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Research report

Disrupted white matter connectivity is associated with reduced cortical thickness in the cingulate cortex in schizophrenia

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ABSTRACT

Introduction: Both impaired white matter connectivity and alterations in gray matter morphometry have repeatedly been reported in schizophrenia. Neurodevelopmental models propose a close linkage between gray matter alterations and white matter deficits. However, there are no studies investigating alterations in cortical thickness in relation to white matter connectivity changes.

Methods: This combined diffusion tensor imaging (DTI) – surface based morphometry study examined a potential linkage between disruption in white matter connectivity and alterations in cortical thickness. Cortical thickness was analyzed using the FreeSurfer software package (version 4.0.5, http://surfer.nmr.harvard.edu) in a sample of 19 patients with schizophrenia and 20 healthy controls.

Results: Whole brain node-by-node correlational analysis revealed a highly significant association ($r = -.8$, $p < .0001$) between disturbed white matter connectivity in the superior temporal cortex and diminished cortical thickness in the posterior part of the cingulate cortex (Brodmann area 23/31).

Conclusions: This result indicates a significant linkage between disturbed white matter connectivity and reduced cortical thickness in a relevant node of the default mode network that is held to be of high pathophysiological relevance in schizophrenia. The result moreover provides support for the assumption of a neurodevelopmental pathogenesis of the disorder.

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1. Introduction

The disorder of schizophrenia is characterized by a diversity of symptoms. Alterations in brain structure and volume as well as a disrupted connectivity in cortical and subcortical pathways have been hypothesized as pathophysiological mechanisms (Honea et al., 2005; Kumari et al., 2008; Pettersson-Yeo et al., 2011). Apart from increased lateral ventricle size volume reductions in predominantly temporal lobe areas as well as gray matter density reductions in the frontal and temporal lobe are the most frequent findings (Honea et al., 2005; Shenton et al., 2001). More recent studies

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indicate that these volume and density deficits go along with morphometric alterations in surface structure, as well. Using surface based analysis methods which allow automatic measurements of cortical surface with submillimeter precision these studies reported alterations in gyrification and cortical thickness in patient populations at various stages of the illness: Studies with multi-episode, adult onset schizophrenia patients found decreased cortical thickness mainly in prefronto–temporal areas (Kuperberg et al., 2003; Nesvag et al., 2008). Patients with adult onset schizophrenia in the short/medium course of the illness seem to have reduced cortical thickness in a network comprising mainly frontal and temporo-occipital areas, as well as posterior cingulate and smaller parietal cortex areas (Rimol et al., 2010; Schultz et al., 2010a). In first episode (FE) schizophrenia, cortical thinning was detected in predominantly frontal, cingulate and temporal cortex areas (Crespo-Facorro et al., 2011; Fornito et al., 2008; Gutierrez-Galve et al., 2010; Narr et al., 2005; Schultz et al., 2010b).

Apart from evidence for alterations in gray matter volume and surface based morphometry there is an increasing number of findings showing alterations in white matter structure and volume in schizophrenia (Kyriakopoulos et al., 2008). A mounting body of evidence indicates that patients exhibit disruptions in various white matter tracts, and predominantly within long association fibers connecting frontal and temporal cortex areas (Kubicki et al., 2007). A recent meta-analysis based on a systematic search for voxel-based diffusion tensor imaging (DTI) fractional anisotropy (FA) studies identified the left frontal deep white matter and the left temporal deep white matter as most consistently affected by the disorder (Ellison-Wright and Bullmore, 2009).

The majority of all DTI studies investigated FA which reflects a combination of estimates of axial white matter diffusivity (i.e., diffusivity parallel to the axon) and radial diffusivity (i.e., diffusivity perpendicular to the axon). Dysmyelination which is being discussed as one central pathophysiological process in schizophrenia has been shown to be associated with an increase in radial diffusivity with no change in axial diffusivity (Song et al., 2002). However, alterations in radial diffusivity have barely been investigated up to now (Seal et al., 2008). Triggered by these considerations, our own recent study investigated potential alterations in radial diffusivity in patients relative to healthy controls (Koch et al., 2011). The analyses revealed an increased radial diffusivity in the white matter of the superior temporal gyrus. This indicates that white matter microstructure in the temporal cortex may be predominantly affected by the disorder which is in accordance with the result of a recent meta-analysis on studies investigating FA differences between people with schizophrenia and healthy people (Ellison-Wright and Bullmore, 2009).

Of note, structural changes in gray and white matter have also been detected in high-risk subjects, first-episode and early course patients (Kyriakopoulos and Frangou, 2009; Lawrie et al., 2008; Steen et al., 2006) indicating that morphometric abnormalities may exist prior to illness onset and might even increase the risk for the subsequent emergence of clinical symptoms. This assumption is in concordance with the neurodevelopmental hypothesis of schizophrenia which posits an early disruption in the normal development of the brain (Fatemi and Folsom, 2009). According to the mechanical models of brain development cortical gyrification and variation in cortical thickness are considered to be the neurodevelopmental consequences of axonal tension exerted between linked areas (Hilgetag and Barbas, 2006; Van Essen, 1997). Consequently, an early white matter disruption - one potential psychopathological mechanism of schizophrenia - should go along with alterations in gyrification and cortical thickness at an early developmental stage. The linkage between disruption in white matter and alteration in cortical thickness has so far been barely investigated in schizophrenia. Against the background of these considerations the present study aimed to investigate whether the recently detected disruption in white matter microstructure (Koch et al., 2011) is related to an alteration in gray matter thickness. To our best knowledge, this is the first study examining a potential relation between changes in white matter and cortical thickness in patients with schizophrenia. We expected increased radial diffusivity in the left temporal cortex to go along with decreased gray matter thickness in an anatomically connected brain network.

2. Methods

2.1. *Participants*

The study included 19 right-handed (Annett, 1967) chronically ill patients (12 male, 7 female) with a DSM-IV diagnosis of schizophrenia and 20 right-handed healthy subjects (12 male, 8 female). On average, patients were 35.2 (SD = 11.5) years old and had a mean education of 10.58 (SD = 2.06) years. In the healthy controls mean age was 29.7 (SD = 9.1) and mean education 12.70 (SD = .92) years. There was no significant difference between the groups in terms of age [t(37)=1.62, n.s.] but a significant difference regarding education [$t(37) = -4.12$, $p < .01$, corrected for unequal variances]. Diagnosis was established by the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (First et al., 1996) and confirmed by two independent clinical psychiatrists (R.G.M.S. and Ch.S.). Patients were free of any concurrent psychiatric diagnosis and had no neurological conditions. They were in remission from an acute psychotic episode and, apart from one patient who was unmedicated, on stable medication with atypical antipsychotics. Psychopathological status of the patients was assessed by the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Ratings were 15.4 (SD = 4.7) on the positive subscale, 18.8 (SD = 6.8) on the negative subscale, and 35.8 (SD = 7.6) on the general psychopathology scale.

Volunteer subjects were recruited by email and public advertisement. They were screened by comprehensive assessment procedures for medical, neurological, and psychiatric history. Exclusion criteria were current and potentially interfering medical conditions, any current or previous neurological or psychiatric disorder, and first-degree relatives with axis I psychiatric or neurological disorders. All participants gave written informed consent to a study protocol approved by the Ethics Committee of the Friedrich-Schiller-University Medical School.

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