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Cortical Thickness correlates of minor neurological signs in patients with first episode psychosis

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ABSTRACT

Neurological soft signs (NSS) are subtle abnormalities of motor and sensory function that are present in the absence of localized brain pathological lesions. In psychoses they have been consistently associated with a distinct pattern of cortical and subcortical brain structural alterations at the level of the heteromodal cortex and basal ganglia. However, a more specific and accurate evaluation of the cytoarchitecture of the cortical mantle could further advance our understanding of the neurobiological substrate of psychosis.

We investigated the relationship between brain structure and NSS in a sample of 66 patients at their first episode of psychosis. We used the Neurological Evaluation Scale for neurological assessment and high-resolution MRI and Freesurfer to explore cortical thickness and surface area. Higher rates of NSS were associated with a reduction of cortical thickness in the precentral and postcentral gyri, inferior-parietal, superior temporal, and fusiform gyri. Higher rates of NSS were also associated with smaller surface areas of superior temporal gyrus and frontal regions (including middle frontal, superior and orbito-frontal gyri). Finally, more sensory integration signs were also associated with larger surface area of the latero-occipital region.

We conclude that the presence of NSS in psychosis is associated with distinct but widespread changes in cortical thickness and surface area, in areas crucial for sensory-motor integration and for the fluid execution of movement. Studying these morphological correlates with advanced neuroimaging techniques can continue to improve our knowledge on the neurobiological substrate of these important functional correlates of psychosis.

INTRODUCTION

Minor neurological signs, or neurological soft signs (NSS) are subtle abnormalities of motor and sensory function that are present in the absence of localized brain damage, in contrast with the "hard" sensory or motor neurological impairments that can result from focal lesions for example in primary sensory or motor areas. They have been proposed to represent biological markers for psychiatric disorders, including affective and non-affective psychoses (Tosato & Dazzan, 2005). Although not localized to specific brain regions, their presence in psychoses has now been consistently associated with a distinct pattern of cortical and subcortical brain structural alterations, including at the level of the heteromodal cortex and basal ganglia in a number of studies, including in work from our group (Bachmann *et al.*, 2014, Chan and Gottesman, 2008, Dazzan *et al.*, 2004, Gay *et al.*, 2013). At cortical level, neurological signs in patients with psychosis have been particularly associated with volume reductions of prefrontal, and precentral and postcentral gyri, and more occasionally with superior and middle temporal gyri, as also confirmed by a recent meta-analysis (Dazzan et al., 2004; Thomann et al., 2009; Zhao et al., 2014).

Still, these studies used voxel-based measures of regional volume only. In contrast, more recent approaches can provide an estimate of cortical morphology beyond volume, and generate measures of both cortical thickness and surface area, two important components of volume. These measures offer a more specific and accurate, albeit indirect, evaluation of the cytoarchitecture of the cortical mantle. For example, cortical thickness is considered to represent

a measure of dendritic arborization and pruning, while surface area provides information about gyrification and folding (Wagstyl *et al.*, 2015). Since they originate from different progenitor cells and reflect distinct developmental trajectories (Ecker et al., 2015), studying them together is crucial to understanding the neurobiological basis of the relationship reported between cortical volumes and minor neurological signs.

To date, only few studies to date have examined the relationship between minor neurological signs and cortical thickness and surface area in psychosis, and none has specifically evaluated patients at illness onset (Hirjak et al., 2016, 2014; Kong et al., 2015). In fact, those that have examined this relationship have used small samples of patients with a chronic illness, or alternatively healthy controls (Kong *et al.*, 2015). Indeed, even in one study that evaluated 28 patients with recent onset schizophrenia, this was defined with a duration of up to 2 years (Hirjak *et al.*, 2014; Hirjak et al., 2016). In these patients, the authors found that higher neurological signs scores were negatively correlated with thinner cortex of somatosensory and motor areas, and thicker cortex of temporal areas. However, studying these relationships in patients at their first psychotic episode can advance these findings as it limits the potential confounding effects of long term pharmacological treatment, and of long term illness duration. This is exactly what we have done in this study, which expand our previous work in a new, large cohort of patients with first episode psychosis, providing the first evaluation of cortical thickness correlates of neurological signs at psychosis onset.

