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Cortex Morphology in First-Episode Psychosis Patients With Neurological Soft Signs

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Schizophrenia is a complex brain disorder associated with numerous etiological factors and pathophysiological pathways leading to multiple clinical outcomes. Compelling evidence suggests that deviations in neurodevelopmental processes are a major risk factor of schizophrenia. The identification of patients with high neurodevelopmental deviance is an important issue as it could help to identify homogeneous subgroups of patients with similar pathophysiological pathways, a key step to decipher the etiology of this complex condition. Several clinical arguments suggest that schizophrenia patients with Neurological Soft Signs (NSS)—ie, observable defects in motor coordination, motor integration, and sensory integration—would have high neurodevelopmental deviance. Based on the analysis of magnetic resonance imaging of 44 first-episode psychosis patients, we compared the cortex morphology, a marker of brain development, in patients with NSS vs patients with nonsignificant NSS. The cortex morphology was automatically assessed from three-dimensional global sulcal index (g-SI, the ratio between total sulcal area and outer cortex area) and regional sulcal indexes (r-SI, the ratio between the area of pooled labeled sulci and the total outer cortex area). Patients with NSS were found to have a lower g-SI in both hemispheres and a lower r-SI in left dorsolateral prefrontal and right lateral occipital cortices. Exploratory analyses revealed correlations between NSS dimensions and r-SI in distinct cortical areas, including dorsolateral and medial prefrontal cortices, lateral temporal, occipital, superior parietal, and medial parieto-occipital cortices. These findings provide evidence of distinct neurodevelopmental pathways in patients with NSS as compared with patients with nonsignificant NSS.

Key words: schizophrenia/first-episode psychosis/cortical folding/neurodevelopment/naive patient/NSS

Introduction

Schizophrenia is a complex brain disorder associated with numerous etiological factors and pathophysiological pathways leading to multiple clinical outcomes. Compelling evidence suggests that deviations in neurodevelopmental processes, involving the interplay of genetic and environmental factors during key stages of brain development (early prenatal and adolescent periods), are a major risk factor of schizophrenia.[1] The identification of patients with high neurodevelopmental deviance is an important issue as it could help to identify homogeneous subgroups of patients with similar pathophysiological pathways, a key step to deciphering the etiology of this complex condition.

Several arguments suggest that schizophrenia patients with Neurological Soft Signs (NSS)—ie, observable defects in motor coordination, motor integration, and sensory integration[2]—would have high neurodevelopmental deviance. Indeed, NSS are clinical markers associated with obstetric complications and neurodevelopmental delay.[3] In addition, NSS have been reported at all stages of schizophrenia, including first-episode psychosis patients and antipsychotic naive patients.[3] Besides, early-onset patients have been shown to have more NSS than adult-onset patients[4] as well as increased neurodevelopmental deviance.[5]

Despite such converging findings, however, cerebral evidences showing higher neurodevelopmental deviations

in the brains of schizophrenia patients with NSS are still lacking.

Structural magnetic resonance imaging (MRI) could help to provide such evidences. MRI studies have previously reported brain volume abnormalities in schizophrenia patients with NSS,[2] particularly in the cerebello-thalamo-prefrontal network.[6] Nevertheless, the pathophysiological interpretation of such volumetric variations is not straightforward as they can be attributed to different factors, including cortical surface morphology and cortical ribbon thickness[7] that have been shown to rely on distinct developmental[8] and genetic[9] factors. Recent works have shown that the complementary study of cortex morphology (gyrification/sulcation) could help providing clues of neurodevelopmental deviations.[10] Hence, visual inspection of the cingulate cortex revealed an abnormal paracingulate sulcus in patients when schizophrenia is established[11] as well as in prodromal stages,[12] suggesting an impaired maturation around 36 weeks of gestation, when the paracingulate sulcus develops. More recently, using regional three-dimensional sulcal indexes[13] to capture the complex and variable morphology of the cerebral cortex, we detected abnormal sulcation in early-onset schizophrenia patients, a clinical subgroup with increased developmental deviance,[14] as well as sulcal variations between subgroups of schizophrenia patients with different hallucination phenomenology.[15]

In this context, we tested the hypotheses that schizophrenia patients with NSS have higher neurodevelopmental deviations than patients with nonsignificant NSS, resulting in different cortical morphology between the 2 subgroups of patients.

Materials and Methods

Participants

Forty-four subjects (12 women, 32 men; mean ± SD age = 26.0 ± 5.7 years) were recruited within the "Sainte-Anne First Episode study". Inclusion criteria were: age 18–45 years, significant psychotic symptoms reaching "psychosis threshold",[16] and no previous psychotic episodes. Patients were included in the study at their first consultation or admission, and were periodically reassessed in a longitudinal design, so that DSM-IV diagnoses were given with respect to duration criteria. Psychosis threshold was defined by a total score at Brief Psychiatric Rating Scale >50, including hallucinatory behavior score >3, conceptual disorganization >4, unusual thought content score >4, emotional withdrawal score >4. Each patient met the DSM-IV diagnostic criteria for schizophrenia (n = 37) or schizophrenia-spectrum disorder including schizo-affective disorder (n = 6) or schizophreniform disorder (n = 1). The duration between intake/consent into the study and MRI scanning was less than 3 days. Exclusion criteria were a previous treated or untreated psychotic episode; serious medical and neurological disorders; head injury; mental retardation; substance dependence or abuse during the last year. After a complete description of the study, all subjects gave their written informed consent. The procedures of the study fulfilled the recommendations of the Helsinki Declaration and followed French ethical regulations.

