NeuroImage 85 (2014) 518–526

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Functional abnormalities in the left ventrolateral prefrontal cortex during a semantic fluency task, and their association with thought disorder in patients with schizophrenia

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ARTICLE INFO

Article history:
Accepted 17 April 2013
Available online 24 April 2013

Keywords:
Schizophrenia
Verbal fluency task (VFT)
Near-infrared spectroscopy (NIRS)
Semantic processing abnormality
Prefrontal hemodynamic response
Thought disorder

ABSTRACT

Thought disorder is one of the primary symptoms in schizophrenia, yet the neural correlates and related semantic processing abnormalities remain unclear. We aimed to investigate the relationship between functional prefrontal abnormalities and thought disorder in schizophrenia using 2 types of verbal fluency tasks: the letter fluency task (LFT) and the category fluency task (CFT). Fifty-six adult patients with schizophrenia and 56 healthy controls matched for age, gender, and IQ participated in the study. During completion of the 2 types of verbal fluency tasks, we measured oxy- and deoxy-hemoglobin concentration ([oxy-Hb] and [deoxy-Hb]) signal changes over a wide area of the bilateral prefrontal cortex, using a 52-channel near-infrared spectroscopy (NIRS) system. Thought disorder scores were evaluated using the positive and negative syndrome scale. CFT performance was significantly higher than LFT performance in both groups, while there was no significant difference in any prefrontal NIRS signal changes between the 2 tasks in either group. In both versions of verbal fluency task, healthy controls exhibited a significantly greater NIRS signal change than did patients with schizophrenia. On the CFT only, left ventrolateral prefrontal NIRS [deoxy-Hb] signals were significantly associated with thought disorder scores in patients with schizophrenia. Our results suggest that left ventrolateral prefrontal abnormalities in category fluency might be related to thought disorder in schizophrenia. This could lead to an improved understanding of the neural mechanisms within the left ventrolateral prefrontal cortex involved in mediating semantic processing, as well as the relationship between semantic processing abnormalities and thought disorder in schizophrenia.

Introduction

Thought disorder, or thought "disorganization," is considered to be one of the main symptoms of schizophrenia (Bleuler, 1911/1956). It commonly manifests as language that is difficult to make sense of. The severity of thought disorder is heterogeneous in schizophrenia, and cognitive neuropsychological studies suggest that thought disorder may result from semantic processing abnormalities (Aloia et al., 1998; Goldberg et al., 1998). Verbal fluency tasks (VFT) require subjects to produce as many words as possible based on certain cues, and have been widely used to evaluate deficits in semantic processing. Imaging studies (magnetic resonance imaging and positron emission tomography) have also revealed distinct brain abnormalities related to VFT performance in schizophrenia (Frith et al., 1995; Yurgelun-Todd et al., 1996). One review article on functional neuroimaging (Costafreda et al., 2006) pointed out that VFT consistently elicited activations in the left ventrolateral prefrontal cortex (PFC), which corresponds to Broca's area or the inferior frontal gyrus. While a number of researchers have investigated the relationship between the neural correlates of semantic processing and thought disorder in schizophrenia (Assaf et al., 2006), the details, particularly with regard to VFT, have yet to be elucidated.

The 2 versions of VFT are classified according to the type of cue used: one requires the subject to generate words belonging to a specific semantic category (category fluency task; CFT), while the other requires the generation of words beginning with a specific letter (letter fluency task; LFT). The LFT and CFT make equivalent demands on the executive system (Ruff et al., 1997), with the CFT additionally requiring the involvement of the semantic system (Henry and Crawford, 2005). Recent studies elucidated that CFT performance was one of the candidates for

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http://dx.doi.org/10.1016/j.neuroimage.2013.04.050

the endophenotype of schizophrenia itself (Hurford et al., 2011; Magaud et al., 2010; Snitz et al., 2006). As thought disorder in schizophrenia is strongly associated with impaired semantic processing (Kerns and Berenbaum, 2002; Spitzer, 1997), CFT is thought to be more associated with thought disorder than LFT; however, neuropsychological findings between VFT and thought disorder to date have been somewhat inconsistent (Barrera et al., 2005; Bokat and Goldberg, 2003; DeFreitas et al., 2009; Docherty et al., 2011; Doughty and Done, 2009). Furthermore, no study has investigated the relationship of neural activity during both types of VFT with thought disorder in schizophrenia.

Near-infrared spectroscopy (NIRS) is a non-invasive optical technique, with high temporal resolution (≥10 Hz), used to measure the relative concentrations of oxy- and deoxy-hemoglobin ([oxy-Hb] and [deoxy-Hb]) in the cerebral cortex, a measurement reflective of neural activity. This technique allows subjects to be seated comfortably in a well-lit room, and enables continuous, simultaneous measurements to be made over time, thereby allowing the assessment of cortical activity associated with human behavior and cognition. These advantages suggest that NIRS could potentially be developed into a method for bedside monitoring in patients with psychiatric disorders.

To date, the majority of NIRS studies have employed only 1 version of VFT, and have revealed a prefrontal functional abnormality in schizophrenia (Reif et al., 2011; Suto et al., 2004; Takizawa et al., 2008). Three studies (Ehlis et al., 2007; Ikezawa et al., 2009; Kubota et al., 2005) did use both versions of VFT, but evaluated limited areas of the cortex, and did not specifically investigate the relationship between VFT performance and thought disorder in schizophrenia. To expand upon these earlier studies, we covered a wide area of the bilateral prefrontal cortex (PFC) using 52-channel NIRS system in order to investigate the functional abnormalities and their spatiotemporal relationship with thought disorder in schizophrenia.