Based on the above-mentioned evidence of an association between neurological signs and smaller volumes of frontal and parietal sensory-motor areas, we hypothesized that higher rates of

minor neurological signs would be associated with reductions in cortical thickness and surface area of these same regions.

METHODS

We evaluated a sample of 66 individuals aged 18 – 65, who presented to inpatients and outpatients services of the South London and Maudsley NHS Foundation Trust with a first episode of a functional (i.e. in absence of any organic cause) psychotic illness (meeting ICD10 criteria for a diagnosis of non-affective (F20-F29) and affective (F30-F33) psychosis (World Health Organization, 1992)) (Reis Marques *et al.*, 2014). The mean duration of illness (including the duration of untreated illness) was 37 weeks Ethical permission was obtained from the Institute of Psychiatry, Psychology and Neuroscience Ethics Committee, and written informed consent was obtained from all participants after a complete description of the study.

Patients were excluded if they reported a history of head trauma or injury with loss of consciousness longer than 1 h; current or past organic psychosis; learning disabilities or lack of English fluency (for details, see Reis Marques *et al.*, 2014). All patients underwent clinical and Magnetic Resonance Imaging (MRI) assessments, as soon as possible after their first contact with services. Characteristics of the sample are shown in Table 1. From the original sample, five subjects did not complete two or more subscales of the Neurological Evaluation Scale and one subject had an MRI scan that failed processing (see below), and these subjects were therefore excluded from further analyses.

[Table 1]

[Table 2]

Clinical and neurological assessment

Diagnosis was made using the Operational Criteria (OPCRIT) (McGuffin *et al.*, 1991), according to the International Statistical Classification of Diseases and Related Health Problems - 10th Revision (ICD-10) criteria, using patient clinical notes for the month after their first contact with psychiatric services. All diagnoses were performed by qualified psychiatrists, subject to comprehensive training and achievement of good inter-rater reliability testing (kappa=0.91). Patients with a diagnosis of Bipolar disorder or Major Depression with psychotic symptoms were included in the affective psychosis group, while patients with Schizophrenia, Schizophreniform Disorder and Psychosis not Otherwise Specified formed the non-affective psychosis group.

Severity of psychotic symptoms was evaluated on the day of MRI using the Positive and Negative Syndrome Scale (PANSS) (Kay *et al.*, 1987). Information on antipsychotic drugs dose were collected during face-to-face interviews, from clinical notes and from interviews with the clinical team. All participants were treated with second generation antipsychotic (43% with Olanzapine, 31% with Risperidone, 17% with Aripiprazole and 9 % with Quetiapine). Antipsychotic doses were converted into chlorpromazine equivalents, according to defined criteria (Atkins, 1997, Woods, 2003), to estimate the total chlorpromazine-equivalent exposure. This was calculated by summing all daily doses from the first day of treatment with antipsychotics up to the day of MRI (mean exposure was 47 days).

An expanded version of the Neurological Evaluation Scale (NES) (Buchanan and Heinrichs, 1989, Dazzan *et al.*, 2004) was used to evaluate neurological function. The scale was administered as soon as possible after initial presentation. This expanded version consists of four subscales corresponding to different functional domains. Specifically, the "*Primary neurological dysfunction*" subscale (reflecting a dysfunction that can be identified by a standard neurological examination, such as reflexes, abnormal eye movement, and lateralising limb pyramidal signs); the "*Sensory Integration dysfunction*" subscale (examining the integration of sensory information and including signs such as extinction, right/left confusion, and audio-visual integration); the "*Motor Coordination dysfunction*" subscale (evaluating motor incoordination with tests such as tandem walk, finger-to-thumb opposition and finger-to-nose test); and finally, the "*Motor Sequencing dysfunction*" subscale (estimating difficulties in performing complex motor sequences with tests like the fist-edge-palm). Each item is evaluated on a scale ranging from 0 (i.e. no abnormality) to 2 (i.e. marked impairment) and 1 as an intermediate criterion. The total score can vary from 0 to 52, with higher scores highlighting more pronounced impairment. The scale was administered in a standardized and fixed order.