Each patient underwent a clinical evaluation using a structured lifetime psychiatric interview (DIGS 3.0) and a psychopathology assessment using Positive and Negative Symptom Scale (PANSS). Seventeen patients had never received any antipsychotic treatment before inclusion. Twenty-seven patients had received low dosage of antipsychotic (olanzapine [n = 11]; risperidone [n = 13]; clozapine [n = 1]; amisulpride [n = 1]; chlorpromazine [n = 1]); the mean (±SD) life-span cumulative chlorpromazine equivalent dose[17] for previously treated patients was 380 ± 445 mg.

Neurological Examination

A comprehensive standardized neurological examination,[18] including the evaluation of 23 Neurological Soft Signs (NSS) (four-level rating), was then administered to each patient. This scale encompasses 3 main factors[18]: sensory integration ("Hand face test", graphesthesia, constructive apraxia, stereognosia, and right/left recognition), motor integration (balance, romberg, finger to nose, gait), and motor coordination (rapid alternative movements of foot, hand, finger opposition, foot and hand dysrythmia, fist edge palm). During the same examination, extrapyramidal symptoms were evaluated using the Simpson Angus rating scale (SA) and the Abnormal Involuntary Movement Scale (AIMS). Inter-rater reliability score was evaluated, with a score of 0.82[18] for the whole neurological evaluation, and an internal consistency of 0.85 Cronbach's α).[18]

The presence of NSS was defined from the normal distribution of total NSS score among healthy subjects: a patient was considered to have significant NSS if his/her total NSS score was greater than 10 as 95% of healthy subjects have a total NSS score between 0 and 10.[18] Patients with a total NSS score between 0 and 10 were therefore considered to have nonsignificant NSS.

Details of demographic and clinical data are reported in table 1.

MRI Acquisition

Individual high-resolution anatomical inversion recovery T1-weighted images (3D spoiled gradient recalled [SPGR]) were acquired on a 1.5T GE MR (General Electric Health Care, Milwaukee, Wisconsin) using the following parameters: TR/TI/TE: 10.3/450/2.2 ms; flip

Table 1. Demographic and Clinical Characteristics of the Study Subjects

Demographic and Clinical Characteristics	Whole Sample (n = 44)	Patients With NSS (n = 19)	Patients With Nonsignificant NSS (n = 25)	Difference (Patients With NSS vs Patients With Nonsignificant NSS, mean [SD])	
				t/χ^2	P value
Age, years	**26.0 (5.7)**	**29.7 (6.1)**	**23.1 (3.5)**	***t* = 4.53**	**$<10^{-4}$**
Gender, male/female	32/12	13/6	19/6	$X^2 = 0.31$	.56
Level of education, years	13.7 (2.1)	14.4 (1.9)	13.2 (2.1)	t = 1.88	.07
PANSS	87.4 (21.3)	92.7 (20.9)	83.0 (21.0)	$t = 1.49$	.14
Age at onset, years	**23.6 (5.4)**	**26.5 (6.1)**	**21.5 (3.6)**	***t* = 3.27**	**.002**
Duration of Untreated Psychosis (DUP), years	2.4 (3.5)	3.4 (5.0)	1.6 (1.7)	$t = 1.60$	.12
Previously treated subjects, n (%)	27 (61%)	12 (63%)	15 (60%)	$\chi^2 = 1.79$	.18
Life-span cumulative exposure to antipsychotics in treated patients, chlorpromazine equivalents mg	380 (445)	326 (309)	423 (536)	$t = -0.56$	.58
AIMS	0.6 (2.2)	1.3 (3.2)	0.05 (0.2)	$t = 1.82$	.08
SA	2.7 (2.8)	3.6 (2.9)	2.0 (2.6)	$t = 1.79$	.08
NSS, total score	**10.9 (6.3)**	**16.7 (5.0)**	**6.5 (2.5)**	***t* = 8.91**	**$<10^{-4}$**
NSS, motor coordination subscore	**5.3 (3.8)**	**8.3 (3.5)**	**3.0 (2.1)**	***t* = 6.19**	**$<10^{-4}$**
NSS, motor integration subscore	**2.3 (2.1)**	**3.7 (2.4)**	**1.3 (1.1)**	***t* = 4.30**	**10^{-4}**
NSS, sensory integration subscore	**1.8 (1.7)**	**2.5 (2.0)**	**1.3 (1.3)**	***t* = 2.28**	**.03**
NSS, laterality subscore (handedness)	0.9 (1.2)	0.9 (1.1)	0.9 (1.3)	$t = 0.24$	.82

Note: Variables significantly different between patients with NSS from patients with nonsignificant NSS (ns-NSS) are indicated by boldface.

