Progress in Neuro-Psychopharmacology & Biological Psychiatry xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

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

Relationship between the prefrontal function and the severity of the emotional symptoms during a verbal fluency task in patients with major depressive disorder: A multi-channel NIRS study

Xiaomin Liu [a,b], Gaoxiang Sun [b], Xiaoqian Zhang [b], Bo Xu [b], Chenyu Shen [a,b], Lujie Shi [a,b], Xiangyun Ma [a,b], Xiajin Ren [a,b], Kun Feng [b], Pozi Liu [b,*]

[a] Medical Center, Tsinghua Unversity, Beijing, China
[b] Department of Psychiatry, Yuquan Hospital, Tsinghua University, Beijing, China

A R T I C L E I N F O

Article history:
Received 15 January 2014
Received in revised form 2 May 2014
Accepted 9 May 2014
Available online xxxx

Keywords:
Anxious symptom
Major depressive disorder
Near-infrared spectroscopy (NIRS)
Neurocognition
Obsessive–compulsive symptom
Prefrontal cortex

A B S T R A C T

Multi-channel near-infrared spectroscopy (NIRS) is a noninvasive and low-cost functional neuroimaging technique in psychiatric research, and it has been wildly used for detecting the spatiotemporal characteristics of brain activity. In order to evaluate the clinical value of NIRS data in the assistant diagnosis of major depressive disorder (MDD), prefrontal cortex (PFC) hemoglobin concentration exchange of 30 MDD patients combined with anxious and obsessive–compulsive symptom was detected by NIRS under voice fluency task (VFT), then the relationship between the severity of depressive, anxious and obsessive–compulsive symptom assessed by Hamilton Rating Scale for Depression (HAMD), Hamilton Anxiety Rating Scale (HAMA) and Yale-Brown Obsessive Compulsive Scale (Y-BOCS) with NIRS data in PFC was analyzed. Hypoactivation in lateral and lower PFC of MDD patients was confirmed in this study. Furthermore, Spearman correlation found that oxy-hemoglobin concentration ([oxy-Hb]) exchange in right-lateral PFC was associated with the severity of anxiety, while bilateral PFC and antero-medial PFC were associated with severity of depression. Meanwhile, no statistical correlation was observed on the severity of obsessive–compulsive symptom. The results prompted that MDD patients with anxiety and obsession–compulsion symptom showed a PFC hypoactivation state in NIRS. Furthermore, the function of right-lateral PFC was associated with anxiety symptom, while bilateral PFC and antero-medial PFC were associated with depression symptom. Different from depression and anxiety, obsession–compulsion may have a different biological character in PFC function.

1. Introduction

Major depressive disorder (MDD) is a severe and common mental disorder with a lifetime prevalence of 6.7 per 100 (Waraich et al., 2004), which is characterized by anatomical and functional brain abnormalities, especially a loss of top-down control over limbic structures (Savitz and Drevets, 2009). Neurophysiological abnormalities in multiple areas of the prefrontal cortex (PFC), the amygdala, and related parts of the striatum and thalamus have been identified in MDD patients by several neuroimaging studies (Alvarez and Emory, 2006; Drevets, 2000). Involved in attention, cognition control and motivation, PFC plays an important role in regulatory function over the limbic system in the pathophysiology of depression (Diekhof et al., 2011; Etkin et al., 2011). A relative hypoactivity of PFC that implicates hypometabolism and hypoperfusion was observed in mood disorders compared with healthy control (Townsend and Altshuler, 2012), which has been identified by a series of functional neuroimaging researches such as functional magnetic resonance imaging (fMRI) and metabolic positron emission tomography (PET) studies (Savitz and Drevets, 2009; Videbech, 2000).