As there are no clearly defined cut-off scores with high discriminant values for NES, consistently with our previous work (Dazzan *et al.*, 2004), participants were divided into two groups, with "High" and "Low" neurological signs based on the median of their scores on the NES, for each NES subscale (i.e. Primary, Sensory Integration, Motor Coordination, Motor Sequencing) as well as for the total NES score (Table 2). There were no significant differences in age, level of education, gender, total PANSS score or antipsychotic exposure between patients in the High and Low score groups, for any of the NES subscales or in the Total score (Table 2). Individuals

with an affective psychosis were significantly more likely to be in the High score than Low score groups for all NES subscales as well as the Total score (Table 2).

Structural MRI acquisition

All MRI scans were acquired in a 3-T Signa HDx scanner (General Electric) at the Centre for Neuroimaging Sciences, Institute of Psychiatry, Psychology and Neuroscience (London, United Kingdom). A sagittal 3-dimensional magnetization-prepared rapid-acquisition gradient-echo volumetric scan was obtained from each subject. The scan had an image matrix size of 256 × 256 × 166 voxels, with an in-plane voxel size of 1.02 × 1.02 mm and a slice thickness of 1.2 mm (echo time, 2.848 milliseconds; repetition time, 6.988 milliseconds; inversion time, 650 milliseconds; excitation flip angle, 20°; 1 data average). Full brain and skull coverage was required for the MRI data sets.

Structural MRI processing

T1-weighted images were used to evaluate cortical thickness across the entire cerebral cortex. Images were processed with Freesurfer, version 5.3.0 (http://freesurfer.net/fswiki), which provides automated analysis and visualization of brain structures from structural neuroimaging data (Fischl and Dale, 2000, Fischl *et al.*, 1999, Fischl *et al.*, 2004). The images were reconstructed with the "recon-all" command line in FreeSurfer version 5.3.0. This consists of several stages which comprise registering the images with the Talairach atlas, segmentation based on voxel intensity and the characteristics of the tissues around them (neighbour

constraints), generation of the outer boundaries of the white matter, redefinition of this surface is then refined to follow the intensity gradients between the white and grey matter (white matter surface), generation of the pial surface following the intensity gradients between grey matter and CSF, intensity normalisation, tessellation of the grey matter-white matter boundary and the grey matter-CSF boundary, and automated topology correction (Fischl *et al.*, 1999). The quality of the reconstruction of each image was checked manually and modified if needed according to Freesurfer guidelines (http://freesurfer.net/fswiki/FsTutorial/TroubleshootingData). Thirty-seven subjects showed imprecise boundary in the pial surface, and 19 presented inaccuracies in white matter segmentation. For these subjects, the Recon-all command was re-ran to implement manual corrections. One subject was excluded from the analysis as these corrections could not be successfully implemented.

Statistical analyses

Between-group differences were tested with parametric tests as appropriate, all using Statistical Package for Social Science 22 (SPSS Com., USA).

Differences in cortical thickness and cortical surface area between subjects with High and Low neurological signs were explored in a whole-brain vertex-wise analysis for each NES subscale, as well as for total NES score. Age at time of MRI scan and level of education were included in the models as covariates of no interest. Average cortical thickness and surface were also included as covariates of no interest in the respective analyses, in order to account for differences in head size (which strictly correlates with gender) (Lüders et al., 2002; Sowell et al., 2003). Query,

Design, Estimate Contrast (QDEC) interface was used to run the analyses (included in Freesurfer 5.3.0 package). Finally, correction for multiple comparisons with permutation testing with Monte Carlo simulation and cluster analysis was used to identify statistically significant differences in cortical thickness and surface area between groups. The fundamental hypothesis of this approach is that random oscillation of cortical thickness differences are unlikely to cluster in space; thus the analysis is repeated 10,000 times with arbitrary group labels in order to generate a distribution under the null hypothesis of no difference between groups (Nichols and Holmes 2002; Pereira et al. 2012; Oertel-Knochel et al. 2013). The simulation yields the minimum cluster size for the comparison based on a probability threshold that we set at $p < 0.05$. Thus we report differences when significant at $p<0.05$ after correction for multiple comparisons.

RESULTS

Group Scores for Neurological Soft Signs

The total score for NES as well as the median for each subscale are reported in Table 2. Differences between patients with high and low NSS for social demographic and clinical characteristics at each subscale are shown in Table 1. Twenty subjects were above the median of all four subscales, while 30 were below the median for all subscales. None of the participants was drug-free at time of the neurological evaluation.

