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Reduced prefrontal activation during performance of the Iowa Gambling Task in patients with bipolar disorder

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ABSTRACT

The Iowa Gambling Task (IGT) is a complex decision-making task in which monetary wins and losses guide the development of strategies. The objective of this study was to evaluate hemodynamic responses of patients with bipolar disorder (BD) during performance of the IGT using near-infrared spectroscopy (NIRS). Participants comprised 13 patients and 15 healthy control subjects who were matched for age, sex, handedness, and intelligence quotient. Relative changes in oxygenated and deoxygenated hemoglobin (oxy-Hb and deoxy-Hb) levels in the frontal region were measured using a 46-channel NIRS system. All subjects were evaluated using NIRS during a verbal fluency task (VFT) and the IGT. During performance of the IGT, BD patients showed significantly decreased oxy-Hb levels in the bilateral orbitofrontal cortex (OFC) and left prefrontal cortex (PFC) compared with normal control subjects. However, during the VFT, patients with BD showed no significant changes in oxy-Hb levels compared with control subjects. Changes in oxy-Hb levels in the bilateral OFC and the PFC during the IGT were negatively correlated with total scores on the Hamilton Rating Scale for Depression (HAM-D). Although the IGT was useful for differentiating patients with BP from control subjects, no significant differences in autonomic activity were observed.

1. Introduction

Mood disorders, such as major depressive disorder (MDD) and bipolar disorder (BD), have been evaluated using near-infrared spectroscopy (NIRS) during the performance of various tasks, including a verbal fluency task (VFT; Kameyama et al., 2006; Matsuo et al., 2007; Kubota et al., 2009; Noda et al., 2012) and a working memory task (Schecklmann et al., 2011). Compared with functional magnetic resonance imaging (fMRI), NIRS does not detect changes in deep brain structures and has inferior spatial resolution, although it has fewer restrictions. In particular, NIRS is less sensitive to motion artifacts, and due to the absence of magnetic effects of computer and monitors, it can be applied even to newborn babies.

BD is a chronic and debilitating mood disorder that is associated with substantial morbidity and mortality (Oquendo et al., 2000), with odds ratios for suicide attempts of 6.2 among patients with BD and 3.1 among patients with MDD (Chen and Dilsaver, 1996). Thus, clinical evaluations of impulsivity are critical in patients with BD.

The Iowa Gambling Task (IGT) is a prototypic tool for the investigation of processes that underpin incentive-related decision-making. It is a clinically sensitive tool that emulates real-world financial decision-making by requiring participants to select cards arranged in four decks. Each card has a monetary value that is revealed only after selection, and can either be a gain or a loss. The aim of the task is to optimize net gains across several trials. Two decks have higher rewards (gains) but also higher risks (losses) and can result in disadvantageous monetary losses over time. The other two decks have lower rewards and risks, making them advantageous in the long term. Differences in IGT performance have been observed in individuals with neuropsychiatric disorders that are characterized by problems in impulse control and emotion regulation.

Several fMRI studies have used the IGT as a measure of impulsivity (Lawrence et al., 2009; Hartstra et al., 2010; Li et al., 2010). Only one study, however, has reported fMRI and blood oxygen measurements during performance of the IGT in patients with BD (Frangou et al., 2008). In that study, patients with BD

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showed attenuated activation in both ventral and dorsal prefrontal cortices (PFCs) and increased activity in the lateral temporal and polar regions.

The somatic marker hypothesis (SMH; Damasio, 1996) provides a relevant theoretical framework for studying decision-making processes and the role of psychophysiological reactions in the anticipation of rewards or losses. It postulates that unconscious bodily states ("somatic markers") guide our behavior. In particular, pathological gamblers show decreases in heart rate (HR) after losses and wins. Although the absence of HR increases after wins indicates that reward sensitivity is decreased in pathological gamblers (Goudriaan et al., 2006), no previous reports have evaluated the SMH in patients with BD.

The aim of the present study was to evaluate PFC activation during the IGT and the VFT, which require differing brain activations. Compared with the VFT, the IGT demonstrates impulsivity and presumably relies more on attentional and working memory processes. It may help to differentiate BD patients from healthy controls. A second aim was to determine whether sympathetic and parasympathetic activation showed changes in BD patients during performance of the IGT.

2. Methods

2.1. Subjects

Twenty-eight individuals were included in this study (see Table 1). These included 13 patients with BP-II disorders during euthymic or subdepressive episodes and 15 healthy controls. Premorbid intelligence quotient (IQ) was estimated using the Japanese version of the National Adult Reading Test (Matsuoka et al., 2006). Executive functions were evaluated according to the Behavioral Assessment of the Dysexecutive Syndrome (BADS; Wilson et al., 1996). Participants were assessed as being right-handed according to the Edinburgh Handedness Index if they used their right hand for $>85\%$ of items (Oldfield, 1971). All subjects were right-handed according to the Edinburgh Handedness Index and were native speakers of Japanese.

Diagnoses were performed by experienced psychiatrists and were confirmed using the Structured Clinical Interview for DSM-IV (SCID-I). Patients ranged in age from 19 to 45 years. Subjects with a history of head injury or neurological disorders were excluded. None of the included patients received electroconvulsive therapy in the 3 months before the study. However, two patients suffered from co-morbid panic disorder, one suffered from social anxiety disorder, and one suffered from gender identity disorder.

At the time of testing, 11 patients were receiving neuroleptic medications; all were receiving lithium, valproate alone or a combination of these medications; one patient was receiving a selective serotonin reuptake inhibitor (SSRI); and eight patients were receiving second-generation antipsychotics.

Table 1
Demographic, clinical and behavior performance of participants.