Near-infrared spectroscopy (NIRS) is a kind of optical functional brain imaging technique, which has been raised to a very high level in the field of neuroscience research since the pioneering work by Jöbsis in 1977 (Jöbsis, 1977). Compared with other functional neuroimaging technologies such as fMRI, PET and single-photon emission computed tomography (SPECT), NIRS is a noninvasive and bedside measurement. NIRS allows measurement of changes induced by brain activity by means of probing the concentration and oxygenation of hemoglobin in the brain cortex non-invasively, using near infrared light between 650 nm and 950 nm (Lloyd-Fox et al., 2010; Quaresima et al., 2012). It

Abbreviations: deoxy-Hb, relative concentration of deoxy-hemoglobin; DLPFC, dorsolateral prefrontal cortex; DSM, Diagnostic and Statistical Manual of Mental Disorder, text revision (DSM-TR); HAMA, Hamilton Anxiety Rating Scale; HAMD, Hamilton Rating Scale for Depression; NIRS, near-infrared spectroscopy; [oxy-Hb], relative concentration of oxy-hemoglobin; PFC, prefrontal cortex; [t-Hb], relative concentration of oxy-hemoglobin plus deoxy-hemoglobin; VFT, voice fluency task; Y-BOCS, Yale–Brown Obsessive Compulsive Scale.

* Corresponding author at: Department of Psychiatry, No. 5 Shijingshan Road, Shijingshan District, Beijing100049, China. Tel.: +86 1088257755x6111; fax: +86 83658195.
E-mail address: liupozi@tsinghua.edu.cn (P. Liu).

http://dx.doi.org/10.1016/j.pnpbp.2014.05.005
0278-5846/© 2014 Published by Elsevier Inc.

has been proved that an optically measured hemoglobin signal in NIRS strongly correlates with the fMRI blood oxygenation level dependent (BOLD) signals and is repeatable and reproducible (Boas, 2004; Ye et al., 2009). NIRS has been used to investigate several psychiatric disorders, including schizophrenia, obsessive–compulsive disorder, depression, bipolar disorder, dementia, post-traumatic stress disorder, panic disorder, and pervasive developmental disorder (Okada et al., 2013; Quaresima et al., 2012; Takeshi et al., 2010). Suto et al. (2004) using a 48-channel NIRS system showed that the depression group was characterized by a smaller [oxy-Hb] increase in PFC during the first half of the verbal fluency task period compared with the normal group. Then, several NIRS studies demonstrated frontal lobe dysfunction in MDD patients (Kameyama et al., 2006; Pu et al., 2008). Moreover, frontal lobe dysfunction was also observed in schizophrenia (Suto et al., 2004; Takeshi et al., 2008, 2010) and panic disorder (Nishimura et al., 2009).

Researches investigating cross-sectional relationship between depression symptom severity and brain function patients assessed by cerebral blood flow (CBF) and metabolism did not obtain consistency yet. For example, Noda et al. (2012) explored the possible relationship between the severity of depression symptom and [oxy-Hb] change by NIRS, and the results showed that a mean [oxy-Hb] increase in the right dorsolateral prefrontal cortex (DLPFC) demonstrated a significant negative correlation with the symptom severity. Whereas, Kameyama et al. (2006) showed no correlation between activity of frontal lobe and frontal lobe with depression symptom severity in bipolar patients by NIRS. And Milak et al. (2005) found a positive correlation between large bilateral ventral cortex metabolism and depression severity in MDD patients by PET. To clarify the relationship between depression severity and brain activity, more studies should be warranted.

To our knowledge, nearly 6 studies (Marumo et al., 2009; Milak et al., 2005; Morinage et al., 2007; Nishimura et al., 2009; Périco et al., 2005; Sakai et al., 2006) have evaluated the correlation between the severity of anxiety symptoms and regional blood blow, and all these studies were inconsistent. Three of them (Morinage et al., 2007; Périco et al., 2005; Sakai et al., 2006) obtained positive results, while, the other three studies (Marumo et al., 2009; Milak et al., 2005; Nishimura et al., 2009) didn't show any difference. This confliction was probably due to choosing different technologies, individual difference, and different evaluating methods. In NIRS studies, Nishimura et al. (2009) investigated patients with panic disorder, finding that [oxy-Hb] changes in the left inferior prefrontal cortex were significantly associated with the frequency of panic attacks; and Marumo et al. (2009) found that mean [oxy-Hb] changes during the emotional-activation task period showed no significant correlation with trait anxiety score assessed by State-Trait Anxiety Inventory in the whole sample; then Morinage et al. (2007) observed that right frontal [oxy-Hb] increases were significantly correlated with the Temperament Character Inventory Harm Avoidance subscale.

