

Bipolar mood tendency and frontal activation using a multichannel near infrared spectroscopy

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Abstracts

This study aims to examine the association of frontal functioning with subclinical bipolar spectrum by a newly developed convenient method. We investigated subclinical bipolar tendency and frontal lobe activation during word productions using multi-channel near infrared spectroscopy. Participants: 44 healthy university students (mean ages 20.5 years old, and 29 female) gave their written informed consent, and we strictly protected privacy and anonymity was carefully preserved. A 13-items self-report questionnaire (Mood Disorders Questionnaire; MDQ) and a 16-channel near-infrared spectroscopy were used to compare frontal activations between two samples divided by median (4 points) of the total MDQ scores and to analyze correlations between relative changes of cerebral blood volume and bipolarity levels. There was no case suspected as bipolar disorders by MDQ screening (mean 3.4, max 10). Significant differences in lower activations were noted in the right and left prefrontal cortex (PFC) with higher bipolarity scores using the specific software to analyze the NIRS waveform ($P < 0.05$). Total MDQ were correlated significantly with frontal activation negatively in many channels; therefore, we conducted multiple linear regression to select significant frontal activations using the MDQ as a dependent variable. Stepwise method revealed that activation in left lateral PFC was negatively associated to bipolar tendency, and this regression model was significant ($R^2 = 0.10$, $F = 4.5$, $P = 0.04$). Differences in frontal functioning suggest that subclinical bipolar tendencies might be related to left lateral PFC activations. It should be confirmed whether the identical pattern can be identified for clinical subjects with bipolar disorders.

Introduction

Subclinical bipolar mood liability in youth can be related to aggression, irritability, impul-

sive behavior, self-harm, drug abuse, unstable relationships, and loss of academic activity. Detection and prevention of bipolar tendencies early is important for the mental health of children and adolescents. Although it is ideal to examine a clinical patient who is experiencing actual illness, it is also necessary for mental health professionals to assess subclinical status. According to recent evidence related to the spectrum of bipolarity, this study included non-clinical participants of young adults to screen bipolar mood liability. It is particularly interesting that some brain mechanisms underlying bipolarity have been investigated, and recent advances in neuroimaging might enable us to explore the neural bases of mood conditions. For instance, earlier functional magnetic resonance imaging (fMRI) studies of mania have demonstrated decreased functioning of the ventrolateral prefrontal cortices (vlPFC),^{1,4} as well as increased activation of the amygdala.⁵ Foland-Ross *et al.*⁶ reported that vlPFC hypoactivation might represent a trait-related neural disturbance in bipolar disorder (BD). In contrast, Robinson *et al.*⁷ proposed state-related amygdala activity and prefrontal hyperactivation when BD patients are asymptomatic, given the reciprocal relation between the PFC and limbic structures. Using near-infrared spectroscopy, Kameyama *et al.*⁸ reported that blood volume changes occurring with BD were smaller than healthy controls during the early period of a verbal fluency task, larger than major depression and control groups during the late period of this task, characterized by a preserved but delayed pattern. Near-infrared spectroscopy (NIRS) and the newly developed optic brain functional imaging are promising techniques because of their non-invasiveness and convenience. NIRS employs near-infrared light emitted and detected on the skull skin.⁹ It allows the monitoring of hemodynamic changes, which include both cerebral blood volume changes and oxygenation state, using a small apparatus with a high time resolution of about 0.1 s. It also allows the monitoring of changes in both oxygenated hemoglobin concentration [o-Hb] and deoxygenated hemoglobin concentration [d-Hb]. NIRS is suitable for studies of higher brain function because it enables measurements in a natural setting compared with other brain imaging techniques. For example, subjects can undergo an NIRS examination in the sitting position, with their eyes open, or while speaking.¹⁰ Taking advantage of these characteristics, several NIRS studies on psychiatric disorders, such as schizophrenia,^{11,12} depression,¹³ eating disorders,^{14,15} and ADHD disorder,¹⁶ have been conducted. These characteristics of NIRS have also enabled the investigation of subjective experiences in healthy subjects such as conversation, subjective sleepiness, and psychological fatigue.¹⁷⁻¹⁹ The present study aimed to examine cortical activation using a verbal fluency

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Key words: Bipolar spectrum; mood liability; frontal functioning; campus health.