[Table 3 and Table 4]

Neurological Soft Signs and Cortical Thickness and Surface Area

Primary Neurological Dysfunction

Participants with High Primary Neurological Dysfunction showed significantly thicker cortex in the left superior-parietal gyrus ($p=0.03$) (Figure 1 and Table 3) compared to those with Low Primary Neurological Dysfunction. Moreover, individuals with High Primary Neurological Dysfunction had a significantly smaller surface area of the left lingual gyrus ($p<0.001$), superior temporal sulcus, rostral middle frontal gyrus ($p<0.001$) and pars triangularis of the inferior frontal gyrus ($p=0.03$), than those with Low Primary Neurological Dysfunction (Figure 2 and Table 4). All areas reported survived correction for multiple comparisons.

Sensory Integration Dysfunction

Compared to those with Low Sensory Integration Dysfunction signs, patients with High Sensory Integration Dysfunction had a thinner cortex in the precentral ($p<0.001$) and postcentral ($p = 0.03$) gyri of the left hemisphere (Figure 1 and Table 3). Furthermore, patients with High Sensory Integration Dysfunction had larger surface area of the right latero-occipital area ($p<0.001$), compared to those with Low Sensory Integration Dysfunction on this NES subscale (Figure 2 and Table 4). All areas reported survived correction for multiple comparisons.

Motor Coordination Dysfunction

Individuals with High Motor Coordination Dysfunction signs showed a significantly thinner cortex in the left inferior parietal ($p<0.001$), superior temporal ($p=0.01$) and fusiform ($p<0.001$) gyri than those with Low Motor Coordination Dysfunction (Figure 1 and Table 3). Participants with High Motor Coordination Dysfunction also showed smaller surface area of the right superior frontal ($p<0.0001$) and latero-orbito-frontal ($p<0.0001$) gyri, compared to those with Low Motor Coordination Dysfunction (Figure 2 and Table 4). All areas reported survived correction for multiple comparisons.

Motor Sequencing Dysfunction

There were no differences in cortical thickness or surface area between patients with High and

Low Motor Sequencing Dysfunction.

Total neurological Dysfunction

There were no differences in cortical thickness or surface area between patients with High and Low Total neurological dysfunction.

DISCUSSION

This is the first study that has investigated the relationship between neurological signs and cortical thickness and surface area in patients at the first onset of psychosis. We have shown that higher rates of neurological signs are associated with a reduction of cortical thickness in areas important for motor function as well as sensory and emotional processing, including the precentral and postcentral gyri, inferior-parietal, superior temporal, and fusiform gyri. Furthermore, we have shown that higher rates of primary and motor signs are also associated with smaller surface areas of superior temporal gyrus and frontal regions (including middle frontal, superior and orbito-frontal gyri). Interestingly, more sensory integration signs were additionally associated with larger surface area of the latero-occipital region.

We found that higher rates of sensory integrative signs were associated with thinner cortex of left postcentral and precentral gyri. These findings are consistent with previous reports of thinner precentral and postcentral regions in individuals in more advanced stages of schizophrenia and worse neurological function (Hirjak *et al.*, 2014, Kong *et al.*, 2015). The postcentral gyrus is the site of the primary somatosensory cortex, which receives sensory information from the somatic senses, and plays an important role in language processing, attention, spatial working memory and touch (Bellani *et al.*, 2010). Relevant to this, this area has also been found to be smaller in volume and altered in neuronal function (as abnormal BOLD response in functional MRI studies) in patients with psychosis and more neurological signs (Heuser *et al.*, 2011, Schroder *et al.*, 1999, Thomann *et al.*, 2009). The finding that in our study sensory integrative signs were also associated with a thinner cortex of the precentral gyrus is consistent with our previous report of smaller volume in this area in patients with first episode psychosis and more difficulties in

sensory integration (Dazzan *et al.*, 2004). The precentral gyrus is the site of the primary motor area, which controls voluntary movements. The pyramidal neurons in this area project to subcortical structures and control somatic movements, and integrate complex sensory and motor information (DeLong, 2000). Interestingly, more sensory integration difficulties were also associated with larger surface area of the latero-occipital region. This area plays a central role in object perception and recognition and in the integration of different perceptual elements, and has been found to show abnormal activity during visual masking and contour integration tasks in patients with schizophrenia (Silverstein *et al.*, 2015).

