4.3. Limitations

Some comment upon methodological considerations is necessary. First, the continuous-wave NIRS enables measurement of Hb concentration changes not as absolute values but as measures relative to pre-task baseline. Therefore we cannot empirically rule out the possibility that the present findings may be due to a difference in prefrontal blood volume during the pre-task period (i.e., *hyper*perfusion in the pre-task period in schizophrenia). However, PET studies have found significant *hypo*perfusion during the resting state in the frontal areas of schizophrenia as compared to healthy controls (Hill et al., 2004). More recently, a near-infrared time-resolved spectroscopy study replicated a hypoperfusion in the resting state in patients with schizophrenia (Hoshi et al., 2006). Thus, decreased activation during the cognitive task was not likely to be due to a saturated hemodynamic state in the pre-task baseline in schizophrenia. Second, although we did not find a significant correlation between [oxy-Hb] change and dose of medication, we cannot fully rule out the possible effect of antipsychotics in the observed prefrontal activation in schizophrenia patients. Third, our study design was cross-sectional and used chronic patients. Investigations into longitudinal relationship between NIRS and functional outcome should be an important next step. Fourth, spatial resolution for detecting hemodynamic response from the scalp surface using NIRS is lower than that of fMRI and PET. Future investigations should conduct a simultaneous measurement of NIRS and fMRI, which is technically possible (Strangman et al., 2002b), using a cognitive task directly segregating frontopolar, dorsolateral, and ventrolateral prefrontal cortex (Koechlin et al., 1999).

Further, the difficulty in making a real-time measurement of the accurate differential pathlength factor (DPF) in vivo is one of the major considerations regarding data accuracy of NIRS method. In this continuous-wave NIRS system, "hemoglobin concentration change*DPF" ($\Delta C*L$) is calculated as a solution to the simultaneous equations based on the modified Beer–Lambert law.

It should be also noted that controversies exist regarding DPF in NIRS measurement. Some researchers have estimated the DPF value by one-channel time-resolved NIRS system and have incorporated it into the calculation of the modified Beer–Lambert law. However, if one uses a one-channel time-resolved NIRS system, one could detect the sum of 'partial optical pathlengths' within the cerebral and extracerebral tissues' in another session, but could not make a real-time measurement of the precise 'optical pathlength within the cerebral tissue' (Hoshi, 2003). Since commonly used NIRS systems employ the multiple wavelengths, the incorporation of one constant DPF value of a certain wavelength estimated from one-channel time-resolved NIRS system into the calculation of the modified Beer–Lambert law in all the multi-channels would not necessarily mean the improvement of accuracy. It is for this reason that we examined the NIRS signals including DPF ($\Delta C*L$) with clinical evaluation in schizophrenia, according to the previous researches that have reported the results of $\Delta C*L$ closely agreed with various clinical data (Fallgatter et al., 1997; Kameyama et al., 2006; Matsuo et al., 2002; Suto et al., 2004).

Meanwhile, Zhao et al. (2002) used a Monte Carlo simulation to report the estimated DPF in various brain regions and suggested that the estimated DPF variation in the forehead region of adult humans was regarded as roughly homogeneous (in accordance with Ferrari et al., 1993). Also, from a practical point of view, the characteristics of time course pattern in the NIRS signals ($\Delta C*L$) of the prefrontal cortex was found to be significantly different between mental disorder groups and healthy control group during verbal fluency task, but not during motor activation task (finger tapping that is cognitively less-demanding task) (Kameyama et al., 2006; Suto et al., 2004). These results suggest that only the difference of DPF could not account for the between-group difference in the NIRS signals ($\Delta C*L$) of the prefrontal cortex during verbal fluency task.

However, to improve the accuracy of NIRS data, when feasible, the technology for the real-time measurement of the estimated DPF at each channel and the incorporation into the calculation of the modified Beer–Lambert law would be an issue for the future NIRS study.

4.4. Conclusions

In conclusion, our study suggested reduced hemodynamic response in frontopolar sub-region of prefrontal cortex during executive task and its relationship with functional impairment in patients with schizophrenia. NIRS may be a candidate biological marker for objectively monitoring the functional level in schizophrenia which may be potentially useful not only for clinicians, but also for consumers and families with severe mental illness such as schizophrenia.

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Japan Society for the Promotion of Science and the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labor and Welfare had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Contributors

Ryu Takizawa, Kiyoto Kasai, Masato Fukuda designed the study and wrote the protocol. Ryu Takizawa and Kiyoto Kasai undertook the statistical analysis. Ryu Takizawa, Kiyoto Kasai, Yuki Kawakubo, and Kohei Marumo conducted data acquisition. Ryu Takizawa, Kiyoto Kasai, Shingo Kawasaki, and Hidenori Yamasue analyzed the data. Ryu Takizawa and Kiyoto Kasai wrote the first draft of the manuscript, and the other authors revised it critically for important intellectual content. All authors have approved the final version of the manuscript.

Conflict of interest

Drs. Kasai, Kawasaki, and Fukuda have potential conflict of interest (please see below for details). Other authors have no relevant conflict of interest.

Dr. Kiyoto Kasai: Since July 31, 2003 through present, the University of Tokyo and The Research and Developmental Center, Hitachi Medical Corporation has had an official contract for a collaborative study on clinical application of near-infrared spectroscopy in psychiatric disorders, which has been approved by the Research Promotion Office, University of Tokyo Hospital. The principal investigator of this study is Kiyoto Kasai. For this study, Hitachi Medical Corporation provided a project grant (JPY 300,000/year) and material support (temporary rental of a near-infrared spectroscopy (Optical Topography) machine, ETG-4000).

