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A selective review of structural connectivity abnormalities of schizophrenic patients at different stages of the disease

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ABSTRACT

Schizophrenia has long been hypothesized to result from a disconnection syndrome due to a disruption of the association fibers of the brain. However, only with the advent of *in vivo* neuroimaging, a formal disconnectivity hypothesis for schizophrenia has been developed. Diffusion tensor MRI, a non-invasive technique which is sensitive to features of tissue microstructure and to the anatomy of the white matter fibers, has gained a crucial role in the field. Here, we provide a state-of-the-art review of structural connectivity abnormalities detected in schizophrenia and discuss the most relevant findings at preclinical, first episode drug-naïve, and chronic stages. Imaging studies showed white matter alterations from the preclinical to the chronic stage of the disease, which involve the corticospinal tracts, interhemispheric connections, long association white matter tracts, cerebello-thalamo-cortical circuit, and limbic system. Such abnormalities were found to be associated with the psychiatric and cognitive manifestations of the disease and to predict, at least partially, the patient clinical evolution and response to treatment.

Contents

1. Introduction

Schizophrenia (SZ), a severe psychiatric disorder, has long been hypothesized to result from a disconnection syndrome. Wernicke (1906) first proposed that SZ might be associated with a disruption of the association fibers of the brain. However, only with the advent of *in vivo* neuroimaging it was possible to achieve an experimental evidence for this

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hypothesis (Volkow et al., 1988; Friston and Frith, 1995), and to identify the possible pathological substrates.

Structural magnetic resonance imaging (MRI) studies have shown reductions of gray matter (GM) volume in the brain of patients with SZ compared to healthy controls, although increased GM volumes of some subcortical regions have also been reported (Levitt et al., 2010). Structural connectivity, in terms of white matter (WM) fiber integrity, has been investigated with both conventional and advanced MRI techniques. To date, however, the majority of studies evaluating WM regional abnormalities in SZ is based on sequences and post-processing algorithms developed for GM volumetry assessment, which may not represent the optimal approach to image WM alterations (Sullivan and Pfefferbaum, 2006). Diffusion tensor (DT) MRI is a non-invasive technique which is sensitive to features of tissue microstructure, such as axonal density and axonal fiber orientational coherence. Diffusion is anisotropic in WM, and DT MRI-derived maps allow visualizing anisotropic structures that are consistent with the anatomy of the major WM fiber bundles of the brain (Pierpaoli et al., 1996). Furthermore, the anatomy of structural connectivity can be further investigated with DT MRI tractography, which allows the *in vivo* reconstruction of WM tracts, by measuring the diffusivity characteristics of water along different directions on a voxel-by-voxel basis (Basser et al., 2000). Once a WM region of interest (ROI), a WM voxel or a WM tract is identified, measures of WM integrity can be obtained by measuring fractional anisotropy (FA), an index of the degree to which water diffusion has a common orientation, and mean diffusivity (MD), a measure of the magnitude of water diffusion in all directions (Basser et al., 1994).

Recently, a massive number of studies on WM in SZ patients has been published. Unfortunately, the results of these studies are frequently contrasting. A recent meta-analysis (Ellison-Wright and Bullmore, 2009) reviewed 15 studies which investigated FA with a voxel-wise approach in a total of 407 patients affected by SZ or related diagnoses (schizoaffective disorder and first episode psychosis – FEP). Two major clusters of altered WM integrity have been found in the left frontal and temporal lobes in 12 of these 15 studies (Ellison-Wright and Bullmore, 2009). Such a pattern of abnormalities suggests that two brain networks might be disrupted in SZ patients: the cerebello-thalamo-cortical circuit and the temporal network interconnecting the frontal lobe, insula, hippocampus/amygdala, and occipital lobe. In keeping with these findings, another meta-analysis showed that treated and untreated SZ patients have decreased FA or reduced WM volume (WMV) of the interhemispheric fibers, anterior thalamic radiations, inferior longitudinal fasciculus (ILF), inferior fronto-occipital fasciculus (IFOF), cingulate bundle and fornix (Bora et al., 2012). The most significant clusters of abnormalities were found in the anterior limb of internal capsule bilaterally and right temporal lobe (Bora et al., 2012). The DT MRI abnormalities found in SZ patients agree with postmortem studies which identified WM alterations in these patients, including microstructural abnormalities of myelin and oligodendrocytes (Uranova et al., 2001). Furthermore, the onset of SZ usually occurs during late adolescence or early adulthood suggesting a possible altered WM maturation in these patients (Feinberg, 1982). Although the findings of the two meta-analysis largely overlap (Ellison-Wright and Bullmore, 2009; Bora et al., 2012), they reviewed clinically heterogeneous populations formed by patients at different stages of SZ, with different treatment exposure, and different clinical diagnosis.

