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Minor physical anomalies and neurological soft signs in patients with schizophrenia and their siblings

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ABSTRACT

Neurological soft signs (NSSs) and minor physical anomalies (MPAs) are consistently found at higher rates in individuals with schizophrenia compared to healthy controls. However, limited research has been conducted on these traits among the biological relatives of these patients. We aimed to identify the possible origins of these traits in schizophrenia by exploring them in patients with schizophrenia, their healthy siblings and normal controls. Ninety-six patients with schizophrenia, their 66 non-psychotic siblings and 52 healthy subjects were studied. Measures included the Neurological Evaluation Scale, a structured examination for detection of minor physical anomalies, stroop and verbal fluency tests for cognitive assessment, and scales for assessment of disease severity in patients; the Scale for the Assesment of Negative Symptoms and the Scale for the Assesment of Positive Symptoms. Increased rates of NSSs and high MPA scores were found in both the patients and their siblings as compared to normal controls. MPAs in several body regions were similar (eyes, ears, hands and feet) or correlated (innercanthal width and head circumference) between patients and their respective siblings. However, there was little similarity in palate and tongue anomalies between these subjects. These results suggest that NSSs and MPAs might represent two distinct markers of risk for schizophrenia. MPAs at different locations may also represent distinct pathological processes, such that palate and tongue abnormalities are more likely to represent non-familial rather than familial factors compared to other abnormalities.

1. Introduction

Minor physical anomalies (MPAs) are subtle morphological variations developing during early gestation and evident throughout one's individual life. These anomalies having common embryonic ectodermal origins with brain, are assumed to be markers of fetus' central nervous system (CNS) maldevelopment. This idea is plausible in the context of the 'neurodevelopmental hypothesis' of schizophrenia, which argues that schizophrenia originates from faulty brain development. MPAs have been consistently found at a higher frequency in patients with schizophrenia than in healthy individuals. There is little evidence for the etiological origins of these anomalies: i.e. Whether they are genetically or environmentally determined (Compton and Walker, 2009). Research on MPAs in relatives of patients has potential to illuminate this issue; however these studies produced mixed results. Several studies report that patients' relatives have MPA frequencies similar to those in healthy controls (Green et al., 1994; Gourion et al., 2003), while others report that they have elevated MPAs similar to patients (Ismail et al., 1998, 2000; Gourion et al., 2004a).

Neurological soft signs (NSSs) – including motor dyscoordination and mildly impaired sensory integration – are consistently found at high frequency in patients with schizophrenia and their relatives (Buchanan and Heinrichs, 1989; Bombin et al., 2005). NSSs have been shown to be markers of CNS maldevelopment as they are observable in first-episode patients (Dazzan and Murray, 2002; Bachmann et al., 2005), even prior to antipsychotic administration (Keshavan et al., 2003; Scheffer, 2004; Chen et al., 2005); and as they are found consistently at high rates in healthy children who later develop schizophrenia, long before overt manifestations of the illness (Walker and Lewine, 1990). NSSs were found to show a graded pattern of severity across investigated populations; patients having the most, healthy controls having the least, and first degree relatives having intermediate degree of these anomalies (Rossi et al., 1990),which indicates that the origin of NSSs is at least partly genetic and these anomalies might be endophenotypes (Cannon, 2005).

In this study, we investigated the rate and type of minor physical anomalies (MPAs) in patients with schizophrenia, their non-psychotic

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siblings and healthy controls. Direct comparisons between patients and their respective siblings for each subset of the MPAs were made in order to test whether these traits have a familial nature and possibly help identification of vulnerability in genetically high-risk subjects. Relation of these anomalies with neurological soft signs (NSSs) and neurocognitive functioning was also assessed for each group. Finally, we tested the usefulness of investigated traits in phenotypic characterization of schizophrenic patients.