Those patients with more motor coordination problems showed thinner cortex of inferior parietal lobule (IPL), fusiform, and superior temporal gyri. The IPL is an area involved with perceptual functions, as well as in social cognition, working memory, sustained attention (Palaniyappan and Liddle, 2012). However, evidence from patients with IPL lesions also shows that this region is involved in the ability to initiate movements towards a visual target, suggesting it also operates as a sensorimotor interface (Mattingley *et al.*, 1998). Its relationship with more motor signs is supported by various studies that found this region to be smaller in volume and thickness in patients with psychosis (Heuser *et al.*, 2011, Hirjak *et al.*, 2014) and in individuals without psychosis (Hirjak *et al.*, 2016). This is not surprising since the IPL is directly connected to regions important for the execution of motor task, including premotor areas, the anterior cingulate and the dorsolateral prefrontal cortex. We found that motor coordination problems were also associated with a thinner cortex of the superior temporal and fusiform gyri. The superior temporal gyrus is functionally identified as the primary auditory cortex. However, in this region perceptual and motor processes are closely integrated to influence coordinative

stability. This is supported for example by evidence that activity of this area during the execution of finger-thumb opposition is modulated by both the presence of movement and the nature of the coordination (Oullier *et al.*, 2005). Together with the fusiform gyrus, and the inferior-parietal area, these regions could play a crucial role in the recognition and interpretation of sensory information needed for coordinative stability. In addition to thickness reductions, we found that patients with coordination deficits also had smaller surface area of the superior frontal and orbito-frontal gyri. The latter is part of a cortical-subcortical loop, and is involved in social and emotional behavior and, relevant to our findings, plays an important role in executive function (Bonelli and Cummings, 2007). Crucially, patients with orbito-frontal dysfunction have difficulties inhibiting their motor behavior during task execution when requested.

Subjects with more Primary signs showed thicker cortex in the left superior-parietal gyrus. The superior-parietal area is associated with sensory input and motor output signals, and is thought to provide coherent internal evaluation of the state of both the external world and one's own body (Gay *et al.*, 2013). Although the increased thickness may appear somewhat counterintuitive, this finding is similar to what reported by Hirjak and colleagues (2014), who found an association between more neurological signs and increased thickness of parietal areas in individuals with recent onset (within two years) schizophrenia. As suggested by these authors, this increase in thickness in early illness stages could reflect a compensatory mechanism that would allow to maintain optimal sensorimotor and language functions, in face of alterations in other primary frontal and parietal regions (Cobia *et al.*, 2012). Individuals with more Primary signs also showed a smaller surface area of the left lingual, superior temporal sulcus, rostral-middle frontal, and pars triangularis surface. The involvement of frontal areas is not surprising, since the

primary subscales evaluates a number of frontal release signs which appear in relation to frontal lobe pathology. The smaller area of the pars triangularis is particularly interesting, as this area has been found to be activated during action observation but not during imitation, and one of the signs evaluated in the primary subscale is mirror movements during the execution of the finger-thumb opposition test. The lingual area is considered fundamental in the integration of visual-sensory aspects (Dazzan *et al*, 2004). Together with the bank of superior temporal sulcus, these regions are involved in linking sensory encoding and motor output, functions that are important for the execution of tests included in this scale.

Taken together, our findings support the presence of a distributed pattern of cortical morphological alterations that underlie minor neurological signs reported in psychosis. This is not surprising considering that these signs are by definition not focal, but rather seem to reflect a deficit in the ability of various brain regions to integrate not only information from different sensory modalities, but also the sensory and motor information needed for the fluent execution of coordinated movement. Here we confirm our previous findings on the volume correlates of neurological signs in first episode psychosis, showing that these signs are also associated with other morphological features such as thickness and surface area. Cortical thickness and surface area analyses are of increasing interest in psychiatric disorders, as well as in normal development and neurodegenerative disorders, as they provide more detailed information about the different components of any observed volume change. Cortical thickness and surface area have different genetic origins, and distinct developmental trajectories (Panizzon *et al.*, 2009, Raznahan *et al.*, 2011). While cortical thickness is thought to reflect dendritic arborisation and pruning (Huttenlocher, 1990), surface area is thought to reflect folding and gyrification, which occur

