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White matter microstructure in ultra-high risk and first episode schizophrenia: A prospective study

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ABSTRACT

There is increasing evidence of white matter (WM) pathology in schizophrenia, but its role at the very early stage of the disorder remains unclear. In an exploration of WM microstructure in ultra-high risk (UHR) subjects and first episode schizophrenia (FES), 34 FES, 27 UHR and 26 healthy control (HC) subjects underwent a magnetic resonance imaging (MRI) tract based spatial statistics (TBSS) investigation. Whole brain fractional anisotropy (FA), mean diffusivity (MD), radial (RD) and axial diffusivity (AD) values were extracted. UHR subjects who later developed psychosis showed lower FA compared with HC in the corpus callosum (CC), the left superior and inferior longitudinal fasciculus, the left inferior fronto-occipital fasciculs (IFO), and the forceps; RD was significantly higher in the CC, the forceps, the anterior thalamic radiation bilaterally, and the cingulum bundle. FES, compared to HC, showed a significant FA reduction of the CC, the superior and inferior longitudinal fasciculi bilaterally, the IFO bilaterally, the corona radiate bilaterally, and the forceps; while RD was found to be significantly increased in the left superior longitudinal fasciculus. UHR who later developed psychosis had WM abnormalities affecting brain pathways that are crucial for intra- and inter-hemispheric connections.

1. Introduction

Abnormalities in connectivity have been proposed as a key feature of schizophrenia (Friston and Frith, 1995; Guo et al., 2015; Laidi et al., 2015). Recent studies suggest that white matter (WM) abnormalities are evident at the first episode of illness (Rigucci et al., 2013), in people at ultra-high risk (UHR) of developing psychosis (Crossley et al., 2009; Benetti et al., 2009), and even among adolescents who report psychotic experiences (O'Hanlon et al., 2015). Although there is not a specific localization of these abnormalities; frontal, fronto-temporal and fronto-limbic connections, including the superior longitudinal fasciculus (SLF), cingulum bundle, uncinate fasciculus and corpus callosum (CC), seem to be affected in the early course of the disorder (Samartzis et al., 2014).

Diffusion tensor imaging (DTI) allows the in vivo study of WM organization at a microstructural level, measuring the direction and degree of water diffusion as well as its anisotropy. Anisotropy (commonly reported as fractional anisotropy (FA)) can be altered by pathologic factors, such as demyelination and axonal membrane deterioration, and so is often used as an index of WM integrity. The diffusivity along axons provides complementary information regarding WM structure. The axial (parallel) diffusivity (AD) corresponds to the amount of diffusion measured along the direction of principal diffusion, while the radial (perpendicular) diffusivity (RD) corresponds to the average diffusion in the perpendicular plane. An increase in RD, which reflects the diffusion of water perpendicular to a fiber, is generally considered a marker of reduced myelination (Song et al., 2005). In contrast, a decrease in AD, which reflects the diffusion of water parallel to a fiber, is often considered a marker of axonal injury (Budde et al., 2009). Finally, mean diffusivity (MD) is a non-specific measure of integrity and is considered a marker of overall diffusion. Alterations in this measure can result from changes in intra- or extra-cellular space, including extra-cellular edema, and therefore be temporary and

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reversible (Bosch et al., 2012). Studies of WM microstructure in UHR subjects have so far been scarce and inconclusive. One study reported a reduction of FA in the WM of the frontal lobe (Peters et al., 2009), while another found a reduction in the SLF (Karlsgodt et al., 2009). Peters et al. (2008, 2010), who used tractography to assess the uncinate and arcuate fasciculi, cingulum bundle, and corpus callosum (CC), did not find any differences between UHR and healthy control subjects. So far, only one previous DTI investigation has subdivided UHR subjects in terms of their clinical outcome (Bloemen et al., 2010). In this study, UHR subjects who later became psychotic (UHR-P) showed lower FA in the WM lateral to the right putamen and in the left superior temporal gyrus, but higher FA in the left posterior temporal WM, compared with UHR subjects who did not become psychotic (UHR-NP) (Bloemen et al., 2010). A region of interest (ROI) approach, in which the UHR-P group was compared with both the UHR-NP group and controls, showed a significant regional reduction in the genu of the CC (Walterfang et al., 2008a, 2008b). A recent longitudinal investigation revealed a progressive FA reduction in UHR-P subjects that was not evident in UHR-NP subjects (Carletti et al., 2012).

The objective of the present study was to comprehensively investigate WM microstructure in UHR subjects, first episode schizophrenia (FES) patients and healthy controls. Based on the literature, we hypothesized that WM abnormalities would be present in FES patients and in UHR subjects who developed a psychotic disorder. We used Tract-Based Spatial Statistics (TBSS) to investigate WM integrity. A range of diffusion metrics, including AD, RD, as well as MD and FA, was used to provide a greater degree of information on the diffusion properties related to axonal integrity and myelination.