2. Methods

2.1. Setting and sample

This is a cross-sectional study in consecutive outpatients of the psychiatry department of Cerrahpaşa Medical Faculty, University of Istanbul (Istanbul, Turkey), in the period January 2008–February 2009. A total of 213 subjects were included in the study. Patients ($n=96$) were eligible for the study if they were between 18 and 60 years of age and they had received a diagnosis of schizophrenia according to Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR, American Psychiatric Association Washington DC, 2000). Patients' healthy siblings ($n=66$) included 26 sisters and 40 brothers. Non-psychiatric controls ($n=51$) were selected from hospital staff. Exclusion criteria for all participants included active substance abuse or dependence, mental retardation, and history of neurological disease or clinically significant head injury. Exclusion criteria for siblings also included any personal history of psychotic or mood disorders. Controls were excluded if they endorsed any personal or family history (in first- or second-degree relatives) of psychotic or mood disorders. Personal history of these disorders was assessed using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID; First et al., 1996). Family history was assessed informally by participants' verbal responses to several questions. The interviews and assessments of subjects were performed by one of the authors (C.A).

2.2. Procedures and materials

The research was approved by the Istanbul University, Cerrahpaşa Medical Faculty's Ethics Committee, and all participants provided written informed consent. During a single outpatient visit, the following information was collected: patients' gender, age, marital status, educational attainment, age of disease onset, treatment response, number of hospitalizations, family history for psychotic disorders. After obtaining demographic and treatment information, the the Scale for the Assesment of Negative Symptoms (Andreasen, 1983) and the Scale for the Assesment of Positive Symptoms (Andreasen, 1984) were administered in order to assess the severity of psychopathology. The SAPS, a 34-item scale used to assess positive symptoms in schizophrenia, is designed for use in conjunction with the 25-item SANS, which is used to assess negative symptoms; scoring ranges from 0 (no abnormality) to 5 (severe). Ratings from the SAPS and SANS (Andreasen, 1982) are divided into three symptom dimensions, including positive (hallucinations and delusions), negative symptoms (affective flattening, alogia, avolition-apathy, and anhedonia-asociality), and disorganization dimension (inappropriate affect, bizarre behavior, and formal thought disorder) (Andreasen et al., 1995). The validity and reliability of SAPS and SANS have been established in Turkish (Erkoç et al., 1991a, 1991b).

The Neurological Evaluation Scale (NES) is a 26-item instrument designed to measure NSS in schizophrenia (Buchanan and Heinrichs, 1989). Evaluators administer the scale based on the original scoring instructions, and items are scored 0 (no abnormality), 1 (mild but definite impairment), or 2 (marked impairment). Two items –the suck and snout reflexes– are scored 0 (absent) or 2 (present). Fourteen items are assessed bilaterally, and right and left scores were summed for bilateral items. The possible ranges of these total scores were 0–76. Conceptually based subscales also were calculated: sensory integration, motor coordination, and sequencing of complex motor tasks (Buchanan and Heinrichs, 1989).

MPAs were recorded using a structured scale adapted from one previously described instruments (Yoshitsugu et al., 2006). In this scale, the following items from the Waldrop scale were refined: 1) head circumference; 2) epicanthus; 3) innercanthal width; 4) lowseated ears; 5) adherent ears; 6) ear asymetry; 7) heightened palate; 8) furrowed tongue; 9) curved fifth finger; 10) transverse palmar crease; 11) long third toe. Both qualitative (e.g., low seated ears) and quantitative (i.e., head and facial measurements) measures were recorded by the assessor in a standardized manner. Items excluding head circumference and innercanthal width were coded as present or absent. Total MPA score was derived by summing all qualitative items. Four regions -eyes, mouth, ears and limbs- were assessed to derive subscale/regional scores (coded as present if at least one anomaly was detected at that region or absent if no anomaly was recorded) in addition to the total score.