Abbreviations: PANSS, Positive and Negative Symptom Scale; AIMS, Abnormal Involuntary Movement Scale; SA, Simpson Angus rating scale; NSS, Neurological Soft Signs.

angle: 15°; bandwidth: 11.9 kHz; 142 axial sections of 1.2 mm thickness; field of view: 240 × 240 mm; voxel size: 0.93 × 0.93 × 1.2 mm; matrix: 256 × 256; acquisition time: 6 min 58 s. These MRIs were adapted to the reconstruction of the fine individual cortical folds.[13]

Measure of Cortex Morphology

In order to assess both global and regional cortex morphology, the raw MRI data were subjected to automatized estimation of three-dimensional surface-based sulcus areas by means of a three-step procedure.[13] This approach has been previously applied to the investigation of cortical folding abnormalities in patients with psychiatric or neurogenetic condition.[10]

First, an automated pre-processing step skull-striped T1 MRI and segmented the brain tissues (cerebrospinal fluid [CSF], gray matter [GM], and white matter [WM]) and calculated, in each hemisphere, the total intracranial volume (= GM + WM + CSF volumes) and the area of the outer cortex from non-normalized images. The hemispheric outer cortex area was defined as the area of a smooth envelope of the brain mask that wrapped around the hemisphere but did not encroach into sulci. The envelope was obtained with a morphological closing of the brain mask; an isotropic closing of 5 mm was used to ensure the boundary smoothness. The cortical folds were then automatically segmented throughout the cortex from the skeleton of the GM/CSF mask (see figure 1), with the cortical folds corresponding to the crevasse bottoms of the "landscape," the altitude of which is defined by intensity on MRI. This definition provides a stable and robust sulcal surface definition that is not affected by variations in the cortical thickness or span, as well as the GM/WM contrast.[19] The cortical folds were then converted to a graph-based representation of the cortex containing information related to shape (area, depth, and length) and spatial organization (position and orientation). No spatial normalization was applied to the MRI data to overcome potential bias due to the sulcus shape deformations induced by the warping process.

Second, the area of each cortical fold was computed as the sum of all of the triangular areas defining the fold mesh. The global sulcal index (g-SI) for each hemisphere was measured as the ratio between the total sulcal area

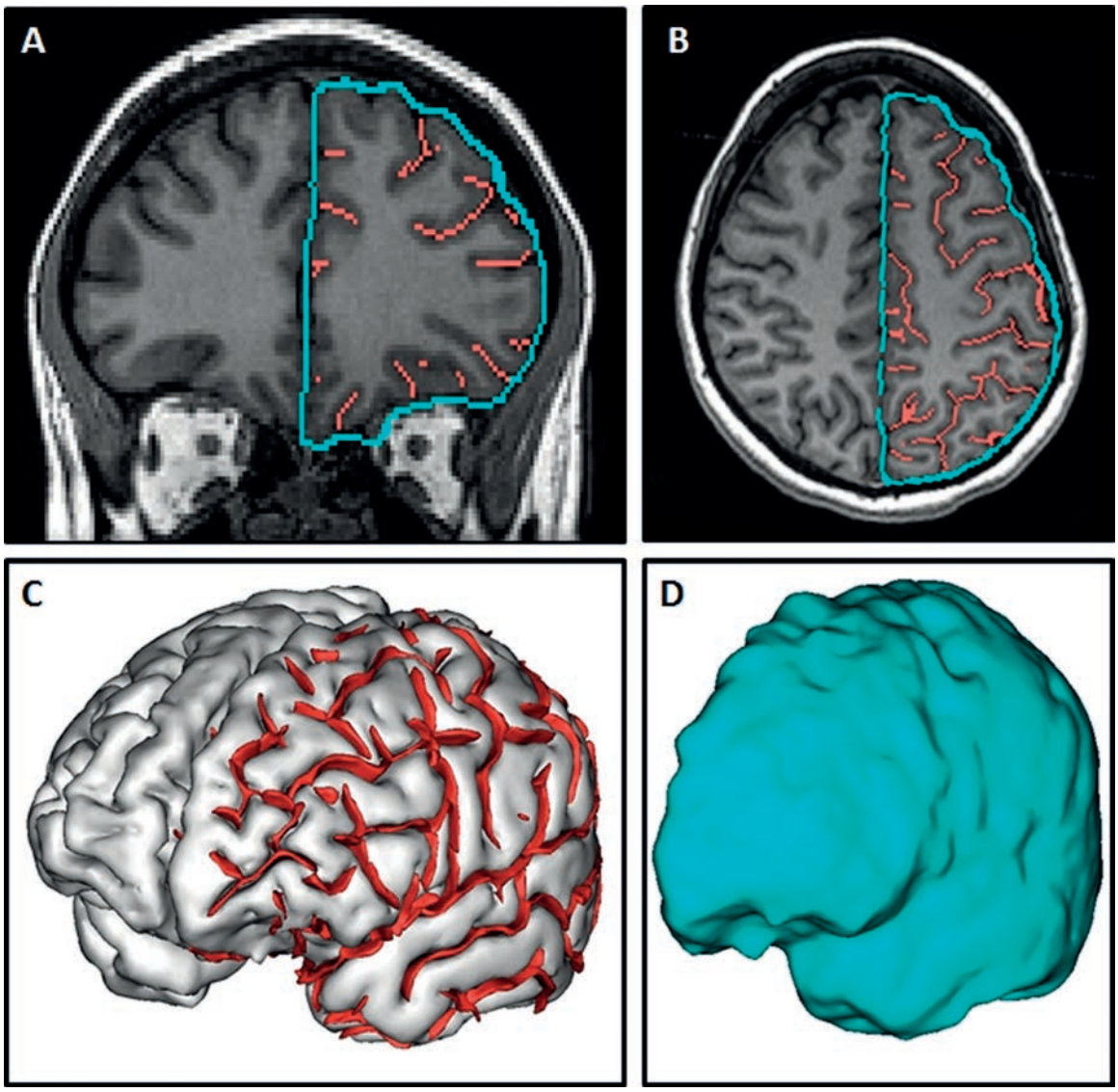

Fig. 1. Three-dimensional segmentation of the cortical folds and global sulcal index (g-SI). Automatically segmented cortical folds (A, B, C; in red) and smooth envelope of the brain mask (A, B, D; in blue) represented on two-dimensional magnetic resonance imaging slices (A: coronal, B: axial) and using mesh-based three-dimensional reconstruction (C: cortical sulci and brain surface, D: brain hull surface).

