Psychiatry Research: Neuroimaging 261 (2017) 91–95

Contents lists available at ScienceDirect

Psychiatry Research Neuroimaging

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

# Increased white matter radial diffusivity is associated with prefrontal cortical folding deficits in schizophrenia

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ARTICLE INFO

*Keywords:*
Prefrontal cortical folding
Radial diffusivity
Schizophrenia

ABSTRACT

The neuronal underpinnings of cortical folding alterations in schizophrenia remain unclear. Theories on the physiological development of cortical folds stress the importance of white matter fibers for this process and disturbances of fiber tracts might be relevant for cortical folding alterations in schizophrenia. Nine-teen patients with schizophrenia and 19 healthy subjects underwent T1-weighted MRI and DTI. Cortical folding was computed using a surface based approach. DTI was analyzed using FSL and SPM 5. Radial diffusivity and cortical folding were correlated covering the entire cortex in schizophrenia. Significantly increased radial diffusivity of the superior longitudinal fasciculus (SLF) in the left superior temporal region was negatively correlated with cortical folding of the left dorsolateral prefrontal cortex (DLPFC) in patients, i.e. higher radial diffusivity, as an indicator for disturbed white matter fiber myelination, was associated with lower cortical folding of the left DLPFC. Patients with pronounced alterations of the SLF showed significantly reduced cortical folding in the left DLPFC. Our study provides novel evidence for a linkage between prefrontal cortical folding alterations and deficits in connecting white matter fiber tracts in schizophrenia and supports the notion that the integrity of white matter tracts is crucial for intact morphogenesis of the cortical folds.

## 1. Introduction

The highly folded cerebral cortex is a unique feature of the primates` brain. Gross alterations of cortical folding such as lissencephaly leading to intellectual disability and motor retardation demonstrate the relevance of the intact formation of the cortical folds. The process of cortical folding takes place in utero and is, to a large extent, completed at the time of birth (Zilles et al., 2013). Moreover, the pattern of the cortical folds is usually largely stable over the life-span (Armstrong et al., 1995). Hence, deviations of cortical folding might be regarded as an indicator of altered brain maturational processes. Schizophrenia is conceptualized as neurodevelopmental disorder (Rapoport et al., 2005) and the investigation of cortical folding is thus a promising approach to increase our understanding of the neurobiology of the disorder. A growing number of MRI studies explored cortical folding in schizophrenia in vivo and demonstrated cortical folding alterations in terms of both hypo- and hypergyrification in several cortical areas (s. for review (White and Hilgetag, 2011) and overview for more recent studies in (Nanda et al., 2014)). Increased cortical folding in mainly occipito-temporal areas has been shown in first episode patients (Harris et al., 2004b; Schultz et al., 2010a) whereas predominantly decreased folding in terms of a lower local gyrification index in mainly prefrontal, middle temporal and parietal regions (i.e., precuneus) has been found in chronic patients (Nesvag et al., 2014; Palaniyappan et al., 2011). In high risk states increased prefrontal folding as indicated by a higher local gyrification index seems to be a risk factor for the conversion to psychosis (Harris et al., 2007, 2004a). Moreover, cortical folding alterations seem to be genetically driven as both increased cortical folding in frontal regions as well as slightly decreased cortical folding (as assessed by calculation of the regional local gyrification index) in anterior and posterior cingulate regions has been detected in non-affected first degree relatives (Falkai et al., 2007; Nanda et al., 2014). Finally, cortical folding defects also seem to be of major clinical relevance as reduced cortical folding in terms of a smaller local gyrification index in bilateral insular, frontal, and temporal regions has been shown to predict poor treatment response (Palaniyappan et al., 2013) and an alteration in the structural covariance of specific folding patterns has been shown to be linked to

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http://dx.doi.org/10.1016/j.pscychresns.2017.01.011
Received 16 September 2016; Received in revised form 6 January 2017; Accepted 26 January 2017
Available online 04 February 2017
0925-4927/ 

illness severity (Palaniyappan et al., 2015). In the overall view findings on altered cortical folding in schizophrenia are still rather heterogeneous with previous studies providing evidence for both decreased and increased cortical folding. On a closer inspection there seems to be a tendency towards increased cortical folding in high-risk and first episode patients and decreased cortical folding in chronic patients or patients at a later stage of the illness. Predominantly the decreased folding in more chronic patients seems to be psychopathologically relevant. Despite this relevance the pathomechanism underlying cortical folding deficits in schizophrenia is poorly understood. In line with theories which consider cortical shape as a product of underlying patterns of connectivity first evidence (Schaer et al., 2013) showed alterations in cortical folding to be directly associated with altered white matter structural connectivity. Although this association was found in patients with autism it can be assumed that similar mechanisms underlie folding alterations in schizophrenia considering that disrupted white matter connectivity is a frequent finding in schizophrenia (Tamnes and Agartz, 2016).

To investigate this presumed relationship and its relevance for the disorder of schizophrenia we explored a potential association between a previously reported disruption in white matter fiber tract diffusivity and cortical folding in patients with schizophrenia.