In order to assess the executive frontal functions, the stroop and the verbal fluency tests (number of animal names generated in 1 minute) were performed. The stroop test was conducted according to standard procedures (Perret, 1974). Briefly, each patient was requested to perform two tasks. The first 'colour task' required the patient to read the words of colour names, which was printed in colours different from the meaning of the words. The second 'colour-word task' required the patient to read the printed colour of the words. Time for completion of each tests, the numbers of correct and incorrect responses were recorded.

2.3. Data analysis

To compare continous variables between three groups, if the data showed non-normal distribution, we used one-way analysis of variance (ANOVA), if not, we used Kruskal-Wallis ANOVA; each was followed by post-hoc tests. The Mann-Whitney *U* test was used to compare ordinal data between independent groups. Categorical variables were compared with chi-square tests. For the correlational analyses of ordinal variables, Spearman's correlation coefficients were used, followed by partial correlation analyses to control for sociodemographic variables if the correlation was significant. Patients and their respective healthy siblings were also compared for significant differences of frequencies of each qualitatively assessed MPA using the McNemar test. Finally, stepwise regression analyses were carried out to predict group membership (schizophrenia versus controls) based on the predictor variables. The statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS), version 11.5. Statistical significance was established as $p<0.05$.

3. Results

3.1. Sample characteristics

Gender, age and educational attainment for the assessed groups are shown in Table 1. There was not a significant difference across groups in terms of gender, age and educational attainment.

3.2. Neurological soft signs and cognitive tests

Table 2 shows whether the difference in Neurological soft signs (NSS) and neuropsychological tests are statistically significant between patients, healthy siblings and healthy controls.

Total NSS score was significantly higher in patients compared to their siblings and healthy controls (Kruskal-Wallis; $\chi^2=91.7$, $p=0.0001$). Two of the NSS subscales (sensory integration and motor coordination) showed a graded pattern of severity between groups; i.e. highest scores in patients with schizophrenia, intermediate scores in healthy siblings and lowest scores in healthy controls.

Patients had significantly higher number of errors in stroop test I and II; they were significantly slower in completing these tests and they could count significantly fewer animal names compared with both healthy controls and healthy siblings.

When patients and respective siblings were compared for NSS scores and neurocognitive performance using Spearman correlational analyses, significant correlations between these groups were observed in 'motor coordination' subscale score ($r=0.27$; $p=0.028$), 'sequencing complex motor acts' subscale score ($r=0.28$; $p=0.021$), Stroop I test time ($r=0.3$; $p=0.01$), Stroop II test time ($r=0.4$; $p=0.001$) and Stroop II error count ($r=0.24$; $p=0.04$). However, these correlations disappeared when these variables were subsequently controlled for age or educational attainment and for both using partial correlation analyses.

3.3. Minor physical anomalies

Table 3 shows the comparisons of patients and healthy siblings with healthy controls for the frequencies of MPAs assessed qualitatively, with

Table 1
Basic demographic characteristics of the three groups.

Characteristic	Subjects ($N=213$)			
	Patients [$n=96$]	Siblings [$n=66$]	Controls [$n=51$]	P^*
Gender				
vh*Male, n (%)*	59 (61.5)	40 (60.6)	32 (62.7)	0.97[1]
Female, n (%)	37 (38.5)	26 (39.4)	19 (37.3)	
Age (year), mean ± SD	39.6 ± 12.0	37.0 ± 12.6	38.3 ± 10.3	0.39[2]
Education (year), mean ± SD	9.2 ± 3.5	9.6 ± 3.8	8.1 ± 4.1	0.12[2]

*Statistical comparison of the demographics across groups by [1]Chi-square test and [2]Kruskal-Wallis ANOVA.

Table 2
Neurological soft signs (NSS) and neurocognitive tests in patients ($N=96$), healthy siblings ($N=66$) and healthy controls ($N=51$).

