and

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three BFCRS factors (Impulsivity, Oppositionism and Inhibition). Scores resulting from these factor analyses were also used in further analyses.

Cognitive tests were grouped according with their main cognitive processes in seven cognitive functions. All neuropsychological variables were converted to z-scores, based on the means and standard deviations of the control group. Z-scores were averaged to calculate each of the cognitive functions and a global cognitive score. Internal consistency of these functions was estimated by means of Cronbach alpha. All cognitive scores were calculated such that higher values indicated better performance. Performances on motor scores and cognitive functions were compared by one-way ANOVA (Scheffé post-hoc test).

To explore the relationships between motor domains and cognitive functioning, Pearson coefficient correlation analyses were carried out in the three groups of the study. Furthermore, to examine the value of motor domains in the prediction of cognitive functioning, individual motor domains entered as dependent variables and cognitive functions as independent variables in multiple regression models using stepwise entry procedure. Multicollinearity among independent variables was examined by means of Tolerance and the Variance Inflation Factor (VIF).

The significance level was set at $\alpha = 0.05$, and the statistical analyses were carried out using the IBM SPSS package (v.20) (IBM Corp., 2011).

3. RESULTS

The three groups in the study did not show significant differences in age and years of education. FEP patients and healthy controls were predominantly male regarding the unaffected siblings group ($x2= 6.14$, $p\leq 0.046$) (Table 1). The FEP patients had not been exposed to antipsychotic medication until the onset of the illness. DSM-5 diagnoses of FEP patients were schizophrenia spectrum disorders (schizophreniform and schizoaffective disorders) (n=21, 42%), brief psychotic disorder (n=14, 28%) and bipolar disorder with psychotic symptoms (n=15, 30%) (Table 1).

Total scores in the 4 motor domains and 2 NES subscales (coordination and sequencing) showed significantly higher motor abnormalities in FEP patients than unaffected siblings and healthy controls. Integration and 'other SS' subscales of NES

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showed significantly higher motor abnormalities in FEP patients than healthy controls but not regarding unaffected siblings (Table 2).

Cronbach's alphas of the cognitive functions ranged between 0.616 (Attention) and 0.749 (Working memory). There were significant differences in cognitive functions among groups as follows: Patients showed significantly lower estimated premorbid intelligence than healthy controls and significantly lower performance in the 7 cognitive functions and global cognition. Patients showed significantly poor performance compared to their unaffected siblings in all cognitive functions and global cognition, except for visual memory. And unaffected siblings showed significantly poor performance in attention, social cognition and global cognition regarding healthy controls (Table 3).

Pearson correlation coefficients between total scores and subscores in motor scales (NES, SAS, BARS and BFCRS) and cognitive functions in the 3 groups are shown in Supplementary Table 1. We also calculated partial correlations including as control variable the total exposure to antipsychotics in CPZ equivalents in the patients group, to confirm that the significant correlations observed were not due to the treatment effects. We found that the significant correlations observed between cognitive scores and the BARS and BFCRS scores were not significant after controlling the exposure to antipsychotics. The significant associations found between NES scores and cognitive functions did not change with respect to Pearson correlations after controlling the cumulative exposure to antipsychotics (Supplementary Table 2).

Results from regression models showed that attention was significantly associated with NES total score in patients and with NES sequencing in patients and siblings. Speed of processing was associated with NES integration score and BARS total score in patients. Verbal memory was significantly related to NES integration score in patients. Visual memory was significantly associated with NES 'other SS' and SAS total score in patients. Working memory was significantly associated with NES integration in siblings and NES sequencing in controls and executive function with NES total score and NES 'other SS' in healthy controls. Finally, social cognition showed significant associations with NES total score and NES 'other SS' in siblings. Individual cognitive functions entered in regression analyses after allowing for the effect of the remaining cognitive functions. Neither SAS factors (Hypokinesia and Rigidity) nor BFCRS scores

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(Total scores and 3 factors) showed significant associations with any cognitive function or global cognition in the three diagnostic groups. VIF scores in all regression analyses were lower than 10.