	Bipolar depression ($n=13$)	Healthy controls ($n=15$)	Group difference p-value
Age (years)	38.4 ± 7.3	32.9 ± 7.7	0.068
Sex (female/male)	f:m=7:6	f:m=7:8	0.705
Edinburgh handedness inventory (%)	93.8 ± 9.6	98.7 ± 3.5	0.108
Estimated premorbid IQ	101.5 ± 9.6	106.3 ± 9.7	0.201
GRID HAM-D21 total score	12.2 ± 6.6	1.3 ± 1.8	$p<0.001$
YMRS	2 ± 2.0	0.3 ± 0.8	0.011
BADS	100.1 ± 12.2	107.3 ± 11.1	0.116
Iowa Gambling Task	−4.3 ± 13.0	3.1 ± 27.8	0.378
Total cards number	81.0 ± 7.1	84.5 ± 8.5	0.262
Verbal fluency	8.2 ± 2.6	11.6 ± 3.5	0.008
Antidepressive medication	1	0	
Antipsychotic medication	8	0	
Mood stabilizing agents	13	0	
Benzodiazepine use	11	0	

HAM-D, Hamilton Rating Scale for Depression; YMRS, Young Mania Rating Scale; BADS, Behavioural Assessment of the Dysexecutive Syndrome.

Clinical ratings were assessed using the Hamilton Rating Scale for Depression (HAM-D; Hamilton, 1960) and the Young Mania Rating Scale (YMRS; Young et al., 1978).

Fifteen healthy volunteers (23–43 years of age) were recruited as controls after they responded to an advertisement in Kanazawa. Control subjects had no history of psychiatric or neurological disorders and no first-degree relatives with bipolar diagnoses. They were not taking any drugs and were interviewed with the SCID-I. Table 1 summarizes the demographic characteristics of the patients and controls. The patients did not differ significantly in age, gender, handedness, estimated premorbid IQ, or BADS.

The study was approved by the local research ethics committees, and after complete disclosure of the study details, all participants gave written informed consent. Upon completion of the experiment, all participants received 5000 yen as compensation for participation.

2.2. Task procedure

2.2.1. VFT

A letter version of the VFT was used as the target task, and the word repetition task (WRT) was used as the control task (CT). Subjects were asked to generate as many words as possible using the initial syllables /te/, /i/, or /shi/ in this order.

Three repetitions of VFT and WRT tasks were conducted in the following order: WRT, VFT, WRT, VFT, WRT, VFT, and WRT. The duration of the WRT was 80 s and that of the VFT was 60 s. Subjects were instructed to repeat "hai" during the WRT, which means "yes" in Japanese.

2.2.2. IGT

A computerized version of the IGT (Version 2.0, 2002, Antoine Bechara) was used. Subjects were instructed to select 100 cards arranged in four decks with the intention of gaining simulated monetary rewards. In each trial, subjects used a mouse to select cards from one of the four decks; the amounts won or lost in the trial, and total cumulative earnings were recorded. After NIRS measurements, subjects continued to play until the game had been completed.

Unknown to the subjects, deck A had frequent small punishments, deck B had infrequent but larger punishments, deck C had frequent small rewards, and deck D had infrequent large rewards. Subjects were asked to select a card from a deck of their choice taking their own time. The control task (CT) was designed to match the sensorimotor demands of the IGT, and subjects were instructed to select cards from the decks in the sequence A-, B-, C-, D-, A-, B-, C-, D. Both the IGT and the CT were performed for 60 s. Five repetitions of the IGT and six repetitions of the CT were conducted in the following order: CT, IGT, CT, IGT, CT, IGT, CT, IGT, CT, IGT, and CT (Fig. 1).

Performance was measured by the net global outcome scores (net scores), which were calculated by subtracting the total number of cards selected from the disadvantage decks (A+B) from the total number of cards selected from the advantage decks (C+D).

2.3. NIRS measurements

A 46-channel NIRS imaging system (ETG-4000; Hitachi Medical Corporation, Tokyo, Japan) was used to measure relative changes in oxygenated and deoxygenated hemoglobin (oxy-Hb and deoxy-Hb) levels at infrared wavelengths of 695 and 830 nm according to the modified Beer–Lambert law (Cope et al., 1988). This method allowed calculation of signals that reflected changes in arbitrary units of Hb (mM-mm; Maki et al., 1995).

Intensities of diodes were modulated at frequencies in the range of 1–10 kHz to prevent cross-talk between channels and wavelengths. The distance between the injectors and the detectors was 30 mm. A pair of three × three arrays with five injectors and four detectors (probe 1), and three × five arrays with eight injectors and seven detectors (probe 2) were placed bilaterally on the prefrontal and temporal surface regions (Fig. 2A and B). The lowest probes were positioned along the Fp1–Fp2 line according to the international 10–20 system used in electroencephalographic measurements. Correspondence between these NIRS channels and measurement points on the cerebral cortex was confirmed using a multi-subject study of anatomical cranio-cerebral correlations (Okamoto et al., 2004) and is presented according to the virtual registration method (Tsuzuki et al., 2007).

The sampling rate was 0.1 s and data were analyzed using the integral mode. Subsequently, the sum and average block design data were calculated by fitting the baseline. The mean pre-task baseline was estimated over a 10-s period immediately before the task period, and the mean post-task baseline was determined over the

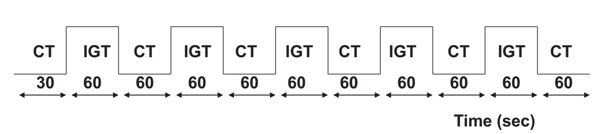

Fig. 1. Experimental design. A total of 5 block trials of the Iowa Gambling Task (IGT) and 6 block trials of the control task (CT) were performed.