Dr. Shingo Kawasaki: His contribution to this study was in part thorough his role as an employee of Hitachi Medical Corporation. Since May 17, 2002 through present, Gunma University and Hitachi Group (Advanced Research Laboratory, Hitachi Ltd. and the Research and Developmental Center, Hitachi Medical Corporation) have had the official contract for a collaborative study on clinical application of near-infrared spectroscopy in psychiatric disorders. The principal investigator of this study is Masato Fukuda. For this study, Hitachi Group provides a project grant (JPY 1,000,000–1,500,000/year) and material support (temporary rental of a near-infrared spectroscopy (Optical Topography) machine, ETG-4000). Since July 31, 2003 through present, Tokyo University and Hitachi Medical Corporation (Application Development Office, Optical Topography Group) have had an official contract for a collaborative study on clinical application of near-infrared spectroscopy in psychiatric disorders. The principal investigator of this study is Kiyoto Kasai. For this study, Hitachi Medical Corporation provided a project grant (JPY 300,000/year) and material support (temporary rental of a near-infrared spectroscopy (Optical Topography) machine, ETG-4000).

Dr. Masato Fukuda: Since May 17, 2002 through present, Gunma University and Hitachi Group (Advanced Research Laboratory, Hitachi Ltd. and The Research and Developmental Center, Hitachi Medical Corporation) has had an official contract for a collaborative study on clinical application of near-infrared spectroscopy in psychiatric disorders. The principal investigator of this study is Masato Fukuda. For this study, Hitachi Group provided a project grant (JPY 1,000,000–1,500,000/year) and material support (temporary rental of

a near-infrared spectroscopy (Optical Topography) machine, ETG-4000).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.schres.2007.10.025.

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Decreased cortical reactivity underlies subjective daytime light sleepiness in healthy subjects: A multichannel near-infrared spectroscopy study

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Abstract

Daytime sleepiness is considered to be one of the main problems in modern society. Of the four aspects of sleepiness, namely, subjective sleepiness, performance decrease, sleep propensity, and arousal decrease, subjective sleepiness is the most difficult to assess. Brain mechanisms underlying subjective light sleepiness in daytime were investigated in healthy subjects using multichannel near-infrared spectroscopy (NIRS), which enables the noninvasive measurement of regional cerebral blood volume (rCBV) changes under natural conditions. Forty right-handed healthy volunteers participated in this study. Relationships were investigated between subjective sleepiness and anxiety, assessed using the Stanford Sleepiness Scale (SSS) and State-Trait Anxiety Inventory (STAI), respectively, and cerebral cortex reactivities assessed as oxygenated and deoxygenated hemoglobin concentration ([oxy-Hb] and [deoxy-Hb], respectively) changes during a verbal fluency task using a 24-channel NIRS machine. SSS score correlated negatively with an [oxy-Hb] increase in the bilateral frontal channels mainly in the middle and last third of the verbal fluency task period. Subjective light daytime sleepiness in healthy subjects is considered to be related to decreased prefrontal reactivities in the later part of cognitive activation.

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Keywords: Near-infrared spectroscopy; Sleepiness; Alertness; Verbal fluency task; Frontal lobe function; Anxiety; Neuroimaging

1. Introduction

Sleepiness is considered to be one of the main problems in modern society because it often precipitates accidents in the workplace, traffic on roadways, and during military, exercises, and can even cause disasters such as traffic accidents human injuries causing a loss of life and meltdowns in nuclear power stations (Åkerstedt, 1995; Dement and Gelb, 1993; Léger, 2000; Metlaine et al., 2005). Sleepiness is measured in terms of four aspects (Curcio et al., 2001): subjective sleepiness, performance decrease, sleep propensity, and arousal decrease.

Although the latter three aspects of sleepiness can be assessed quantitatively using neuropsychological, behavioral, and neurophysiological methods, respectively, subjective sleepiness is still difficult to assess.

Brain mechanisms underlying sleepiness have been studied in the resting and activation states. In studies examining sleepiness in the resting state, the relationship between cerebral blood flow, determined by positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), and alpha activity, determined by electroencephalography (EEG), was investigated (Oakes et al., 2004; Feige et al., 2005; Goldman et al., 2002; Laufs et al., 2003a, 2006; Goncalves et al., 2006). These studies showed that alpha wave power determined by EEG in the resting state correlates negatively with blood flow in the cerebral cortex including the frontal lobe

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and correlates positively with blood flow in subcortical structures including the thalamus. These findings suggest that sleepiness is related to a decreased cerebral cortex activity and an increased subcortical activity.

In most of the studies of sleepiness in the activation state, the subjects were examined after sleep deprivation using fMRI, and inconsistent results were obtained. Increased cerebral blood flow has been reported during verbal learning (Drummond et al., 2000), short-term attention (Portas et al., 1998), divided attention (Drummond et al., 2001), and grammatical reasoning tasks after total sleep deprivation (Drummond et al., 2004). In contrast, decreased cerebral blood flow has been reported during arithmetic (Drummond et al., 1999) and verbal working memory tasks (Mu et al., 2005a,b). In addition, both increased and decreased cerebral blood flows have been reported during verbal (Chee and Choo, 2004; Habeck et al., 2004) and nonverbal (Bell McGinty et al., 2004) item recognition tasks. These inconsistent results are interpreted as follows: enhanced activation represents the compensatory recruitment of resources and attenuated activation may reflect the cognitive dysfunction associated with performance deficits after sleep deprivation (Drummond et al., 2005).

