Behavioural Brain Research 292 (2015) 19–25

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Local brain gyrification as a marker of neurological soft signs in schizophrenia

Dusan Hirjak[a,*], Katharina M. Kubera[a], Robert C. Wolf[a,b], Anne K. Thomann[c], Sandra K. Hell[a], Ulrich Seidl[d], Philipp A. Thomann[a]

[a] Center for Psychosocial Medicine, Department of General Psychiatry, University of Heidelberg, Germany
[b] Department of Psychiatry, Psychotherapy and Psychosomatics, Saarland University, Homburg, Germany
[c] Department of Internal Medicine II, Medical Faculty Mannheim, Heidelberg University, Germany
[d] Center for Mental Health, Klinikum Stuttgart, Germany

HIGHLIGHTS

- There is a significant association between NSS performance and LGI in recent-onset schizophrenia patients.
- Cortical folding patterns may play a role in the development of NSS in schizophrenia.
- Investigation of LGI may help to explain subtle motor symptoms in schizophrenia spectrum disorders.

ARTICLE INFO

Article history:
Received 30 March 2015
Received in revised form 22 May 2015
Accepted 27 May 2015
Available online 29 May 2015

Keywords:
Neurological soft signs
Schizophrenia
Magnetic resonance imaging
Local gyrification index
Freesurfer

ABSTRACT

Patients with psychiatric disorders of significant neurodevelopmental origin, such as schizophrenia and autism frequently experience genuine motor abnormalities, such as neurological soft signs (NSS). Previous MRI studies in patients with schizophrenia have shown that NSS are associated with abnormal cortical, thalamic and cerebellar structure and function. So far, however, no neuroimaging study focused on the role of the local gyrification index (LGI) in the pathophysiology of NSS. This study sought to explore the relationship between NSS and folding patterns of the cerebral cortex that are thought to be established during early brain development. In this study, whole brain high-resolution magnetic resonance imaging (MRI) at 3 Tesla was used to investigate the LGI in 33 patients with recent-onset schizophrenia. Cortical reconstruction was performed with the Freesurfer image analysis suite. NSS were examined on the Heidelberg Scale and related to LGI. Age, gender, years of education and medication were considered as potential confounding variables. In summary, higher NSS scores were positively associated with morphological changes of LGI predominantly in parietal and occipital areas. Our results confirm the hypothesis of a significant relationship between LGI changes and the NSS expression in schizophrenia. Investigation of LGI may help to explain subtle motor symptoms such as NSS in schizophrenia.

1. Introduction

Schizophrenia patients frequently experience genuine, not drug induced, subtle motor phenomena, such as neurological soft signs (NSS) [1,2]. NSS include a variety of discrete abnormalities in sensory integration, motor coordination and sequencing of complex motor acts [3–5]. A higher prevalence of NSS in schizophrenia may reflect disorder-specific abnormalities of motor circuits [6] and a neurodevelopmental origin of motor function established during early brain development. In particular, recent neuroimaging studies of NSS in patients suffering from schizophrenia have revealed structural and functional alterations in cortical and subcortical brain areas (see the meta-analysis by Zhao et al. [7] for further details). These findings strongly support the hypothesis that NSS may be related to a disrupted cortico-cerebellar-thalamic-cortical circuit (CCTCC) as conceptualized in the model of cognitive dysmetria [8]. Correspondingly, NSS have been discussed as potential indicators of vulnerability to psychotic disorders and as endophenotypes for schizophrenia [9,10].

* Corresponding author at: Center for Psychosocial Medicine, Department of General Psychiatry, University of Heidelberg, Voßstraße 4, D-69115 Heidelberg, Germany. Tel.: +49 62215637539; fax: +49 6221565327.
E-mail address: dusan.hirjak@med.uni-heidelberg.de (D. Hirjak).

http://dx.doi.org/10.1016/j.bbr.2015.05.048
0166-4328/

In the last decade, the development of powerful 3D-based image-processing techniques (e.g. surface based morphometry – SBM) based on T1-weighted structural MRI scans has made it possible to compute the local gyrification index (LGI) automatically [11,12]. LGI is defined as the amount of cortex buried within the sulcal folds as compared with the amount of visible cortex in circular regions of interest [11,12]. The development of cortical folding starts during prenatal life and undergoes only minor changes in adolescence [13,14]. Therefore, LGI might represent a useful cytoarchitectural parameter to assess early defects in fetal neurodevelopment [14–16]. Defects in fetal neurodevelopment comprising the CCTCC might give rise to subtle sensorimotor abnormalities. Correspondingly, subtle sensorimotor deficits such as NSS could be seen as a result of changes in early corticogenesis in brain regions of the CCTCC. Furthermore, NSS have been suggested to be an external marker of underlying neuronal dysfunction that is linked with an elevated risk for developing schizophrenia. Along these lines, comprehensive characterization of cortical folding changes that are presumed to underlie NSS may illustrate the phenotypic significance of subtle sensorimotor abnormalities when investigating the pathogenesis of schizophrenia. Eventually, the investigation of NSS may prove to be useful for this purpose, especially when used in combination with modern structural neuroimaging parameters such as LGI, to improve neurobehavioural characterization and stratification of mental disorders with prominent occurrence of sensorimotor symptoms, such as schizophrenia and autism. However, to the best of our knowledge, there have been no MRI studies investigating whether NSS are associated with certain LGI characteristics in schizophrenia patients. Since NSS may serve as external markers of psychosis vulnerability [17–19], clarification of the brain structure underlying NSS is crucial for a further understanding of developing schizophrenia.