Contributions: TU designed the study, wrote the protocol, and wrote the first draft of the manuscript; TU and YI performed statistical analyses and managed the health examination; all authors contributed to and have approved the final manuscript.

Conflict of interest: the authors declare no potential conflict of interest.

Funding: Funding for this study was provided by a Grant-in-Aid for scientific research, KAKEN (C), 21591504, 2009-2011. The Japan Society for the Promotion of Science had no further role in study design, in the collection, analysis and interpretation of data, in the writing of the report, or in the decision to submit the paper for publication.

Conference presentation: the summary of this data has been presented at the World Psychiatric Associations Regional Meeting in Bali on September 13-15 2012.

Received for publication: 18 December 2014.

Accepted for publication: 12 March 2015.

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Mental Illness 2015; 7:5767
doi:10.4081/mi.2015.5767

task, which has been applied widely in clinical and nonclinical samples as a standard and specific paradigm to activate the frontal lobe. We used a newly developed multi-channel NIRS machine specified for frontal regions to explore differences in frontal activation according to the bipolar mood swing tendency. In addition, we examined correlations among frontal functioning and bipolarity score measured by self-report. Subclinical bipolar tendency might be expressed identically or continuously with previous clinical findings with respect to their NIRS characteristics.

Materials and Methods

Participants

The study participants were 44 healthy uni-

versity students (32 females, 2 left-handed), with a mean age of 20.5 years (18-24 years, $SD=2.0$). They were all Japanese, and two students were left-handed. None of the participants had any significant medical/psychiatric history. The participants were voluntarily recruited as subjects for this scientific study, and were paid 1600 yen for a 2 hours exam as a co-operator as per the official provision. All subjects gave written informed consent prior to their participation in the study, which conformed with the provisions of the Declaration of Helsinki revised in Edinburgh in 2000. Privacy and anonymity of all participants were carefully preserved. The data was collected from August to December in 2009 and 2010.

Mood Disorders Questionnaire

The Mood Disorders Questionnaire (MDQ) is a three-part self-report questionnaire that screens for a lifetime history and a current symptoms of manic or hypomanic episodes: the first part contains 13 items to assess symptoms related to bipolar mood swings; the second part is a question about the co-occurrence of two or more symptoms; and the third part is a 4-Lickert scale about the extent to which symptoms have caused functional impairment.²⁰ One of the Japanese versions of MDQ was developed by the Niigata University Group,²¹ and it was completed by all participants. The 13-item self-report questions for symptoms were scaled as to two level (yes 1, no 0) in the present study. We defined a positive MDQ screen as a minimum of seven of 13 co-occurring symptoms resulting moderate or more functional impairment; however, no bipolar disorder was suspected from use of this MDQ.

Near-infrared spectroscopy

Near-infrared spectroscopy (NIRS, Figure 1) allows the calculation of changes in Hb parameters, including [o-Hb] and [d-Hb], by measuring the attenuation of near-infrared light at an approximate 800 nm wavelength. Neural activation induces regional hemodynamic changes in brain tissue, almost identical in pattern to spontaneous cerebral neural activity. Cortical activation is typically detected as an [o-Hb] increase or an [d-Hb] decrease; however, the direction of change in [d-Hb] can be ambiguous in the frontal lobe.²² Mainly changes in [o-Hb] at a depth of 2-3 cm from the scalp, that is, the surface of the cerebral cortex, are correlated with positron emission tomography (PET) hemodynamic changes and blood-oxygenation-level-dependent signal changes in fMRI.²³⁻²⁵ NIRS does not measure cerebral luminescence but measures the attenuation of irradiated light intensity. Therefore, the combination of optical irradiation and photon detection determines the resolution. It characteristically measures not the 1:1 combination of irradiation and detection,

but the light from one light source with 2 or more detectors arranged geometrically in the measurement system of NIRS. Thus, information on which detector measures the signal of which portion becomes important. Some methods are available for judging this channel separation. The first method, time division multiple access, makes a light source turn on in order, and separates the signal on a time axis. The second method, frequency division multiple access, is for modulating and irradiating two or more light sources with different frequencies and separating a signal based on frequency information after detection. The third

method is code division multiple access (CDMA), using spectrum diffusion attenuation, which is applied in such applications as global positioning system or mobile phone. A new machine, OEG-16 (Spectratech, Inc, Yokohama, Japan), uses CDMA and is very convenient and portable. It can generate NIRS data under natural conditions noninvasively, and artifacts induced by hair can be avoided because of the adjustments only on the front of the head. The OEG-16 measures 16 channels on the frontal lobe (according to Brodman's map, provides data on 10, 11, 12, 44, 45, and 46). Its time resolution is 0.5 s, and space res-