	Patients (Sch)	Siblings (S)	Healthy Controls (HC)	P[3]
Total NSS[1] score	17 (11–24)[2]	8 (5.75-11)	6 (4–8)	0.0001 **(HC, S<Sch)**
NSS sensory integration	3 (2–4)	1 (1–3)	1 (0–2)	0.0001 **(HC<S<Sch)**
NSS motor coordination	1 (0–2)	0 (0–1)	0	0.0001 **(HC<S<Sch)**
NSS sequencing complex motor tasks	3 (1–6)	1 (0–3)	1 (0–2)	0.0001 **(HC, S<Sch)**
NSS other tests	9 (6.5-12.5)	3 (5–7)	4 (2–6)	0.0001 **(HC, S<Sch)**
Verbal fluency (number of animal reported in 1 minute)	12.5 ± 3.7	15.8 ± 3.3	16.6 ± 3.2	0.0001 **(HC, S>Sch)**
Stroop I test time (sec)	43 ± 20	32 ± 6.7	32.2 ± 14.6	0.0001 **(HC, S<Sch)**
Stroop II test time (sec)	53.2 ± 17.8	40 ± 10.7	40.8 ± 11.8	0.0001 **(HC, S<Sch)**
Stroop I test number of errors	0 (0–1)	0	0	0.002 **(HC, S<Sch)**
Stroop II test number of errors	2 (1–4)	1 (0–2)	1 (0–2)	0.0001 **(HC, S<Sch)**

[1] NSS = Neurological soft signs according to Neurological Evaluation Scale. [2]Median and interquartil range. [3]For the statistical analyses, Kruskal-Wallis ANOVA and post-hoc Tukey's HSD tests were used. In Post-hoc Tukey's HSD test, "<" shows that there is statistical significance between groups ($p<0.05$).

respective odds ratios. Table 3 also shows comparisons of quantitatively assessed MPAs between three groups.

Patients with schizophrenia had significantly higher total MPA scores when compared to their healthy siblings and healthy controls. Total MPA scores were highest in patients, lowest in healthy controls and intermediate in healthy siblings (Table 3).

The most frequent MPA noted in patient group were furrowed tongue (53%) and heightened palate (49%). They were also significantly more frequent among patients compared to healthy siblings (heightened palate, $\chi^2=10.9$, df = 1, $p=0.001$; furrowed tongue, $\chi^2=10.2$, df = 1, $p=0.001$).

No subject had epicanthus, and long third toe was detected only in one healthy control. Curved fifth finger and ear asymetry were significantly more frequent in patients and healthy siblings than in healthy controls. Innercanthal width and head circumference were significantly greater in patients and healthy siblings than in healthy controls. Transverse palmar crease, cuspidal ear, ear lobe adherence and low-seated ears were more frequent in both patients and healthy siblings compared to controls (most of these had OR greater than 1.5), though not at the level of significance. Strabismus was more frequent in patients compared to both controls and healthy siblings.

Comparisons were also made for three of the body regions investigated (mouth, ears and limbs). Compared to healthy controls, we detected significantly higher rates of physical anomalies at mouth, ears and limbs in patients. Compared to healthy controls, siblings had higher rates of physical anomalies at ears and limbs (though results were not at the level of significance for ears), while they had similar rates of anomalies at the mouth region.

Table 3 shows results of correlational analyses for the quantitatively assessed MPAs between patients and their respective healthy siblings. Patients and their respective healthy siblings were also compared for significant differences of frequencies of the qualitatively assessed MPAs using the McNemar test. When patients and respective siblings were compared separately for total MPA scores, innercanthal width and head circumference using Spearman correlational analyses, significant correlations between pairs were observed only for the innercanthal width ($r=0.66$; $p=0.0001$). However, since innercanthal width and head circumference were found to be gender-dependent variables in the present sample, a second step correlational analyses were performed between same-gender patient and sibling pairs ($N=33$) and it was revealed that head circumference was significantly correlated between pairs ($r=0.6$; $p=0.0001$). The correlation for the innercanthal width remained significant in this analysis.

