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Cortical magnetization transfer abnormalities and connectome dysconnectivity in schizophrenia

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ABSTRACT

Macroscale dysconnectivity in schizophrenia is associated with neuropathological abnormalities. The extent to which alterations in cortical myelination as revealed in vivo by magnetization transfer ratio (MTR) are related to macroscale dysconnectivity remains unknown. We acquired magnetization transfer imaging (MTI) data and diffusion weighted imaging (DWI) data from 78 schizophrenia patients and 93 healthy controls for MTR extraction and connectome reconstruction to examine the possible link between cortical myelination and macroscale dysconnectivity. Our findings showed significant cortical MTR disruptions in several prefrontal areas in schizophrenia patients, including bilateral rostral middle frontal areas, right pars orbitalis, and right frontal pole. Furthermore, cortical MTR alterations between patients and controls were significantly correlated with the level of regional disconnectivity. Together, our findings provide evidence that microstructural neuropathological abnormalities in schizophrenia are predominately present in prefrontal areas of the cortex and are associated with alterations in structural connectome architecture at the whole brain network level.

1. Introduction

Schizophrenia is a severe psychiatric disorder that is characterized as a disorder of brain connectivity (Fornito et al., 2012; Stephan et al., 2009; van den Heuvel and Fornito, 2014). In the past two decades, empirical magnetic resonance imaging (MRI) studies have provided a large body of evidence for disruptions of interregional connectivity (Ellison-Wright and Bullmore, 2009; Fitzsimmons et al., 2013; Fornito et al., 2012; Klauser et al., 2017). Connectome studies focused on brain network topology offer further support for this hypothesis by presenting converging evidence of decreased network efficiency (Zalesky et al., 2011), less centralized frontal and parietal hubs (van den Heuvel et al., 2010), and reduced rich club organization in schizophrenia (Collin et al., 2014; van den Heuvel et al., 2013).

In terms of microscale neuropathology in schizophrenia, a wide range of histological alterations have been observed in the cerebral cortex (for a review, see Bakhshi and Chance, 2015). Findings include increased neuronal density (Dorph-Petersen et al., 2009; Selemon, 2004; Selemon et al., 1998, 1995; Yang et al., 2011), decreased neuron size (Chana et al., 2003; Rajkowska et al., 1998), reduced dendritic spines density (Garey et al., 1998; Glantz and Lewis, 2000; Glausier and Lewis, 2013; Penzes et al., 2011) and reduced oligodendroglia density (Uranova et al., 2001, 2004; Vostrikov et al., 2013). Alterations in neuronal, synaptic and dendritic density have been suggested to underlie gray matter changes as revealed by neuroimaging studies (Fornito et al., 2009a, 2009b) and oligodendrocyte and myelination dysfunction have been linked to perturbations of white matter connectivity in schizophrenia (Cassoli et al., 2015). In a recent study, we confirmed the pattern of abnormalities in spine density of pyramidal neurons across the cortex to be associated with the pattern of white matter connectivity changes in schizophrenia (van den Heuvel et al., 2016).

Magnetization transfer ratio (MTR) obtained by means of magnetization transfer imaging (MTI) provides an estimate of in vivo brain microstructure, in particular myelination levels (Whitaker et al., 2016), a technique that could complement post-mortem investigations of neuronal structure. MTR detects subtle changes in protons that are tightly bound to macromolecular structures, such as myelin, cell membrane proteins, and phospholipids (Wolff and Balaban, 1994). Indeed, MTR reductions in white matter have been shown to be associated with myelin loss in demyelinating diseases such as multiple sclerosis (Chen et al., 2008, 2007; Derakhshan et al., 2014; Dousset et al., 1992; Schmierer et al., 2007, 2004), making MTR a suitable metric for demyelination in neurological conditions. In schizophrenia, several studies have revealed MTR changes in temporal (Foong et al., 2000) and occipital white matter

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(Palaniyappan et al., 2013), the occipito-frontal fasciculus (Kubicki et al., 2005), and the right uncinate fasciculus (Mandl et al., 2010).

MTR has also been used to assess the microstructure of gray matter. MTR studies have verified region-specific cortical myelination patterns in the healthy human brain (Whitaker et al., 2016) with high myelin levels in primary cortices (Glasser et al., 2014; Shafee et al., 2015) and MTI-derived myelination estimates have been observed to be associated with oligodendroglia-related genes in the healthy human brain (Whitaker et al., 2016). Studies in schizophrenia have reported MTR changes in frontal and temporal regions (Bagary et al., 2003; Foong et al., 2001; Price et al., 2010), insula (Bagary et al., 2003), and the cingulate gyri (Price et al., 2010). It remains unknown whether such neuropathological alterations as revealed by intracortical MTR changes are associated with disruptions in macroscale white matter connectivity.

In the current study, we use MTR measurements to characterize neuropathological abnormalities in schizophrenia. Based on the aforementioned findings of cortical microscale alterations associated with macroscale connectivity changes in schizophrenia (van den Heuvel et al., 2016), we hypothesize that cortical MTR abnormalities may relate to macroscale dysconnectivity in the structural connectome. To test this hypothesis, we use a set of MTI data, diffusion weighted imaging (DWI) data and T1-weighted imaging data in 78 schizophrenia patients and 93 healthy controls for MTR extraction and structural connectome reconstruction. We demonstrate cortical MTR differences between schizophrenia patients and healthy controls and show that these cortical MTR alterations correlate with global white matter connectivity disruptions.

