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Reduced language lateralization in first episode schizophrenia: A near infrared spectroscopy study

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ABSTRACT

Background: Diminished functional lateralization in language-related areas is found in chronic schizophrenia (SZ). However, whether this reduced lateralization exists at the early stage of SZ remains unclear. The present study aimed to investigate language lateralization in first episode schizophrenia (FES) using near infrared spectroscopy (NIRS) during a letter version of verbal fluency test (VFT).

Methods: A total of 28 FES patients and 33 healthy controls (HCs) underwent NIRS while performing a VFT. Six regions of interests (ROIs) were defined: the bilateral frontal-, inferior frontal gyrus (IFG), and temporal regions. Laterality index (LI) was calculated and compared between the two groups in ROIs. In addition, we investigated whether language lateralization was correlated with severity of clinical symptoms.

Results: Across all ROIs, LI was significantly reduced in FES patients ($p = 0.037$) compared to controls in the IFG region. In addition, LI was not found to be correlated with VFT performance, the PANSS positive, negative or general psychopathology subscales.

Conclusions: Our study demonstrated a diminution of leftward functional lateralization in the IFG during a VFT in FES patients. This is the first NIRS study to report reduced functional lateralization in patients at the early stage of schizophrenia.

1. Introduction

Brain asymmetry is a phenomenon of hemispheric specialization and is a feature of normal neurodevelopment (Hutsler and Galuske, 2003). For instance, the left hemisphere is strongly involved in language perception and production, tool use, complex motor actions, and arithmetic, while the right hemisphere specializes in attention, visuospatial ability, geometrical patterns, faces, and language prosody (reviewed in [Ocklenburg et al., 2015]). Various disorders have been shown to be associated with reduced lateralization of the left side of the brain. These disorders include autism, depression, attention deficit hyperactivity disorder, Tourette's syndrome, and schizophrenia (SZ) (Klimkeit and Bradshaw, 2006; Sommer et al., 2001a,b).

SZ is a devastating disorder characterized by brain structural (Olabi et al., 2011) and functional (Chou et al., 2014) deficits. Reduced leftward functional lateralization is evidenced by several functional magnetic resonance imaging (fMRI) studies demonstrating reduced leftward lateralization during language-related activation in patients with SZ (Alary et al., 2013; Bleich-Cohen et al., 2012; Dollfus et al., 2005; Li et al., 2009; Oertel et al., 2010; Royer et al., 2015; Sommer et al., 2003; van Veelen et al., 2011). A similarly well-established finding is reduced structural asymmetry in language areas. For instance, several studies using structural MRI reported an absence or reversal of this leftward asymmetry in patients with SZ (DeLisi et al., 1997; Kawasaki et al., 2008; Li et al., 2012; Li et al., 2009; Oertel et al., 2010; Sheng et al., 2013). However, other studies have failed to corroborate these findings (Chapple et al., 2004; Hadjulis et al., 2004; Takao et al., 2010). Crow (1997) proposed that the main symptoms of SZ (hallucinations and thought disorders) arise from this reduced left hemispheric dominance for language. Moreover, several studies have reported an association between the extent of language lateralization and the severity of symptoms (Kircher et al., 2002; Sheng et al., 2013;

Abbreviations: SZ, schizophrenia; FES, first episode schizophrenia; NIRS, near infrared spectroscopy; VFT, verbal fluency test; HC, healthy control; ROI, region of interest; IFG, inferior frontal gyrus; LI, laterality index; fMRI, functional magnetic resonance imaging; MINI, mini international neuropsychiatric interview; PANSS, positive and negative syndrome scale; SD, standard deviation; LPBA, LONI Probabilistic Brain Atlas; FDR, false discovery rate; CFT, category fluency task; LFT, letter fluency task

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Sommer et al., 2001a,b; Weiss et al., 2006). In a meta-analysis, Ocklenburg et al. (2013) concluded that reduced language lateralization is a strong trait marker for the experience of auditory hallucinations in patients with SZ. However, other studies have failed to find a correlation between reduced language lateralization and psychotic symptoms (Bleich-Cohen et al., 2009; Razafimandimby et al., 2007; Sommer et al., 2007; van Veelen et al., 2011).

So far, most neuroimaging studies focusing on language lateralization have been carried out in patients with chronic SZ. As changes in brain function (Chou et al., 2015a; Koike et al., 2011) and structure (Olabi et al., 2011) are progressive in SZ, it is unclear whether the reduced hemispheric dominance for language is already present at illness onset. Limiting enrolment to patients with first-episode schizophrenia (FES) eliminates confounding by illness duration, longstanding substance abuse, and/or treatment effects. This type of design also may provide more generalizable results regarding the nature of the disorder than studies of patients with chronic SZ.

To date, only a few fMRI studies have addressed these issues. In the study conducted by Bleich-Cohen et al. (2009), it was found that patients with FES who are medicated had significantly reduced lateralization indices in language-related regions, especially in the inferior frontal gyrus (IFG), and in the superior temporal regions. Similarly, van Veelen et al. (2011) studied 35 drug-naïve patients with FES and found that lateralization indices were significantly reduced especially in the IFG and the superior temporal regions. Therefore, the question of whether or not reduced lateralization exists at the early stages of SZ remains unanswered.