Table 3
The frequency (percentage) of minor physical anomalies (MPAs), total MPA scores, head circumference and telecanthus width in patients with schizophrenia, non-psychotic siblings and healthy controls.

Minor physical anomalies	Patients ($n=96$) (Sch)		Siblings ($n=66$) (S)		Controls ($n=51$) (C)	ANOVA	Comparison of patient-sibling pairs[c]	Correlational analyses of patient-sibling pairs[d]
Eye								
Epicanthus	0%		0%		0%	-	-	-
Strabismus	6.3%	(OR = 3.3)	1.5%	(OR = 0.7)	2%	-	N.S.	-
Ear	53.1%	**(OR = 2.5*)**	47%	(OR = 2.1)	31.4%			
Low-seated ear	6.3%	(OR = 3.3)	3%	(OR = 1.5)	2%	-	N.S.	-
Ear lob adherence	37.5%	(OR = 1.5)	39.4%	(OR = 1.7)	27.5%	-	N.S.	-
Ear asymetry	26%	**(OR = 4.1**)**	21.2%	**(OR = 3.1*)**	7.8%	-	N.S.	-
Cuspidal ear	**9.4%***		6.1%		0%	-	N.S.	-
Mouth	80.2%	**(OR = 7.1**)**	41.5%		37.3%			
Heightened palate	49%	**(OR = 5.1**)**	23.1%	(OR = 1.6)	15.7%	-	$P=0.0001$	-
Furrowed tongue	53.1%	**(OR = 2.7**)**	27.7%	(OR = 0.9)	29.4%	-	$P=0.0001$	-
Hands-feet	40.6%	**(OR = 3.1**)**	43.9%	(OR = 3.7**)	17.6%			
Transverse palmar crease	6.3%		**9.1%***		0%	-	N.S.	-
Curved fifth finger	37.5%	**(OR = 2.8*)**	36.4%	**(OR = 2.6*)**	17.6%	-	N.S.	-
Long third toe	0%		0%		2%	-	N.S.	-
Head circumference (cm)	56.6 ± 2.0		56.2 ± 2.1		55.6 ± 2.0	.031 (C<S,Sch)[a]		nsf
Innercanthal width (mm)	394 ± 40.4		385.3 ± 44.6		363.3 ± 33.8	0001 (C<S,Sch)[a]		$P=0.0001$
Total MPA score	2 (1–3)[b]		1 (1–3)		1 (0–2)	.0001 (C<S<Sch)[b]		$P=0.07$

Comparisons of MPA frequencies (patients vs. controls and siblings vs. controls) with odds ratios (OR) were presented. Statistical comparisons (patients vs. controls and siblings vs. controls) using chi-square test were also presented *$p<0.05$; **$p<0.01$. Quantitative measures between groups (head circumference, telecathus width and total MPA scores) were compared using Kruskal-Wallis ANOVA[b] and one-way ANOVAs[a]. Included also are the comparisons of patient-sibling pairs with respect to minor physical anomaly frequencies using McNemar test[c]. Spearman correlational analyses[d] were performed between patient-sibling pairs for head circumference, telecathus width and total MPA scores. Total MPA scores in the table were presented as median and interquartile range.

When patients and respective siblings were compared for the presence of each of the MPAs using the McNemar test, only the anomalies of heightened palate and furrowed tongue were found significantly more frequent in patients compared to their respective siblings.

3.4. Associations between neurological soft signs and minor physical anomalies

Total NSS scores were not significantly correlated with total MPA score in the overall sample using Spearmen correlations. When the three groups were assessed separately, total NSS scores were not associated with total MPA scores in any of the groups.

3.5. Associations of patients' symptoms with NSSs, MPAs and neurocognitive functioning

Total NSS score was significantly associated with SANS score ($r=0.6$; $p=0.0001$); and the disorganization dimension ($r=0.38$; $p=0.0001$). In general, both negative symptoms and disorganized symptoms were directly associated with all of the NSS subscales. Controlling for the effects of age, gender and educational status using partial correlations had no effect in these associations.