2. Methods

2.1. Subjects

A total of 171 subjects participated in this study, including 78 schizophrenia patients and 93 healthy controls. Subjects were included as part of the Genetic Risk and Outcome of Psychosis (GROUP) cohort study at the University Medical Center Utrecht, the Netherlands. The affiliated medical ethics committee approved the study and written informed consent was obtained from each subject before study participation. Two patients and four controls were excluded because no MTI or DWI data was acquired. Detailed demographics of the remaining subjects (i.e., 76 patients and 89 controls) are listed in Table 1. A higher proportion of males were included in the patient group (42 males and 47 females in controls, 62 males and 14 females in schizophrenia patients). All subjects went through an extensive psychiatric assessment procedure to determine the presence or absence of psychopathology, by using the Comprehensive Assessment of Symptoms and History (CASH) (Andreasen et al., 1992). Patients met Diagnostic and Statistical Manuals for Mental Disorders Fourth Edition (DSM-IV) (American Psychiatric Association, 2000) criteria for schizophrenia or related spectrum disorders. Control subjects were eligible for inclusion if they had no current or lifetime psychiatric disorder and no first- or second-degree relatives with a psychotic disorder.

At the time of scanning, 60 out of 76 patients were taking typical or atypical antipsychotic medication. The type and daily dose of antipsychotic medication were recorded and converted to a haloperidol equivalent dose using conversion rates (Kroken et al., 2009). The severity of symptoms was estimated using the Positive And Negative Syndrome Scale (PANSS) (Kay et al., 1987). The presence and severity of subclinical symptoms in controls were assessed using the Community Assessment of Psychic Experiences (CAPE) (Stefanis et al., 2002). For all subjects, total IQ was assessed using four subtests of the Dutch version of Wechsler Adult Intelligence Scale (WAIS), including Vocabulary, Comprehension, Block Design and Picture Arrangement (Stinissen et al., 1970). The Word Learning Task (WLT) was performed to assess verbal learning and memory abilities (Brand and Jolles, 1985). Statistical analyses on group differences in demographic and clinical characteristics were performed by using two-sample *t*-test for continuous variables and chi-squared tests for categorical variables (Table 1).

Table 1
Demographic and clinical characteristics.

	Controls ($N = 89$)	Patients ($N = 76$)	*P*
Age in years, mean (SD), [range]	26.6 (7.7) [17–49]	26.3 (5.4) [16–43]	0.79[a]
Gender, M/F	42/47	62/14	<0.0001[b]
DSM-diagnosis			
Schizophrenia, N (%)	–	51 (67.1)	–
Schizophreniform disorder, N (%)	–	3 (4.0)	–
Schizoaffective disorder, N (%)	–	10 (13.2)	–
Other[c], N (%)	–	9 (11.8)	–
Bipolar disorder, N (%)	–	3 (4.0)	–
IQ, mean (SD) [range]	114.6 (15.2) [83–144]	93.2 (13.5) [63–128]	<0.0001[a]
PANSS symptoms			
Total, mean (SD) [range]	–	61.6 (18.1) [32–107]	–
Positive, mean (SD) [range]	–	15.2 (5.5) [7–29]	–
Negative, mean (SD) [range]	–	15.5 (6.1) [7–31]	–
General, mean (SD) [range]	–	30.9 (8.9) [17–59]	–
CAPE subclinical symptoms			
Total, mean (SD) [range]	0.34 (0.22) [0–1.05]	–	–
Positive, mean (SD) [range]	0.19 (0.21) [0–1.00]	–	–
Negative, mean (SD) [range]	0.46 (0.32) [0–1.50]	–	–
General, mean (SD) [range]	0.52 (0.30) [0–1.63]	–	–
Antipsychotic medication			
Typical/atypical/none/unknown, N[d]	–	4/56/10/6	–
Haloperidol equivalent dose (mg), mean (SD) [range]	–	9.4 (6.4) [0.75–32]	–
WLT[e]			
Delayed recall correct items, mean (SD) [range]	21.10 (13.80) [0–36]	19.83 (8.11) [0–36]	0.50[a]
Immediate recall correct items, mean (SD) [range]	7.01 (4.97) [0–15]	6.16 (3.25) [0–14]	0.22[a]
Retention rate, mean (SD) [range]	0.81 (0.17) [0.2–1.17]	0.74 (0.23) [0.09–1.4]	0.07[a]

Note: DSM, Diagnostic and Statistical Manuals; PANSS, Positive And Negative Syndrome Scale; CAPE, Community Assessment of Psychic Experiences; WLT, Word Learning Task.
[a] Two-sample *t*-test.
[b] Chi-square test, statistically different between two groups.
[c] Other diagnoses include brief psychotic disorder, psychotic disorder not otherwise specified, and delusional disorder.
[d] "Typical": haloperidol, perfluridol and perfenazine; "atypical": risperidone, olanzapine, quetiapine, clozapine, aripiprazole; "none": no current antipsychotic treatment.
[e] Data were missing 10 schizophrenia patients and 25 controls.

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