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Left fronto-temporal dysconnectivity within the language network in schizophrenia: An fMRI and DTI study

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ABSTRACT

Schizophrenia is a mental disorder characterized by language disorders. Studies reveal that both a functional dysconnectivity and a disturbance in the integrity of white matter fibers are implicated in the language process in patients with schizophrenia. Here, we investigate the relationship between functional connectivity within a language-comprehension network and anatomical connectivity using fiber tracking in schizophrenia. We hypothesized that patients would present an impaired functional connectivity in the language network due to anatomical dysconnectivity. Participants comprised 20 patients with DSM-IV schizophrenia and 20 healthy controls who were studied with functional magnetic resonance imaging and diffusion tensor imaging. The temporal correlation coefficient and diffusion values between the left frontal and temporal clusters, belonging to the language network, were individually extracted, in order to study the relationships of anatomo-functional connectivity. In patients, functional connectivity was positively correlated with fractional anisotropy, but was negatively correlated with radial diffusivity and/or mean diffusivity, in the left arcuate fasciculus and part of the inferior occipitofrontal fasciculus, determined as the fronto-temporal tracts. Our findings indicate a close relationship between functional and anatomical dysconnectivity in patients with schizophrenia. The disturbance in the integrity of the left fronto-temporal tracts might be one origin of the functional dysconnectivity in the language-comprehension network in schizophrenia.

1. Introduction

Schizophrenia is a mental disorder characterized, in large part, by symptoms involving language, such as auditory verbal hallucinations and disorganized thoughts (DeLisi, 2001). These symptoms might be the result of a disruption in the connectivity between interconnected brain regions that regulate language processes. This notion has been termed “functional connectivity”, reflected by the strength of temporal correlation coefficients between distinct brain regions (Zhou et al., 2009). Functional neuroimaging studies have posited that patients with schizophrenia, compared with healthy controls, present an altered fronto-temporal functional connectivity (Friston and Frith, 1995), with greater involvement of the left hemisphere (Ford et al., 2002; Wolf et al., 2007; Li et al., 2010).

The functional dysconnectivity observed in patients with schizophrenia might be the consequence of disturbed anatomical connectivity. White matter (WM) bundles allow for fast and efficient communication between distinct brain regions. These bundles can be highlighted by diffusion tensor imaging (DTI) and, specifically, by diffusion tractography, which represents the spatial organization of human WM (Mori et al., 1999). These cerebral imaging methods allow us to collect information on the number/density or the degree of myelination of bundles using fractional anisotropy (FA) or radial diffusivity (RD) and mean diffusivity (MD), respectively (Basser and Pierpaoli, 1996; Beaulieu, 2002). Studies of tract-based DTI in schizophrenia have revealed alterations in WM integrity within the fiber bundles that are implicated in the language functional networks (Fitzsimmons et al., 2013): the uncinate, inferior occipitofrontal and arcuate fasciculi, constituting the fronto-temporal tracts (Duffau, 2008; Kubicki et al., 2013).

Through different cognitive processes, including language, recent studies have established a relationship between functional and diffusion data, based mainly on brain activation and diffusion parameters in WM regions (Schultz et al., 2012; Fitzsimmons et al.,

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2013; Leroux et al., 2013). Overall, these findings revealed that functional deficits in patients with schizophrenia were linked to deficits in WM integrity. Nevertheless, these studies did not seek to identify anatomo-functional relationships using functional connectivity and fiber tracking. In a previous study, WM regions adjacent to functional clusters belonging to the language network were investigated without using specific fiber tracts connecting functional regions (Leroux et al., 2013). Although Jeong et al. (2009) highlighted a relationship between functional and anatomical connectivity, their method, Tract-Based Spatial Statistics (TBSS), did not allow for the evaluation of the neural connections within a functional cerebral network while it is involved in a specific cognitive process.