(ie, the sum of the areas of all segmented cortical folds) and the total outer cortex area:

$$\text{g-SI}^{\text{hemisphere}} = \frac{\sum_{\text{sulcus} \in \text{hemisphere}} A_{\text{sulcus}}}{A_{\text{brain hull}^{\text{hemisphere}}}}$$

(with A_{sulcus}, the sulcus surface area and $A_{\text{brain hull}^{\text{hemisphere}}}$, the brain hull area).

Of note, ventricle area was not included in the g-SI. A cortex with extensive folding has a large g-SI, whereas a cortex with low degree of folding has a small g-SI. At constant outer cortex area, the g-SI increases with the number and/or area of sulcal folds, whereas the g-SI of a lissencephalic cortex is zero. G-SI describes the burying of the cortex and is therefore slightly different from the classical gyrification index (GI), the ratio of the whole gyral contour length to the outer, exposed surface,[20] which embodies additional information (included in the whole gyral contour length) related to the cortex thickness and the sulcal opening. In addition, the classical GI captures the shape of the cortical folds, which are complex three-dimensional structures from measures on two-dimensional MRI slices,[20] while the g-SI is based on measures derived from a three-dimensional reconstruction of the sulcal surface.[13]

In a third step, a new automatic recognition algorithm based on a Bayesian framework to jointly identify and register sulci[21] (validated from 62 MRI with sulci

manually labeled; mean recognition rate: 86%) was used to label the sulci in each hemisphere. Regional cortex folding was assessed by computing a regional sulcal index (r-SI), which was defined for twelve predefined regions (lateral face: dorsolateral prefrontal cortex [DLPFC], pre-central sulcus, central sulcus, sylvian fissure, superior parietal cortex, inferior parietal cortex, temporal cortex, occipital cortex; medial face: medial frontal cortex, medial parieto-occipital cortex, basal temporal cortex; ventricle) as the ratio between the area of pooled labeled sulci (estimated from the sum of area of the mesh defining each sulcus) and the total outer cortex area in the corresponding hemisphere. Hence, the r-SI increases with the depth and the length of a sulcus. These twelve regions were defined a priori using the standard regional grouping of Brainvisa software (ie, "sulcal_root_color" sulcus nomenclature).

Image processing was performed with the "T1_MRI_segmentation" pipeline of Brainvisa 4.0 using the default settings. For each subject, all of the image-processing steps were visually checked and no gross segmentation error (eg, cortical ribbon thinning, gyrus or sulcus missing) or sulcus labeling error was detected. Some minor segmentation errors, mostly observed in the margin between occipital lobes and cerebellum, were corrected manually in each patient, blind to subgroup membership. G-SI and r-SI were computed automatically, without any manual intervention.

Statistical Analyses

Quantitative (respectively qualitative) demographic and clinical characteristics comparisons between patients with NSS and patients with nonsignificant NSS were based on bilateral Student *t* (respectively χ^2) tests.

Comparisons between subgroups of patients as well as dimensional analyses for each NSS functional dimension (motor integration, motor coordination, and sensory integration)[18] were performed on sulcal indexes and global brain tissue volumes (hemispheric intracranial volumes, hemispheric GM and WM volumes normalized to intracranial volume).

Between-group differences in g-SI and brain volumes were analyzed for each hemisphere using univariate linear models. Age, gender, and number of years of education, as an IQ approximation, were a priori added as confounding covariates in the statistical models to control for previously detected confounding effects of age,[13] gender,[22] and IQ[23] on sulcal anatomy. When a significant main effect of group was detected, analysis was continued by post hoc paired comparisons using Tukey's HSD test with Bonferroni correction.

Dimensional analyses were performed separately for each NSS functional dimension using univariate linear models with NSS dimension subscore, age and years of education as numeric covariates and gender as factor.

In order to specify the direction and strength of the association with age, number of years of education and NSS scores, the standardized coefficient (beta) relative to these quantitative covariates in the linear regressions is provided: a positive (respectively negative) beta denotes a positive (respectively negative) partial correlation.

In addition, explorative regional post hoc comparisons between patients with NSS and patients with nonsignificant NSS, as well as dimensional analyses, were performed on the 12 predefined hemispheric region r-SI using the previous statistical models.

Shapiro tests were used to check that the linear model residuals were normally distributed. Statistical significance was probed with *F* tests in the linear model and with t tests in the paired post hoc analyses. A two-tailed *P* value of less than .05 was considered statistically significant. All the statistical analyses were carried out with R 2.9 software (http://www.r-project.org/).

