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Left-hemisphere lateralization for language and interhemispheric fiber tracking in patients with schizophrenia

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ABSTRACT

Background: It has been suggested that the degree of hemispheric specialization (HS) depends on the structural connectivity between the two hemispheres, that is to say the corpus callosum (CC). Studies, performed only on healthy participants, investigated this anatomo-functional relationship. Nevertheless, it has never been studied in schizophrenia. We therefore propose to study the anatomo-functional relationships between the integrity of interhemispheric connectivity and leftward functional lateralization for language in patients with schizophrenia compared with healthy participants, driven by a multimodal approach combining fMRI and DTI-based fiber tractography. We hypothesized that reduced leftward functional lateralization for language in patients with schizophrenia could be related to a callosal hypoconnectivity.
Materials and methods: Seventeen patients based on the DSM-IV, and 17 controls were included. The functional laterality index and interhemispheric diffusion values between homologue temporal regions, belonging to the language network, were individually extracted in order to study the anatomo-functional relationships.
Results: In the patients, higher mean and radial diffusivity (RD) values (thicker myelin sheaths) were associated with less leftward lateralization. In contrast, the controls presented higher RD values and lower fractional anisotropy values (axonal loss) with more leftward lateralization.
Conclusions: Our study revealed a relationship between the CC and the HS for language, but did not provide evidence clarifying the direction of the relationship between callosal connectivity and functional lateralization for language. In particular, the present findings showed that the loss of integrity in interhemispheric callosal fibers was associated with reduced leftward cerebral dominance for language in patients with schizophrenia.
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1. Introduction

The corpus callosum (CC) is the major commissure of white matter (WM) connecting the two cerebral hemispheres (Sperry, 1968). It consists of approximately 200–350 million fibers in humans, allowing the transfer of high-level cognitive, somatosensory and motor information through its various callosal pathways (Aboitiz and Zaidel, 1992; Aboitiz et al., 1992; Aboitiz and Montiel, 2003). In this respect, it is suggested that the CC plays a fundamental role in the development and maintenance of hemispheric specialization (HS) (Gazzaniga, 2000, 2005). The best documented HS concerns the leftward cerebral asymmetry underlying language functions (Broca, 1861). It has been suggested that the degree of HS depends on the structural connectivity between the two hemispheres, that is to say the CC (Ringo et al., 1994; Gazzaniga, 2000). Based on this assumption, a smaller CC corresponds to greater lateralization. In other words, interhemispheric connectivity may act as an essential anatomical substrate for HS, measured through functional asymmetries. Nevertheless, this hypothesis still has to be elucidated.

Anatomical imaging studies revealed that, compared with controls, patients with schizophrenia showed WM structural and integrity modifications characterized by smaller CC size (Rotarska-Jagiela and Linden, 2008) associated with a reduced number of fibers (Freitag et al., 2013) and degree of myelination (Clemm von et al., 2014). The authors interpreted these findings as indicating lower interhemispheric connectivity. Knöchel et al. (2012), investigating the structure and integrity of CC, highlighted similar results suggesting interhemispheric hypoconnectivity in schizophrenia.

With regard to HS for language, healthy right-handed participants showed a pattern of "typical" cerebral lateralization characterized by left hemisphere (LH) dominance for linguistic functions (Gazzaniga,

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2000). Moreover, it has already been suggested that right-handedness is associated with left-hemispheric dominance for language (Knecht et al., 2000). These findings are less obvious in schizophrenia since about one third of patients present rightward lateralization for language (Dollfus et al., 2005). Previous studies, using functional magnetic resonance imaging (fMRI), suggested reduced leftward functional lateralization for language in patients with schizophrenia, owing to either increased right hemisphere activation (Sommer et al., 2001), decreased LH activation (Dollfus et al., 2005) or more bilateral activation (Bleich-Cohen et al., 2012). Our previous work, based on a functional laterality index, highlighted decreased leftward hemispheric lateralization in patients with schizophrenia compared with controls, in a functional network specifically involved in a language task (Alary et al., 2013a; Royer et al., 2015). In addition, this reduced functional cerebral lateralization could be a biomarker for schizophrenia (Alary et al., 2013b). Consequently, in order to evaluate the relationships between leftward functional lateralization and the CC, in the current study we selected only participants with right-handedness associated with leftward functional lateralization for language.