The objective of the current study was to investigate the relationship between activity in the prefrontal sub-regions during the 2 types of VFTs and thought disorder in patients with schizophrenia, and to test whether NIRS could potentially be used clinically to assess the severity of thought disorder in schizophrenia. We hypothesized that VFT performance and task-related NIRS signals would be attenuated during both versions of the VFT in schizophrenia, and that the prefrontal NIRS signal during the VFT would be associated with thought disorder.

Methods

Subjects

Fifty-six Japanese adult patients with schizophrenia (27 men and 29 women), and 56 healthy Japanese adults (27 men and 29 women), matched for age, participated in the study (Table 1). The exclusion criteria for both groups were neurological illness, traumatic brain injury with any known cognitive consequences or loss of consciousness for more than 5 min, a history of electroconvulsive therapy, and alcohol/substance abuse or addiction. An additional exclusion criterion for the control group was a history of psychiatric disease, or a family history of axis I disorders in any first-degree relatives. Any patients with schizophrenia who had other psychiatric or physical comorbidities were excluded. Patients were recruited from among outpatients and inpatients at the University of Tokyo Hospital. They were diagnosed with schizophrenia according to the DSM-IV criteria (American Psychiatric Association, 1994). All patients were medicated with psychotropic drugs (chlorpromazine equivalent dose 768.3 ± 658.0 mg/day) (see Table 1). None of the patients were in an acute phase, but all had some residual psychiatric symptoms at the time of NIRS measurement. Psychiatric symptoms were evaluated by trained psychiatrists (R.T. and K.K.) using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). We calculated the total PANSS scores of the patients by using a five-factor model with confirmatory factor analysis (van der Gaag et al., 2006a). In this study, the disorganization factor score was used as the primary measure for analysis, as an index of thought disorder. This was the total score of items that showed consistent and unique loadings on the disorganization factor (van der Gaag et al., 2006b).

All subjects were right-handed, as defined by the Edinburgh Inventory (Oldfield, 1971). Premorbid IQs were estimated using the Japanese version of the National Adult Reading Test (Matsuoka et al., 2006). These measures were not significantly different between patient and control groups (Table 1). Socioeconomic status (SES) and parental SES were assessed using the Hollingshead scale (Hollingshead, 1965). Written informed consent was obtained from all subjects prior to their participation in our study, and all protocols were approved by the Ethics Committee of Medicine, The University of Tokyo (Institutional Review Board number: 630).

Activation tasks

Changes in the concentrations of [deoxy-Hb] and [oxy-Hb] were measured during a verbal fluency task, as described previously (Takizawa et al., 2008, 2009a). The task consisted of a 30-s pre-task baseline, a 60-s activation period, and a 70-s post-task baseline. Subjects were instructed to repeat the Japanese syllables /a/, /i/, /u/, /e/, and /o/ during both the pre- and post-task baseline periods. During the LFT, subjects were instructed to produce as many words as possible beginning with a designated syllable, for 20 s each (first; /to/, /a/, or /na/, second; /i/, /ki/, or /se/, and third; /ta/, /o/, or /ha/). In the CFT, subjects were asked to produce as many words as possible within a given semantic category for 20 s each (first: “birds,” “fish,” or “insects”; second: “sweets,” “fruits,” or “vegetables”; third: “vehicles,” “stationery items,” or “home appliances”). Subjects were instructed using an auditory cue at the start and end of the task or baseline period, as well as at the task category change. Before beginning a task session, subjects were given audiovisual, on-screen instructions regarding how to repeat the Japanese syllables during the baseline periods (at a frequency of 1 Hz), and how to provide an answer during the task periods. Each subject performed a practice trial to ensure that they understood the instructions. The total number of correct words produced during the tasks was defined as a measure of task performance. The trial order was counterbalanced among participants.

NIRS measurements

The 52-multi-channel NIRS machine (ETG-4000; Hitachi Medical Corporation) measures relative changes in [oxy-Hb] and [deoxy-Hb] using 2 wavelengths (695 nm and 830 nm) of infrared light, based on the modified Beer–Lambert law. The distance between pairs of detector probes was set at 3.0 cm. A channel (ch) was defined as the measurement area between a pair of source-detector probes. As described previously (Takizawa et al., 2008, 2009b), the probes of the NIRS machine were fixed with 3 × 11 thermoplastic shells, and placed at 52 measuring points, with the lowest probes positioned along the T4–Fpz–T3 line, according to the international 10–20 system used in electroencephalography. These points are labeled ch 1–52, starting from the right-posterior to the left-anterior (Fig. 2). This arrangement can measure [oxy-Hb] and [deoxy-Hb] from the bilateral prefrontal, and superior temporal cortical surface regions. We estimated the cortical localization of each channel according to the virtual registration method (Tsuzuki et al., 2007; Tzourio-Mazoyer et al., 2002).

Each participant was seated in a chair in front of a desk for all measurements. Subjects were asked to avoid body movements, including head movements, biting, and strong blinking, during the NIRS measurements, in order to minimize artifacts from perfusion changes unrelated to the study task.

The time resolution of the NIRS apparatus was set at 0.1 s [Hb], and changes were analyzed using the first-order correction to exclude changes unrelated to the task, such as very slow oscillations or baseline