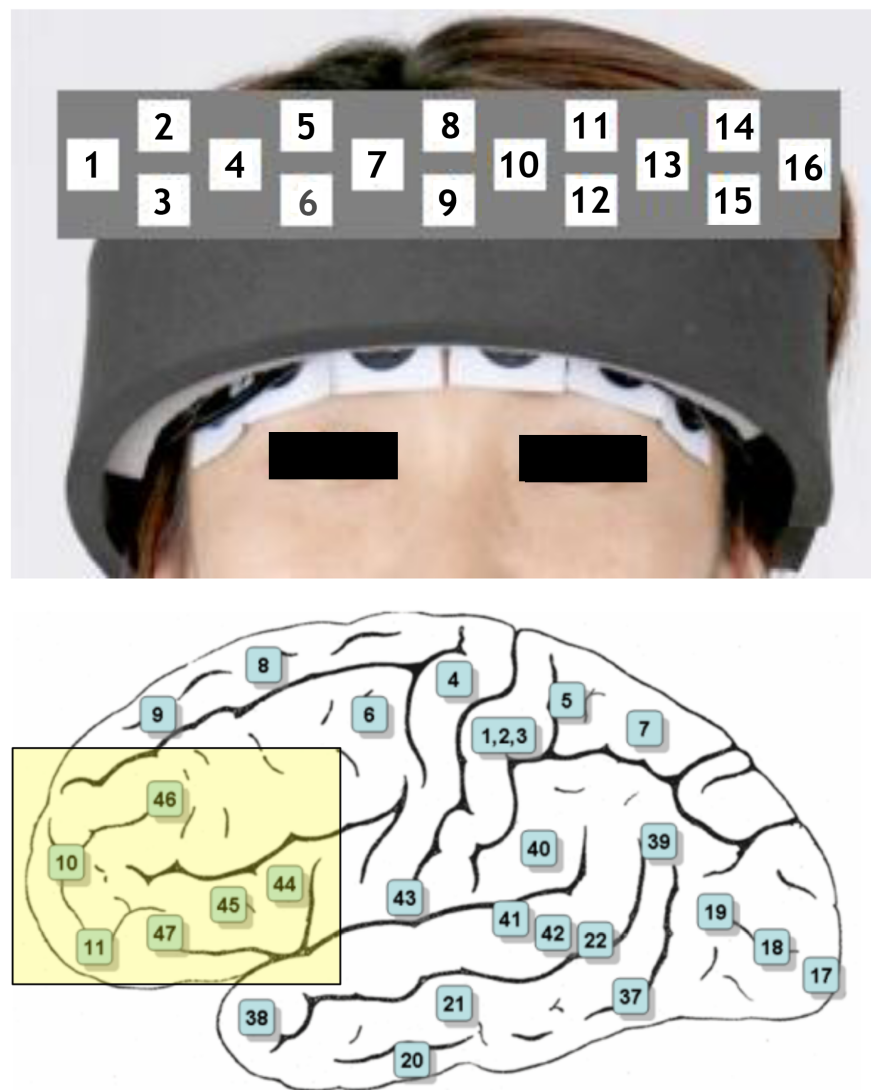


Figure 1. Measuring points and headset (Spectratech, Inc.) and correspondent brain regions (yellow square) according to the Brodman's areas.

olution is 2 cm. A headset was placed on the participant's head according to the 10/20 system, by which a central hole was coordinated with Fz. The measurement points for channels 1 to 8 were placed from the right lateral to the central pole. For channels 9 to 16, the measurement points were placed from the ventral/rostral to the left lateral (refer to the video content). These placements provided for relative changes in Hb concentration, and the values obtained were in arbitrary units (concentration \times path length). Details of NIRS methodology have already been described in major publications in Japan.²⁶

