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Abnormal white matter microstructure and increased extracellular free-water in the cingulum bundle associated with delusions in chronic schizophrenia

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ABSTRACT

Background: There is growing evidence to suggest that delusions associated with schizophrenia arise from altered structural brain connectivity. The present study investigated whether structural changes in three major fasciculi that interconnect the limbic system – the cingulum bundle, uncinate fasciculus and fornix – are associated with delusions in chronic schizophrenia patients.

Methods: Free-water corrected Diffusion Tensor Imaging was used to investigate the association between delusions and both microstructural changes within these three fasciculi and extracellular changes in the surrounding free-water. Clinical data and diffusion MRI scans were obtained from 28 healthy controls and 86 schizophrenia patients, of whom 34 had present state delusions, 35 had a lifetime history but currently remitted delusions, and 17 had never experienced delusions.

Results: While present state and remitted delusions were found to be associated with reduced free-water corrected fractional anisotropy (FA_T) and increased free-water corrected radial diffusivity (RD_T) in the cingulum bundle bilaterally, extracellular free-water (FW) in the left cingulum bundle was found to be specifically associated with present state delusions in chronic schizophrenia. No changes were observed in the remaining tracts.

Conclusions: These findings suggest that state and trait delusions in chronic schizophrenia are associated with microstructural processes, such as myelin abnormalities (as indicated by decreased FA_T and increased RD_T) in the cingulum bundle and that state delusions are additionally associated with extracellular processes such as neuroinflammation or atrophy (as indicated by increased FW) in the left cingulum bundle.

1. Introduction

Delusions are described as "fixed beliefs that are not amenable to change in light of conflicting evidence" (American Psychiatric Association, 2013) and are one of the most distinctive and common symptoms of schizophrenia. It has long been suggested that delusions represent a misinterpretation or misperception of sensory experiences resulting from abnormal neural connectivity. Frith et al. (2000) suggested that certain delusions might result from an abnormal connectivity between the frontal lobe and the parietal cortex, leading to a misattribution of internally generated events to external sources. It has been proposed that this abnormal fronto-parietal communication might be the result of structural changes in frontally extending white matter tracts that connect these distant cortical regions (Whitford et al., 2014a).

Other studies have focused on connectivity within the limbic system. The limbic system is a complex network of interconnected gray matter structures including the amygdala, hippocampus, hypothalamus, thalamus, basal ganglia, and cingulate gyrus (Mega et al., 1997). While the

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limbic system plays a role in behavior, motivation and olfaction, its principal functions are in emotional regulation and memory (Salcman, 1978). The limbic system is interconnected by three major white matter fasciculi, namely the cingulum bundle, uncinate fasciculus, and fornix. The cingulum bundle connects the anterior cingulate cortex with the nucleus accumbens, the amygdala and the medial dorsal thalamus (Nestor et al., 2007), and is involved in memory, emotion and attention (Catani and Thiebaut de Schotten, 2008). The uncinate fasciculus is a ventral limbic connection that originates in the temporal lobe and projects into orbital, medial and ventral regions of the frontal cortex (Catani et al., 2002; Price et al., 2008). The uncinate fasciculus has been reported to be involved in memory (Cohen, 2011; Schott et al., 2011), emotion, and inhibition (Price et al., 2008). The fornix connects the hippocampus with the mammillary bodies, thalamus and nucleus accumbens (Davies et al., 2001; Takei et al., 2008), and is thought to be primarily involved in memory functions (Catani and Thiebaut de Schotten, 2008; Takei et al., 2008).

There is growing evidence to suggest that abnormalities in the structural and functional connectivity of the limbic system may be a causal factor in the development of delusions in individuals with schizophrenia. With regards to functional connectivity, Javanbakht (2006) suggested that delusions emerge from a fronto-limbic imbalance resulting from an increase in limbic dopamine, which has been observed during psychotic episodes of schizophrenia but not during remission. According to this account, a hyperactive limbic system attributes enhanced emotional importance to internal and external events (Javanbakht, 2006). This in turn leads to a breakdown of the prefrontal cortex's ability to differentiate internally from externally generated events and thereby gives rise to the development of delusions. Support for the involvement of the limbic system in the development of delusions comes from an fMRI study which reported that disrupted functional connectivity in fronto-limbic structures were associated with acute psychotic states (Schott et al., 2015). Additionally, a positron emission tomography (PET) study reported an association between metabolic changes in brain circuits of the limbic system and the development of psychosis in schizophrenia (Tamminga et al., 1992).

With regards to structural connectivity, findings from several Diffusion Tensor Imaging (DTI) studies have noted correlations between severity of white matter abnormalities in the constituent fasciculi of the limbic system and severity of delusions in patients with schizophrenia (Bracht et al., 2014; Chan et al., 2010; Fitzsimmons et al., 2014; Whitford et al., 2014a, 2014b). Given the established association between structural and functional connectivity within the limbic system (Cohen et al., 2008), it is feasible that abnormalities in structural connectivity could underpin the observed abnormalities in functional connectivity, which could, in turn, lead to the development of delusions.