Multi-channel near-infrared spectroscopy (NIRS) is a recently developed functional neuroimaging technology that allows non-invasive measurements of the spatio-temporal characteristics of neural activity in frontotemporal regions (Strangman et al., 2002). While NIRS has lower spatial resolution than fMRI, it has several advantages over existing imaging techniques, including positron emission tomography, single-photon emission computed tomography, and fMRI, because it is noninvasive, easy to perform, tolerates small movements, is inexpensive, and provides excellent time resolution (Ferrari and Quaresima, 2012). Moreover, NIRS provides a bedside measurement of oxy-hemoglobin ([oxy-Hb]) and deoxy-hemoglobin ([deoxy-Hb]) concentrations, which are thought to indicate regional cerebral blood volumes and show strong correlations with fMRI signals (Sato et al., 2013). Many studies of patients with SZ have used NIRS (Ehlis et al., 2007; Ikezawa et al., 2009; Suto et al., 2004), but to our knowledge, no previous NIRS studies have investigated language lateralization in patients with FES. Therefore, we aimed to investigate language lateralization in patients with FES. We hypothesized that patients with FES would have decreased leftward hemispheric functional lateralization during a verbal fluency test (VFT).

2. Materials and methods

2.1. Study participants

A total of 28 outpatients and inpatients (11 men and 17 women) were recruited at the Taichung Veterans General Hospital. Patients who fulfilled the criteria for SZ listed in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision were recruited and the diagnoses were validated using the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) by board-certified psychiatrists (P.H.C and W.H.L). All patients were experiencing their first episode of psychosis and had received no > 12 weeks of previous antipsychotic medication (Fannon et al., 2000). Eight patients were taking risperidone, 6 used paliperidone, 5 used olanzapine, 3 used aripiprazole, 3 used amisulpride, 1 used quetiapine and risperdal, 1 used haloperidal, and 1 was drug-naïve. Some FES patients also participated in our previous study (Chou et al., 2015b).

Thirty-three healthy individuals (HCs) (15 men and 18 women) were recruited as control subjects and were screened using the MINI. All study participants were right-handed, which was defined as > 70 points on the Edinburgh Inventory (Oldfield, 1971). Subjects who had a history of substance abuse or dependence, mental retardation, neurological disorders, or a medical condition with the potential to affect brain structure or function were excluded. Controls were excluded if there was a personal history of any axis I or II disorder. This study complied with the Declaration of Helsinki, and was approved by the Institutional Review Board of Taichung Veterans General Hospital (approval No. CF13044). All participants received a complete explanation of the study and provided written informed consent.

2.2. Clinical measurements

The Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) was used to assess symptoms on the same day as the NIRS measurements. Patients' antipsychotic dosage are presented as chlorpromazine-equivalent doses (Inada and Inagaki, 2015).

2.3. Cognitive testing

The participants completed 160-s block-design VFTs (letter version). We selected the VFT because previous fMRI studies have used VFT and demonstrate decreased lateralization in frontal regions in patients with SZ (Sommer et al., 2001a,b; Weiss et al., 2006). In addition, VFTs have widely been used in previous NIRS studies (Huang et al., 2016; Quan et al., 2015; Takizawa et al., 2014). Details regarding the VFT may be found in our previous study (Chou et al., 2016). In brief, each 160-s block comprises three different time periods: a 30-s pre-task period, a 60-s task period, and a 70-s post-task period. In the pre- and post-task periods, patients were instructed to fix their gaze to the center of the screen and repeatedly count from one to five to control for and remove task-related motion artifacts. During the 60-s task period, the participants were instructed to say as many words as possible that started with a phonological syllable presented as an audible instruction by a computer. The task period comprised three continuous 20-s sub-periods, which were initiated by a single syllable selected from nine possible options (1st subperiod: /ㄅ(b)/, /ㄆ(p)/, or /ㄉ(d)/; 2nd subperiod: /ㄊ(t)/, /ㄌ(l)/, or /ㄋ(n)/; 3rd subperiod: /ㄇ(m)/, /ㄈ(f)/,or /ㄗ(dz)/). We chose these syllables because they appear at the beginning of a moderate number of Chinese words. Transitions between the 20-s sub-periods were immediate to encourage continuous performance. Before beginning each task session, subjects were provided with instructions on how to answer correctly by experienced researchers (P.H.C, W.R.L., and W.H.L). Each subject performed three practice trials to ensure that they understood the instructions. We then recorded the total number of correct words generated during the task as an index of VFT performance.

2.4. NIRS instrument

We used a 52-channel NIRS instrument (ETG-4000; Hitachi Medical Co., Tokyo, Japan) to measure changes in [oxy-Hb]. The NIRS probe attachments are thermoplastic 3 × 11 shells set within the 52 channels (Fig. 1). The lowest probe line was set along the Fp1–Fp2 line, as defined by the international 10–20 system used in electroencephalography. The distances between pairs of source and detector probes were set to 3.0 cm. We defined the measurement area between each probe-set pair as one ‘channel,’ which was sufficient to obtain data from depths of 20 to 30 mm under the scalp. These depths approximately correspond to the surface of the cerebral cortex. The NIRS instrument measures changes in both [oxy-Hb] and [deoxy-Hb] (in mM) using two wavelengths (695 and 830 nm) of near-infrared light. The calculations are based on the Beer–Lambert law (Jobsis, 1977). We could not measure the absolute path length from the scalp to the cerebral cortex. We thus recorded the hemoglobin concentrations from baseline to the