Considering the importance of the prevention of accidents due to sleepiness, studies of daytime light sleepiness, that is, declined alertness, are required in healthy subjects in the activation state under their natural conditions. As far as we have surveyed, however, there have been no studies focusing on subjective light sleepiness in daytime under natural conditions, that is, not after sleep deprivation, using an activation design. Near-infrared spectroscopy (NIRS), one of the more recently available functional brain imaging techniques, is considered to be suitable for such studies because it enables measurement in a natural setting as compared with other functional brain imaging techniques such as PET and fMRI (Strangman et al., 2002; Boas et al., 2004; Fallgatter et al., 2004). It allows the monitoring of cerebral blood volume changes, as an increase in oxygenated hemoglobin concentration ([oxy-Hb]) and a decrease in deoxygenated hemoglobin concentration ([deoxy-Hb]), in subjects in a sitting position with their eyes open. There is only one study in which NIRS was employed for examining sleepiness (Moosmann et al., 2003). In that study [deoxy-Hb] showed a positive correlation with the alpha wave power measurement 8 s before.

Here, we examined the association between subjective daytime light sleepiness, alertness, and frontal lobe reactivity during cognitive and motor activations using multichannel NIRS, which enables measurement in a natural experimental setting, in healthy subjects. We hypothesize that subjective sleepiness negatively correlates with frontal lobe reactivity during cognitive activation because sleepiness has been shown to be related to a decreased cerebral cortex activity if examined in ordinary daily living, as contrasted to increased cerebral cortex activity due to compensatory mechanism after sleep deprivation, as mentioned above. We also examined the relationship between subjective anxiety and frontal lobe reactivity at the time of the study because light sleepiness and anxiety are assumed to be inversely interrelated as indicated, for example, by sleep disturbance as one of the six main symptoms included in the criteria of

generalized anxiety disorder (APA, 2000) and by both the sleep-inducing and anxiolytic effects of most benzodiazepines (e.g., Rudolph and Möhler, 2006).

2. Materials and methods

Forty healthy volunteers participated in this study (20 males and 20 females; age: mean, 33.6 years; S.D., 8.4; range, 23–52; years of education: mean, 16.8 years; S.D., 2.4; range, 12–22). All the subjects were determined to be right-handed using the Edinburgh Handedness Inventory scale (Oldfield, 1971). All the participants were interviewed by one of the experimenters to evaluate their depressive mood. They had no history of any sleep disorder including sleep apnea, major psychiatric disorder including major depressive disorder and anxiety disorder, neurological disorder, substance abuse, head injury, or major physical illness, and they were not on any psychotropic medications at the time of the study. This study was approved by the Institutional Review Board of Gunma University Graduate School of Medicine. Written informed consent was obtained from all the subjects prior to the study. Twenty-nine of the forty subjects also participated in our previous study (Kameyama et al., 2004).

Their subjective sleepiness and subjective state of anxiety at the time of the study were evaluated immediately after the task as the score of the Stanford Sleepiness Scale (SSS) (Hoddes et al., 1971) and as the state anxiety score of the Japanese version of the State-Trait Anxiety Inventory (STAI) (Spielberger et al., 1970; Nakazato and Mizuguchi, 1982), respectively. SSS is one of the most frequently employed scales to assess the subjective perception of daytime sleepiness in healthy subjects. It consists of a seven-point scale ranging from 1 (*feeling active and vital; alert; wide awake*) to 7 (*lost struggle to remain awake*). Respondents select one option that best describes how sleepy they feel during the test. STAI is one of the most frequently employed scales to assess the state and trait subjective anxiety in healthy subjects and consists of a four-point scale ranging from 1 to 4. We used the state anxiety score of STAI for the subjective anxiety of the subjects at the time of examination. The experiments were conducted in the daytime, that is between 10 a.m. and 7 p.m. (mean, 2:30 p.m.; S.D., 2.4 h). The subjects were instructed to keep their eyes open throughout the experiment which was monitored by the experimenter.

2.1. Activation tasks

Hemoglobin concentration changes were measured during cognitive and motor activations. Each subject sat on a comfortable chair in a daylight room with his or her eyes open throughout each measurement. Cognitive activation consisted of a 30-s pretask baseline, a 60-s verbal fluency task, and a 60-s posttask baseline. During the verbal fluency task, the subjects were instructed to verbally generate as many words whose initial syllable was either /a/, /ka/, or /sa/ as they could. These three initial syllables were employed in the above-shown order and changed every 20 s during the 60-s task to decrease the time during which the subjects remained silent. The number of words generated during the verbal fluency task was determined as a measure of task performance. The subjects were instructed to repeat the syllables /a/, /i/, /u/, /e/, and /o/ during the pretask and posttask baseline periods as the Japanese counterparts of A, B and C in English.

Motor activation was employed as a control task unrelated to cognitive activity and consisted of a 30-s pretask rest, a 40-s left-finger-tapping task, and a 30-s posttask rest. The left-finger-tapping was selected because skilled movement of the dominant hand, that is, right-finger-tapping, may cause exceptionally smaller or larger brain activations than other unskilled movements. The subjects were instructed to tap their four fingers with their thumb in turn as quickly and accurately as they could. They practiced the left-finger-tapping after receiving the instructions for the task, and it was confirmed that they could perform the task correctly.

2.2. NIRS measurements

2.2.1. NIRS machine

In this study, changes in [oxy-Hb] and [deoxy-Hb] were measured using a 24-channel NIRS machine (Hitachi ETG-100) at two wavelengths of near-infrared light (i.e., 780 and 830 nm) whose absorption was measured,

and [oxy-Hb] and [deoxy-Hb] were calculated. The distance between the pair of emission and detector probes was 3.0 cm, and it was considered that the machine could measure points at a depth of 2–3 cm from the scalp, that is, the surface of the cerebral cortex (Hock et al., 1997; Toronov et al., 2001).