4. DISCUSSION

Three main results were obtained from this study. First, higher scores on NSS but not on extrapyramidal (parkinsonism and akathisia) and catatonic signs showed significant associations with worse cognitive performance in the three study groups (FEP patients, their unaffected siblings and healthy controls). Second, extrapyramidal signs showed significant associations with cognitive impairment in FEP patients but not in their unaffected siblings and healthy controls. And third, catatonic signs did not show any significant association with cognitive functioning in the 3 study groups.

Despite higher NES total score was significantly associated with worse cognitive performance, these associations were with different cognitive functions in the three study groups. While higher NES total score in FEP patients was associated with worse attentional performance, it was associated with poorer social cognition in unaffected siblings and with worse executive performance in healthy controls. Second, within NES subdomains, higher NES sequencing score showed significant associations with worse cognitive functioning in the three diagnostic groups (with poorer attentional performance in FEP patients and unaffected siblings, and with poorer working memory in healthy controls). Similarly, higher scores on NES 'other SS' subscale was associated with poorer visual memory in FEP patients, with worse social cognition in siblings and with worse executive function in healthy controls. Moreover, higher scores on NES integration showed significant associations with poorer performance on verbal memory and speed of processing in FEP patients and with worse performance on working memory in their siblings. And NES coordination score was only significantly associated with worse social cognition in the unaffected siblings group.

FEP patients but not their unaffected siblings and healthy controls had significant associations between greater parkinsonism (SAS total score) and impairment in visual memory and speed of processing and akathisia (BARS total score) with visual memory.

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There is one single study assessing the associations between the whole motor domains and cognitive functioning in schizophrenia (Docx et al., 2012). This study was focused specifically on psychomotor syndrome and they found that 'motoric' NSS but not catatonic, parkinsonism and psychomotor slowing correlated with cognitive impairment. However, comparison of these results with our own are limited by differences in sample composition (chronic versus FEP patients) and motor and cognitive assessment procedures. They only used two NES subscales ('coordination' and 'sequencing') but not 'integration' and 'other SS' subscales, and regarding cognitive assessment only four standard neuropsychological measures. Moreover, they did not include siblings and healthy control groups. Despite these differences, both studies found that higher scores in NES sequencing was significantly associated with poorer performance in attention in patients and poorer working memory functioning was significantly associated with NES coordination (Docx et al., 2012) but NES integration in our study. And these results are in agreement with former results from our own group demonstrating that neurologic frontal signs proposed by Luria were significantly associated with poor cognitive performance in schizophrenia patients (Cuesta et al., 1996) and that NSS have high predictive power for cognitive impairment in psychosis (Cuesta et al., 2002).

Studies focused on the relationships between subsets of motor domains and cognitive impairment in schizophrenia and other samples of patients with psychosis have been predominantly reported for NSS, less frequently reported for extrapyramidal signs and not specifically addressed regarding catatonic signs, except the above mentioned article (Docx et al., 2012). A meta-analysis of 14 studies reporting correlations between NSS and cognitive measures in schizophrenia patients (Chan et al., 2010) concluded that NSS and cognitive domains share 10% of their variance. Specific significant relationships between 'sensory' and 'motor' NSS and several cognitive functions, such as spatial, executive and language performance were found and sensory NSS were significantly related to IQ test performance (Chan et al., 2010). Moreover, these results were in agreement with the largest epidemiological cohort of FEP patients to date reporting that higher scores on all NSS domains were significantly associated with worse cognitive performance in all cognitive functions (Mellacqua et al., 2012).

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A review of literature concluded that tardive dyskinesia was associated with greater cognitive impairment in patients with schizophrenia compared to those without tardive dyskinesia (Paulsen et al., 1994), and other authors reported that these findings are specifically related to orofacial (Waddington and Youssef, 1996) and limb-trunk tardive dyskinesia (Wu et al., 2013). Initial results from CATIE study did not support this association after adjustment for confounding variables, such as exposure to typical antipsychotic or anticholinergic drugs (Miller et al., 2005). However, when data from CATIE study were reanalyzed by including only those patients not receiving any antipsychotic or anticholinergic medication for at least the preceding two weeks, greater severity of extrapyramidal signs was significantly associated with worse cognitive test performance . And these findings remained significant even after accounting for other variables such as severity of psychopathology, sedation, akathisia and dyskinesia (Fervaha et al., 2015). These results are in agreement with a recent longitudinal study from our group on an antipsychotic naïve sample of patients with psychosis, since we found that parkinsonism was strongly associated with deficits in memory, executive and attention performances (Cuesta et al., 2014).

