Journal of Affective Disorders 214 (2017) 44–52

Contents lists available at ScienceDirect

Journal of Affective Disorders

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

Research paper

Different functioning of prefrontal cortex predicts treatment response after a selective serotonin reuptake inhibitor treatment in patients with major depression

Koji Masuda[a], Mari Nakanishi[a], Kana Okamoto[a], Chiwa Kawashima[a], Harumi Oshita[b], Ayako Inoue[a], Fuku Takita[a], Toshihiko Izumi[a], Yoshinobu Ishitobi[a], Haruka Higuma[a], Masayuki Kanehisa[a], Taiga Ninomiya[a], Yoshinori Tanaka[a], Jotaro Akiyoshi[a,*]

[a] Department of Neuropsychiatry, Oita University Faculty of Medicine, Hasama-Machi, Oita 879-5593, Japan
[b] Department of Applied Linguistics, Oita University Faculty of Medicine, Hasama-Machi, Oita 879-5593, Japan

ARTICLE INFO

Keywords:
Antidepressant
Major depressive disorder
Automatic thought
Frontal cortex
Temporal cortex
Near-infrared spectroscopy

ABSTRACT

Background: Major depressive disorder (MDD) is often resistant to treatment with usual approaches. Patients with MDD have shown hypofunction of the frontotemporal cortex in verbal fluency test (VFT)-related near-infrared spectroscopy (NIRS).

Methods: We examined whether the reactions to drug treatment in treatment-naive patients with MDD could be predicted by NIRS outcomes at the initial investigation. All subjects underwent psychological testing to determine levels of anxiety and depression. VFT was used to examine the functioning of the frontotemporal lobes. We administered selective serotonin reuptake inhibitors (SSRIs) for 12 weeks. Subjects included 28 patients with MDD with response to SSRIs (Response group), 19 with no response (Non-Response group), and 63 age-, sex-, and education years-matched healthy controls (HC).

Results: We found in the frontotemporal region that hemodynamic responses were significantly smaller in patients with Response and Non-Response groups than in HC before treatment. We also found in the medial frontal region that hemodynamic responses were significantly larger in patients with Response groups than in patients with Non-Response group before treatment. Patients with MDD scored significantly higher anxiety and depressive states than those in HC on several measures. The Response and Non-Response groups also had higher scores in future denial, threat prediction, self-denial, past denial, and interpersonal threat sections of Anxiety Cognition Scale (DACS). According to the stepwise regression analysis, one variable was determined as independent predictors of response: confusion (Post-POMS).

Limitations: The number of patients and healthy controls was relatively small, and we will increase the number of participants in future studies. NIRS has reduced spatial resolution, which confuses the identification of the measurement position when using NIRS alone.

Conclusion: Cognitive vulnerabilities are associated with predictors of SSRI treatment response. Different hemodynamic activities in the frontotemporal cortex predict response to SSRI treatment in MDD.

1. Introduction

Major depressive disorder (MDD) is a widespread psychiatric disease that is associated with a significant loss of productivity and quality of life and a substantial morbidity and mortality (Bostwick and Pankratz, 2000; Kessler et al., 2005). Depression is not only ranked as the 11th most important cause of worldwide burden by DALY (Ferrari et al., 2013), but current predictions indicate that by 2030 depression will be the leading cause of disease burden globally according to WHO.

Brain imaging has proved to be a strong tool to clarify the pathophysiology and possible etiology of MDD, with many studies highlighting the critical role of dysfunction in an extended network. F^{18}-fluorodeoxyglucose positron emission tomography represents brain regions that predict antidepressant treatment response in MDD. Studies have shown that the regional cerebral metabolic rate of glucose in various parts of the temporal lobe region (Little et al., 1996, 2005; Saxena et al., 2003), various parts of the anterior cingulate (Brannan et al., 2000; Kennedy et al., 2001; Little et al., 2005); various

* Corresponding author.
E-mail address: akiyoshi@oita-u.ac.jp (J. Akiyoshi).

http://dx.doi.org/10.1016/j.jad.2017.02.034
Received 30 July 2016; Received in revised form 18 February 2017; Accepted 28 February 2017
Available online 04 March 2017
0165-0327/

parts of the prefrontal cortex (PFC) (Brody et al., 2001; Kennedy et al., 2001; Saxena et al., 2003; Little et al., 2005); and various parts of the midbrain (Milak et al., 2009) predicted treatment response. Anterior cingulate activity measured with electroencephalography (Pizzagalli et al., 2001) and prefrontal cortical function assessed with P300 latency (Kalayam and Alexopoulos, 1999) have been reported to predict treatment response.

A treatment-related effect in depression is a hyperactive PFC, especially in response to negative stimuli on functional magnetic resonance imaging (fMRI) (Wang et al., 2012). Antidepressants normalize the hypoactive baseline PFC response, especially in response to negative stimuli (Hamilton et al., 2012). Neural activity in the lateral PFC controls limbic responses to emotional stimuli and inhibits augmented emotional reactivity. Normalized PFC activation following treatment may increase the capacity for top-down control of emotional procedures. Attenuation of PFC activity is reported during cognitively demanding conditions such as the Stroop task, emotional oddball task, go/no go task, and self-judgment task (Lemogne et al., 2010; Wagner et al., 2010) in depressed patients, whereas augmentation of PFC activation is found in studies using affective paradigms such as passive viewing of emotional faces, emotion recognition task, and backward masking of emotional faces following treatment (Samson et al., 2011; Victor et al., 2013; Diener et al., 2012). Added neuronal sources from PFC are enlisted by medicated MDD subjects mainly during automatic emotion regulation approaches while, during voluntary emotion regulation, MDD subjects showed decreased PFC activation relative to health controls (HC) (Godlewska et al., 2012). fMRI studies have detected brain circuits with different functional activity while patients with MDD handle affective stimuli. Recently, resting-state fMRI has become increasingly prevalent to study the pathophysiology of MDD. Among studies comparing pre- and post-treatment scans, numerous studies found decreased activity or connectivity of frontal cortical brain regions (Lai and Wu, 2012; Alexopoulos et al., 2012).