Verbal fluency task

This standardized activation task is employed internationally for NIRS measurements, and it has been confirmed that this method provides widespread frontal activation reliably.²⁷⁻²⁹ The frontal activation task was a modified version of the verbal fluency task. A subject sat on a comfortable chair in a quiet room with their eyes open throughout the measurement. The activation task consisted of a 15-s pre-task baseline, a 30-s verbal fluency period, and a 15-s post-task baseline. During the verbal fluency period, the subjects were instructed to verbally generate as many words as they could whose initial Japanese syllable (mora) was either /a/, /ki/, or /ha/. These three initial syllables were used in the above-mentioned order and changed every 10 s during the 30-s verbal fluency period to reduce the time during which the subjects remained silent. The number of words generated during the verbal fluency period was determined as a measure of task performance. During the pre-task and post-task baseline periods, the subjects were instructed to repeat the syllables /a/, /i/, /u/, /e/, and /o/ as the Japanese counterparts of A, B, and C in English. Two sets of this task were performed, and the respective data were superimposed and averaged.

Data analysis

The continuous waveforms of the Hb changes on all 16 channels were acquired from all subjects during the paradigm. The individually averaged Hb waveforms were obtained as the average sum of two trials; a baseline realignment for 5 s before and after the task periods, and a task segment averaging two sets of 15-s image viewing periods. Thereafter, the grand average values of the baseline and task segments for each channel were calculated for all data. Figure 2 indicates grand average waveforms for three parameters; the red polygonal line indicates the relative changes in [o-Hb], the blue indicates those of [d-Hb], and the green indicates the changes in the total-Hb (sum of o- and d-Hb).

We used only [o-Hb] values as cerebral blood volume changes for statistics, based on

previous reports.^{8,30} Topography (video content) was presented on the frontal portion according to the time course. In this grand average data, channels that carried significant activation were analyzed between the pre-task and task periods using the t-test (<http://www.brsystems.jp>). Differences in the mean values were tested by combined variance, as the number of samples for the two periods was not equal.

Combined variance:

$$Ue2 = \{ (na - 1) ua2 + (nb - 1) ub2 \} / \{ na + nb - 2 \}$$

Variance and numbers of sample a: ua2 and na

Variance and numbers of sample b: ub2 and nb

$$T\text{-value: } t0 = (mXa - mXb) / \sqrt{Ue2(1/na + 1/nb)}$$

Average of each sample: mXa, mXb

In the next step, differences were investigated according to dissociative tendencies followed by the t-test for each channel during the task period between the sample grand average data divided by the MDQ median scores (*high* and *low*, median = 4, mean = 3.4). In the last step, the relationships between the [o-Hb] changes and the MDQ scores were investigated using a simple correlation (nonparametric

Spearman's correlation coefficient; two-tailed). And the channels, with significantly correlated changes with bipolarity, were detected by and a linear regression analysis. The specific imaging software was used to analyze the NIRS parameters (Data Viewer ver.1.1a, BR Systems Inc., Tokyo, Japan). The other statistical analyses were conducted using SPSS version 17.0 (SPSS, Inc., Tokyo, Japan).

Results

Group comparison

Figure 2 shows grand average waveforms for the Hb changes for two groups according to the MDQ median scores (median = 4, mean = 3.4, max = 10; 26 students scored lower than 3 points on the right, and the 18 students over 4 points on the left side). The red polygonal line represents the relative changes in [o-Hb], the blue shows those of [d-Hb], and the green shows the changes in the total-Hb (sum of o-Hb and d-Hb). Their values are presented as arbitrary units (mMol \cdot mm).

Comparisons of activations between these

Table 1. Comparisons of activation between cases with high vs. low Mood Disorders Questionnaire.