2.3. Probe positions and measurement points

The probes of the NIRS machine were placed on the subject's frontal region. The frontal probes measured hemoglobin concentration changes at 24 measurement points in a 9 cm × 9 cm area, with the lowest probes positioned along the Fp1–Fp2 line according to the international 10/20 system used in electroencephalography. The measurement points were labeled Channel 1 to Channel 24 from top to bottom. The correspondence between the probe positions and the measurement points on the cerebral cortex was confirmed by superimposing the probe positions on a magnetic resonance image of a three-dimensionally reconstructed cerebral cortex of a representative subject in the healthy control group, and the correspondence was also supported by a multisubject study of anatomical craniocerebral correlation (Okamoto et al., 2004).

2.4. Measurement parameters

The absorption of near-infrared light was measured with a time resolution of 0.1 s. The obtained data were analyzed using the "integral mode". The pretask baseline was determined as the mean across the last 10 s of the 30-s pretask period, the posttask baseline was determined as the mean across the last 5 s of the 50 and 5-s posttask periods for the cognitive and motor activations, respectively, as described previously (Suto et al., 2004; Ito et al., 2005; Kameyama et al., 2006). Linear fitting was applied to the data between these two baselines. The moving average method was used to exclude short-term motion artifacts in the analyzed data (moving average window: 5 s).

2.5. Data analysis

The waveforms of [oxy-Hb] and [deoxy-Hb] changes were acquired from all the subjects in all 24 channels during the cognitive and motor activations. NIRS data that clearly contained motion artifacts determined by a close observation of the subjects were excluded from further analyses.

2.6. Cognitive activation task

Hemoglobin concentration ([Hb]) data in the channels with low signal-to-noise (S/N) ratios were excluded from further statistical analysis when their standard deviations during the pretask period exceeded 0.012. The S/N ratios of [Hb] data in five channels, namely, channels 1–3 and 5–6, were lower than this criterion because the channels positioned over hair-covered areas tended to show low ratios owing to the paucity of near-infrared light detected.

[Hb] data during the cognitive activation were analyzed in two steps. In the first step, the channels with significant [Hb] changes were identified. The individually averaged [Hb] waveforms were divided into the following three time segments: the 'pretask' segment for 10 s before the verbal fluency period, the 'task segment' for 60 s during the task period, and the 'posttask' segment for 60 s after the task period. The averages of [Hb] data within the three segments were calculated and analyzed using one-way repeated measures of analysis of variance (RANOVA) with significance level correction using the false discovery rate method (Singh and Dan, 2006). The channels were considered to be activated by the verbal fluency task when the segment factor in the RANOVA showed a significant effect and their [Hb] values during the pretask and task segments were significantly different as determined by the post hoc *t*-test with Bonferroni correction.

In the second step, for the channels with significant [Hb] changes, the relationships of the [oxy-Hb] and [deoxy-Hb] changes with subjective sleepiness and anxiety were analyzed using multiple regression analyses with the averages of [oxy-Hb] and [deoxy-Hb] during the task period as dependent variables, and the scores of SSS and STAI, task performance, sex and age of the subjects as independent variables, in order to exclude the effects of sex, age, and task performance in this task (Kameyama et al., 2004). When the regression coefficients were significant, the time courses of the relationship between [Hb]

changes and the independent variables were examined in more detail by dividing the task period into three time segments along the time course, that is, "task 1", "task 2", and "task 3" segments for the first, second, and third 20-s periods, respectively. After averaging [oxy-Hb] and [deoxy-Hb] data for each subject over these three time segments, multiple regression analysis was similarly conducted.

2.7. Motor activation task

[Hb] data obtained during motor activation were analyzed similarly to [Hb] data obtained during cognitive activation, except that the task period was divided into two time segments, that is, "task 1" and "task 2" segments for the former and latter 20-s periods, respectively.

3. Results

3.1. Behavioral data

The SSS and STAI scores and task performances of the verbal fluency task are listed in Table 1. The performance of the verbal fluency task marginally correlated with SSS score (rho = −0.31, *P* = 0.052) but not with STAI score (rho = −0.104, *P* = 0.524). There were no significant correlations between SSS and STAI scores (rho = 0.025, *p* = 0.88).

3.2. Cognitive activation task

3.2.1. [Hb] changes during the task (Fig. 1)
[Hb] during the verbal fluency task significantly increased in seventeen channels (i.e., channels 7 and 9–24; *F* = 5.9–47.7, *P* < 0.02) for [oxy-Hb] but not in any channel for [deoxy-Hb].

3.2.2. Correlations of [Hb] changes with subjective sleepiness and anxiety
In the multiple regression analysis [oxy-Hb] changes during the verbal fluency task negatively correlated with task performance in four channels (i.e., channels 7, 13, 17, and 20; beta = −0.412 to −0.292, *P* = 0.008–0.044), SSS score in eight channels (i.e., channels 7, 12–13, 15–17 and 20–21; beta = −0.501 to −0.312, *P* = 0.001–0.043), subjects' age in two channels (i.e., channels 21 and 24; beta = −0.378, *P* = 0.024–0.028), and subjects' sex in eight channels (i.e., channels 12–13, 15–17, and 19–21; beta = −0.373 to −0.315, *P* = 0.02–0.044). [oxy-Hb] changes did not correlate with STAI score in any channel.