Among the patients, total MPA scores were not significantly associated with any of the following items: age, educational attainment, age of onset, number of hospitalizations, neuropsychological test scores, total NSS scores, NSS subscales scores or any of the 'severity of illness' parameters (SANS, SAPS and disorganization dimension).

3.6. Regression analysis

Age, gender and variables showing an odds ratio greater than 2 or a p less than 0.05 in the bivariate analyses between patients and controls (total NSS scores, verbal fluency, stroop I test time/number of errors, stroop II test time/number of errors, head circumference, total MPA score, innercanthal width and presence of strabismus, furrowed tongue, heightened palate, low-seated ears, ear asymetry, cuspidal ears and curved fifth finger; see Tables 1, 2 and 3) were entered in the stepwise logistic regression analysis that was performed to predict group membership of subjects (patients $n=89$ versus healthy controls $n=46$). Continuous predictors had been mean-centered before interactions were made in order to avoid multicollinearity. Following variables were shown to be independent predictors of schizophrenia: Total NSS score, total MPA scores and head circumference. This final regression model (Table 4) predicted 90% of patients and 85% of healthy controls accurately ($\chi^2=113$, df$=3$, $p=0.0001$).

4. Discussion

In the present study, overall minor physical anomaly (MPA) scores were found to be greater in patients than controls, and siblings of patients had scores in between these groups. However, when each of the MPAs were investigated separately, different patterns of distribution across groups were observed for the investigated body regions (i.e. mouth, limb and ear). In general, *limb* and *ear* anomalies were found more frequently in both patients and their siblings compared to controls. Patients and their respective siblings also had a fairly correlated amount of anomalies in limb and ear regions. *Mouth* anomalies, however were prevalent only in patients (furrowed tongue in 53% and heightened palate in 49% of the patients) and these anomalies did not show correlation between patients and their respective siblings. Also, when tongue and palate anomalies were excluded from the statistical analyses, the difference between patients and their healthy siblings for the total MPA score completely disappeared. *Head circumference* and *innercanthal width* were found to be significantly greater in patients and healthy siblings than controls, and these parameters seemed to be correlated between patients and their respective siblings (such that siblings of patients with greater head circumference and innercanthal width had these measurements greater or vice versa).

Table 4
Independent predictors of schizophrenia.

	B	*Wald* χ^2	*p*	Odds ratio
Neurological soft signs (total score)	0.48	21.8	0.0001	1.6
Minor physical anomalies (total score)	1.19	12.2	0.0001	3.2
Head circumference	0.51	7.4	0.006	1.6

These findings provide clues for a novel idea that minor physical anomalies at different localizations might represent different pathological origins; i.e. familial versus non-familial. In this study, ear and limb anomalies as well as greater head circumference and innercanthal width were found to be correlated between patients and their healthy siblings. This indicates that these traits might in deed reflect a familial (or at least partly genetic) predisposition for schizophrenia in an individual. Similar correlations of MPAs between patients and siblings were reported at eyes, hands (Compton et al., 2007) and ears (Ismail et al. 2000; Compton et al. 2007) in previous studies. In contrast, mouth anomalies (palatal and tongue anomalies) which we determined as highly specific to patients with schizophrenia might represent a direct link with a specific disease process, and/or might be markers of a "second hit" distinguishing genetically predisposed individuals who will develop the disease from those who will not. This latter finding is in line with the concept proposed by Waddington et al. (1999), which states that mouth and particularly the palatal anomalies referred to also as 'midline anomalies' represent a pathological brain morphogenesis, as evidence has been found for intimate developmental relationship between the craniofacial region and fetal midline and temporal lobe brain structures. An early insult in the first trimester thus might eventually lead to a faulty development of these closely related structures. In parallel with this, in a study involving patients with schizophrenia, healthy controls and unaffected first-degree relatives of patients with schizophrenia, Turetsky et al. (2007) found that male patients had smaller posterior nasal volumes than both male relatives and male controls, and they concluded that posterior nasal volume decrement is an abnormality –potentially environmentally rather than genetically mediated- that appears to be specific to male schizophrenic patients. They finally concluded that posterior nasal volume might be a specific craniofacial abnormality that may potentially distinguish genetically vulnerable men who go on to develop schizophrenia from those who do not. This is similar to our conclusion in that mouth and posterior nasal area might both represent 'midline structures' mentioned above.