The relationships between catatonic signs and cognitive functioning in psychosis remain understudied but there were not significant associations between these two domains neither in chronic schizophrenia population (Docx et al., 2012) nor in the present study with FEP patients. Thus, catatonic signs seem to be unrelated to cognitive performance not only in chronic and FEP patients but also in unaffected siblings and healthy subjects as we found in this study.

NSS (Chan et al., 2010; Neelam et al., 2011) and abnormal movements (Koning et al., 2010) are more common in schizophrenia and psychosis than in their first-degree relatives and in first-degree relatives of schizophrenia patients than in healthy controls. This led to some authors to propose NSS as endophenotypes of schizophrenia (Chan and Gottesman, 2008; Whitty et al., 2009). However, the relationships between MAs and cognitive functioning in first-degree relatives of schizophrenia patients has been scarcely investigated. We found in this study a different pattern of relationships between NSS and cognitive functioning in patients, their unaffected siblings and healthy controls. These results were in agreement with those reported by Mellacqua et al. (2012) in their comparison of associations between neurological and cognitive

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dysfunctions in FEP patients and healthy controls though they did not include a first-degree relative group.

The significant correlations observed between extrapyramidal and catatonic signs (BARS, BFCRS and SAS scores) and cognitive functions disappeared after controlling for the treatment; this was an expected finding considering the extrapyramidal effects of the antipsychotics, which can obscure the relationships between motor assessments and cognitive domains, such as speed of processing and executive functions.

Despite there is a great overlap between signs of motor domains, it is widely accepted that NSS are non-localizing, maturational signs, that are associated with neurodevelopmental dysfunctions though they are also related to the beginning and course of the schizophrenia illness (Peralta and Cuesta, 2017). However, other motor signs such as catatonic ones might be core motor dysfunctions associated with the beginning of psychosis and hypothetically to their underlying neurobiological dysfunction. In fact, our team reported recently that catatonic signs and dyskinesia at drug-naïve state and parkinsonism, akathisia, NSS and catatonic signs at 6-month of outcome in FEP patients were significantly associated with poorer long-term psychosocial functioning. Moreover, higher scores on parkinsonism, akathisia, neurological soft signs and catatonic signs at 6-month of FEP but not dyskinesia showed significant associations with poorer long-term psychosocial functioning (Cuesta et al., 2017 in this Issue). Similarly, it has been recently reported that gesture performance and nonverbal social perception at baseline predicted negative symptoms, functional outcome, and functional capacity at 6-month follow-up (Walther et al., 2016).

Taken together, it seems NSS are the MAs most related to cognitive functioning in general population but both the vulnerability to psychosis (unaffected siblings) and the psychosis illness might confer different patterns of associations between motor and cognitive domains. Thus, a complex combination of the effects of the risk to develop the illness and the illness at their different stages in the frame of individual brain resilience may result in different structuration of the underlying widely distributed cognitive networks.

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The results of the present study should be interpreted in light of some limitations. First, our study design was cross-sectional and motor abnormalities might change along the course of the first-episode of psychosis. Longitudinal studies should be undertaken to account for this variability. Second, despite there were significant differences in gender composition between patients and siblings, gender effect was introduced as covariate in multiple regression procedures to minimize this potential bias. Third, our patients were receiving antipsychotic medications for the treatment of the FEP at the time of motor and cognitive assessments. However, their exposition period was quite short and chlorpromazine equivalent total doses were included as covariates in the statistical analyses. In our study, we decided to include separately MAs in regression procedures to avoid bias related to though it is acknowledged that motor domains are significantly related (Jahn et al., 2006; Peralta et al., 2011) Future studies should be specifically addressed to disentangle overlaps among MAs. Fifth, as cognitive domains are strongly correlated and multicollinearity should not be discarded. However, the estimates of multicollinearity in the regression procedures allowed us to reduce as much as possible this effect. Finally, motor assessment scales were designed to identify abnormalities in patients and a possible floor effect might account for the very low scores in akathisia and catatonic abnormalities in unaffected siblings and healthy subjects.