Further multiple regression analysis, in which the verbal fluency task period was divided into three time segments, demonstrated in more detail the time courses of the correlations of [oxy-Hb] changes with SSS score: task 2 (beta = −0.385, *P* = 0.023) and task 3 (beta = −0.463, *P* = 0.004) time segments in Channel 7, task 1 (beta = −0.338, *P* = 0.035) and task 3 (beta = −0.342, *P* = 0.033) segments in Channel 12, task 1 (beta = −0.468, *P* = 0.004), task 2 (beta = −0.463, *P* = 0.003) and task 3 (beta = −0.485, *P* = 0.002) segments in Channel 13, task 2 (beta = −0.304, *P* = 0.05) and task 3 (beta = −0.335, *P* = 0.029) segments in Channel 15, task 2 (beta = −0.313, *P* = 0.045) segment in Ch 16, task 1 (beta = −337, *P* = 0.035), task 2 (beta = −0.326, *P* = 0.04) and task 3 (beta = −0.377,

Table 1
Summary of subjects

Case no.	Sex	Age	SSS	STAI	VFT
1	M	27	2	45	12
2	M	27	2	47	35
3	M	27	3	22	14
4	M	28	1	26	18
5	M	29	2	44	20
6	M	29	2	33	16
7	M	29	2	41	17
8	M	31	2	45	6
9	M	36	2	41	13
10	M	38	2	38	19
11	M	39	3	52	12
12	M	40	2	52	16
13	M	40	3	55	21
14	M	41	3	38	14
15	M	41	6	44	18
16	M	42	3	39	22
17	M	43	2	50	13
18	M	44	2	42	15
19	M	47	2	44	20
20	M	50	4	51	15
21	F	23	3	36	15
22	F	24	2	34	17
23	F	24	2	30	17
24	F	24	4	31	12
25	F	26	3	41	25
26	F	26	3	54	16
27	F	27	3	40	14
28	F	27	3	45	14
29	F	27	5	48	15
30	F	28	1	44	19
31	F	28	1	39	20
32	F	28	4	40	13
33	F	28	5	48	13
34	F	29	2	46	17
35	F	29	3	51	15
36	F	32	2	46	19
37	F	41	2	43	9
38	F	43	3	44	18
39	F	50	1	39	20
40	F	52	1	45	17
Mean		33.6	2.6	42.3	16.5
S.D.		8.4	1.1	7.3	4.7

$P = 0.017$) segments in Channel 17, and task 2 (beta = -0.365, $P = 0.019$) and task 3 (beta = -0.475, $P = 0.002$) segments in Channel 20. An example of the correlation for task 3 in Channel 20 is shown in Fig. 2.

3.2.3. Motor activation task (Fig. 3)

[Hb] changes during the left-finger-tapping task were not significant in any of channels for either [oxy-Hb] or [deoxy-Hb] ($F = 0.4$–2.1, $P > 0.11$), and there were no significant correlations between [Hb] changes and SSS or STAI scores (rho = 0.01–0.29, $P > 0.07$).

4. Discussion

In this study, we examined the relationship of subjective daytime sleepiness and subjective state anxiety with cerebral cortex reactivity in healthy subjects during the verbal fluency task and a left-finger-tapping task using a multichannel NIRS machine. The results obtained were as follows: (1) task performance correlated negatively with [oxy-Hb] changes during cognitive activation; (2) subjective light sleepiness correlated negatively with an [oxy-Hb] increase in bilateral frontal channels mainly in the middle and the last third of cognitive activation; and (3) no such relationships of brain activity with subjective light sleepiness and subjective anxiety were observed during motor activation. These results suggest that subjective light sleepiness in daytime is related to the decreased reactivity of the bilateral frontal cortices during the later part of the cognitive task.

The negative correlation between subjective sleepiness and frontal cortical reactivity in this study is in agreement with the results of previous studies in which sleepiness was examined in the resting state (Oakes et al., 2004; Feige et al., 2005; Goldman et al., 2002; Laufs et al., 2003a, 2006; Goncalves et·al., 2006) and with the results of some activation studies after sleep deprivation (Drummond et al., 1999; Mu et al., 2005a,b), as described in the introduction. In these sleep deprivation studies, decreased brain activity may have been due to task performance decline resulting from sleepiness. In this study, however, the significant negative partial correlation between task performance and frontal cortical reactivity in a multiple regression analysis suggests that frontal cortical reactivity decreased even when we excluded the effects of task performance decline and anxiety.

The negative correlation between subjective sleepiness and frontal cortical reactivity in this study is in disagreement with the results of other activation studies that demonstrated increased brain activity (Drummond et al., 2000, 2001, 2004; Portas et al., 1998). This discrepancy can be explained by the different degrees of sleepiness at the time of the examination. The subjects were examined in moderate to severe sleepiness after a long sleep deprivation in previous studies, whereas the subjects were examined only in light sleepiness, that is, during declined alertness, in this study. Increased brain activity can be explained by strong compensatory efforts to overcome intense sleepiness after sleep deprivation.