2. Methods

2.1. Subjects

All consecutive patients referred to acute psychiatric care and to the outpatient psychiatric service of Sant'Andrea Hospital of Rome between October 2010 and December 2014 were enrolled if they met the following requirements:

2.1.1. FES

(i) Age between 18 and 35; (ii) presenting their first episode of non-affective psychosis according to DSM-IV-TR criteria for schizophrenia, schizophreniform disorder or brief psychotic disorder; (iii) receiving adequate antipsychotic treatment for less than 2 weeks. Consensus diagnosis was carried out using the Structured Clinical Interview for DSM-IV (SCID-I) (First et al., 1997) by two senior psychiatrists. Duration of untreated psychosis (DUP) was defined as the time from the first continuous (present most of the time) psychotic symptom to initiation of adequate antipsychotic treatment. The first identifiable positive symptom was determined using data gathered from multiple sources, including medical records and direct interviews with both the patient and family members.

2.1.2. UHR

Ultra high risk subjects were enrolled if they met psychosis risk syndrome criteria (McGlashan et al., 2010), i.e., attenuated psychotic symptoms (APS), brief intermittent psychotic symptoms (BIPS) or functional decline and family history of schizophrenia (genetic risk and deterioration, GRD). At 12-, 24- and 36-month follow-up, subjects were assessed for potential transition to psychosis according to the Structured Interview for Psychosis-Risk Syndromes (SIPS) criteria for the presence of a psychotic syndrome (severe and psychotic positive symptoms that are seriously disorganizing or dangerous and/or occur for at least 1 hour per day at an average frequency of 4 days per week over 1 month) (McGlashan et al., 2010).

Major exclusion criteria were (i) current or past diagnosis of autistic disorder or other pervasive developmental disorder; (ii) history of severe head injury; (iii) severe medical conditions or major neurological disorders, including mental retardation and dementia, that could impair neuropsychological task performance or that could produce psychotic symptoms; and (iv) any current or past drug abuse.

2.1.3. Controls

Twenty-six healthy volunteers were recruited as controls by word of mouth in the same catchment area. None had a history of psychiatric disease, mental retardation, neurological disorder, or general medical illnesses, including substance dependence, as determined by an abbreviated version of the Comprehensive Assessment of Symptoms and History (CASH) (Andreasen et al., 1992). Controls were age-, gender-, handedness-, and education-matched to the patients. Clinical records and family interview confirmed the absence of psychosis in first degree relatives. Written informed consent was obtained from all participants after providing complete description and explanation of the study. Ethical approval was obtained. The study followed the Declaration of Helsinki and Good Clinical Practice guidelines.

2.2. Psychopathological assessment

Criteria for a prodromal syndrome were determined using the validated Italian version of the Scale of Prodromal Symptoms (SOPS) (Comparelli et al., 2011), which consists of 19 items in the following four symptom domains: positive, negative, general and disorganized. The raters (A.C. and V.C.) are expert clinicians trained in the administration of the SIPS/SOPS. Cohen's κ for inter-rater reliability was 0.91 ($p < 0.0001$).

Two specialists (I.M and G.M.) who were unaware of the purpose of the study rated symptom severity using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Handedness was assessed by the Edinburgh Inventory (Oldfield, 1971).

2.3. MRI acquisition and image processing

2.3.1. MRI acquisition

The median time elapsed from admission to MRI acquisition was 4 ± 1.5 days for FES. A single MRI scan of all subjects was acquired on a 1.5 Tesla MR scanner (Magnetom, Siemens, Erlangen, Germany). The imaging protocol comprised a 3D T1-weighted magnetization-prepared rapid acquisition gradient echo (MP-RAGE) sequence (repetition time (TR)=1110 ms; echo time (TE)=3.49 ms; matrix size=256 × 192; section thickness=1 mm), a FLAIR sequence (TR=10,000 ms; TE=125 ms; matrix size=256 × 192; section thickness=5 mm) and diffusion tensor imaging (DTI) data acquired using a 12-direction sequence (TR=9400; TE=9; matrix size=128 × 128; section thickness=1.9 mm).

2.3.2. White matter analysis

DT images were corrected for the effects of head movements and eddy currents using the eddy-correct function (FSL, Oxford, UK) (Smith et al., 2004). The registered images (b0 and the 12 directions files) were skull-stripped using the FSL Brain Extraction Tool. Fractional anisotropy (FA) maps were calculated using DTIFit (FMRIB Software Library's Diffusion Toolbox), which fits a DT model at each voxel.

To perform voxelwise analyses of FA images, we used Tract Based Spatial Statistics (TBSS) v.1.2 (Smith et al., 2006), All FA images were coregistered to the Montreal Neurological Institute-152 space FA

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