### 1.1. Objectives and hypothesis

More specifically, we performed a correlational analysis between a DTI derived indirect measure of myelination ("radial diffusivity") and fine grained cortical folding covering the entire cortex in a well characterized sample of patients with schizophrenia and healthy controls. In this sample we demonstrated in two previous studies significantly increased radial diffusivity – as an indirect indicator of disturbed myelination - in the superior temporal cortex confined to parts of the superior and inferior longitudinal fasciculus (Koch et al., 2013, 2011). For our current analysis we extracted the radial diffusivity values from these voxels in order to perform a node-by-node correlational analysis with cortical folding. We hypothesized a negative correlation between radial diffusivity and cortical folding, i.e., we expected higher radial diffusivity to be associated with stronger alterations in cortical folding.

## 2. Subjects and methods

### 2.1. Participants

We studied 19 patients with schizophrenia and 19 healthy controls. All participants were right-handed (Annett, 1967). Diagnoses were established by a clinical psychiatrist (C. Chr. S.) based on the Structured Clinical Interview for DSM-IV and were confirmed by an independent psychiatrist (R. G. M. S.). All patients met DSM-IV criteria for schizophrenia and had no second psychiatric diagnosis. They were on stable medication, mostly with second-generation antipsychotics.

Healthy volunteers were screened for major medical, neurological and psychiatric history. None of the healthy subjects had a current or history of a psychiatric disorder or first-degree relatives with a psychiatric disorder according to DSM-IV. Exclusion criteria for all participants were neurological disease or damage and medical disorders potentially influencing neurocognitive function. All participants gave written informed consent to the study approved by the Ethics Committee of the Friedrich-Schiller University. Sociodemographic and psychopathological data are given in Table 1.

### 2.2. MRI acquisition

We acquired high-resolution anatomical T1-weighted scans on a 3 T Siemens Magnetom Vision whole-body system using a magnetisation prepared rapid gradient echo sequence, MPRAGE; sagittal orientation (TR =2300 ms, TE =3.03 ms, TI =900 ms, flip angle, 9°, FOV =256 mm, matrix 256×256 mm, number of sagittal slices 192, acceleration factor (parallel acquisition techniques, PAT) =2, acquisition time (TA) =5 min 21 s) with a slice thickness of 1 mm and isotropic resolution of 1×1×1 $mm^3$.

All scans were inspected for motion artefacts and a neuroradiologist confirmed absence of gross pathological findings.

**Table 1**
Demographic and clinical data.

| Diagnostic groups | Healthy controls | Patients | p |
|---|---|---|---|
| **Age (y)** | 29.0 (8.7) | 35.1 (11.5) | 0.077 |
| **Sex (m/f)** | 12/7 | 12/7 | |
| | **Patients subgroups** | | |
| | **Patients with low radial diffusivity** | **Patients with high radial diffusivity** | |
| **Age (y)** | 36.3 (12.9) | 33.67 (10.3) | 0.632 |
| **Sex (m/f)** | 6/4 | 6/3 | |
| **PANSS total** | 66.6 (15.4) | 69.8 (17.1) | 0.664 |
| **PANSS pos** | 14.8 (4.2) | 16.0 (5.3) | 0.592 |
| **PANSS neg** | 19.0 (6.7) | 18.5 (7.2) | 0.891 |

### 2.3. Diffusion tensor imaging procedure

Diffusion imaging data were collected with the same coil in the same scanner. Diffusion-weighted images were obtained using echo-planar imaging (TR =8000 ms, TE =83 ms, FOV =256 mm, with an in-plane resolution of 2 mm, a slice thickness of 2 mm, number of slices 71, an iPAT factor of 3, and a phase partial fourier of 6/8). Diffusion-sensitising gradient encoding was applied in 30 different directions with a diffusion-weighing factor of $b$ = 1000 s/$mm^2$ and one $b_0$ ($b$ =0) image. Images were acquired parallel to the anterior–posterior commissure.

### 2.4. MR scan processing and calculation of cortical folding

We used the FreeSurfer software package (version 4.0.5, http://surfer.nmr.harvard.edu) for processing of images (Dale et al., 1999; Fischl et al., 1999). The implemented processing stream comprises the removal of non-brain tissue, transformation to Talairach-like space, and segmentation of gray/white matter tissue. White and gray matter boundary is tessellated and topological defects are automatically corrected. After intensity normalization, transition of gray/white matter and pial boundary is identified by detecting the greatest shift in intensity through surface deformation. The entire cortex of each subject was then visually inspected and any inaccuracies in segmentation were manually edited.

As a highly local measure for cortical folding absolute mean curvature has been used (Gaser et al., 2006; Luders et al., 2006). This measure allows the exact in vivo quantification of cortical folding at about 300000 points of the whole cortical mantle. Mean curvature has already been used in several studies in schizophrenia (Fornito et al., 2008; Schultz et al., 2010a, 2012; White et al., 2003) (for a detailed methodical description see (Schultz et al., 2010a)).

### 2.5. DTI processing and data extraction

The diffusion-weighted images were computed using standard procedures as implemented in FSL (FMRIB Software Library, FMRIB, Oxford, UK, http://www.fmrib.ox.ac.uk/fsl/) and SPM5 (for a detailed methodical description see (Koch et al., 2011)).