The time courses of the association between subjective sleepiness and frontal cortical reactivity offer some indications of the nature of the association. In this study, a negative correlation was observed mainly in the middle and the last third of the 60-s verbal fluency task. Although the subjects did not feel strong sleepiness during this task period subjectively, this negative correlation may be explained by a gradual attenuation of attention function during this task period because attentional function was reported to negatively correlate with cerebral blood flow in the frontal lobe in a study using simultaneous fMRI and EEG monitoring (Laufs et al., 2003b). If attention attenuation is more enduring owing to stronger sleepiness, it might be a risk factor for cognitive dysfunction, psychiatric health, and quality of life in the general population (Theorell-Haglow et al., 2006; Ohayon and Vecchierini, 2005) via frontal lobe dysfunction, as demonstrated in this study.
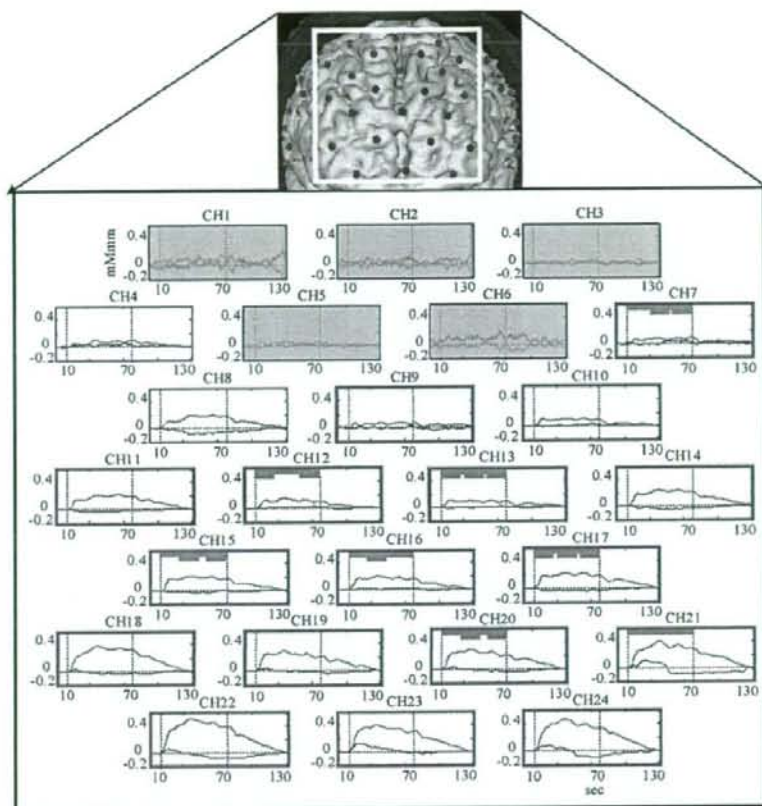
Fig. 1. Grand averaged waveforms of oxygenated and deoxygenated hemoglobin concentration ([oxy-Hb] (red line) and [deoxy-Hb] (blue line), respectively) changes during 60-s verbal fluency task (between two dotted vertical lines) measured using 24-channel NIRS machine over frontal region. Channels excluded from the analyses because of low signal-to-noise ratios are shaded in gray. Channels with significant [oxy-Hb] changes during the task period are indicated by red frames. The long and short green thin lines above the waveforms of [oxy-Hb] indicate the time segments showing significant correlations with SSS score and averaged [oxy-Hb] changes during three task segments as a whole and during each divided task segment, respectively.
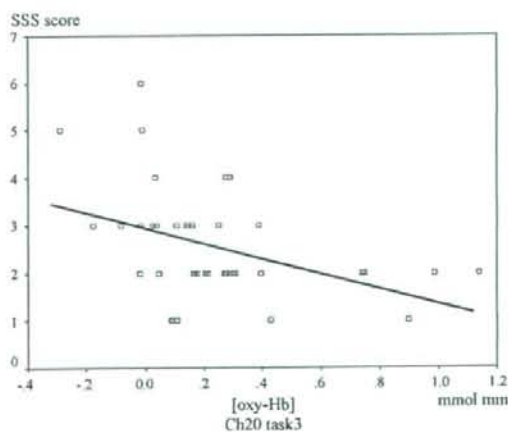

Fig. 2. Example of correlation between [oxy-Hb] changes during verbal fluency task and SSS score.

The lack of significant correlations between frontal lobe reactivity and subjective sleepiness during motor activation, as contrasted to cognitive activation, is another important finding of this study. The discrepancy can be explained as follows: (1) frontal activation by repeated behavior, namely, only maintaining finger-tapping during motor activation, is different from that by nonrepeated behavior, namely, finding new words during the verbal fluency task; (2) motor activation is related to the motor cortex in the frontal lobe but not to the prefrontal cortex, the reactivity of which was measured in this study; and (3) the lack of the baseline task during motor activation as contrasted to simple repetition of vowels during cognitive activation. As indicated by the time courses showing significant correlations during cognitive activation, that is, only in the middle and the last third of the task period, the first explanation is favored.

There are several limitations of this study. First, sleepiness was assessed only subjectively, not electrophysiologically (e.g., by EEG) or behaviorally (e.g., by multiple sleep latency test).
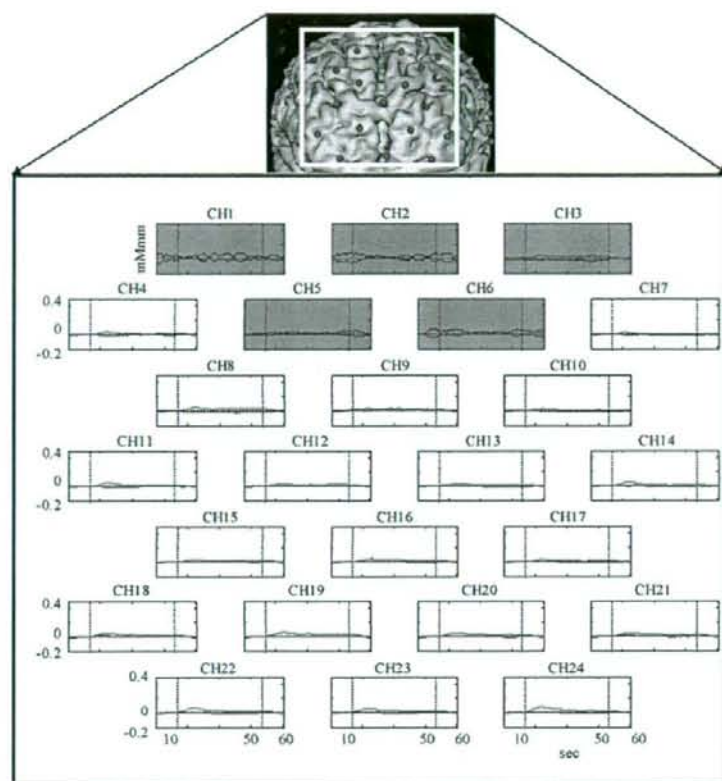
Fig. 3. Grand averaged waveforms of [oxy-Hb] (red line) and [deoxy-Hb] (blue line) changes during 40-s left-finger-tapping task (between two dotted vertical lines) measured using 24-channel NIRS machine over frontal region shown in Fig. 1.

