



## Functional and structural brain asymmetries in patients with schizophrenia and bipolar disorders



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### ABSTRACT

**Objectives:** This study aimed to compare the functional and gray matter asymmetries in patients with schizophrenia (SZ), patients with bipolar disorders (BD), and healthy controls (HCs) to test whether decreased leftward functional hemispheric lateralization and gray matter volume asymmetry could mark the boundary between schizophrenia and bipolar disorder.

**Methods:** A total of 31 right-handed SZ and 20 right-handed BD underwent a session of functional MRI with a speech listening paradigm. Participants were matched with HCs for gender, age, and education. Functional laterality indices (FLI) and gray matter volume asymmetry indices (GVAI) were computed from the individual functional language network. Correlations between the FLI and GVAI indices were also examined.

**Results:** SZ exhibited significantly decreased leftward functional hemispheric lateralization whereas BD did not. The GVAIs did not differ significantly between SZ and HCs or between BD and HCs. There were positive correlations between GVAIs and FLIs in all groups.

**Conclusions:** Loss of laterality for language comprehension with retention of gray matter volume asymmetry indicates that gray matter loss alone will not account for the pathophysiology of schizophrenia. Impaired leftward functional hemispheric lateralization for language but not gray matter volume asymmetry can be considered a biomarker of SZ.

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## 1. Introduction

Specificity of cerebral markers in patients with schizophrenia (SZ) or bipolar disorders (BD) must be considered in light of the debate on the nosological delimitation of the two disorders (Lake and Hurwitz, 2007). Few functional magnetic resonance imaging studies investigating language networks have sought to identify cerebral biomarkers to discriminate these patient groups (McIntosh et al., 2008; Maïza et al., 2010; Whalley et al., 2012). Nevertheless, some authors have reported

**Abbreviations:** AHRS, Auditory Hallucinations Rating Scale; ARS, Association de Recherche pour la Schizophrénie; BD, bipolar disorders; CS, comprehension score; DSM-IV, Diagnostic and Statistical Manual of Mental Disorder 4th edition; FLI, functional laterality index; FLI<sub>int</sub>, intermediate functional laterality index; FWE, family-wise error; GVAI, gray matter volume asymmetry index; GVAI<sub>int</sub>, intermediate gray matter volume asymmetry index; HC, healthy control; HCL-20, hypomania checklist; HRSD, Hamilton Rating Scale for Depression; MNI, Montreal Neurological Institute; MRI, magnetic resonance imaging; nCS, normalized comprehension score; PANSS, Positive and Negative Syndrome Scale; SPM, Statistical Parametric Mapping; SZ, schizophrenia.

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decreased leftward functional lateralization for language in SZ patients (Sommer et al., 2003; Dollfus et al., 2005; van Veelen et al., 2011; Sheng et al., 2013), and one previous study suggested that change in functional hemispheric lateralization for language could be a biomarker of SZ (Alary et al., 2013b). However, gray matter volume changes in language structures in SZ and BD patients have been little investigated (Ratnanather et al., 2013). Therefore, the present study compared functional and gray matter asymmetries among SZ patients, BD patients, and healthy controls (HCs). We hypothesized that decreased leftward functional hemispheric lateralization and gray matter volume asymmetry in a language network would be specifically observed in SZ patients but not in BD patients.

## 2. Materials and methods

### 2.1. Participants

A total of 31 SZ and 20 BD (Diagnostic and Statistical Manual of Mental Disorder 4th Edition; DSM-IV) were included after giving informed written consent and with the agreement of the local ethics

committee. All participants were right-handed. In the current study, we used a sample expanded from a previous study (Alary et al., 2013b) to increase the number of BD and SZ. Moreover, each group of patients was carefully matched with HCs for gender, age, and education level (Table 1). The clinical state of SZ 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). The clinical state of BD was assessed using the Hamilton Rating Scale for Depression (HRSD) (Hamilton, 1960) and the hypomania checklist (HCL-20) (Angst, 1992). All patients were stabilized, with no change in treatment during the preceding month.

## 2.2. Language task

The experimental paradigm consisted of listening to a factual story told in French. The reference task was to listen to the same story in Tamil, a language not known to French nationals. The stimuli were presented in a block design for 5 min, alternating 32-s blocks in French or Tamil (Tzourio et al., 1998). Participants were instructed to listen passively and attentively with the eyes closed. After scanning, participants were asked to answer a comprehension questionnaire (maximal score 20) to evaluate their involvement in the task (Table 1).

## 2.3. Data acquisition

Anatomical T<sub>1</sub>-weighted and T<sub>2</sub>-weighted volumes and functional T2\*-weighted volumes were acquired using a 3-T scanner (IRM Philips Achieva, Netherlands). These data were pre-processed using SPM5 subroutines (Statistical Parametric Mapping, UK), allowing us to obtain the anatomical and functional images used for the following analyses in the MNI template (Montreal Neurological Institute, Canada).

