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Information processing speed mediates the relationship between white matter and general intelligence in schizophrenia

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ABSTRACT

Several authors have proposed that schizophrenia is the result of impaired connectivity between specific brain regions rather than differences in local brain activity. White matter abnormalities have been suggested as the anatomical substrate for this dysconnectivity hypothesis. Information processing speed may act as a key cognitive resource facilitating higher order cognition by allowing multiple cognitive processes to be simultaneously available. However, there is a lack of established associations between these variables in schizophrenia. We hypothesised that the relationship between white matter and general intelligence would be mediated by processing speed. White matter water diffusion parameters were studied using Tract-based Spatial Statistics and computed within 46 regions-of-interest (ROI). Principal component analysis was conducted on these white matter ROI for fractional anisotropy (FA) and mean diffusivity, and on neurocognitive subtests to extract general factors of white mater structure (g_{FA}, g_{MD}), general intelligence (g) and processing speed (g_{speed}). There was a positive correlation between g and g_{FA} ($r = 0.67$, $p = 0.001$) that was partially and significantly mediated by g_{speed} (56.22% CI: 0.10–0.62). These findings suggest a plausible model of structure-function relations in schizophrenia, whereby white matter structure may provide a neuroanatomical substrate for general intelligence, which is partly supported by speed of information processing.

1. Introduction

Several authors have proposed that schizophrenia is the result of impaired connectivity between specific brain regions rather than differences in local brain activity (Wernicke, 1906; Friston, 1998; Friston and Frith, 1995). This dysconnection hypothesis suggests that schizophrenia may be understood in terms of cognition and pathophysiology as aberrant brain integration (Friston, 1998). It has been suggested that abnormalities in white matter microstructure may produce the anatomical substrate for the dysconnectivity hypothesis (Alvarado-Alanis et al., 2015; Weinberger, 1987). White matter deficits are the most consistent neuroimaging findings in this disorder and it has been reported that white matter integrity may be predictive of conversion to schizophrenia and functional outcome (reviewed in Karlsgodt et al., 2012). Furthermore, Kochunov and Hong (2014) reviewed the overlap between the developmental trajectory of cerebral white matter and the onset of schizophrenia linking the neurodevelopmental and neurodegenerative theories with white matter as the strategic component.

Thus far, a number of studies using functional and diffusion tensor MRI (DT-MRI) have provided evidence regarding the dysconnectivity hypothesis by reporting structural and functional connectivity abnormalities between specific brain regions (Samartzis et al., 2014; Schmidt et al., 2015). The most replicated findings are fronto-temporal, corpus callosum and anterior cingulate cortex dysconnectivity to other cortical and subcortical areas (Pettersson-Yeo et al., 2011). As the symptomatology of schizophrenia is so varied, it is unlikely to be attributable to a circumscribed brain deficit, while the dysconnectivity hypothesis may be able to explain its heterogeneous and complex manifestations (Fornito et al., 2012).

Cognitive impairments are a core characteristic of

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schizophrenia (Elvevåg and Goldberg, 2000). For example, patients diagnosed with schizophrenia often show cognitive deficits in numerous domains, such as attention, learning, memory and executive functions (Elvevåg and Goldberg, 2000). Recent evidence suggests that differences in white matter may account for this variance in cognitive performance (Wexler et al., 2009). Complex cognitive functioning depends on synchronised activity between distributed brain networks. Thus, proper speed and efficiency of information transfer between distal brain regions relies on white matter microstructure (Turken et al., 2008). Indeed, information processing speed has been proposed as a key cognitive resource facilitating higher order cognition by allowing multiple cognitive processes to be simultaneously available (Kail and Salthouse, 1994). Individual differences in processing speed are likely to be dependent on structural variations in white matter, which facilitates and constrains communication among nodes of brain pathways (Turken et al., 2008).

Slowed information processing speed has been proposed as a potential endophenotype for schizophrenia (Antila et al., 2011). These deficits have been repeatedly reported in patients and high risk individuals (Badcock et al., 2015; Bora et al., 2009; Dickinson et al., 2007; Mesholam-Gately et al., 2009; Morgan et al., 2014; Muñoz Maniega et al., 2008; Rodríguez-Sánchez et al., 2007; Sprooten et al., 2011). Rodríguez-Sánchez et al. (2007) reported that when processing speed was removed from a multivariate model, the cognitive deficits observed in patients with schizophrenia were no longer significant compared with healthy controls. Furthermore, schizophrenia patients show an accelerated ageing decline in cerebral white matter linked to an accelerated decay in processing speed when compared to healthy participants in cross-sectional and longitudinal studies (Karbasforoushan et al., 2015; Kochunov et al., 2013; Liu et al., 2013; Ritchie et al., 2015). Thus, deficits in speed of information processing represent an important cognitive marker of risk (Gur et al., 2014; Seidman et al., 2010).