Because sleepiness is measured on the basis of four aspects, namely, subjective sleepiness, performance decrease, sleep propensity, and arousal decrease, as stated in the introduction, the results obtained should only be considered as valid for subjective sleepiness. This point is a major problem in this study. Second, the sleepiness of the participants at the time of the NIRS examination was mild: their SSS scores indicated mainly in a state of light sleepiness (i.e., 1–3), which should be interpreted as reflecting declined alertness. The obtained results may not be generalized to the case of moderate to severe sleepiness (i.e., 6–7). Other scales that are more sensitive for evaluating light sleepiness (i.e., visual analogue scale) should be employed in our future study. Third, the subjects' daytime schedule was not controlled, namely, sleep schedule, amount of sleep in the previous night, and daytime activities that may considerably affect daytime sleepiness. In addition, we excluded the participant who had sleep disorder only by clinical interview, but not by any objective test such as polysomnograms. Controlling the nocturnal sleep of the participants is needed in future study. Fourth, brain function was monitored as "reactivity", that is, the activity change from the baseline level, not as baseline activity, owing to the

measurement nature of NIRS. Hence, the results obtained should be interpreted as showing the relationship between subjective sleepiness and brain function reactivity, not activity. Fifth, only the verbal fluency task was employed for cognitive activation. Different results can be obtained using other cognitive tasks, such as the continuous performance test, which enables the monitoring of sustained attention. Sixth, the relationships between subjective sleepiness and frontal lobe reactivity may be causally indirect. For example, the correlations were obtained because the arousal level decrease due to subjective sleepiness caused decreases in frontal lobe reactivity, or because one common factor, such as general fatigue, caused both subjective sleepiness and decreases in frontal lobe reactivity. Such other factors for the possible direct relationship were not examined in this study. Seventh, during the finger-tapping task as the control task, the number of tappings was not monitored: the subjects were only instructed to tap their fingers as fast and accurately as possible. The decline of concentration and attention owing to sleepiness may decrease task performance.

In summary, subjective daytime light sleepiness in healthy subjects under natural conditions was considered to be related

to decreased prefrontal reactivity in the later part of cognitive activation.

Acknowledgments

We thank Dr. Ryu Takizawa of the University of Tokyo and Dr. Ayako Kawakami of Tokyo Medical and Dental University for assistance in data collection and analyses, and Mr. Suguru Hattori of Gunma University for help in statistical analyses.

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Review

Does stimulation of 5-HT$_{1A}$ receptors improve cognition in schizophrenia?

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ARTICLE INFO

ABSTRACT

Cognitive impairment is a key feature of schizophrenia and may be the most important determinant of outcome in schizophrenia. This impairment is diffuse and may reflect abnormalities in frontal cortex, hippocampus and other brain regions. While deficits in glutamatergic, GABAergic, dopaminergic and cholinergic impairment have received the most attention as the basis of this impairment, there are many reasons for considering the role of serotonin (5-HT) in contributing to these deficits. This may be via its influence on dopaminergic, cholinergic, glutamatergic and GABAergic function, as well as various growth factors that have been implicated in schizophrenia. Of the 14 known serotonin receptors, the 5-HT$_{1A}$ receptor is a key candidate for mediating at least some of the influence 5-HT has on cognition. 5-HT$_{1A}$ receptors are upregulated in postmortem specimens from patients with schizophrenia, suggesting a deficit in 5-HT$_{1A}$ function in this disorder. Atypical but not typical antipsychotic drugs stimulate the efflux of dopamine from cortex by a 5-HT$_{1A}$-dependent mechanism. A series of studies from this laboratory involving the 5-HT$_{1A}$ partial agonists tandospirone and buspirone have reported a modest ability of these agents to improve some domains of cognition in patients receiving typical or atypical antipsychotic drugs. Preclinical studies have been mixed in regard to the ability of 5-HT$_{1A}$ partial agonists to improve cognition in various paradigms; some studies report that 5-HT$_{1A}$ antagonists are effective to improve cognition. Aripiprazole, clozapine, olanzapine, perospirone, quetiapine risperidone, and ziprasidone are examples of atypical antipsychotic drugs which are either direct or indirect 5-HT$_{1A}$ agonists which have been shown to improve cognitive function in patients with schizophrenia. Further study is needed to determine the role of the 5-HT$_{1A}$ receptor to improve cognitive function in schizophrenia.