In this study, we performed cortical surface reconstruction on 3 Tesla MRI data of 33 patients with recent-onset schizophrenia using SBM (http://surfer.nmr.mgh.harvard.edu/) allowing for a fine-grained quantification of gyrification in order to explore the relationship between the LGI and the severity of NSS. Since voxel-based morphometry (VBM) is prone to smoothing across neighbouring gyri [20–22], we sought to investigate – independently of smoothing – whether LGI changes match the topography of structural alterations previously reported in VBM studies on NSS in schizophrenia. Specifically, we hypothesized that patients with higher NSS will exhibit significant LGI changes in cortical regions essential for regulating motor activity such as the precentral and paracentral gyrus, the postcentral lobe, and the prefrontal cortex, respectively.

2. Methods and data analysis

2.1. Subjects

A sample of 33 patients was consecutively recruited from the Department of General Psychiatry in Heidelberg, Germany between 2009 and 2013. Our sample consisted of 9 women and 24 men, all right-handed Caucasians with a mean age of 23.11 ± 4.24 and a mean of 12.36 ± 2.48 years of education. 20 subjects have already been included in previous studies of our group [23,24]. Patients were excluded if: (i) they were aged <18 or >35 years, (ii) they had a history of brain trauma or neurological disease, or (iii) they had shown alcohol/substance abuse or dependence within 12 months prior to participation. Diagnoses were made by staff psychiatrists and confirmed using a clinical interview [25] and examination of the case notes by two experienced psychiatrists (PAT and US). All patients fulfilled the ICD-10 criteria [25] for schizophrenia and had an initial onset of psychosis within two years prior to study entry with a mean duration of illness of 8.11 ± 3.98 months (range 2–24 months). At the time of inclusion, all patients were receiving treatment with a single antipsychotic agent according to their psychiatrists' choice. The antipsychotic treatment included clozapine ($n = 9$), olanzapin ($n = 6$), aripiprazole ($n = 6$), quetiapine ($n = 5$), amisulpride ($n = 1$), ziprasidone ($n = 1$) or risperidone ($n = 5$), respectively. The average dose in chlorpromazine (CPZ) equivalents was 489.21 ± 310.28 mg (range: 133–1100) [26]. The mean duration of neuroleptic treatment was 2.65 ± 3.82 months (range 0.25–18 months). All patients gave informed consent to participation, and the study has been approved by the local ethics committee of the Medical Faculty, University of Heidelberg, Germany.

2.2. Clinical assessments

NSS were assessed using the Heidelberg Scale [5] that consists of five items assessing motor coordination (MOCO) [Ozeretski's test, diadochokinesia, pronation/supination, finger-to-thumb opposition, speech articulation], three items assessing integrative functions (IF) [station and gait, tandem walking, two-point discrimination], two items assessing complex motor tasks (COMT) [finger-to-nose test, fist-edge-palm test], four items assessing right/left and spatial orientation (RLSPO) [right/left orientation, graphesthesia, face-hand test, stereognosis], and two items assessing hard signs (HS) [arm holding test, mirror movements]. Items were rated on a 0 (no prevalence) to 3 (marked prevalence) point scale. A sufficient internal reliability and test-retest reliability have been established previously [5,27]. Handedness was assessed on the Edinburgh Inventory [28]. The severity of psychopathological symptoms were assessed with the Brief Psychiatric Rating Scale [29], the Scale for the Assessment of Positive Symptoms [30] and the Scale for the Assessment of Negative Symptoms [31]. Predictors of outcome were rated on the Strauss–Carpenter Scale [32]. Potential extrapyramidal side effects, Parkinsonian signs and abnormal involuntary movement according to Abnormal involuntary movement scale (AIMS) [33] were excluded before study entry by an experienced psychiatrist who was not directly involved in the study.

2.3. MR imaging data acquisition

Participants underwent structural scanning at the German Cancer Research Center (DKFZ), Heidelberg, Germany, on a 3 Tesla Magnetom TIM Trio MR scanner (Siemens Medical Solutions, Erlangen, Germany) using a T1-weighted 3D magnetization prepared rapid gradient echo sequence (MP-RAGE, 160 sagittal slices, image matrix = 256×256, voxel size = $1 \times 1 \times 1\,mm^3$, TR = 2300 msec, TE = 2.98 msec, TI = 900 msec, flip angle = 9°). An experienced neuroradiologist reviewed all MRI brain scans; no gross abnormalities (e.g. tumour, space-occupying cystic lesion greater 3 mm, signs of bleeding, contusion, infarction, major grey or white matter lesions) were found.

2.4. MR image processing

2.4.1. Cortical reconstruction

Freesurfer (for detailed description of the method see (http://surfer.nmr.mgh.harvard.edu/) [34] was used for cortical surface reconstruction [35–37]. Briefly, the stream consists of multiple stages, such as removal of non-brain tissue using a hybrid watershed/surface deformation procedure [38]; affine registration with Talairach space specifically designed to be insensitive to abnormalities and to maximize the accuracy of the final segmentation; tissue classification and correction of the variation in intensity resulting from the B1 bias field [39]; tessellation of the gray matter white matter boundary; automated topology correction, and sur-