Therefore, we reanalyzed our previous data in order to investigate, through several diffusion parameters, the relationships between anatomical connectivity using fiber tracking and functional connectivity within a language-comprehension network involved in the cognitive process. Particular attention was also directed to gender, considered as a confounding factor (Sacher et al., 2013), leading us to match our patient and healthy groups contrarily to what was done in our previous study. The ultimate goal of this investigation was to determine a model of the specific organization of interactions between the activity that is evoked by a language task and WM fibers underlying the specific functional network. We hypothesized that patients with schizophrenia would present an impaired functional connectivity in the language network due to anatomical dysconnectivity.

2. Methods

2.1. Participants

Participants comprised 20 patients diagnosed with schizophrenia, based on the DSM-IV (Diagnostic and Statistical Manual of Mental Disorder 4th edition), and 20 healthy volunteers, matched for gender (14 patients and controls were males), age, and level of education (Table 1). All participants were right-handed based on self-report, and each participant had an Edinburgh Inventory score greater than +33 (Oldfield, 1971). The population studied here overlapped that in the previous study, but there were few different participants in order to match the two groups on gender (Leroux et al., 2013).

All patients were stabilized outpatients with no change in their treatment over the last month, and only one was unmedicated. The psychopathological status of each patient was assessed using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) and the Auditory Hallucination Rating Scale (AHRS) (Hoffman et al., 2003).

The control group did not meet the criteria for lifetime psychotic disorders or substance dependence (including alcohol), as assessed by the MINI (Mini International Neuropsychiatric Interview).

The patients were recruited from the University Hospital (Caen), and healthy volunteers were recruited from the community. All participants were free of auditory deficits, neurological disorders, and cerebral abnormalities. Participants gave their informed, written consent, in accordance with the Declaration of

Table 1
Characteristics of participants.

Characteristics	Patients with schizophrenia	Controls	*P*-value
	n=20	*n*=20	
Gender			
Males *n* (%)	14 (70%)	14 (70%)	–
Age (years) (m ± S.D.)			0.59
[range]	34.8 ± 8.3	33.4 ± 7.6	*t*-test
(*t*-value; d.f.)	[20.8; 59.6]	[22; 45.1]	(−0.55; 38)
Education level			0.25
(years of education) (*m* ± S.D.) [range]	12.2 ± 2.1	12.9 ± 1.9	*t*-test
(*t*-value; d.f.)	[9; 17]	[10; 17]	(1.17; 38)
Comprehension score			
(*m* ± S.D.)	9.7 ± 4.8	16 ± 2.7	0.0001*
[range]	[1; 17]	[7.5; 19]	*t*-test
(*t*-value; d.f.)			(5.09; 38)
Type of medication			
Atypical *N* (%)	13 (65%)	–	–
Typical *N* (%)	6 (30%)		
Duration of illness			
(years) (*m* ± S.D.)	10.2 ± 6.4	–	–
[range]	[1; 28]		
Chlorpromazine equivalent			
(mg/day) (*m* ± S.D.)	368.6 ± 325,3	–	–
[range]	[0; 1250]		
PANSS Subtypes *N* (%)			
Residual	14	–	–
Positive	4		
Negative	1		
Mixed	1		
PANSS positive subscale			
(*m* ± S.D.)	13.5 ± 5.4	–	–
[range]	[7; 24]		
PANSS negative subscale			
(*m* ± S.D.)	13.7 ± 5.6	–	–
[range]	[8; 25]		
PANSS general subscale			
(*m* ± S.D.)	26.7 ± 7	–	–
[range]	[17; 45]		
AHRS (*m* ± S.D.)	8.7 ± 12.8	–	–
[range]	[0; 33]		

PANSS: Positive And Negative Syndrome Scale; AHRS: Auditory Hallucination Rating Scale; *m*: mean; S.D.: standard deviation; d.f.: degree of freedom. Significance level at $P < 0.05$, with * for significant *P*-value. *t*-value corresponding to *t*-test of Student.