Several studies (Kwon et al., 2003; Le Jeune et al., 2010; Millet et al., 2013) revealed either left-sided, right-sided, or bilateral prefrontal cortex hypermetabolism in obsessive–compulsive disorder (OCD) patients by functional brain imaging, which identified the dysfunction of prefrontal cortex in OCD. Within these researches, only Kwon's study was focused on symptom of obsession–compulsion. Based on the PET imaging, it concluded that the severity of symptom has no correlation with PFC (Kwon et al., 2003). Up to now, only two publications on NIRS studies have indicated that PFC, especially frontopolar cortex, showed inhibitory state for children and adults with obsessive–compulsive disorder (Okada et al., 2013; Ota et al., 2013). However, no further discussion on the relationship between the severity of obsessive–compulsive disorder and the function of PFC was investigated by NIRS. Whether the relationship could be used for guiding the clinical practice was still unknown.

Although biomarkers for medical conditions have proliferated over the past decades, objective assessments relate to mental health have lagged behind (Wager et al., 2013). Psychiatric disease traditionally is evaluated by means of self-report, the sole reliance on which hampers diagnosis and treatment. As a simple, economic and non-invasive technology in the field of functional brain imaging, NIRS holds promise for identifying objective measures of psychiatric symptoms.

We hypothesized that the functional activity domains in PFC would be related to specific symptom and the relationship could be observed through NIRS. This result would be used for clinical application. As such, there has been a greater need to adapt clinical imaging methods for noninvasive assays of biochemical processes.

In summary, the first objective of the study was to use NIRS to identify hypoactivation of PFC in MDD patients. The second objective was to investigate the relationship between hypoactivation of the prefrontal cortex by NIRS and the severity of depression, anxiety and obsession–compulsion symptoms, exploring the way of NIRS clinical application.

2. Materials and methods

2.1. Subjects

Thirty right-handed healthy volunteers and thirty Chinese MDD outpatients with depression, anxiety and obsession–compulsion symptoms in Yuquan Hospital were recruited for this study from June 2012 to August 2013. MDD was diagnosed according to the DSM-IV-TR (American Psychiatric Association, 2000), with the score of Hamilton Rating Scale for Depression higher than 21.

All subjects were free of medications, between 18 and 65 years old, and possessed educational level of senior middle school or above. Also subjects with psychiatric symptoms or other psychotic disorder, chronic substance abuse, severe medical illness or cognitive disorders were excluded. The study was approved by the ethic committees of Yuquan hospitals, and written informed consent was obtained from all participants.

2.2. Clinical assessment

Hamilton Rating Scale for Depression (HAMD, 24-item, Hamilton, 1960), Hamilton Anxiety Rating Scale (HAMA, Hamilton, 1956) and Yale–Brown Obsessive Compulsive Scale (Y-BOCS, Goodman et al., 1989a,b) were conducted by trained doctoral-level interviewers to assess behavioral and somatic symptoms associated with depression, anxiety and obsession–compulsion. MDD patients with scores of HAMD, HAMA and Y-BOCS higher than 21, 14 and 10 respectively were included into the group. Demographic characteristics and scores were reflected in the statistical description in Table 1.

2.3. Activation task

Changes of the concentration of hemoglobin ([Hb]) were measured during a cognitive activation task. Each subject sat on a comfortable chair and was instructed to minimize movements such as head movements, biting and eye blinking during measurements, to avoid artifact. Then, they were given practice using category verbal fluency task (Jayakar et al., 2005; Herrmann et al., 2006; Kono et al., 2007;), which consists of a 30 s pre-task period, a 30 s task period and a 30 s post-task period. During the task period, participants were required to verbally list items belonging to given semantic categories (vegetables, four-foot animals, family machines, fruits). These semantic cues were determined according to preliminary results and previous research (Dieler et al., 2012) and the cues were visually presented by software E-prime 2.0 in a computer screen during measurement.

2.4. NIRS measurements

A 52-channel spectrometer (FOIRE-3000, also named SmartNIRS; Shimadzu Corporation, Japan) based on the modified Beer–Lambert Law (Yamashita et al., 1996) was used to measure the relative changes in [oxy-Hb], [deoxy-Hb] and [total-Hb] at three wavelengths of near-infrared light (780, 805 and 830 nm). Relative concentration (mmol/L × cm) of [oxy-Hb], [deoxy-Hb] and [total-Hb], derived from