Here, we provide a state-of-the-art selective review of structural connectivity studies in SZ and discuss the most relevant findings seen at the different stages of the disease. To try to define a possible trajectory of WM alterations in this condition, findings are reported in the following order: people at risk to develop SZ; drug-naïve first episode SZ patients (FES); and treated SZ patients. The search of manuscripts was done in PubMed (http://www.ncbi.nlm.nih.gov/pubmed) using the following key words: "white matter"; and "schizophrenia" or "schizophrenic patients"; and "first episode psychosis" or "drug-naïve" or "treated patients"; and "diffusion tensor MRI" or "structural connectivity" or "structural MRI". Papers using different DT MRI techniques, such as regions of interest, tractrography and voxel-wise approaches, were included. Then, the (relatively) most recent papers were selected and discussed as examples to show the main patterns of WM alterations in the different phases of this condition.

2. White matter abnormalities in individuals at high risk to develop schizophrenia

To investigate vulnerability to psychosis, two different approaches can be used: a) assess individuals with clinical prodromal signs of the disease (i.e., the clinical high-risk strategy) and b) evaluate non-psychotic first-degree relatives of patients with a definite diagnosis of SZ or psychosis (i.e., the genetic high-risk approach) (Fusar-Poli et al., 2011). Among individuals with a clinical high risk (CHR) to develop SZ, there are ultra-high risk (UHR) subjects (who are defined by the presence of prevalent positive clinical symptoms and represent a "late prodromal" syndrome) (Yung et al., 2003, 2004), and "early prodromal" individuals (who present with more subtle symptoms including attenuated psychotic phenomena, a decline in socio-occupational function and a diagnosis of schizotypical personality disorder) (Olsen and Rosenbaum, 2006). The identification of at risk subjects is clinically important in order to make an early diagnosis and intervention, thus reducing the duration of untreated psychosis (DUP), and, ideally, to push forward disease onset.

WMV was found to be reduced in UHR subjects compared to controls in the superior temporal lobe (Witthaus et al., 2008). In these patients compared to controls, DT MRI studies showed decreased FA values of the long association tracts, such as ILF, IFOF and superior longitudinal fasciculus (SLF) (Karlsgodt et al., 2009; Carletti et al., 2012; Clemm von Hohenberg et al., in press), body (Clemm von Hohenberg et al., in press), tapetum (Clemm von Hohenberg et al., in press) and splenium of the corpus callosum (CC) (Carletti et al., 2012; Clemm von Hohenberg et al., in press), stria terminalis (Clemm von Hohenberg et al., in press), right internal (Carletti et al., 2012; Clemm von Hohenberg et al., in press) and external capsules (Carletti et al., 2012), superior and posterior corona radiata (Clemm von Hohenberg et al., in press), cingulum (Clemm von Hohenberg et al., in press), and cerebral peduncles (Clemm von Hohenberg et al., in press). Interestingly, while young controls showed increased FA with increasing age, this was not the case for UHR subjects in regions such as the medial temporal WM and ILF (Fig. 1), suggesting a different WM development at least in the temporal structures (Karlsgodt et al., 2009). When compared with FES patients, UHR patients had a less severe involvement of the fronto-temporal WM regions (Witthaus et al., 2008). While this finding can be explained by the fact that not all UHR patients are going to

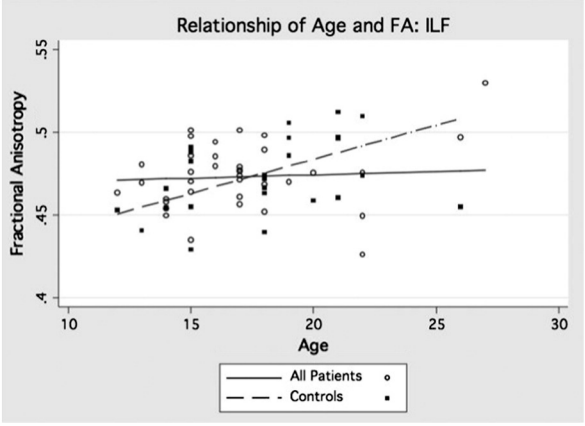

Fig. 1. Scatterplot of the correlations between age and fractional anisotropy (FA) of the inferior longitudinal fasciculus (ILF) in ultra-high-risk (UHR) subjects and healthy controls ($F_{[4,52]} = 3.49$, $p = .022$). Reproduced with permission from Karlsgodt et al. (2009).

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