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MRI diffusion tractography study in individuals with schizotypal features: A pilot study

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ABSTRACT

Diffusion tensor imaging (DTI) studies have identified changes in white matter tracts in schizophrenia patients and those at high risk of transition. Schizotypal samples represent a group on the schizophrenia continuum that share some aetiological risk factors but without the confounds of illness. The aim of the current study was to compare tract microstructural coherence as measured by fractional anisotropy (FA) between 12 psychometrically defined schizotypes and controls. We investigated bilaterally the uncinate and arcuate fasciculi (UF and AF) via a probabilistic tractography algorithm (PICo), with FA values compared between groups. Partial correlations were also examined between measures of subclinical hallucinatory/delusional experiences and FA values. Participants with schizotypal features were found to have increased FA values in the left hemisphere UF only. In the whole sample there was a positive correlation between FA values and measures of hallucinatory experience in the right AF. These findings suggest subtle changes in microstructural coherence are found in individuals with schizotypal features, but are not similar to changes predominantly observed in clinical samples. Correlations between mild hallucinatory experience and FA values could indicate increasing tract coherence could be associated with symptom formation.

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1. Introduction

Schizophrenia is characterised by aberrant connections and can be considered a disorder of dysconnectivity (Friston, 1998; Stephan et al., 2009). Research has identified structural and functional correlates of dysconnectivity, with one such example being altered white matter connectivity (Kanaan et al., 2005; Walterfang et al., 2006; Kubicki et al., 2007; Ellison-Wright and Bullmore, 2009; Peters et al., 2010a; Bora et al., 2011). Diffusion tensor imaging (DTI) enables the visualisation and quantification of white matter tracts (Basser et al., 1994) via encoding the diffusivity of water molecules. The widely used scalar measure, fractional anisotropy (FA—Basser and Pierpaoli, 1996), gives an indication of tract microstructural orientation coherence. Higher values of FA (0–1 scale) are considered as having greater tract coherence since these represent increased directionality of water diffusion and likely to be influenced by factors such as integrity of the fibres, the extent of myelination, and geometric factors including crossing, splaying and curving fibres (Beaulieu, 2002).

Alterations in frontotemporal connections are proposed as key regions in schizophrenia (Friston and Frith, 1995; Lawrie and Abukmeil, 1998), with DTI studies demonstrating changes in tracts such as the arcuate fasciculus (AF) and uncinate fasciculus (UF) (e.g. Mori et al., 2007; Phillips et al., 2009). The changes in tracts are likely due to abnormalities in oligodendrocytes as demonstrated in post-mortem studies examining prefrontal brain regions (Uranova et al., 2007). Clinical symptoms, particularly hallucinations, have been associated with abnormal tracts (e.g. Hubl et al., 2004; Rotarska-Jagiela et al., 2009; de Weijer et al., 2011). The AF connects temporoparietal regions with the frontal cortex and is a key tract between the Broca's and Wernicke's language areas. Consistent with its proposed role in language, there is asymmetry in the AF with greater fibre density

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and FA values in the left hemisphere (Nucifora et al., 2005; Parker and Alexander, 2005; Powell et al., 2006). The UF connects orbitofrontal cortex and temporal lobe and is thought to be involved in episodic memory (Levine et al., 1998). Again, asymmetries in this tract have been reported in tract width (Azadbakht et al., 2010) and FA values (Vernooij et al., 2007; Iturria-Medina et al., 2011). A reduction in normal asymmetry in brain function and structure is the central tenet of Crow's aetiological theory on the failure of dominance in schizophrenia (Crow, 1990, 1997). The theory proposes that schizophrenia is associated with a failure in establishing cortical asymmetry, particularly the normal left hemisphere dominance for language. Crow argues that the dysfunctional development of language dominance could result in a predisposition to psychotic symptoms and problems in communication. DTI studies have shown a reduction in asymmetry, for example in the UF of patient groups compared to controls (Kubicki et al., 2002).

It is uncertain whether changes in white matter occur pre- or post-psychosis onset. To understand the potential progression of change in white matter, groups along the schizophrenia continuum that have been investigated include first-episode (FE) patients (Szeszko et al., 2005; Federspiel et al., 2006; Hao et al., 2006; Price et al., 2007, 2008; Cheung et al., 2008; Luck et al., 2010; Perez-Iglesias et al., 2010) those with genetic proximity (Hoptman et al., 2008; Munoz Maniega et al., 2008) and those with 'at-risk mental states' (Peters et al., 2008, 2010a; Karlsgodt et al., 2009; Carletti et al., 2012). Studies examining individuals with at-risk mental states (ARMS) are particularly informative in understanding aetiological mechanisms. This group are considered at-risk due to presence of intermittent or mild subthreshold psychotic experiences (i.e. ARMS or clinical 'ultra-high risk' UHR; e.g. Yung et al., 1996). Reduced FA values in tracts have been observed in UHR groups, for instance in the superior longitudinal fasciculus (SLF) (Karlsgodt et al., 2009), with such reductions intermediary between FE patients and controls (Carletti et al., 2012). Others have not found regional differences between UHR and controls (Peters et al., 2008) or differences in baseline FA values in those UHR who later go through transition compared to those UHR that do not (Peters et al., 2010b). However in longitudinal studies, UHR patients that go through transition do subsequently present FA reductions compared to non-transition UHR (Carletti et al., 2012). Such studies are critical in determining whether changes in white matter are a risk factor for transition or epiphenomenon of illness.