during embryogenesis (Rakic, 2009). The fact that they reflect different biological processes can therefore provide important information about the neurobiological alterations that underlie any observed volume reduction (or increase). Distributed thinning of the cortex has been consistently reported in patients with schizophrenia in comparison to healthy controls (Gong *et al.*, 2016), and this study confirms that the minor neurological signs found in excess in these patients may be the functional correlates of these widespread alterations.

One of the main strengths of this study is the large number of patients examined, together with the fact that these patients were all at their first episode of psychosis. This is the first study that, to our knowledge, has examined both cortical thickness and surface area to better evaluate the cytoarchitecture of the cortical mantle in relation to neurological function at this early illness stage. This is particularly important, since brain morphological features can be affected by long term exposure to antipsychotic, or to prolonged illness duration, factors that were unlikely to be present in our sample. Still, we could not completely rule out a potential effect of medications on both cortical thickness and surface area as our patients were not completely antipsychotic-naïve. Still, we found no differences in the cumulative exposure to antipsychotics between those "high" and " Low" in NSS. Furthermore, our sample included individuals with both affective and non-affective psychoses. While it could have been potentially interesting to investigate differences or similarities in NSS-related regions across different diagnostic groups, our sample size was not sufficiently large to allow such investigation. Of note, we have previously reported, in a separate, much larger sample of 310 patients with first episode affective and non-affective psychoses that there was no difference across diagnostic groups in total NSS scores or in any of the NSS subscales (Dazzan et al., 2008). Finally, we intentionally did not include in this study a

group of individuals without psychosis. We used this design, as we were interested in the cortical correlates of neurological signs in relation to psychosis. Comparing patients and controls would introduce a main confounder: the fact that patients suffer from psychosis while the controls do not. This would make it difficult to distinguish what is related to neurological signs and what is related to psychosis. For this reason, we believe that comparing two patient groups different only in their level of neurological signs is more informative of the brain differences that characterize the subgroup of patients with a more marked neurological dysfunction.

Conclusion

This study suggests that, already at the first episode of illness, the presence of minor neurological signs is associated with distinct but widespread changes in cortical thickness and surface area, in areas crucial for the integration of sensory and motor information and for the fluid execution of movement. Studying these morphological correlates with advanced neuroimaging techniques and multimodal approaches can continue to advance our knowledge on the neurobiological substrate of these important neurological correlates of psychotic disorders, and of their clinical meaning. This would contribute to identifying a biological basis for the stratification of psychosis patients into more homogeneous, clinically distinct subgroups. The individual biological abnormalities identified could eventually help developing individualized treatments for better clinical outcomes.

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Table 1. Socio-demographic and clinical characteristics of the sample

