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Schizophrenia moderates the relationship between white matter integrity and cognition

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ABSTRACT

Cognitive impairment is a primary feature of schizophrenia, with alterations in several cognitive domains appearing in the pre-morbid phase of the disorder. White matter microstructure is also affected in schizophrenia and considered to be related to cognition, but the relationship of the two is unclear. As interaction between cognition and white matter structure involves the interplay of several brain structures and cognitive abilities, investigative methods which can examine the interaction of multiple variables are preferred. A multiple-groups structural equation model (SEM) was used to assess the relationship between diffusion tensor imaging data (fractional anisotropy of selected white matter tracts) and cognitive abilities of 196 subjects - 135 healthy subjects and 61 patients with schizophrenia. It was found that multiple-indicators, multiple-causes model best fitted the data analysed. Schizophrenia moderated the relation of white matter function on cognition with a large effect size. This paper extends previous work on modelling intelligence within a SEM framework by incorporating neurological elements into the model, and shows that white matter microstructure in patients with schizophrenia interacts with cognitive abilities.

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1. Introduction

Schizophrenia is often accompanied by impairment in general intelligence and in several cognitive domains (Weickert et al. 2000; Wells et al. 2015; Tandon et al. 2009). These include impairment in episodic memory (Leavitt and Goldberg 2009), processing speed (Knowles et al. 2010), verbal fluency (Henry and Crawford 2005), attention (Fioravanti et al. 2005), executive function (Orellana and Slachevsky 2013) and working memory (Barch and Smith 2008; Reichenberg and Harvey 2007). These impairments robustly contrast them with healthy subjects (Tandon et al. 2009; Reichenberg and Harvey 2007; Keshavan et al. 2008).

Cognitive dysfunction appears in the pre-morbid phase of the disorder and progresses, but with a highly variable course (Weickert et al. 2000). In the pre-morbid phase, the dysfunction has an effect size of 0.5 (Woodberry et al. 2008), and predicts the severity of symptoms and functional outcome after onset (Wells et al. 2015), with impairments translating into poor social and occupational skills (Bowie et al. 2008).

Intelligence requires the proper integration of multiple brain areas (Jung and Haier 2007; Deary et al. 2010), one of the principle roles of white matter. The integrity of white matter is often measured using diffusion tensor imaging (DTI), and a large and growing body of DTI studies have reported white matter tract differences in patients with schizophrenia (Keshavan et al. 2008; Chua et al. 2007; Kanaan et al. 2009; Li et al. 2009; Wagner et al. 2015). Fractional Anisotropy (FA) is perhaps the commonest DTI measure employed in this regard, reflecting white matter micro- and macrostructural organisation, and myelination, and has consistently been shown to be reduced in schizophrenia. Mega-analyses (Kanaan et al. 2017, Kelly et al., 2017) and meta-analyses (Vitolo et al. 2017, Bora et al. 2011, Yang et al. 2017) alike confirm FA to be lower than in healthy controls, related to symptoms, and present

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from first onset (Samartzis et al. 2014). As in the healthy (Ohtani et al. 2017), FA has been shown to be related to various measures of cognition in patients with schizophrenia (Knochel et al., 2016, Alloza et al. 2016, Hidese et al. 2017).

This paper aims at extending these findings, now focusing on clarifying whether the relation between white matter structure and cognition differs in patients with schizophrenia as compared to healthy subjects. The presence of this difference might suggest white matter is involved in the cognitive change in schizophrenia. A multiple groups Structural Equation Modelling (SEM) approach was used, as it is an optimal method to evaluate the relationship between several variables, and to design and test a model representing these relations. The model was specified with one latent variable, which was correlated with white matter structural measurements and to neuropsychological test scores. Based on the aforementioned cognitive impairment in patients with schizophrenia, we hypothesised that schizophrenia would moderate the effect of white matter function on cognition and that this moderation would be reflected in the latent variable mean, i.e., we expected a large effect size when comparing the mean of the latent variable between the groups.

2. Methods

2.1. Subjects

The patients were recruited from the inpatient and outpatient clinics of the South London and Maudsley Hospital National Health Service (NHS) Trust. An experienced psychiatrist established the diagnosis of schizophrenia (DSM-IV criteria) using semi-structured interviews and detailed case-note review. The control subjects were matched to the patient group for age, gender, handedness and premorbid IQ using the National Adult Reading Test (Russell et al. 2000). Exclusion criteria for the control group were personal history of mental illness or family history of psychotic illness. Exclusion criteria for both groups were history of head injury with loss of consciousness, neurological illness or current drug or alcohol dependence. Sixty-one subjects with schizophrenia and 135 healthy subjects were assessed using Wechsler's Adult Intelligence Scale (WAIS-III) (Wechsler 1995) prior to MRI scanning (1.5 Tesla MRI). Fractional anisotropy of 48 white matter tracts was acquired. This dataset has previously been analysed for gender differences (Kanaan et al. 2012) and for differences on FA anisotropy between schizophrenics and healthy subjects (Kanaan et al. 2017). The control group was 57% male, the patient group 82% male; the mean years of education in the control group was 14.71 and 12.98 in the patient group (Table 1).

