Discriminant analysis in schizophrenia and healthy subjects using prefrontal activation during frontal lobe tasks: A near-infrared spectroscopy

Michiyo Azechi [a,*], Masao Iwase [a], Koji Ikezawa [a], Hidetoshi Takahashi [a,c], Leonides Canuet [a], Ryu Kurimoto [a], Takayuki Nakahachi [a], Ryouhei Ishii [a], Motoyuki Fukumoto [a,c], Kazutaka Ohi [a,c], Yuka Yasuda [a,b,c], Hiroaki Kazui [a], Ryota Hashimoto [a,b,c], Masatoshi Takeda [a,b]

[a] Department of Psychiatry, Osaka University Graduate School of Medicine, Suita, Osaka, Japan
[b] The Osaka-Hamamatsu Joint Research Center for Child Mental Development, Osaka University Graduate School of Medicine, Suita, Osaka, Japan
[c] CREST (Core Research for Evolutionary Science and Technology), JST (Japan Science and Technology Agency), Kawaguchi, Saitama, Japan

ARTICLE INFO

ABSTRACT

While psychiatric disorders such as schizophrenia are largely diagnosed on symptomatology, several studies have attempted to determine which biomarkers can discriminate schizophrenia patients from non-patients with schizophrenia. The objective of this study is to assess whether near-infrared spectroscopy (NIRS) measurement can distinguish schizophrenia patients from healthy subjects. Sixty patients with schizophrenia and sixty age- and gender-matched healthy controls were divided into two sequential groups. The concentration change in oxygenated hemoglobin (Δ[oxy-Hb]) was measured in the bilateral prefrontal areas (Fp1-F7 and Fp2-F8) during the Verbal Fluency Test (VFT) letter version and category version, Tower of Hanoi (TOH), Sternberg's (SBT) and Stroop Tasks.

In the first group, schizophrenia patients showed poorer task performance on all tasks and less prefrontal cortex activation during all but the Stroop Task compared to healthy subjects. In the second group, schizophrenia patients showed poorer task performance and less prefrontal cortex activation during VFTs and TOH tasks than healthy subjects. We then performed discriminant analysis by a stepwise method using Δ[oxy-Hb] and task performance measures as independent variables. The discriminant analysis in the first group included task performance of TOH, VFT letter and VFT category and Δ[oxy-Hb] of VFT letter. As a result, 88.3% of the participants were correctly classified as being schizophrenic or healthy subjects in the first analysis. The discriminant function derived from the first group correctly assigned 75% of the subjects in the second group. Our findings suggest that NIRS measurement could be applied to differentiate patients with schizophrenia from healthy subjects.

© 2009 Elsevier B.V. All rights reserved.

1. Introduction

Major psychiatric disorders such as schizophrenia are largely diagnosed on symptomatology (World Health Organization, 1992; American Psychiatric Association, 1994). While the validity of diagnostic criteria continues to be debated, major advances have been made in understanding the biology of these disorders. However, identified biological markers of psychiatric diseases, including schizophrenia, are not currently used in their diagnosis.

Candidate biological markers of schizophrenia include pathogenetic factors, physical findings, neurophysiological and neuropsychological functioning, and structural and functional brain imaging. In particular, neuroimaging techniques hold significant advantages and have provided evidence for localized anatomical and functional abnormalities, complemented by the use of cognitive neuroscience (Abou-Saleh, 2006). Abnormalities in the prefrontal cortex as well as other brain regions (Arnold and Trojanowski, 1996; Bogerts et al.,

1990; Carter et al., 1998; Harrison, 2005; Heckers et al., 1998; Laurens et al., 2005; Torrey, 2007) and connections between these regions (Fletcher, 1998; Volkow et al., 1988; Weinberger et al., 1992) have been identified as substrates of the clinical features of schizophrenia. For example, positron emission tomography (PET) and single photon emission computed tomography (SPECT) studies identified prefrontal cortex dysfunction as one of the characteristic features of the disease (Callicot et al., 2000; Carter et al., 1998; Curtis et al., 1998). These studies highlight the prefrontal cortex as a promising brain region in the potential use of functional imaging as a biological marker of psychiatric disorders.

