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Functional hemispheric lateralization for language in patients with schizophrenia

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ABSTRACT

Background: It is widely reported that patients with schizophrenia exhibit decreased hemispheric lateralization. However, no study has evaluated relationships between the hemispheric anatomical and functional asymmetry in language areas. The present study aimed to determine whether decreased leftward hemispheric lateralization could be related to asymmetry of the grey matter volume in patients with schizophrenia. This investigation was the first to use a functional index of laterality to analyze the global functional network specifically involved in the language task.
Methods: Twenty-seven right-handed patients with schizophrenia and 54 right-handed control subjects underwent a session of a functional magnetic resonance imaging (fMRI) with a speech listening paradigm. Functional laterality indices (FLI) were calculated (Wilke, M. and Lidzba, K., 2007. LI-tool: a new toolbox to assess lateralization in functional MR-data. J Neurosci Methods. 163, 128–136). The indices of asymmetry in the volume of grey matter (GVAIs) were computed from the functional language network.
Results: Patients with schizophrenia exhibited significantly decreased leftward hemispheric lateralization. There was a positive correlation between GVAIs and FLIs in healthy subjects, while no such correlation was seen in patients with schizophrenia.
Discussion: This study reports for the first time a significant relationship between the anatomical and functional asymmetry in healthy subjects, but not in patients with schizophrenia. While decreased leftward functional lateralization for language was observed in patients with schizophrenia compared to the control group, this functional abnormality was not related to asymmetry in the volume of grey matter.

1. Introduction

Since Bleuler's description in 1911, the hypothesis has been advanced that schizophrenia is characterized by language disorders, such as auditory verbal hallucinations, and formal thought disorders (Delisi, 2001; Ceccherini-Nelli and Crow, 2004; Li et al., 2009). Structural and functional neuroimaging studies have shown that schizophrenia pathophysiology involves brain language areas, particularly in patients with language disorders. These language disorders could be related to an abnormal left hemispheric dominance for language (Crow, 1997). While the hemispheric specialization for language is normally leftward-lateralized in right-handed controls, several anatomical and functional cerebral studies have suggested that patients with schizophrenia exhibit decreased hemispheric lateralization for language.

Numerous results support the existence of decreased leftward asymmetry in patients with schizophrenia (Shenton et al., 2001), for example, in the occipitoparietal, premotor, and prefrontal regions for patients with a first episode of schizophrenia (Bilder et al., 1994), or in frontoparietal brain regions for male patients with schizophrenia (Guerguerian and Lewine, 1998). Other authors have associated decreased asymmetry in the frontal brain regions with early disease onset (Highley et al., 1998; Maher et al., 1998). Patients with

Abbreviations: AHRS, Auditory Hallucinations Rating Scale; BOLD, blood oxygen level dependent; CS, comprehension score; CSi, individual comprehension score; dof, degree of freedom; DSM IV, diagnostic and statistical manual of mental disorders 4th edition; EPI, echo planar imaging; ET, echo time; FA, flip angle; FLI, functional laterality index; fMRI, functional magnetic resonance imaging; FOV, field of view; FWE, family wise error; FWHM, full width at half maximum; GM, grey matter; GVAI, grey matter volume asymmetry index; HRF, hemodynamic response function; IT, inversion time; LH, left hemisphere; MINI, Mini International Neuropsychiatric Interview; MNI, Montreal Neurological Institute; *n*, number; n-CS, normalized comprehension scores; PANSS, Positive And Negative Syndrome Scale; RH, right hemisphere; ROI, regions of interest; RT, repetition time; SPM5, statistical parametric mapping 5; SD, standard deviation.

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schizophrenia have also been noted to exhibit decreased leftward anatomical asymmetry of the superior temporal gyrus (Delisi et al., 1994; Levitan et al., 1999) or the planum temporale (Sommer et al., 2001a; Kawasaki et al., 2008; Clark et al., 2010), with some schizophrenia patients even showing rightward asymmetry of the planum temporale (Rossi et al., 1992; Pearlson et al., 1996; Barta et al., 1997; Hasan et al., 2011).

Structural brain scans can be used to predict language lateralization in healthy subjects (Josse et al., 2009), but functional magnetic resonance imaging (fMRI) remains the most powerful imaging method for evaluating hemispheric dominance for language. Functional MRI allows the computation of functional cerebral inter-hemisphere differences reflecting the leftward or rightward dominance of activations for a specific task. Right-handed patients reportedly exhibit decreased leftward hemispheric functional lateralization for language compared to control subjects (Dollfus et al., 2005). Using verbal fluency tasks, other studies have localized this decreased lateralization in frontal regions, and found it to be correlated with the severity of auditory verbal hallucinations (Sommer et al., 2001b; Weiss et al., 2006). Decreased lateralization for language has also been reported in patients with negative symptoms (Artiges et al., 2000) and in unmedicated patients (Weiss et al., 2006; van Veelen et al., 2011).

The corpus of the literature, including anatomical and functional studies, has concluded that decreased hemispheric lateralization for language exists in patients with schizophrenia. To date, no study in patients with schizophrenia has evaluated the relationships between the anatomical and functional hemispheric asymmetry in the high-level language areas, particularly those of the semantic network, which is known to be functionally impaired in patients (Dollfus et al., 2005). It remains unknown whether grey matter volume asymmetry underlies the decreased functional leftward lateralization for language. Studies of healthy subjects have demonstrated that leftward functional lateralization is predicted by grey matter volume asymmetry in semantic and phonological regions (Josse et al., 2009). One study examined relationships between anatomical and functional brain changes in patients with schizophrenia, but the analysis was limited to primary language areas (Oertel et al., 2010).