Ch	MQD	Mean	SD	t	P
1	H	0.95	2.66	-0.88	0.38
	L	2.08	5.71		
2	H	0.40	1.53	-1.57	0.13
	L	2.37	6.11		
3	H	0.23	1.85	-1.82	0.08
	L	2.11	4.75		
4	H	0.20	2.66	-1.89	0.07
	L	1.99	3.58		
5	H	-0.07	1.90	-2.07	0.05
	L	1.94	4.36		
6	H	0.06	2.02	-2.13	0.04
	L	1.94	3.80		
7	H	-0.07	2.15	-2.01	0.05
	L	1.49	2.99		
8	H	-0.43	2.36	-2.02	0.05
	L	1.23	3.08		
9	H	0.23	2.74	-1.42	0.16
	L	1.76	4.38		
10	H	0.52	2.38	-1.46	0.15
	L	2.13	5.85		
11	H	0.09	1.40	-2.26	0.03
	L	1.59	2.95		
12	H	1.11	4.37	-0.64	0.53
	L	1.99	4.72		
13	H	1.12	3.18	-0.72	0.47
	L	1.93	4.20		
14	H	0.37	1.26	-1.61	0.11
	L	1.19	2.11		
15	H	1.27	3.04	-0.53	0.60
	L	1.75	2.79		
16	H	0.86	2.72	-0.50	0.62
	L	1.22	1.67		

MDQ, Mood Disorders Questionnaire (divided by the median; H \geq 4, and L <3. H were 18, L were 26); SD, standard deviation.

two groups during task periods are presented in Table 1. The respective t-values and p-values for each channel are presented. Significant differences were obtained on channels (ch) in the prefrontal cortex (PFC); lower in ch5*, 6*, 11* (right to left) with higher bipolarity ($2.1 < t < 2.3$, $*P < 0.05$). However, stricter corrections negated all significances (P-values/numbers of channels). Video contents (video_MDQ_uehara.avi) depict the topography of the [o-Hb] changes (high MDQ on the left and low MDQ on the right side). Red areas represent greater activation. Gradual increases

and fluctuations were generally observed in widespread channels during the task for both groups.

Correlations among frontal activations and bipolar tendencies

The total MDQ scores were negatively correlated with activations in the many channels (ch3-7,11,14,16; $\rho > -0.33$; Figure 3). Therefore, in order to correct the multiplicity, we conducted multiple linear regression analysis to select significant frontal activations using MDQ as a dependent variable. Stepwise

method revealed that activation in ch14 (left PFC) was negatively associated with bipolar tendency ($\beta = -0.31$, $P = 0.04$); this regression model was significant ($R^2 = 0.10$, $F = 4.5$, $P = 0.04$).

Discussion and Conclusions

The present study resulted that youths with highly mood bipolarity showed less activations in bilateral broad prefrontal areas than those with the low grade group based on simple comparisons and correlations among frontal oxy-hemoglobin changes and bipolar scale scores. And a consequent precise analysis indicated the specific relationship between left lateral prefrontal deactivation and bipolar mood tendency.

According to recent fMRI findings while viewing facial expressions, the patients with bipolar disorders (BD) had hypoactivation in the dorsolateral prefrontal cortex (DLPFC) and hyperactivation in the posterior cingulate cortex compared to the healthy group.³¹ And a Japanese NIRS study indicated that both the major depressive disorder and BD groups showed decreased continuous activation in the left DLPFC and left frontopolar cortices (FPCs) during face-to-face conversation; they also showed decreased rapid change in bilateral FPC activation.³² On the other hands, Hajek *et al.*³³ conducted meta-analysis combined voxel based and cognitive performance in BD patients, and commented that the rIFG (right inferior frontal gyrus) hypoactivations were congruent with a BD trait, which may underlie the impaired response inhibition in mania. Euthymic BD subjects may compensate for rIFG hypoactivations by hyperactivations of adjacent cortical areas, therefore, it might be related to comparable performance in inhibitory functions.³³ Regarding clinical findings, BD is often associated with cognitive or executive dysfunction. Biological mechanisms of cognitive deficits in BD are not sufficiently understood although specifically the amygdala and the PFC (known to have a regulatory function over the limbic system) have been evaluated. Based on the previous investigations and our results, the PFC may remain persistently hypoactivated across mood states while amygdala has been activated. As Townsend and Altshuler reviewed,³⁴ emotional lability in mania and depression may reflect disruption of a frontal-limbic functional neuroanatomical network. Differences in frontal activation suggest that subclinical bipolar tendencies might be related to prefrontal, especially left lateral PFC, dysfunction in the present study. It should be confirmed whether the identical pattern is identifiable for clinical subjects with bipolar disorders. In fact, according to some previous