Motor abnormalities not only may paved the way to better understand the common pathophysiological underpinnings of psychiatric disorders (Mittal et al., 2017) but they have also demonstrated to be a transdiagnostic domain that support ours and other research proposals for integration in the Research Domain Criteria (RDoC) matrix as a specific domain (Peralta and Cuesta, 2017). Moreover, motor abnormalities might serve as clinical markers to target and early detect those FEP patients that may have a poor outcome to provide them a more intensive rehabilitation in order to minimise poor long-term psychosocial impairment.

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CONFLICT OF INTEREST

None.

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Contributors

M.J. Cuesta and V. Peralta designed the study and made final diagnosis. L. Moreno, M. Ribeiro and J. López-Ilundain carried on the motor evaluations. R. Lorente-Omeñaca and A. M. Sánchez-Torres performed neuropsychological assessments. M.J. Cuesta analyzed data and drafted the manuscript. P. Lecumberri, M.S. Gómez and T. Cabada participated in statiscal analyses and and contributed to supervise the study.

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Table(s)

Table 1: Demographic characteristics of the sample

	Patients (n=50)	**Siblings (n=21)**	**Controls (n=24)**	**Difference**
Age (years) ± SD	25.5 ± 5.7	24.9 ± 6.6	23.2 ± 5.7	n.s.
Education (years) ± SD	12.6 ± 3.2	13.7 ± 2.7	13.8 ± 2.5	n.s.
Handedness % Right	96	90.5	95.8	n.s.
Sex	15F : 35M	12F : 9M	6F : 18M	x^2= 6.14 p≤ 0.046
Civil status % Single	90	76.2	83.3	n.s.
Age (years) at onset ± SD	24.9 ± 5.4			
Duration of illness (months) ± SD	4.50 ± 3.94			
CASH Positive ± SD	0.48 ± 0.64			
CASH Negative ± SD	0.68 ± 0.83			
CASH Disorganization ± SD	0.39 ± 0.57			
CASH Mania ± SD	0.46 ± 0.81			
CASH Depression ± SD	0.68 ± 0-93			
CPZ_day (mg) ± SD	428.15 ± 299.87			
CPZ_Total exposure (mg) ± SD	15314.78± 21642.54			
DSM 5 Dx Breakdown (%)	Schizophrenia spectrum disorder[a] Brief psychotic disorder Bipolar disorder		21 (42) 14 (28) 15 (30)	

SD: standard deviation. CASH: Comprehensive Assessment Symptom History. Dx: diagnosis. CPZ_day: daily mean chlorpromazine equivalent dose, CPZ_Total exposure: Total chlorpromazine equivalent dose. n.s.= non-significant

[a]= Schizophrenia spectrum disorder included schizophrenia, schizophreniform and schizoaffective disorders

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Table(s)

Table 2: Results and differences of total motor scores and subscores in the three groups

	Patients	Siblings	Controls	Differences		
Variables (x ± SD)				**F-value**	**p-value**	**Post hoc**
NES total	13.42 ± 6.44	8.57 ± 6.09	5.75 ± 4.46	14.85	<0.001	**P>S / P>C**
NES integration	2.5 ± 1.82	1.71 ± 2.02	1.33 ± 1.37	3.95	.022	**P>C**
NES coordination	2.04 ± 2.26	0.81 ± 1.03	0.33 ± 0.86	8.66	<0.001	**P>S / P>C**
NES sequencing	2.86 ± 2.24	1.38 ± 1.68	1.13 ± 1.26	8.47	<0.001	**P>S / P>C**
NES other SS	6.02 ± 3.79	4.66 ± 4.21	2.95 ± 2.61	5.82	.004	**P>C**
SAS total	4.20 ± 3.82	1.57 ± 1.66	0.58 ± 1.13	14.13	<0.001	**P>S / P>C**
BARS total	0.48 ± 0.86	0.00 ± 0.00	0.00 ± 0.00	6.88	.002	**P>S / P>C**
BFCRS total	2.26 ± 3.89	0.33 ± 0.96	0.13 ± 0.61	5.91	.004	**P>S / P>C**

