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Anterior commissural white matter fiber abnormalities in first-episode psychosis: A tractography study

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ABSTRACT

Background: The Anterior Commissure (AC) is an important interhemispheric pathway that connects contralateral temporal lobes and orbitofrontal areas. The role of the AC is not yet well understood, although abnormalities in this white matter tract have been reported in patients diagnosed with chronic schizophrenia. However, it is not known whether changes in the AC are present at earlier stages of the disease.
Methods: Diffusion Magnetic Resonance Images (dMRI) were acquired from 17 First Episode Schizophrenia Patients (FESZ) and 20 healthy controls. The AC was reconstructed using a streamline tractography approach. DMRI measures, including Fractional Anisotropy (FA), Trace, Axial Diffusivity (AD) and Radial Diffusivity (RD) were computed in order to assess microstructural changes in the AC.
Results: FA was reduced, while trace and RD showed increases in FESZ. AD did not show differences between groups.
Conclusion: The observed changes in these dMRI measures, namely reductions in FA and increases in trace and RD, without changes in AD, likely point to myelin abnormalities of this white matter tract, and provide evidence of white matter pathology extant in the early phases of schizophrenia.

1. Introduction

It has been suggested that schizophrenia is associated with a functional disconnectivity of the brain (Wernicke, 1906; Mesulam and Geschwind, 1978; Friston and Frith, 1995; Fornito et al., 2011). According to this theory, functionally specialized brain regions are highly interconnected through white matter tracts and a disconnection in these tracts may lead to dysfunction in the brain. Connectivity of the brain can now be studied in vivo by using functional imaging in resting-state brain networks (Karbasforoushan and Woodward, 2012), and an abnormal interhemispheric connectivity has been reported in schizophrenia (Guo et al., 2013). The commissural fibers are important for the transfer of information, including complex cognitive information between the hemispheres (Moldrich et al., 2010; van der Knaap and van der Ham, 2011). Additionally, the coordinated transfer of information is essential for appropriate cerebral functions. The cerebral hemispheres are connected by the corpus callosum (CC) and the anterior commissure (AC), as well as by the posterior and the hippocampal commissures. The largest of these pathways is the CC, which transfers the majority of interhemispheric information. However, when the CC becomes dysfunctional, the AC plays a compensatory role by providing comprehensive inter-hemispheric communication. This has been demonstrated in several studies, first, in an experiment on rhesus monkey with lesions in the CC (O'Reilly et al., 2013), second, in individuals with agenesis of the CC (Risse et al., 1978), and, third, in individuals with epilepsy and complete resection of the CC (Spencer, 1988). These studies consistently show that the functionality of motor, language and cognition remained

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unaffected as long as the AC was intact. Interestingly, **reduced** interhemispheric functional connectivity **and structural abnormalities in the CC have been reported in chronic and in FESZ patients** (Kubicki et al., 2005; Whitford et al., 2010; Henze et al., 2012; Knochel et al., 2012; Guo et al., 2013; Samartzis et al., 2014), suggesting a pivotal role of the AC in the etiology of this disorder.

The AC and the CC each interconnect specific cortical areas. The major brain areas connected by the AC are the temporal pole, inferior temporal gyrus, superior temporal gyrus, parahippocampal gyrus, fusiform gyrus, amygdala, orbitofrontal cortex and olfactory bulb (Turner et al., 1979; Barbas and Pandya, 1984; Cipolloni and Pandya, 1985; Demeter et al., 1990; Di Virgilio et al., 1999; Schmahmann and Pandya, 2006). The AC is a relatively small fiber tract (diameter of 3.5-4.3 mm^2) (Allen and Gorski, 1992) that is visible on structural MRI and on diffusion tensor magnetic resonance images (dMRI) in the mid-sagittal plane. In comparison to the CC, AC makes up only about 1% of the CC area (Foxman et al., 1986). Due to the small size, until now, the AC of the human and primate brains has mostly been explored in post-mortem preparations, and only very recently using dMRI *in vivo*. Using the dMRI technique the AC was reconstructed in healthy subjects, in adolescents born preterm and in adolescents with bipolar disorder (Catani et al., 2002; Patel et al., 2010; Northam et al., 2012; Saxena et al., 2012). Interestingly, one of the dMRI studies showed that AC fibers can be tracked all the way into the occipital and parietal lobes in humans, suggesting a wider distribution of the AC axons in humans than in primates (Patel et al., 2010). To the best of our knowledge, only one dMRI study, conducted in our laboratory, has explored the AC in patients diagnosed with chronic schizophrenia (Choi et al., 2011) but not in earlier stages of the disease.