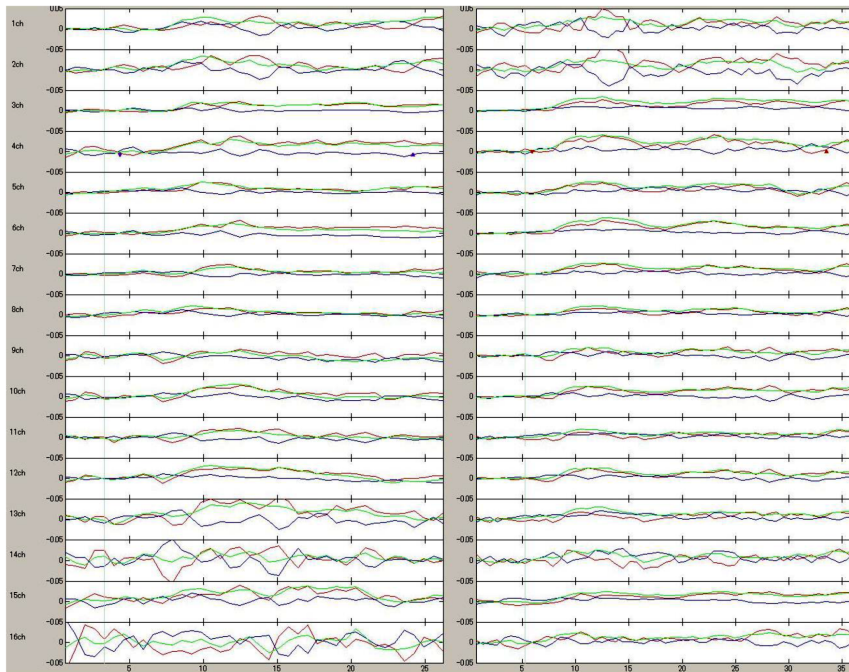


Figure 2. Graphs shows grand average waveforms for the hemoglobin (Hb) changes for two groups according to the MDQ median scores (median = 4, mean = 3.4, max = 10; 26 students scored lower than 3 points on the right, and the 18 students over 4 points on the left side). The red polygonal line represents the relative changes in [o-Hb], the blue shows those of [d-Hb], and the green shows the changes in the total-Hb (sum of o-Hb and d-Hb). Their values are presented as arbitrary units (mMol•mm).

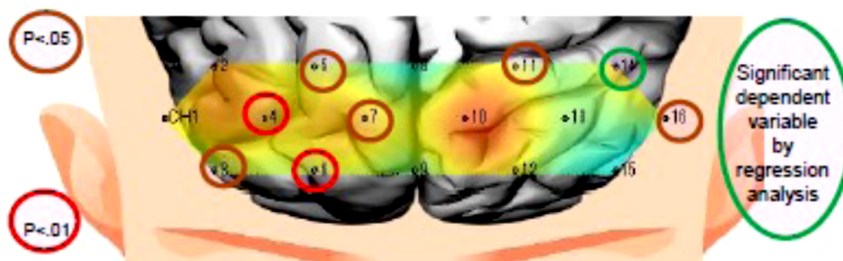


Figure 3. The total MDQ scores were negatively correlated with activations in the many channels (ch3-7,11,14,16; $\rho > -0.33$; see blown and red circles). A multiple linear regression selected significant frontal activations using MDQ as a dependent variable. Stepwise method revealed that activation in ch14 (green circle) was negatively associated with bipolar tendency ($\beta = -0.31$, $P = 0.04$); this regression model was significant ($R^2 = 0.10$, $F = 4.5$, $P = 0.04$).