This study replicated the finding that in patients with schizophrenia, neurological soft signs (NSSs) are associated with negative and disorganization symptoms, and frontal lobe executive functions as shown by stroop and category tests. The relationship between MPAs and cognitive dysfunction in schizophrenic patients is so far, unclear (Ismail et al., 2000). In this study, we could not find evidence for association of MPAs with cognitive performance and disease symptoms. Neurological soft signs and minor physical anomalies were found to be unrelated in our subjects, a finding reported by numerous previous studies (Ismail et al., 2000; Lawrie et al., 2001; O'Reilly et al., 2001; Gourion et al., 2003; Compton et al., 2007; John et al., 2008). So far, significant positive correlations between NSS and MPA scores in patients and their relatives were reported only in two studies (Nizamie et al., 1989; Gourion et al. 2004b). This suggests that NSSs and MPAs may be independent markers of predisposition toward schizophrenia, which also means that they would afford greater predictive validity when used as a composite endophenotype in genetic association studies (Ismail et al., 2000;

Compton et al., 2007; John et al., 2008). In our study, we could classify 90% of patients and 85% of healthy controls accurately by including subjects' total NSS scores, total MPA scores and head circumferences as predictors in a final regression model.

This study confirmed that NSSs show associations with negative and disorganized symptoms in schizophrenia. In contrast, correlations between MPAs and symptom domains were not apparent, consistent with prior reports (Arango et al., 2000; Ismail et al., 2000; Gourion et al., 2003; Compton et al., 2007). The well-replicated relationship between negative symptoms and NSSs suggests that NSSs are a part of the negative symptoms or both share a common ethiopathological process (Whitty et al., 2006).

Our findings on several domains of NSSs (i.e. sensory integration and motor coordination) are consistent with extant literature showing a graded pattern of NSS severity, with healthy relatives having an intermediate number of these anomalies between patients and controls (Rossi et al., 1990; Egan et al., 2001; Schubert and McNeil, 2004; Compton et al. 2007). This suggests that at least part of the NSSs reflect an underlying genetic vulnerability to schizophrenia. In our study, *motor coordination* and *sensorial integration* defects were found to be significantly increased in both patients and their siblings compared to the healthy controls. In parallel with this, previous researchers noted especially motor coordination deficits among the NSS domains to be significantly raised in patients and their relatives (Gourion et al. 2004b; Mechri et al., 2009). Additionally, this was reported as the only NSS domain found abnormal in schizophrenic patients independent of low intelligence (Arango et al., 1999; Dazzan et al., 2008). These findings thus indicate that motor dyscoordination may be particularly specific to the schizophrenic pathology and may as well reflect an underlying genetic vulnerability to schizophrenia.

Several methodological limitations of this study should be considered. The assessor could not be feasibly blinded to participants' group status when assessing NSSs and MPAs. However, standardized instruments were used for both indices. As- the patients were on various antipsychotic medications (and often as combinations) during assessments, potential medication effects on NSSs could not be examined. Antipsychotics have been found to exacerbate particularly motor functions (Gupta et al., 1995; Emsley et al., 2005), however there is strong evidence that neurological abnormalities are present also in antipsychotic-naive patients (Keshavan et al., 2003; Scheffer, 2004; Chen et al., 2005) indicating that NSSs occur independently of antipsychotic side effects. Finally, some healthy siblings of patients were still at high risk age interval, which means that they could be at prodromal or premorbid stage of the illness.

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