DMRI is a well established, noninvasive method to explore brain white matter integrity, and has been applied to thousands of studies, of which about 200 have focused on schizophrenia. It is sensitive to changes in extracellular water movement, and measures used most frequently in clinical DTI studies include Fractional Anisotropy (FA), Trace, Axial Diffusivity (AD) and Radial Diffusivity (RD). FA is a measure of the directionality of water diffusion (Basser et al., 1994) and has highest values in white matter regions of highly myelinated and organized fibers (Beaulieu, 2002). The two other dMRI measures, AD and RD, are believed to be related more, but still indirectly, to neurobiological properties of white matter within the fiber bundle. AD is a measure of diffusion along the length of the axon (e.g., the largest eigenvalue), whereas RD is the average of the two measures of diffusion orthogonal to the axon. Trace is the sum of the AD and the RD and describes the overall diffusivity of water molecules. Trace is increased in the case of any tissue damage, but also as a result of vasogenic edema and inflammation. A series of animal experiments has shown that demyelination of axons is reflected by increased RD and decreased FA, with AD unchanged (Song et al., 2003; Song et al., 2005). Subsequently, dMRI measures have been applied to evaluate the micropathology of multiple diseases.

DMRI has proven useful in investigating changes in white matter prior to and throughout the disease course of schizophrenia (Kubicki and Shenton, 2014). When compared to a healthy control group, changes in dMRI measures describe biological changes in brain tissues by the mean of altered water diffusion. Prior to disease onset, decreases in FA and AD (with no changes to RD and trace) were reported in individuals with 22q11.2 deletions syndrome (22q11DS), a syndrome with an incidence of 30% for developing schizophrenia (Kikinis et al., 2012). These changes in dMRI measures have been interpreted as indicative of changes in axonal integrity, likely a consequence of neurodevelopmental abnormalities. At the time immediately before (clinical high risk phase) and immediately after the first episode of schizophrenia (FESZ), increases in trace and decreases in FA have been interpreted as a possible sign of tissue edema, suggestive of neuroinflammation (Pasternak et al., 2012; Clemm von Hohenberg et al., 2014). It is further hypothesized that neuroinflammation occurs temporarily and gives way later to myelin degeneration in the chronic phase of schizophrenia. Indeed, decreases in FA and associated increases in RD, the signature of abnormalities of the myelin sheath, have repeatedly been reported in FESZ and in patients with chronic schizophrenia (e.g. (Ashtari et al., 2007; Seal et al., 2008; Whitford et al., 2010))

Of interest to the hypothesis of disconnectivity are the structural abnormalities observed in interhemispheric pathways in schizophrenia. Structural abnormalities in the CC have been reported in chronic and in FESZ patients (Kubicki et al., 2005; Whitford et al., 2010; Henze et al., 2012; Knochel et al., 2012; Samartzis et al., 2014), and is one of the most consistent findings in schizophrenia (e.g.(Melonakos et al., 2011)). Since lesion studies suggest that dysfunctional CC is not sufficient to result in cognitive deficits, as long as AC is preserved (Risse et al., 1978; Spencer, 1988; O'Reilly et al., 2013), we explored whether patients with schizophrenia evince abnormalities in AC at the time of first episode. Thus in this study we used dMRI and tractography to reconstruct the AC tract in FESZ patients and healthy controls. We compared dMRI measures, including FA, trace, AD and RD, between the two groups, and assessed microstructural abnormalities of the AC tract in FESZ.

2. Methods

2.1. Subjects

Seventeen first episode schizophrenia patients (13 male/4 females) were diagnosed with FESZ and twenty (15 males/5 females) control subjects were recruited as part of the larger Boston Center for Intervention Development and Applied Research (CIDAR) study (www.bostoncidar.org). Diagnoses were based on a diagnostic interview using the Structured Clinical Interview for the DSM-IV-TR, Research Version (SCID) for ages 18 years and older, (First et al., 2002), or the Kiddie-SCID for subjects 13-17 years of age (Hien et al., 1994). The patients were either not medicated (two patients) or medicated with antipsychotic medication (fifteen patients). All medication dosages were converted to chlorpromazine equivalents (Woods, 2003; Stoll, 2009). **The IQ was estimated using the Wide Range Achievement Test 4 (WRAT-4)** (Wilkinson and Robertson, 2006), **which among others measures the subject's ability to read and comprehend sentences. The WRAT-4 Reading sub-score assesses the subject's IQ at young age before the onset of schizophrenia.** The severity of schizophrenia symptoms was assessed in patients using the Positive and Negative Syndrome Scale (Andreasen, 1983, 1984). Further demographic and clinical information for patients and controls is given in Table 1.This study was approved by the local IRB committees at all participating institutions.

2.2. Image acquisition and processing

Diffusion weighted images (DWI) were acquired on a 3 Tesla System GE Echospeed (General Electric Medical Systems, Milwaukee, WI) scanner. The scan parameters were: TR 17,000 ms, TE 78 ms, FOV 24 cm, 144x144 matrix and 1.7 mm slice thickness. Acquisitions used 51 gradient direction with $b = 900$ s/mm and 8 baseline scans with $b = 0$. The whole brain was imaged in 85 axial slices. The raw data was processed for noise reduction, eddy current and head motion. Tensors were estimated by the least squares method (Basser and Jones, 2002) using 3DSlicer software version 3.6.2 version (http://www.slicer.org/) (Pieper et al., 2004; 2006).

2.3. Tractography of the AC

The AC was reconstructed using ROIs (Region-Of-Interest) based streamline tractography using 3Dslicer software (Fig. 1). Individual ROIs were drawn as described by Choi (Choi et al., 2011), and further modified by adding an exclusion ROI to remove stray fibers. In summary,