Table 1
Characteristics of the subjects.

Variables	Healthy subjects (mean, n = 135)	Patients (mean, n = 61)	p-Value
Age	28.742	33.207	0.012 ^a
Gender			
Male (%)	57%	82%	<0.001 ^b
Female (%)	43%	18%	
Age of onset	NA	20.82	
Education (mean, in years)	14.71	12.98	<0.001 ^a
Handedness			
Right	127	60	0.212 ^b
Left	6	0	
Mixed	1	1	
WAIS-III verbal	108.3 (sd 13.97)	100.6 (sd 14.63)	0.001 ^a
WAIS-III performance	109.1 (sd 11.68)	97.3 (sd 17.27)	<0.001 ^a

n, number of patients; (*) For one patient of the healthy group handedness was not recorded.

^a Wilcoxon-Mann-Whitney test was used for the continuous variables.

^b The correlation of the categorical variables was carried out using Fisher exact test.

2.2. Neuroimaging

A GE Signa 1.5 Tesla LX MRI system (General Electric, Milwaukee, Wisconsin, USA) was used, with a standard birdcage quadrature and an echo planar imaging sequence peripherally gated to the cardiac cycle. Sixty-four images with diffusion gradients ($b = 1300 \text{ s/mm}^2$) were acquired together with seven non-diffusion-weighted images ($b = 0$). The diffusion gradients were uniformly distributed in space (Jones et al. 2002) at each of 60 slices; TR was 15 cardiac R-R intervals with a TE of 107 ms. The acquisition gave isotropic (2.5 mm^3) voxels, which were reconstructed to a $1.875 \times 1.875 \text{ mm}$ in-plane pixel size. Mutual-information image correction was applied, then non-brain tissue was removed and finally fractional anisotropy in each remaining voxel was calculated using in-house software (Catani et al. 2002).

Image processing was conducted using TBSS v1.2 (Smith et al. 2006). The FA images were all aligned to the Johns Hopkins University - International Consortium of Brain Mapping DTI-81 white matter atlas (JHU DTI atlas) (Mori et al. 2008) with FNIRT in FSL (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/>). The "skeletons" of the FA images were thresholded for white matter ($FA > 0.3$) and projected onto the mean of all the FA skeletons. They were further subdivided according to 48 JHU DTI atlas regions, with FA averaged per region per-subject and these regional means compared between groups using IBM SPSS v20 (www.ibm.com/software/analytics/spss).

2.3. Statistical package and assumption testing

The analysis was carried out using R (version 3.3.2). The R lavaan package (version 0.5-23.1097) was used to specify the models and later run the structural equation analysis (Rosseel 2012). The MVN package (version 4.0.2) was used to test normality (Korkmaz, Goksuluk, and Zararsiz 2014).

We had measures for 48 tracts, but focussed on a subset of these in order to follow Kline (2004a, b) recommendation of 10 to 20 observations per indicator (Kline 2004a). The decision on inclusion of variables used a data-driven approach, which consisted of fitting a multiple indicators, multiple causes (MIMIC) model similar in structure to those in Fig. 3, but including all available tract measures and cognitive variables, which were then ranked using a modification indices test. This test is part of the lavaan package and it iteratively removes one indicator at a time from the model further calculating the difference that this removal causes to the chi-square value. Each indicator is then ranked by how much it changes the chi-square. We used only tracts from the right hemisphere, the resulting set of tracts comprising the uncinate, external capsule, superior corona radiata, cingulum body, cingulum hippocampus, superior cerebellar pedunculum and the superior fronto-occipital fasciculus.

We followed standard notation in our diagrams. Boxes were used to represent indicators/variables, circles to represent latent variables and arrows to represent regressions. In the interest of clarity, residuals and correlations between the neurological tracts were not represented in the diagrams. A histogram with the distribution of the variables is available in Fig. 2.

2.4. Assumption testing

A concern that besets SEM analysis is confirmation bias. One way of approaching this issue is by analysing semi-equivalent models and picking the one that fares best both in representing a theory about the relations, and by its performance in fit tests (Kline 2004b). We tested three equivalent models (Reflective, 2g, and MIMIC, see Fig. 1), which Kievit (2012) previously tested using psychological measures in healthy subjects. Psychological and neurological measures will be referred to as p- and n-indicators, respectively.

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