P= Patients. S= Siblings. C= Controls. NES: Neurological Evaluation Scale. SAS: Simpson-Angus Scale. BARS: Barnes Akathisia Rating Scale. BFCRS: Bush-Francis Catatonia Rating Scale. SS: Soft signs

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Table(s)

Table 3: Differences in cognitive functions and global cognition in the three groups

	Patients	Siblings	Controls	Differences		
Variables (mean ± SD)				**F-value**	**p-value**	**Post hoc**
Vocabulary (WAIS)	9.63 ± 2.16	9.90 ± 1.81	10.91 ± 1.80	3.19	.046	**P<C**
Attention	-2.61 ± 1.53	-1.15 ± 1.55	0.00 ± 1.62	22.30	.001	**P<S / P<C /S<C**
Speed of processing	-1.51 ± 0.87	-0.12 ± 0.71	0.01 ± 0.69	36.55	.001	**P<S / P<C**
Verbal memory	-1.02 ± 1.19	-0.21 ± 0.88	-0.01 ± 0.68	9.21	.001	**P<S / P<C**
Visual memory	-1.73 ± 2.37	-0.72 ± 1.68	-0.01 ± 1.00	6.18	.003	**P<C**
Working memory	-1.12 ± 0.87	0.16 ± 0.84	-0.01 ±0.75	17.13	.001	**P<S / P<C**
Executive	-1.20 ± 1.16	-0.21 ± 0.75	0.01 ± 0.76	14.29	.001	**P<S / P<C**
Social cognition	-1.35 ± 1.05	-0.66 ± 0.84	0.01 ± 0.99	14.45	.001	**P<S / P<C / S<C**
Global cognition	-1.49 ± 0.78	-0.42 ± 0.58	0.03 ± 0.54	40.51	.001	**P<S / P<C / S<C**

P= Patients. S= Siblings. C= Controls.

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Table(s)

Dependent variables	PATIENTS						SIBLINGS						CONTROLS					
	Variables in the model	R^2	B	s.e.	t	sign.	Variables in the model	R^2	B	s.e.	t	sign.	Variables in the model	R^2	B	s.e.	t	sign.
NES total	Attention	.10	-1.43	.653	-2.19	.034	Social cognition	.57	-5.09	1.077	-4.73	.001	Executive function	31	-2.20	.753	-2.92	.009
NES integration	Verbal memory	.10	-0.60	.223	-2.69	.010	Working memory	.26	-1.21	.493	-2.45	.025						
	Speed of process.	.19	-0.70	.325	-2.17	.036												
NES coordination							Social cognition	.33	-.62	.214	-2.92	.009						
NES sequencing	Attention	.34	-0.92	.197	-4.68	.000	Attention	.35	-.74	.243	-3.06	.007	Working memory	.22	-.65	.285	-2.31	.032
NES other SS	Visual memory	.10	0.54	.247	2.19	.034	Social cognition	.32	-2.78	.972	-2.86	.011	Executive function	.19	-.99	.463	-2.15	.045
SAS total	Visual memory	.16	0.66	.230	2.87	.006												
SAS Hypokinesia																		
SAS Rigidity																		
BARS total	Speed of process.	.97	-0.34	.134	-2.53	.015												
	Visual memory	.20	0.11	.048	2.31	.026												
Bush-Francis total																		
BF Impulsivity																		
BF Oppositionism																		
BF Inhibition																		

NES: Neurological Evaluation Scale. SAS: Simpson-Angus Scale. BARS: Barnes Akathisia Rating Scale. BFCRS: Bush-Francis Catatonia Rating Scale. SS: Soft signs

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