Two previous studies of cognitive ageing have reported that nearly half the variance in water diffusion parameters across major white matter tracts can be accounted for by a single general factor in a large cohort of healthy subjects in their seventies (Penke et al., 2012, 2010). Moreover, this general factor of white matter fractional anisotropy (FA) was positively correlated with general intelligence, and this was completely mediated by processing speed. However, whether an association between FA and general intelligence holds in schizophrenia – and is mediated by processing speed - has not yet been studied (Penke et al., 2012, 2010; Turken et al., 2008).

The aim of this paper is therefore to examine the relationship between white matter structure and general intelligence in schizophrenia and the possible attenuation effect caused by processing speed. We hypothesise that a general factor of white matter integrity can be extracted from water diffusion parameters measured in a range of major tracts in patients diagnosed with schizophrenia, and this general factor accounts for a substantial amount of variance in general intelligence, with a statistically significant portion of this variance mediated by processing speed.

2. Methods

2.1. Participants

Information about participants has been reported in detail previously (Whalley et al., 2015). Participants were recruited across Scotland as part of the Scottish Family Mental Health Study. DT-MRI data were acquired from a total of 28 individuals diagnosed with schizophrenia aged between 23 and 57 years old, with the diagnosis confirmed using the structured clinical interview for DSM IV (SCID) administered by one of two trained psychiatrists (First et al., 2002). (No control cohort was included in the current analysis.) Exclusion criteria included any major medical or neurological conditions, or any personal history of substance misuse in the last year. Additionally, subjects were excluded if there were MRI safety considerations. A detailed description of the study and written informed consent were given to all recruited individuals. The study was approved by the Multicentre Research Ethics Committee for Scotland (09/MRE00/81).

2.2. SCAN acquisition

MRI data were collected on a Siemens Magnetom Verio 3T scanner running the syngo MR B17 software (Siemens Healthcare, Erlangen, Germany). Whole brain diffusion-weighted MRI scans were acquired using a single-shot spin-echo echo-planar (EP) imaging sequence with diffusion-encoding gradients applied in 56 directions ($b=1000$ s/mm^2); six T_2-weighted ($b=0$ s/mm^2) baseline scans were collected at the beginning of the acquisition scheme. Fifty-five 2.5 mm thick axial slices were acquired with a field-of-view of 240 mm and matrix 96×96 giving 2.5 mm isotropic voxels. The repetition and echo times for the EP sequence were 10,200 and 74 ms respectively. The examination took approximately 12 min.

2.3. Imaging analysis

2.3.1. DT-MRI data preprocessing

DT-MRI datasets were pre-processed using FSL tools (http://www.fmrib.ox.ac.uk/fsl), and were visually assessed at every stage of pre-processing to identify artefacts or errors in the analysis pipeline. All volumes were aligned to the first T_2-weighted EP volume using eddy_correct. This alignment corrects for eddy current induced distortions produced by different diffusion gradient directions and head movement (Horsfield, 1999). Next, brain extraction was performed using FSL's Brain Extraction Tool (BET) (Smith, 2002), which removes non-brain tissue. FMRIB's Diffusion Toolbox (FDT/FSL) (Behrens et al., 2003) was then used to fit a diffusion tensor model to the data to obtain parametric maps of FA and mean diffusivity (MD).

2.3.2. Tract-based Spatial Statistics (TBSS)

Whole brain statistical analysis of each subject's FA and MD data was performed using Tract-based Spatial Statistics (TBSS; Smith et al., 2007, 2006) as part of the FSL software package. First, the FA data were non-linearly registered into standard space (FMRIB58_FA) to make local comparison possible while controlling for overall white matter structure. Next, a mean of all FA volumes was obtained and an FA skeleton created. The mean FA skeleton was threshold at 0.2 in order to exclude voxels that were grey matter or CSF (Smith et al., 2006). Then each subject's aligned FA and MD data were projected onto the mean FA skeleton to account for misalignments between participants. (As assessed using ENIGMA protocols (http://enigma.ini.usc.edu/protocols/dti-protocols/#dtiproj), the cohort-averaged mean-squared projection distance for each subject's FA data to the mean FA skeleton was 0.48 (0.02) mm^2.).

Following the protocol described by the ENIGMA consortium (http://enigma.ini.usc.edu; Jahanshad et al., 2013), an atlas-based segmentation was performed on the FA skeletons using binary masks derived from the John Hopkins University (JHU) white matter atlas available in FSL (see Fig. 1). We extracted 46 white matter structures as indicated by this atlas (see Table 1). Mean FA and MD values were calculated from voxels in each subject's white matter skeleton within these regions-of-interest (ROI), thereby