Results

Global Analyses

Analyses of g-SI revealed significant main effects of group on left $F_{1,37} = 7.67$, $P = .009$) and right ($F_{1,37} = 5.78$, $P = .02$) hemispheres, with a bilateral g-SI decrease in patients with NSS (figure 2).

There was also a significant main effect of gender on left ($F_{1,37} = 6.81$, $P = .01$) and right ($F_{1,37} = 5.10$, $P = .03$) hemispheres, with lower g-SI in females in comparison to males, as well as a significant main effect of years of education on left ($F_{1,37} = 5.93$, $\beta = 0.34$, $P = .02$) and right ($F_{1,37} = 4.33$, $\beta = 0.30$, $P = 0.04$) hemispheres. There was no significant main effect of age and no significant interaction between factors and covariates on left or right hemispheres. Of note, removing of number of years of education or addition of normalized hemispheric GM or WM volumes, outer cortex area, PANSS, cumulative treatment dose or illness duration as covariate in g-SI analyses yielded similar significant effects (except for the right outer cortex area leading to a group effect of $P = .08$ instead of $P = .03$).

The between-group differences in g-SI were not accounted for by differences in outer cortex surface area. Indeed, in the left hemisphere, the outer cortical area was $454.5 \pm 3.1\,cm^2$ in patients with NSS, and $463.1 \pm 2.9\,cm^2$ in patients without significant NSS ($F_{1,37} = 2.36$; $P = .13$). In the right hemisphere, the corresponding areas were $453.6 \pm 3.4\,cm^2$ and $461.7 \pm 2.9\,cm^2$ ($F_{1,37} = 2.27$; $P = 0.11$).

There was no between-group difference for hemispheric intracranial volume, GM, WM, and CSF volumes normalized to intracranial volume.

There was no significant main effect of neurological subscores (sensory integration, motor integration, and motor coordination) neither on g-SI nor on hemispheric brain volume analyses.