Near-infrared spectroscopy (NIRS) is one of functional neuroimaging techniques that has been increasingly employed in psychiatry. NIRS is superior to functional magnetic resonance imaging (fMRI) in that it offers better temporal resolution and subjects can be examined in a sitting position while they speak and move (Ferrari and Quaresima, 2012). NIRS has been established as suggesting auxiliary role of diagnosis of major depressive disorder (Takizawa et al., 2014).

The autonomous nervous system (ANS) can be associated with higher heart rate (Simon et al., 2013). Both NIRS and heart rate variability (HRV) are sensitive to different levels of mental workload (Durantin et al., 2014). Lower prefrontal activation as well as a lower LF/HF ratio at the highest level of difficulty, suggest that these measures are suitable for mental overload detection.

Selective serotonin reuptake inhibitors (SSRIs) have been used as the first-line antidepressant drug treatment of depression and replaced tricyclic antidepressants (TCA) and monoamine oxidase inhibitors (MAOI) due to fewer side effects and widespread availability (Bauer et al., 2008). SSRIs could improve certain cognitive functions on cognitive domains (Baune and Renger, 2014). The four different SSRIs (fluoxetine, sertraline, citalopram, and paroxetine) were effective in auditory–verbal declarative and working memory performance in a case-control design comparing the results of patients with remission to those without remission (Talarowska et al., 2010). We study relating cognitive function to response to SSRI antidepressants.

Brain imaging methods that could predict treatment response to antidepressants have been examined. Although activation and connectivity in these networks distinguishes those with MDD from HC, less is known about the relation between functional brain connectivity and antidepressant treatment outcomes. Therefore, we examine the relationship between changes in near-infrared spectroscopy (NIRS) and SSRI treatment responses in MDD.

Table 1
Results of multivariate analysis of variance(MANOVA).

Dependent variables	F-ratio	Num df	Den df	*p*-value
NIRS response (1–47 CHs)	1.495	94	124	**0.018**
Region				
DL	1.548	38	180	**0.031**
T	1.673	32	186	**0.019**
FP	2.184	18	200	**0.005**
OF	2.708	6	212	**0.015**

MANOVA: multivariate analysis of variance with Pillai methods.
Between-group factor: Group (Healthy Control vs. Response vs. Non-Response).
DL: Dorsolateral prefrontal cortex, T: Temporal cortex, FP: Frontopolar
OF: Orbitofrontal cortex.
F-ratio: approximate F ratio.
Num df: numerator degrees of freedom.
Den df: denominator degrees of freedom.

2. Methods

2.1. Participants

The present study included 47 patients (females, n=26; males, n=21; mean age 48.6 ± 15.0 years) and 63 HCs (females, n=28; males, n=35; mean age 41.7 ± 1.4 years) (Table 1). Japanese patients with MDD were recruited from a group of outpatients in the Department of Neuropsychiatry, Oita Medicine University Faculty in Japan. The patients are drug-naïve only for this episode. All patients were diagnosed on the basis of clinical interviews and all underwent MDD testing according to DSM-IV-TR criteria, including the number of past episodes and the severity of a current depressive episode. The patients did not involve catatonic features, atypical features, and postpartum features. We found no differences of presence of melancholic features between responders and non-responders (71.4% vs 84.2%; $p < 0.49$). No patients with MDD with psychotic features were allowed to participate in the study. Patients were excluded if they had comorbid bipolar disorder, schizophrenia, panic disorder, obsessive-compulsive disorder, post-traumatic stress disorder, social anxiety disorder, generalized anxiety disorder, risk of suicide, substance abuse, drug abuse, personality disorder, or any physical illness. To ensure that the participants were right-handed, all participants completed the Edinburgh handedness inventory (Oldfield, 1971). All subjects provided written informed consent. The symptom score in the 17-Item Hamilton Rating Scale for Depression (HAM-D_{17}) scale score was obtained for each subject in the depression group (Hamilton, 1960). A total of 47 patients received a SSRI alone. 33 patients received escitalopram, 7 received paroxetine, 5 received sertraline, or 2 received fluvoxamine. We tried to use only escitalopram for our studies (Cipriani et al., 2009). However, we selected sertraline and paroxetine because they showed a better neonatal safety profile during breastfeeding as compared with other SSRIs (Orsolini et al., 2015). After a base line evaluation, patients were seen weekly or biweekly by their study psychiatrist for 12 weeks. Clinical response was based on ratings from the HAM-D_{17} by a psychiatrist who was blind to the neurocognitive test data and to the hypotheses being tested in this study. Patients showing a change in HAM-D_{17}≥50% from baseline assessment to end of treatment trial were considered responders and all other patients were considered to be non-responders. This study was performed in accordance with the Declaration of Helsinki and was approved by the Human Ethics Committees of the Oita University Faculty of Medicine.

2.2. Verbal fluency test (VFT)

VFT was used as the neuropsychological task during NIRS, given that VFT is widely used as a test to measure cognitive function in the frontal lobes, is easy to manage for most subjects, and is widely used in NIRS research. The VFT (letter version) consisted of a 30 s pre-task