There is a degree of heterogeneity within the literature on white matter abnormalities and psychosis due to, at least in part, methodological factors including those related to the collection of data (e.g. image acquisition and method of analysis) and those associated with the samples being investigated. Studies have investigated various sources of sample variance including illness duration (Mori et al., 2007), age of onset (Kyriakopoulos and Frangou, 2009), and medication status on FA values (Kanaan et al., 2009). In high risk studies, individuals who meet the ARMS criteria are clinically undifferentiated, so there is potential for lack of diagnostic specificity. In the current study we propose to overcome some of the problems related to using clinical samples by investigating white matter in another sample along the extended phenotype of schizophrenia: individuals with schizotypal features.

Schizotypy is a trait psychosis liability comprising attenuated psychotic symptoms, unusual beliefs, as well as negative-like symptoms such as social withdrawal (e.g. Esterberg and Compton, 2009). Individuals with schizotypal features can be identified in the general population via psychometric measures such as the Schizotypal Personality Questionnaire (SPQ: Raine, 1991). These individuals are at higher risk than the general population for clinical disorders such as schizotypal personality disorder (SPD; see Raine, 2006) and schizophrenia-spectrum disorders (e.g. Gooding et al., 2005). The schizotypal trait provides a means of exploring the mechanisms underpinning risk factors for schizophrenia and psychotic symptoms (Cadenhead and Braff, 2002; Lenzenweger, 2006). Additionally some of the previously mentioned confounds are not present.

One study has examined white matter structures in a related group (those experiencing heightened psychotic-like experiences; Volpe et al., 2008). Higher FA values were found in the left AF in the high psychotic-experience group, whereas the low psychotic-like experience group had higher FA values in the right AF, corpus callosum and fronto-parietal tracts. In a more recent study, various fronto-temporal and other tracts were examined in healthy volunteers (Nelson et al., 2011). Associations between diffusion metrics and the SPQ were examined, with reduced FA values being predictive of higher scores on the Cognitive–Perceptual factor of the SPQ (measure of psychotic-like schizotypal features). Both studies demonstrated that white matter changes commonly found in patients with a diagnosis of schizophrenia are associated with "symptoms" not in need of clinical treatment in healthy individuals. Further studies sampling individuals with increased presence of schizotypal features would be beneficial.

In the current study white matter structures were identified via tractography methods. Two main white matter tracts that have been studied extensively in clinical samples are the AF and UF. Differences in the coherence have been observed in schizophrenia patients (e.g. Burns et al., 2003), as well as being associated with psychotic experiences (e.g. Rotarska-Jagiela et al., 2009). We compared these two tracts bilaterally between individuals with heightened schizotypal features (i.e. those scoring high on the SPQ: High SPQ Group) and Controls. The main hypothesis of this study was that individuals with schizotypal features represent part of the extended phenotype of schizophrenia and would show qualitatively similar white matter abnormalities. Therefore, it was predicted that reduced tract coherence (lower FA) would be found in the High SPQ group compared to Controls. A subsidiary hypothesis was that High SPQ Group would have reduced asymmetries in white matter tracts, most notably in the AF where there is usually a pronounced hemispheric difference (left > right FA values). Finally, in exploratory analyses, schizotypal features and measures of psychosis-proneness were correlated with FA values in the AF and UF.

2. Methods

2.1. Participants and procedure

The sample for the current study was selected from a series of earlier studies (PhD: Schizotypy and the association with brain function and structure: Smallman, 2011). Initially 994 participants completed an online SPQ from universities and colleges in North-West England. From this sample 109 participants were selected for neuropsychological testing, from which 24 participants were selected based on SPQ score for the current study. Controls ($n=12$) were defined as scoring $+0.5$SD or below the mean on total SPQ score from the online sample and individuals with heightened schizotypal features (High SPQ Group, $n=12$) were defined as scoring $+1$SD above the mean. The choice of $+1$SD was sufficient to differentiate from the Controls, but also was determined by availability of high SPQ scoring individuals who fitted inclusion/exclusion criteria (see below), and were willing to undergo brain imaging. At $+1$SD the high scoring group had comparable scores to other studies selecting individuals on the SPQ (e.g. Raine, 1991). Exclusion criteria were current or past history of self-reported psychiatric disorder as assessed by the Mini International Neuropsychiatric Interview (MINI: Lecrubier et al., 1997), history of head trauma with loss of consciousness, non-right motor dominance, and exclusion criteria for magnetic resonance imaging (MRI). Groups were matched on age, sex and IQ.

On the day of testing, in addition to scanning, participants completed two further questionnaires: the Peters et al. Delusions Inventory and Launay-Slade Hallucinatory Scale (see below). Measures of motor dominance and IQ were obtained in an earlier study (Smallman, 2011). Participants were debriefed after

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