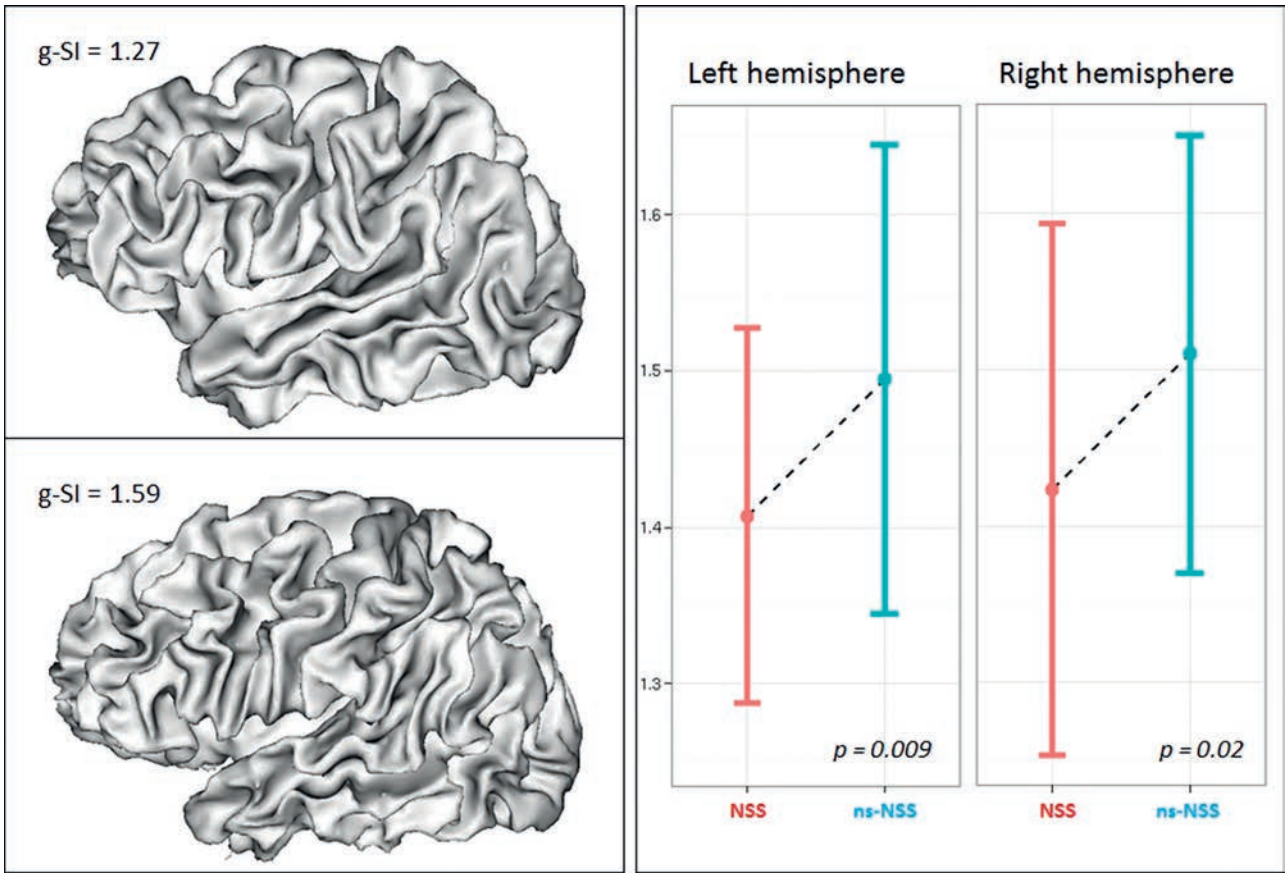

Fig. 2. Neurological Soft Signs (NSS) and hemispheric sulcation. Left: Lateral views of the left hemispheres of 2 subjects illustrating a low and high global sulcal index (g-SI). The gray matter ribbon has been removed to emphasize the folding surface in the depth of the sulci. (Upper) reconstructed left hemisphere of a patient with NSS (NSS) showing a low degree of overall sulcation (g-SI = 1.27); (Lower) a patient with nonsignificant NNS (ns-NSS) and a high degree of overall sulcation (g-SI = 1.59). Right: Bar plots (mean ± 1 SD) of g-SI in NSS (red), ns-NSS (blue) in left and right hemispheres. The data were linearly adjusted by age, gender, and years of education.

Details of global sulcal indexes and brain volume analyses are reported in table 2.

Explorative Regional Analyses

Regional analyses revealed that the decrease in sulcation was not uniform: patients with NSS exhibited lower r-SI in the left DLPFC ($F_{1,37}$ = 7.54; P = .009) and in the lateral right occipital cortex ($F_{1,37}$ = 6.20; P = .02).

In addition, dimensional analyses revealed a main effect of some NSS dimensions on distinct r-SI: motor coordination subscore on the left DLPFC ($F_{1,37}$ = 7.30; β = −0.49; P = .01), left lateral temporal cortex ($F_{1,37}$ = 6.16; β = −0.44; P = .02) and lateral right occipital cortex ($F_{1,37}$ = 6.87; β = −0.49; P = .01); motor integration on the left medial parieto-occipital cortex ($F_{1,37}$ = 6.02; β = 0.42 ; P = .02) and right DLPFC ($F_{1,37}$ = 4.92; β = −0.36; P = .03); sensory integration on the left medial frontal cortex ($F_{1,37}$ = 5.18; β = −0.35; P = .03) and right superior lateral parietal cortex ($F_{1,37}$ = 4.95; β = −0.33; P = .03) (figure 3).

All these regional analyses should be considered as exploratory as none would hold following Bonferroni correction for multiple testing (α corrected = 0.002, ie, 0.05/26).

Discussion

In this first study on cortical morphology and NSS we found that schizophrenia patients with NSS exhibited significant overall reductions of cortical sulcation in both hemispheres as compared with patients with nonsignificant NSS, in line with our hypothesis. Exploratory regional analyses revealed correlations between NSS dimensional subscores and distinct regional cortical sulcation, including dorsolateral and medial prefrontal cortices, lateral temporal, occipital and superior parietal cortices, and medial parieto-occipital cortex. Due to their exploratory nature, however, these regional analyses should be considered with caution before replication.

Table 2. Results of g-SI and Global Volumes Analyses

	NSS	ns-NSS	NSS Versus ns-NSS		
	Mean (SD)		Difference, %	*F*	*P* value
Left Hemisphere					
Global sulcal index (g-SI)	**1.41 (0.12)**	**1.49 (0.15)**	**−5.8**	**7.67**	**.009**
Hemispheric volume, cm^3	526.8 (82.0)	561.27 (68.8)	−6.5	3.74	.06
Normalized GM volume, %	46.8 (4.6)	48.2 (3.9)	−3.0	1.98	.17
Normalized WM volume, %	37.9 (4.3)	38.2 (3.6)	−0.8	0.10	.75
Normalized CSF volume, %	15.3 (3.9)	13.6 (3.3)	+11.2	4.03	.05
Right Hemisphere					
Global sulcal index (g-SI)	**1.42 (0.17)**	**1.51 (0.14)**	**−5.7**	**5.78**	**.02**
Hemispheric volume, cm^3	528.6 (81.8)	561.8 (68.6)	−6.3	3.50	.07
Normalized GM volume, %	46.8 (4.6)	48.1 (3.8)	−2.7	1.65	.21
Normalized WM volume, %	38.1 (4.2)	38.1 (3.6)	+0.2	0.005	.94
Normalized CSF volume, %	15.1 (3.8)	13.9 (3.2)	+8.1	2.17	.15

Notes: Data are presented as means (SD). Variables significantly different between patients with Neurological Soft Signs (NSS) and patients with nonsignificant NSS (ns-NSS) are indicated by boldface (patients with NSS as reference). All results were linearly adjusted for age, gender, and years of education.
Abbreviations: GM, Gray Matter; WM, White Matter; CSF, Cerebrospinal Fluid.