Characteristic		Patients (n = 60)	
		n	*SD*
Age at MRI (mean years)		27.65	7.94
Male/Female		20/40	
Diagnosis (affective psychosis/non-affective psychosis)		23/37	
PANSS Total Score		59.6	
Level of education		2.38	1.30
Total NES score		14.80	11.87
Primary neurological dysfunction		8.30	6.73
Sensory Integration dysfunction		2.43	1.95
Motor Coordination dysfunction		1.11	1.79
Motor Sequencing dysfunction		2.38	2.63
Chlorpromazine equivalent total estimate at MRI date (mg)		10686.94	17029.78
		Statistical comparison	
		t test (df)	*P value*
Primary neurological dysfunction	High group / Low group (26/34)	-7.6 (28.7)	**<0.001**
	Age in years when the MRI was done	0.54 (57)	0.95
	Level of education	1.61 (1) (x^2 *test*)	0.11
	Gender	1.41 (1) (x^2 *test*)	0.71
	Diagnosis	23.2 (1) (x^2 *test*)	**<0.001**
	PANSS Total Score	1.67	0.10
Sensory Integration Dysfunction	High group / Low group (25/35)	10.39 (58)	**<0.001**
	Age in years when the MRI was done	-0.49 (57)	0.62
	Level of education	-0.68 (1) (x^2 *test*)	0.49
	Gender	1.20 (1) (x^2 *test*)	0.68
	Diagnosis	24.0 (1) (x^2 *test*)	**<0.001**
	PANSS Total Score	1.58	0.09
Motor Coordination dysfunction	High group / Low group (23/37)	-7.58 (22)	**<0.001**
	Age in years when the MRI was done	1.47 (57)	0.15
	Level of education	1.14 (1) (x^2 *test*)	0.26
	Gender	1.32 (1) (x^2 *test*)	0.68
	Diagnosis	22.78 (1) (x^2 *test*)	**<0.001**
	PANSS Total Score	1.70	0.11
Motor Sequencing dysfunction	High group / Low group (26/34)	-13.3 (31.4)	**<0.001**
	Age in years when the MRI was done	-0.44 (57)	0.66
	Level of education	0.79 (1) (x^2 *test*)	0.43
	Gender	1.40 (1) (x^2 *test*)	0.70
	Diagnosis	23.57 (1) (x^2 *test*)	**<0.001**
	PANSS Total Score	1.60	0.98
Total	High group / Low group (29/31)	-7.57 (32.4)	**<0.001**
	Age in years when the MRI was done	-1.01 (57)	0.32
	Level of education	0.22 (1) (x^2 *test*)	0.83
	Gender	1.41 (1) (x^2 *test*)	0.71
	Diagnosis	23.18 (1) (x^2 *test*)	**<0.001**
	PANSS Total Score	1.67	0.10

Table 2. Mean, Median and Cut off for each neurological subscale

Neurological signs	Mean	Median (25^{th},75^{th} percentiles)	Patients above/below the median (*n*)
Primary neurological	8.30	7 (4, 11)	26/34
Sensory Integration	2.43	2 (1, 4)	25/35
Motor Coordination	1.11	0 (0, 2)	23/37
Motor Sequencing	2.38	2 (0, 4)	26/34
Total	14.80	12 (7, 19)	29/31

Table 3 Anatomical structures showing significant differences in cortical thickness between patients with high and low scores in NSS subscales; numbers refer to brain areas in figure 1

Anatomical area	Size (mm^2)	Location of cluster centre (x, y, z)
Thicker cortex in subjects high for *Primary neurological dysfunction*		
Left superior-parietal gyrus (1)	784.49	-6.8 -80.6 34.9
Thinner cortex in subjects high for *Motor Coordination dysfunction*		
Left pre-central gyrus (2)	1224.64	-13.5 -13.7 61.4
Left post-central gyrus (3)	771.32	-36.0 -29.4 61.1
Thinner cortex in subjects high for *Motor Sequencing dysfunction*		
Left inferior-parietal gyrus (4)	4022.45	-28.2 -62.8 38.1
Left superior-temporal gyrus (5)	1100.43	-63.3 -38.9 12.8
Left fusiform gyrus (6)	969.68	35.8 -73.5 -8.2

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Table 4 Anatomical structures showing significant differences in cortical surface between patients with high and low scores in NSS subscales; numbers refer to brain areas in figure 2

Anatomical area	Size (mm^2)	Location of cluster centre (x, y, z)
Smaller surface area in subjects high for *Primary neurological dysfunction*		
Left lingual gyrus (1)	5570.95	-26.5 -43.2 -3.6
Left superior-temporal sulcus (2)	2796.07	-60.7 -33.4 5.9
Left rostral-middle-frontal gyrus (3)	2511.72	-24.9 25.4 29.7
Left pars triangularis (4)	1517.62	-48.5 33.6 -2.5
Larger surface area in subjects high for *Motor Coordination dysfunction*		
Right lateral-occipital gyrus (5)	3130.23	27.1 -77.8 -2.7
Smaller surface area in subjects high for *Motor Sequencing dysfunction*		
Right superior-frontal gyrus (6)	139802	7.5 0.8 54.9
Right lateral-orbito-frontal gyrus (7)	5789.71	41.8 25.0 -12.8

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Table 4 Anatomical structures showing significant differences in cortical surface between patients with high and low scores in NSS subscales; numbers refer to brain areas in figure 2

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