Few studies have addressed the question of a possible relationship between CC characteristics and leftward functional lateralization. Studies have only been conducted in healthy participants and they reported anatomo-functional relationships between the degree of leftward lateralization and CC features, but the results were still contradictory (Westerhausen et al., 2006; Josse et al., 2008; Haberling et al., 2011; Kompus et al., 2011). Westerhausen et al. (2006) showed that mean diffusivity (MD, measured by diffusion tensor imaging, DTI) was lower in the CC (meaning thicker myelin sheaths) in participants who were strongly left-lateralized for language, compared with moderately left-lateralized, bilateral or right-lateralized participants, but the groups did not differ with respect to the area of the CC. On the other hand, Josse et al. (2008), investigating only healthy participants with a null or negative lateralization index (suggesting no lateralization or leftward lateralization for language), found that the CC midsagittal surface area was positively correlated with left language lateralization in the posterior temporal and inferior frontal regions. Similarly, Kompus et al. (2011) revealed that anterior CC size was positively correlated with functional asymmetry for episodic encoding and retrieval in the frontal lobes, suggesting a larger anterior CC associated with a greater leftward asymmetry pattern. However, Haberling et al. (2011) highlighted findings somewhat in conflict with these previous works. Indeed, they showed lower integrity of the callosal area in healthy participants, through lower fractional anisotropy (FA) values (meaning axonal loss) associated with typical cerebral asymmetry, that is to say leftward-cerebral dominance for language.

Thus, the light of these findings and to the best of our knowledge, this anatomo-functional relationship between interhemispheric callosal connectivity and the degree of functional lateralization for language has never been investigated in schizophrenia. Therefore, this study aimed to investigate the anatomo-functional relationships between the integrity of interhemispheric connectivity and leftward functional lateralization for language in patients with schizophrenia compared with healthy participants, driven by a multimodal approach combining fMRI and DTI-based fiber tractography. Otherwise, as a sexual dimorphism in the CC was described both in healthy individuals (Sacher et al., 2013) and in patients with schizophrenia (Crow et al., 2007), we evaluated these anatomo-functional relationships in taking into account the gender. We hypothesized that reduced leftward functional lateralization for language in patients with schizophrenia could be related to a callosal hypoconnectivity.

In the present study, we propose to evaluate CC integrity through its interhemispheric callosal fibers, using DTI-based tractography which reflects the interhemispheric connectivity or communications more than CC area. The callosal fibers were specifically evaluated between the homologue temporal regions belonging to a language comprehension network. Moreover, we used a direct and robust measure of functional cerebral lateralization (Wilke and Lidzba, 2007) reflecting hemispheric lateralization for language.

2. Materials and methods

2.1. Participants

Seventeen patients (13 males) diagnosed with schizophrenia (Diagnostic and Statistical Manual of Mental Disorder 4th edition, DSM-IV) were selected, based on a self-reportedly right-handed (Edinburgh Inventory score greater than +33) (Oldfield, 1971) with leftward functional lateralization for language determinated by a functional lateralization index (see below data analyses). Seventeen healthy volunteers (13 males) were included in the study, which were matched for gender, age and level of education (Table 1).

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 with 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).

Table 1
Characteristics of participants.

Characteristics	Patients with schizophrenia N = 17	Controls N = 17	*p*-Value
Gender			1
Males N (%)	13 (76.5%)	13 (76.5%)	Pearson chi-square test
Age (years) (m ± SD) [range]	34.8 ± 8.5 [20.8; 59.6]	36.5 ± 9.5 [24.5; 56.1]	0.59 *t*-test
Education level (years of education) (m ± SD) [range]	12.4 ± 2.2 [9; 17]	12.7 ± 2.1 [10; 17]	0.76 *t*-test
Comprehension score (m ± SD) [range]	8.9 ± 4.6 [2; 17]	15.1 ± 3.6 [7.5; 19]	0.0001* *t*-test
Type of medication			
Atypical N (%)	12 (70.6%)	–	–
Typical N (%)	5 (29.4%)		
Duration of illness (years) (m ± SD) [range]	10.7 ± 6.7 [1; 28]	–	–
Chlorpromazine equivalent (mg/day) (m ± SD) [range]	321.8 ± 269,4 [0; 1060]	–	–
PANSS subtypes N (%)			
Residual	13	–	–
Positive	3		
Negative	1		
PANSS positive subscale (m ± SD) [range]	11.9 ± 4.7 [7; 23]	–	–
PANSS negative subscale (m ± SD) [range]	13.2 ± 4.7 [8; 24]	–	–
PANSS general subscale (m ± SD) [range]	24.4 ± 5.3 [17; 35]	–	–
PANSS total (m ± SD) [range]	49.5 ± 11.3 [35; 80]	–	–
AHRS (m ± SD) [range]	5.2 ± 10.1 [0; 32]	–	–

Significance level at $p < 0.05$ with * for significant *p*-value. PANSS: Positive And Negative Syndrome Scale; AHRS: Auditory Hallucination Rating Scale; m: mean; SD: standard deviation.

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