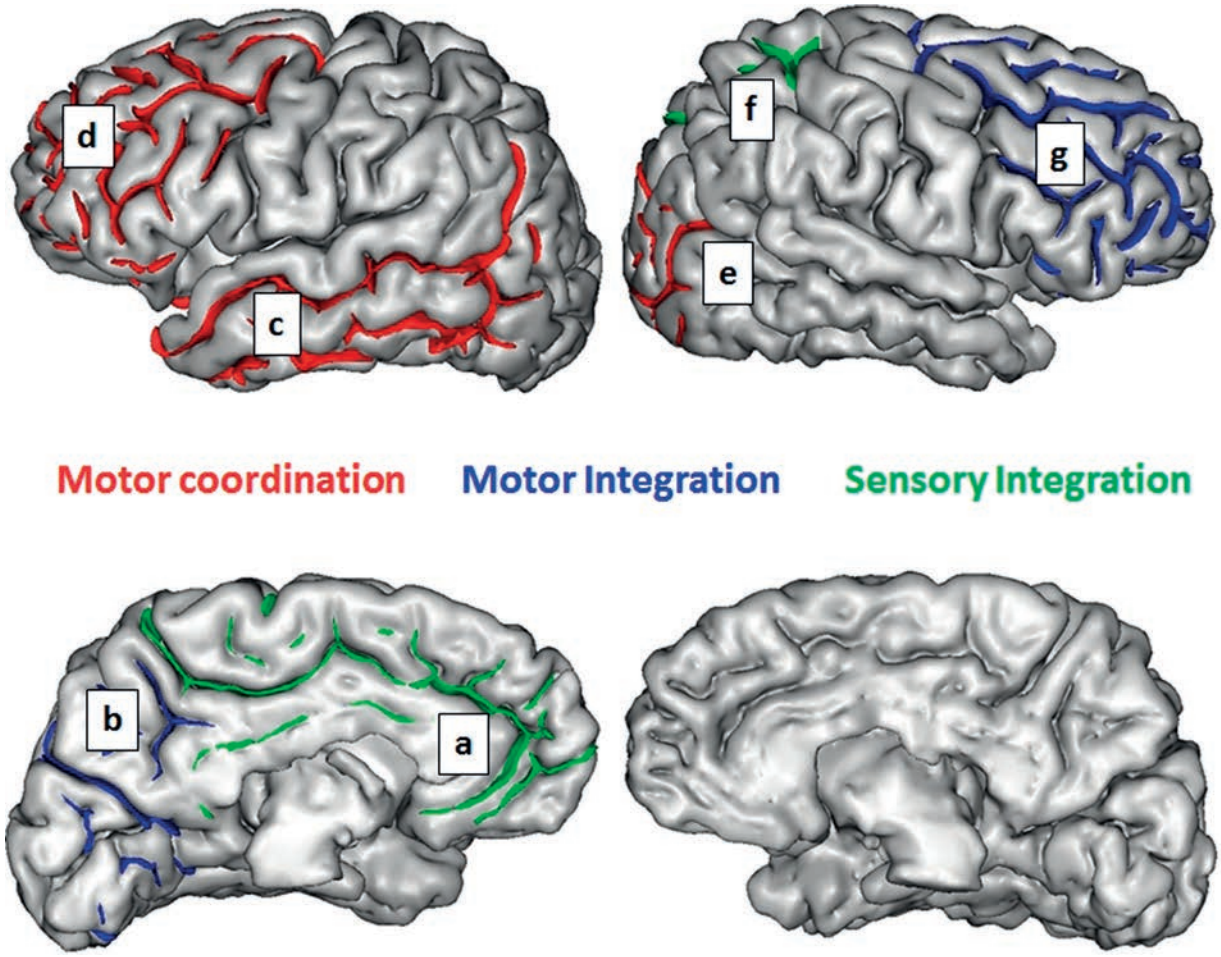

Fig. 3. Neurological Soft Sign (NSS) dimensions and regional sulcation. In each region, cortical sulci are color-coded depending on the main effect of NSS dimensions on the corresponding regional sulcal index (r-SI): red for significant (P uncorrected < .05) effect of motor coordination, blue for motor integration and green for sensory integration. Data are provided for the (a) left medial frontal cortex, the (b) left medial parieto-occipital cortex, (c) the left lateral temporal cortex, (d) the left dorsolateral prefrontal cortex, the (e) lateral right occipital cortex, the (f) right superior lateral parietal cortex and the (g) right dorsolateral prefrontal cortex. The relative position of the cortical regions involved is represented on reconstructed hemispheres of 1 subject.

Cortex Morphology, Neurodevelopment, and NSS

In this study, the putative neurodevelopmental differences between the patients with NSS and patients with nonsignificant NSS were investigated from the analysis of the cortical morphology.[10] Indeed, the mature sulco-gyral pattern is considered to result from early processes that shape the cortex anatomy from a smooth lissencephalic structure to a highly convoluted surface. This complex folded surface has been shown to be an early marker of later functional development.[24] Moreover, obstetrical complications have recently been associated with cortical folding decrease in adult brain.[25] The precise mechanism underlying the cortex folding is still unknown but several factors probably contribute to prenatal processes that influence the shape of the folded cerebral cortex, including cortical growth, apoptosis, differential expansion of superior and inferior cortical layers, differential growth of the progyral vs the prosulcal regions and/or variations of white matter connections.[26] Because of the lack of consistent morphological data,[10,26] it is impossible to rule out the possibility that smaller changes in sulcal span, depth or thickness due to abnormal postnatal brain development could lead to changes in (regional) sulcation. In addition to these early developmental factors, later neurodegenerative processes might also contribute to the cortical morphology.[10] Nevertheless, g-SI reductions in patients with NSS would probably not be explained by neurodegenerative processes, as no correlations with illness duration or treatment dose were found. For these reasons, it is therefore assumed that the different cortical sulcation observed in the 2 patient subgroups probably relate to perturbations of early cortical development and support distinct pathophysiological and neurodevelopmental pathways. This interpretation is in line with clinical studies showing that NSS are associated with early disturbances in brain development.[2,3] For instance, neurological abnormalities at early adulthood have been found to correlate with neuromotor dysfunction at age 6.[27] Furthermore, a retrospective study found high rates of abnormal movements in early childhood (within 2 years of life) in children who later developed schizophrenia,[28] suggesting that early precursors of NSS can be observed in children who subsequently develop schizophrenia. In addition, NSS have been shown to be associated with minor physical anomalies, a marker of early developmental deviations.[29]