## 2.4. Data analysis

A map of “French minus Tamil” blood oxygen level-dependent (BOLD) signal contrast was generated for each subject with SPM5. Then, two mean *t*-maps were generated: one with the data from SZ and their respective, matched HCs, and one with the data from the BD and their respective, matched HCs (SPM5, one-sample *t*-test, threshold at  $p < 0.05$ , corrected by family-wise error, FWE,  $k = 200$  voxels, excluding the cerebellum). Both maps were symmetrized to yield two masks, one for SZ and their matched controls (mask 1,  $n = 62$ ) and one for BD and their matched controls (mask 2,  $n = 52$ ). To compute the functional laterality indices (FLIs) and gray matter volume asymmetry indices (GVAIs), the individual contrast maps were masked with either mask 1 or mask 2 (Fig. 1).

**Table 1**

Characteristics of patients with schizophrenia (SZ) or with bipolar disorders (BD) and their matched controls (HCs).

	SZ (n = 31)	HCs matched with SZ (n = 31)	BD (n = 20)	HCs matched with BD (n = 32)
Age, y	33.9 ± 5.9	35.2 ± 9.3	44.7 ± 9.3	42.1 ± 7.7
Male sex, n (% of total)	20 (64.5)	20 (64.5)	9 (45)	15 (47)
Education level, y	12.3 ± 1.9	12.4 ± 2.3	12.5 ± 2.5	12.2 ± 2.0
Edinburgh score	93.8 ± 10.6	94.0 ± 13.7	96.0 ± 9.1	93.8 ± 11.8
Comprehension score	9.8 ± 4.6 <sup>a</sup>	14.5 ± 2.5	11.7 ± 4.0 <sup>b</sup>	14.1 ± 3.2
Illness duration, y	8.8 ± 4.9	–	16.2 ± 10.2	–
Total PANSS	57.3 ± 16.0	–	–	–
AHRS score	13.9 ± 13.6	–	–	–
HRSD score	–	–	3.4 ± 3.4	–
HCL-20 score	–	–	2.5 ± 3.7	–
FLIs	−0.23 ± 0.4 <sup>a</sup>	−0.40 ± 0.2	−0.34 ± 0.4	−0.30 ± 0.4
GVAIs	−0.42 ± 0.4	−0.55 ± 0.3	−0.50 ± 0.4	−0.44 ± 0.5

Significance level at  $p < 0.05$ ; mean ± standard deviation unless otherwise noted.

PANSS = Positive and Negative Syndrome Scale; AHRS = Auditory Hallucinations Rating Scale; FLIs = functional laterality index; GVAIs = gray matter volume asymmetry index.

<sup>a</sup> Statistical significance between SZ and HCs matched with SZ.

<sup>b</sup> Significance between BD and HCs matched with BD.

## 2.5. FLIs

The FLIs were computed according to the bootstrap approach of Wilke and Lidzba's toolbox (Wilke and Lidzba, 2007). Considering the 5000 most activated voxels in both hemispheres of the brain and discarding the clusters smaller than 50 voxels, the intermediate FLIs (FLI<sub>int</sub>) were calculated with the following formula:

$$FLI_{int} = \frac{\text{Right activation} - \text{Left activation}}{\text{Right activation} + \text{Left activation}}$$

Then, the final FLI was generated as the threshold weighted mean of the FLI<sub>int</sub> (Wilke and Schmithorst, 2006):

$$FLI = \frac{\sum (FLI_{int} \times \text{threshold})}{\sum \text{threshold}}$$

The index resulted in negative values for predominantly leftward lateralization and positive values for rightward lateralization.

## 2.6. GVAIs

The calculation of the GVAIs was adapted from the threshold independent method used for the FLIs (Wilke and Lidzba, 2007). The masked individual contrast maps were thresholded and applied on the individual gray matter map to obtain the gray matter volumes for each participant (Fig. 1). This last step was repeated at 100 different thresholds, equally distributed from 0 to the maximum *t*-value (Wilke and Schmithorst, 2006; Wilke and Lidzba, 2007). For each threshold, an intermediate GVAI (GVAI<sub>int</sub>) was calculated with the following formula:

$$GVAI_{int} = \frac{\text{Right GM volume} - \text{Left GM volume}}{\text{Right GM volume} + \text{Left GM volume}}$$

Then, final GVAI was generated, as the threshold weighted mean of the GVAI<sub>int</sub>:

$$GVAI = \frac{\sum (GVAI_{int} \times \text{threshold})}{\sum \text{threshold}}$$

The index resulted in positive values for rightward structural asymmetry and negative values for leftward structural asymmetry.

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