Near-infrared spectroscopy (NIRS), a brain functional measuring technique, can measure changes in the concentration of oxygenated Hemoglobin ([oxy-Hb]), deoxygenated Hemoglobin ([deoxy-Hb]) and total Hemoglobin ([total-Hb]), which are presumed to reflect regional cerebral blood flow (Jobsis, 1977). These hemodynamic parameters are assumed to be a stable marker of cerebral oxygenation changes induced by cognitive tasks (Nakahachi et al., 2008; Suto et al., 2004; Takizawa et al., 2008;). NIRS is advantageous for clinical application over other neuroimaging techniques such as PET, SPECT and functional magnetic resonance imaging (fMRI), due to its non-invasive nature, high time resolution, portable and simple mounting, low cost, robustness against motion artifacts, short time of measurement and little training required for operation and data analysis. Therefore, the prefrontal dysfunction in schizophrenia has been frequently investigated with NIRS in a clinical setting. Studies in the frontal cortex have demonstrated a significant smaller increase in the prefrontal activation during the Verbal Fluency test (Ikezawa et al., 2009; Kubota et al., 2005; Suto et al., 2004; Takizawa et al., 2008; Watanabe and Kato, 2004), the Random Number Generation task (Hoshi et al., 2006) and the Tower of Hanoi task (Ikezawa et al., 2009) in patients with schizophrenia compared to healthy control subjects. However, patients with schizophrenia showed no differences during divergent thinking task (Folley and Park, 2005), and possibly a larger increase during the unilateral finger tapping task (Suto et al., 2004) or letter number span test (Watanabe and Kato, 2004). These studies suggest that NIRS measurement of frontal lobe activity may represent a biological marker of schizophrenia on which frontal lobe tasks are employed.

Despite the potential benefit of NIRS measurement of frontal lobe activity as a biological marker of schizophrenia, to our knowledge, discriminant analysis with NIRS has not previously been applied to distinguish schizophrenia patients from healthy subjects. The present study aimed to evaluate whether the NIRS measurement in the frontal cortex could reliably distinguish patients with schizophrenia from control subjects and to identify the task which would provide the highest correct classification rate.

2. Methods

2.1. Subjects

Subjects were assigned to two independent groups according to the order of study inclusion. The first group consisted of a total of 60 subjects, including 30 patients with schizophrenia and 30 age- and gender-matched healthy control subjects. The period of study for this group was from November 2006 to May 2007.

The second group for the prospective validation also consisted of 60 subjects: 30 with schizophrenia and 30 age- and gender-matched healthy control subjects. The period of study for this group was from June 2007 to April 2008.

The patients were inpatients and outpatients of the Department of Psychiatry, Osaka University Hospital. Each patient underwent a Structured Clinical Interview for DSM-IV (SCID) (First et al., 2002), and two or more experienced psychiatrists reached a consensus diagnosis of schizophrenia according to the DSM-IV (American Psychiatric Association, 1994) and ICD-10 for research (World Health Organization, 1992) on the basis of SCID and all other sources of clinical data. At the time of study, in the first group, 2 patients were medication naïve and 28 patients were medicated (2 patients were receiving typical antipsychotics, 11 patients were receiving atypical and 15 patients were receiving both types of antipsychotics). In addition, 11 patients were taking anxiolytics and 2 patients were taking antidepressants. In the second group, all patients (except one from which medication data was missing) were on medication (4 patients were receiving typical antipsychotics, 14 patients were receiving atypical antipsychotics and 11 patients were receiving both types of antipsychotics). In addition, 23 patients in the second group were taking anxiolytics and 3 were taking antidepressants (Table 1).

Advertisements were posted at local hospitals to recruit healthy subjects. Healthy subjects were diagnostically interviewed and assessed to verify that they had neither personal nor family history of psychiatric disease, and had taken no antipsychotics. All of the healthy subjects had at least no fourth-degree relative with a psychiatric disorder and had an estimated IQ of 70 or greater. All patients were physically healthy at the time of recruitment, and none had a history of head trauma, serious medical or surgical illness, or alcohol/substance abuse disorder. All procedures were approved by the ethical committee of the Osaka University hospital.

All participants provided written informed consent according to the Declaration of Helsinki after they were given a complete explanation of the study procedures.

2.2. Tasks and procedure

The cognitive paradigm employed in the present study consisted of the letter and category versions of the Verbal Fluency Test (VFT), Tower of Hanoi (TOH), Sternberg's Task (SBT), and the Chinese character version of the Stroop Task part III (SRT). These frontal activation tasks comprised a 30-s pre-task baseline period, a 60-s or 120-s task period, and a 60-s post-task baseline periods (Fig. 1). These procedures were similar to that of Suto et al. (2004), Ito et al. (2005) and Kameyama et al. (2006) except for the use of a 120-s task period for SBT or STR instead of the 60-s used in their studies. We used a longer interval for these two tasks to enable a more satisfactory [oxy-Hb] activation compared to the baseline in the pre-task period. This is described in detail elsewhere (Ikezawa et al., 2009).

2.2.1. Verbal Fluency Test letter and category versions

For the pre- and post-task baseline periods of the VFT letter and category versions, the subjects were instructed to repeat the voice vowels (/a/, /i/, /u/, /e/ and /o/ (Phonetic Alphabet)) constantly. During the VFT periods, they were instructed to alternately produce as many Japanese nouns as possible