Several factors contribute to developmental processes that influence the shape of the folded cerebral cortex, including structural connectivity through axonal tension forces.[10] This mechanical constraints lead to a compact layout that optimizes the transit of neuronal signals between brain regions, suggesting that the between-group differences in cortical sulcation detected here could be related, at least in part, to differences in white matter connectivity and network functioning.[30] Such an interpretation is consistent with the view that NSS are related to nonlocalizing neurological abnormalities that the result from network disturbances and impaired connections, but do not result from an impairment within a specific brain region.

Sulcation of Associative Cortex and Integrative Processes

Exploratory analyses of regional sulcation revealed decreased local folding surface in the left DLPFC in patients with NSS in comparison to patients with nonsignificant NSS. The involvement of the DLPFC is consistent with its role in the control of sensory conflict[31] as well as in attentional processes, working memory, and problem solving, which have been reported to be altered in patients with NSS.[32]

Exploratory regional analyses also revealed correlations of NSS subscores[18] with regional sulcation in cortical regions subserving functions that have been reported to be altered in patients with NSS.[2] Hence, the motor coordination subscore, which is based on motor sequence tasks requiring both planning of motor acts and its storage in working memory, correlates with the regional sulcation of the left DLPFC, a region involved in motor planning and working memory. Correlations were found between the sensory integration subscore and the right lateral parietal cortex, including the associative Brodmann areas 5 and 7, classically involved in multimodal integration. Finally, as anticipated,[2] the motor integration subscore was found to correlate with the sulcation of the left medial parieto-occipital cortex, and not the prefrontal cortex. Involvement of the parieto-occipital cortex, and in particular the associative Brodmann areas 5 and 7, is probably related to motor integration tasks—such as balance, romberg, finger to nose[18]—requiring both motor responses and multimodal sensory integration. The involvement of these integrative brain regions is consistent with the contribution of complex neurocognitive processes in NSS, requiring the integration of distributed cerebral sites and systems.[32] In addition, the region-specific correlation of NSS subscores support the anatomo-clinical validity of the domains explored using this NSS scale.[18]

Methodological Issues

The results of this study are best understood in the context of some methodological issues. Cortical folds are complex and variable three-dimensional structures,[33] and their shape is difficult to reliably describe from two-dimensional MRI slices.[20] The use of 3D mesh-based sulcal indexes[13] has provided an accurate assessment of the cortex morphology as in our previous studies in schizophrenia.[13,14] This study focused on sulcation as cortical sulci can be reliably defined using simple geometric properties[19] while the gyri are relatively difficult to reliably

define from a pure geometrical point of view, especially for the borders not limited by sulci.[34]

In this study, a categorical approach to NSS, rather than a correlation approach, was used to investigate the effects of NSS on g-SI. This categorical approach was used to test the hypothesis that patients with NSS and patients without significant NSS were distinct subgroups of schizophrenia with different neurodevelopmental pathways. At variance with our theoretical hypothesis, the alternate correlation approach would support a continuum between schizophrenia patients with low, or null, NSS score and patients with high NSS.

As in previous NSS studies,[35,36] the control group was composed of patients with nonsignificant NSS, which allows to specifically study the correlates of NSS regardless of the disease. Comparison with healthy subjects would require a balanced design including both healthy subjects with nonsignificant NSS and healthy subjects with NSS. The recruitment of healthy subjects with NSS, however, would be very difficult as only 5% of healthy subjects have significant NSS. Of note, in a previous study, healthy subjects with an age similar to that of current patients were found to have a mean g-SI of 1.6,[13] which is greater than g-SI measured in patients with nonsignificant NSS (g-SI ~ 1.5) and patients with NSS (g-SI ~ 1.4).

As indicated in table 1, age at inclusion and age at onset were higher in patients with NSS as compared with patients with nonsignificant NSS. This difference should have a limited effect on the results as age at inclusion was entered as confounding covariate in the statistical analyses and its effect on the g-SI was found to be nonsignificant. Of note, the difference in age at onset has previously been detected in a prospective study of NSS in a large sample of first-episode patients with schizophrenia,[37] which reported that a higher level of NSS was related to an older age at onset.

Possible effects of years of education of the patient were controlled in the analyses. Controlling for parents years of education and socioeconomic status would have been relevant because schizophrenia itself is associated with reduced education and socioeconomic status.

Only first-episode patients were investigated in this study in order to limit possible chronicization and medication effects on both NSS and brain anatomy.[38,39] In addition, the enrolment of in- and outpatients without substance abuse in the last year (particularly frequent at the early stage of the disease) should limit this potential confound.

The identification of schizophrenia subgroups with high neurodevelopmental deviations, like patients with NSS, should optimize the possibility for translating the high heritability of schizophrenia into the search for structural genomic variants because these variants have been consistently reported to affect genes implicated in brain development.[40]

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