Reduced fractional anisotropy (FA; Mori and Zhang, 2006) and increased radial diffusivity (RD; Song et al., 2005) have repeatedly been reported in patients with schizophrenia (Prasad et al., 2015; Seal et al., 2008). Abnormal axial diffusivity (AD), on the other hand, has not been linked to schizophrenia as reliably as FA and RD changes (Seal et al., 2008). Two of the more common interpretations of these white matter findings in schizophrenia are changes to the myelin sheath surrounding the axons (Kubicki et al., 2005; Muller and Schwarz, 2006; Uranova et al., 2007) and neuroinflammation (Laan et al., 2009; Pasternak et al., 2012; van Berckel et al., 2008). Distinguishing between these two pathologies is of utmost importance to our understanding of the neurobiological basis of schizophrenia and for the development of more effective treatments (Pasternak et al., 2009).

At this time, it is not possible to differentiate myelin changes from neuroinflammation with common DTI metrics. Both pathologies lead to a decrease in FA (Pasternak et al., 2009), and while an increase in RD is typically associated with myelin alterations (Song et al., 2005), RD measures can also be contaminated by inflammation (Lodygensky et al., 2010; Wang et al., 2014). Pasternak et al. (2009) developed a novel technique, termed free-water (FW) imaging, to address this problem by differentiating between diffusion properties of brain tissue, such as white matter fiber bundles, and surrounding free-water such as cerebrospinal fluid. Changes to the myelin sheath impact the diffusion of water molecules in close proximity to the axon (Song et al., 2005), whereas neuroinflammation increases the fractional volume of water molecules diffusing freely in the extracellular space (Syková and Nicholson, 2008) where microglia modulate immune defense (Schwartz et al., 2006). Thus, neuroinflammation is associated with excessive extracellular free-water, which can be partialled out to yield improved DTI indices such as free-water corrected fractional anisotropy (FA_T), free-water corrected radial diffusivity (RD_T) and free-water corrected axial diffusivity (AD_T), all of which provide a more precise estimation of tissue changes (Pasternak et al., 2012).

The aim of the present study was to investigate the diffusion properties of white matter fiber tracts of the limbic system in relation to delusions in patients with schizophrenia. For this purpose, FA_T, RD_T, AD_T and FW of the cingulum bundle, uncinate fasciculus and fornix were compared between schizophrenia patients with present state delusions, schizophrenia patients with remitted delusions, schizophrenia patients without a lifetime history of delusions, and healthy controls.

2. Materials and methods

2.1. Participants

The data for this study were obtained from the Australian Schizophrenia Research Bank (ASRB). Details on the original data collection process are provided elsewhere (Loughland et al., 2010). Data were analyzed for 115 participants, consisting of 28 healthy controls (HC) and 87 individuals who had been diagnosed with schizophrenia according to the DSM-IV (American Psychiatric Association, 1994). Diagnostic and clinical information were acquired by conducting the Diagnostic Interview for Psychosis (DIP; Castle et al., 2006). Exclusion criteria included an inability to converse fluently in English, intellectual disability (IQ < 70), movement disorders, a present diagnosis of substance dependence, electroconvulsive therapy within the past six months, brain injury and/or organic brain disorders. One statistical outlier, defined as a value greater than three standard deviations from the sample mean, was identified for FW in the SZ_{D+PS} group and was therefore excluded from further analyses. A subset of the participant sample has been reported on previously in the context of two studies exploring associations between auditory verbal hallucinations and FA in the arcuate fasciculus (McCarthy-Jones et al., 2015), and in the inferior occipito-frontal fasciculus (Oestreich et al., 2015).

Of the 86 schizophrenia patients, 69 had a lifetime history of delusions, which was operationalized as a total score > 0 on the lifetime ratings of the DIP items #58 (other primary delusions), #59 (delusions of passivity), #60 (persecutory delusions), #61 (delusions of influence), #62 (primary delusional perception), #63 (grandiose delusions) and #64 (bizarre delusions). Of these 69 patients, 34 (SZ_{D+PS}) had present state delusions (i.e. delusions present during the past month), while 35 (SZ_{D+LT}) had a lifetime history but currently remitted delusions (i.e., no delusions within the past month). The remaining 17 schizophrenia patients (SZ_{D-}) reported no lifetime history or present state delusions.

Data on the duration of antipsychotic drug use were available for 81 out of the 86 patients with schizophrenia (see Table 1). Lifetime history of alcohol or substance abuse was assessed with DIP items #74 (lifetime diagnosis of alcohol abuse/dependence) and #78 (lifetime diagnosis of drug abuse/dependence), respectively. Hallucinations were assessed with DIP items #49–53. Thought disorder was assessed with the DIP items #54–57. Depression was measured by the DIP items #20 (dysphoria), #21 (loss of pleasure) and #22 (suicide). Negative symptoms were assessed using the DIP items #90 (restricted affect), #91 (blunted affect) and #97 (negative formal thought disorder).

The 28 healthy control participants were screened for a family history of mental disorders and did not have a history of movement or