NIRS studies for mental illness disorders, the BD group showed gradually increased change (preserved but delayed pattern) in bilateral FPC activation during the same verbal fluency task compared with major depressive disorder (overall reduced pattern) or schizophrenia (the initial gentler slope or post-task reactivation pattern).^{30,35,36}

The present study conducted with only healthy young participants, therefore, further study must be undertaken to examine continuum of the previous findings both participants with bipolar disorders and subclinical bipolar spectrum in a larger sample. In particular, it should be investigated whether a deactivation in left lower PFC could be important for prevention or early detection based on a prospective study. Also, the task paradigm for the NIRS should be improved for evaluative and preventive applications.

References

- Altshuler LL, Bookheimer SY, Townsend J, et al. Blunted activation in orbitofrontal cortex during mania: a functional magnetic resonance imaging study. *Biol Psychiatry* 2005;58:763-9.
- Altshuler L, Bookheimer S, Proenza MA, et al. Increased amygdala activation during mania: a functional magnetic resonance imaging study. *Am J Psychiatry* 2005;162:1211-3.
- Foland LC, Altshuler LL, Sugar CA, et al. Increased volume of the amygdala and hippocampus in bipolar patients treated with lithium. *Neuroreport* 2008;19:221-4.
- Mazzola-Pomietto P, Kaladjian A, Azorin JM, et al. R Bilateral decrease in ventrolateral prefrontal cortex activation during motor response inhibition in mania. *J Psychiatr Res* 2009;43:432-41.
- Bermpohl F, Dalanay U, Kahnt T, et al. A preliminary study of increased amygdala activation to positive affective stimuli in mania. *Bipolar Disord* 2009;11:70-5.
- Foland-Ross LC, Bookheimer SY, Lieberman MD, et al. Normal amygdala activation but deficient ventrolateral prefrontal activation in adults with bipolar disorder during euthymia. *Neuroimage* 2012;59:738-44.
- Robinson JL, Monkul ES, Tordesillas-Gutiérrez D, et al. Fronto-limbic circuitry in euthymic bipolar disorder: evidence for prefrontal hyperactivation. *Psychiatry Res* 2008;164:106-13.
- Kameyama M, Fukuda M, Yamagishi Y, et al. Frontal lobe function in bipolar disorder: a multichannel near-infrared spectroscopy study. *Neuroimage* 2006;29:172-84.
- Boas DA, Dale AM, Franceschini, MA. Diffuse optical imaging of brain activation: approaches to optimizing image sensitivity, resolution, and accuracy. *Neuroimage* 2004;23:275-88.
- Suda M, Fukuda M, Sato T, et al. Subjective feeling of psychological fatigue is related to decreased reactivity in ventrolateral prefrontal cortex. *Brain Res* 2009;1252:152-60.
- Grignon S, Forget K, Durand M, Huppert T. Increased left prefrontal activation during staring/mutism episodes in a patient with resistant catatonic schizophrenia: a near infrared spectroscopy study. *Cogn Behav Neurol* 2008;21:41-5.
- Takizawa R, Kasai, K, Kawakubo Y, et al. Reduced frontopolar activation during verbal fluency task in schizophrenia: a multichannel near-infrared spectroscopy study. *Schizophrenia Res* 2008;99:250-62.
- Matsuo K, Onodera Y, Hamamoto T, et al. Hypofrontality and microvascular dysregulation in remitted late-onset depression assessed by functional near-infrared spectroscopy. *Neuroimage* 2005;26:234-42.
- Suda M, Uehara T, Fukuda M, et al. Dieting tendency and eating behavior problems in eating disorder correlate with right frontotemporal and left orbitofrontal cortex: a near-infrared spectroscopy study. *J Psychiatry Res* 2010;44:547-55.
- Uehara T, Fukuda M, Suda M, et al. Cerebral blood volume changes inpatients with eating disorders during word fluency using multi-channel near infrared spectroscopy. *Eat Weight Disord* 2007;12:183-90.
- Ehlis AC, Bahne CG, Jacob CP, et al. Reduced lateral prefrontal activation in adult patients with attention-deficit/hyperactivity disorder (ADHD) during a working memory task: a functional near-infrared spectroscopy (fNIRS) study. *J Psychiatry Res* 2008;42:1060-7.