The present study aimed to analyze the decreased leftward hemispheric lateralization over the entire network involved in a specific language task. The hypothesis was that patients with schizophrenia would present decreased functional lateralization that could be explained by grey matter volume asymmetry. As task performance and language disorders can impact functional activation, these two factors were considered confounding variables. This study was also the first use of a functional laterality index to enable the integrality of the functional network specifically involved in the language task (Wilke and Lidzba, 2007).

2. Materials and methods

2.1. Subjects

Twenty-seven patients with DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th ed., Washington, DC) schizophrenia and 54 control subjects were recruited. All subjects gave their informed written consent, and our local ethics committee (Nord Ouest CPP, France) approved the study. Subject groups were matched by age, gender, and education level. All subjects were right-handed, presented a positive Edinburgh Inventory score (scores $> +60$; Table 1) (Oldfield, 1971), and spoke French as their first language.

The diagnosis of schizophrenia was established by clinicians according to DSM-IV criteria with the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998). Each patient's clinical state was evaluated with the Positive And Negative Syndrome Scale (PANSS) (Kay et al., 1987) and the Auditory Hallucinations Rating Scale (AHRS) (Hoffman et al., 2003) (Table 1). All schizophrenic patients were stabilized, with no treatment modification during the six months before their inclusion.

Table 1
Characteristics of the patients and healthy control subjects.

	Patients ($n = 27$)	Controls ($n = 54$)	p
Age (mean ± SD)	33.17 ± 6.50	35.15 ± 9.25	0.32
Gender (% male)	66.67	62.96	0.74
Level of education in years (mean ± SD)	12.15 ± 1.90	13.39 ± 3.19	0.07
Oldfield scores (mean ± SD)	92.39 ± 13.20	93.02 ± 14.94	0.85
CS (mean ± SD)	9.63 ± 5.01	15.24 ± 2.83	<0.001*
GVAI	−0.028 ± 0.020	−0.027 ± 0.016	0.91
Illness duration in years (mean ± SD)	8.75 ± 4.96		
Positive PANSS (mean ± SD)	14.00 ± 5.31		
Negative PANSS (mean ± SD)	14.42 ± 5.33		
AHRS (mean ± SD)	13.28 ± 12.82		

n, number; SD, standard deviation; CS, comprehension score; GVAI, grey volume asymmetry index; PANSS, positive and negative syndrome scale; AHRS, auditory hallucinations rating scale. $^{*}p < 0.05$.

2.2. Task

We used a paradigm that was designed with e-prime 2.0, and that is well known to activate language areas (Tzourio et al., 1998). Auditory stimuli, recorded on a digital audiotape, were delivered binaurally through air-conducting earphones and using an Ifis system software server 1.1. Presentation of the stimulus followed a block design with nine alternating 32-second blocks of speech in either French (4 blocks) or Tamil (5 blocks), an unknown language for all participants. The task consisted of listening to a factual story in French, and the reference task was listening to the same story in Tamil. The trial lasted 4 minutes 48 seconds. All subjects were instructed to passively and attentively listen to the story.

Shortly after scanning, subjects were asked to answer a 16-item questionnaire, which was used to calculate a comprehension score (CS) for each subject. Out of 20 points, the mean scores ± standard deviation were 9.63 ± 5.01 for patients and 15.24 ± 2.83 for control subjects (t-test, $p < 0.001$).

2.3. Image acquisition and functional image pre-processing

Neuroimaging data were acquired on a 3 Tesla scanner (IRM Intera Philips Achieva Quasar Dual, Philips Medical System, Netherlands). Anatomical T1-weighted volumes were determined using a 3-dimensional spoiled gradient echo sequence with high spatial resolution (3D-FFE-TFE; 256×256 mm^2 matrix size with 180 contiguous slices; field of view (FOV): 256 mm; voxel isotropy: 1 mm^3; sagittal slice orientation; inversion time (IT): 800 ms; repetition time (RT): 20 ms; echo time (ET): 4.6 ms; flip angle (FA): 10°). A T_2-weighted scan was acquired for each participant (T_2-TSE sequence; 256×256 matrix size with 81 contiguous slices; FOV: 256; isotropic resolution: 2 mm; sagittal slice orientation; RT: 5500 ms; ET: 80 ms; FA: 90°; SENSE factor: 2). With respect to T_2^*-weighted functional volumes, an EPI-BOLD sequence was applied (64×64 matrix size with 31 contiguous slices; FOV: 240; isotropic resolution: 3.75 mm; axial slice orientation; RT: 2000 ms; ET: 35 ms; FA: 80°).

The collected data were pre-processed using SPM5 software (Statistical Parametric Mapping, Wellcome Department of Cognitive Neurology, London, UK, http://www.fil.ion.ucl.ac.uk/spm). For each participant, the native T1-weighted volumes were segmented into grey matter (GM), white matter, and cerebrospinal fluid compartments, and normalized with the SPM5 default parameters. Next, the deformations induced by non-linear spatial normalization were corrected via application of a