- Suda M, Takei Y, Aoyama Y, et al. Frontopolar activation during face-to-face conversation: an in situ study using near-infrared spectroscopy. *Neuropsychologia* 2010;48:441-7.
- Suda M, Fukuda M, Sato T, et al. Subjective feeling of psychological fatigue is related to decreased reactivity in ventrolateral prefrontal cortex. *Brain Res* 2009;1252:152-60.
- Suda M, Sato T, Kameyama M, et al. Decreased cortical reactivity underlies subjective daytime light sleepiness in healthy subjects: a multichannel near-infrared spectroscopy study. *Neurosci Res* 2008;60:319-26.
- Hirschfeld RM, Williams JB, Spitzer RL, et al. Development and validation of a screening instrument for bipolar spectrum disorder: the Mood Disorder Questionnaire. *Am J Psychiatry* 2000;157:1873-5.
- Murayama K, Imai Y, Uenoyama Y, et al. [An investigation of the mental health examination in Niigata University]. *Campus Health* 2009;46:320-1. [Article in Japanese].
- Sato T, Ito M, Suto T, et al. Time courses of brain activation and their implications for function: a multichannel near-infrared spectroscopy study during finger tapping. *Neurosci Res* 2007;58:297-304.
- Ohmae E, Ouchi Y, Oda M, et al. Cerebral hemodynamics evaluation by near-infrared time-resolved spectroscopy: correlation with simultaneous positron emission tomography measurements. *Neuroimage* 2006;29:697-705.
- Toronov V, Webb A, Choi JH, et al. Investigation of human brain hemodynamics by simultaneous near-infrared spectroscopy and functional magnetic resonance imaging. *Med Phys* 2001;28:521-7.
- Mehagnoul-Schippier DJ, van der Kallen BF, Colier WN, et al. Simultaneous measurements of cerebral oxygenation changes during brain activation by near-infrared spectroscopy and functional magnetic resonance imaging in healthy young and elderly subjects. *Hum Brain Mapp* 2002;16:14-23.
- Fukuda M, ed. *Clinical evaluation of NIRS data*. Tokyo: Nakayama Shoten; 2011.
- Kono T, Matsuo K, Tsunashima K, et al. Multiple-time replicability of near-infrared spectroscopy recording during prefrontal activation task in healthy men. *Neurosci Res* 2007;57:504-12.
- Schecklmann M, Ehlis AC, Plichta MM, et al. Functional nearinfrared spectroscopy: a long-term reliable tool for measuring brain activity during verbal fluency. *Neuroimage* 2008;43:147-55.
- Kakimoto Y, Nishimura Y, Hara N, et al. Intrasubject reproducibility of prefrontal cortex activities during a verbal fluency task over two repeated sessions using multi-channel near-infrared spectroscopy. *Psychiatry Clin Neurosci* 2009;63:491-9.
- Suto T, Fukuda M, Ito M, et al. Multichannel near-infrared spectroscopy in depression and schizophrenia: cognitive brain activation study. *Biol Psychiatry* 2004;55:501-11.
- Garrett AS, Miklowitz DJ, Howe ME, et al. Changes in brain activation following psychotherapy for youth with mood dysregulation at familial risk for bipolar disorder. *Prog Neuropsychopharmacol Biol Psychiatry* 2014;56C:215-20.
- Takei Y, Suda M, Aoyama Y, et al. Near-infrared spectroscopic study of frontopolar activation during face-to-face conversa-

- tion in major depressive disorder and bipolar disorder. *J Psychiatr Res* 2014;57:74-83.
33. Hajek T, Alda M, Hajek E, et al. Functional neuroanatomy of response inhibition in bipolar disorders--combined voxel based and cognitive performance meta-analysis. *J Psychiatr Res* 2013;47:1955-66.
34. Townsend J, Altshuler LL. Emotion processing and regulation in bipolar disorder: a review. *Bipolar Disord* 2012;14:326-39.
35. Takizawa R, Fukuda M, Kawasaki S, et al. Neuroimaging-aided differential diagnosis of the depressive state. Joint Project for Psychiatric Application of Near-Infrared Spectroscopy (JPSY-NIRS) Group. *Neuroimage* 2014;85:498-507.
36. Kinou M, Takizawa R, Marumo K, et al. Differential spatiotemporal characteristics of the prefrontal hemodynamic response and their association with functional impairment in schizophrenia and major depression. *Schizophr Res* 2013;150:459-67.