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Contents

1. Introduction

Cognitive impairment is almost universal in patients with schizophrenia, with over 85% of patients with this disorder showing clinically significant impairment in some but not all domains of cognition, including attention, working memory, declarative

memory, speeded motor performance, and executive function [1]. It is well established that this impairment is the strongest determinant of functional outcome in schizophrenia [2]. Typical antipsychotic drugs have minimal benefit on cognition in schizophrenia in most studies (see Ref. [3] for review). Conversely, most, but not all studies have found that atypical antipsychotic drugs, e.g. aripiprazole, clozapine, quetiapine, olanzapine, risperidone, and ziprasidone have greater efficacy to improve cognition than the typical antipsychotic drugs, e.g. haloperidol [4–6]. These drugs share in common the ability to block serotonin (5-HT)$_{2A}$ receptors and to block dopamine (DA) receptor transmission. With

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the exception of aripiprazole and the main metabolite of clozapine, N-desmethylclozapine, which are partial DA agonists, they are D_2 receptor antagonists, with affinities for the D_2 receptor which are weaker than their affinities for the 5-HT_{2A} receptors. We have summarized the evidence concerning differences among the atypical antipsychotic drugs with regard to their ability to improve cognition [4]. Head-to-head comparisons such as a recent study comparing clozapine and ziprasidone [7] sometimes show advantages for one atypical over another but there have been too few such studies to have confidence as to the findings.

There is considerable animal evidence in a variety of paradigms that atypical antipsychotic drugs are more effective than typical antipsychotic drugs in reversing deficits in tasks that involve working memory or long-term memory [8,9]. In addition to being inverse agonists (antagonists) at 5-HT_{2A} receptors, some atypical antipsychotic drugs, including aripiprazole, bifeprunox, clozapine, perospirone, quetiapine and ziprasidone are serotonin (5-HT)$_{1A}$ partial agonists, while others are inferred to be indirect 5-HT_{1A} agonists in that some of the key actions, including the ability to enhance DA and acetylcholine (ACh) efflux in the medial prefrontal cortex, a region known to be important for cognition, are blocked by the 5-HT_{1A} antagonist (N-{2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl}-N-(2-pyridinyl)cyclohexanecarboxamide (WAY100635) ([10–12]). However, these results have not been consistently replicated [13]. It has been suggested the 5-HT_{1A} receptor stimulation can improve memory deficits in depression [14]. Some but not all of the atypical antipsychotic drugs are also 5-HT_{2C}, 5-HT_6, and 5-HT_7 receptor antagonists. These 5-HT receptors, particularly the 5-HT_{2C} and 5-HT_6 receptors, may have an important role in cognition, through their ability to modulate the release of cortical and hippocampal DA and acetylcholine [15]. It is beyond the scope of this article to consider the roles of these other types of 5-HT receptors in mediating the action of atypical antipsychotic drugs to improve cognition. As will be discussed below, there is considerable evidence that 5-HT_{1A} and 5-HT_{2A} receptors have a reciprocal relationship on many neurobiological processes, including the activity of pyramidal neurons in cortex and hippocampus. It seems likely that for schizophrenia, the 5-HT_{2A} receptor is more important than the 5-HT_{1A} receptor in terms of both pathophysiology and mechanism of action of antipsychotic drugs, as there is more and more evidence accumulating for an intimate relationship between 5-HT_{2A} receptor function and glutamatergic activity ([16]. Nevertheless, the role of 5-HT_{1A} receptors remains of keen interest. Based upon these and other data to be considered below, there have now been several reviews of the role of 5-HT_{1A} receptors in schizophrenia, including consideration of their importance for cognitive impairment [17,18].

2. 5-HT_{1A} receptors and 5-HT_{1A} agonist administration in schizophrenia

This background is relevant to understanding studies which have utilized buspirone, a 5-HT_{1A} partial agonist introduced as an anxiolytic, in patients with schizophrenia receiving typical antipsychotic drugs, such as haloperidol [19–22]. Most studies involving buspirone in doses of 10–100 mg/day, report a beneficial effect on psychotic symptoms or parkinsonism, or both [20–22]. These findings are supported by a small, randomized, placebo-controlled, double-blind study of buspirone, conducted by the authors' group [23], which found a trend level improvement in positive symptoms, as measured by the Brief Psychiatric Rating Scale Positive symptom scale, in subjects given buspirone 30 mg/day for 6 months.

A key issue in interpreting the results of 5-HT_{1A} partial agonist administration in preclinical or clinical studies is whether they act on presynaptic or postsynaptic 5-HT_{1A} receptors, both, or possibly, neither, as none of the available agents are entirely specific for 5-HT_{1A} receptors. The presynaptic 5-HT_{1A} receptor is an autoreceptor located on cell bodies of raphe neurons; stimulation leads to inhibition of firing of 5-HT neurons and a decrease in the release of 5-HT from nerve terminals in terminal regions such as the hippocampus [24]. Stimulation of postsynaptic 5-HT_{1A} receptors, located on cortical pyramidal neurons as well as GABAergic interneurons, generally leads to hyperpolarization of neurons, and diminished release of glutamate or GABA. This effect of 5-HT_{1A} receptor stimulation is opposite to the depolarizing effect of stimulation of 5-HT_{2A} receptors. Postsynaptic 5-HT_{1A} receptors are abundant in the hippocampus, frontal cortex, entorhinal cortex and the amygdala, all of which have been implicated in various aspects of schizophrenia. Postsynaptic 5-HT_{1A} receptors have been shown to inhibit the entry of CA^{++} into nerve terminals, which should serve to reduce/inhibit the release of neurotransmitters such as GABA, ACh and glutamate [25]. The reciprocal effects of 5-HT_{1A} and 5-HT_{2A} receptors on cortical neurons are the most likely basis for the similarity in clinical and preclinical studies of the effects of 5-HT_{1A} agonists and 5-HT_{2A} antagonists. There is extensive evidence indicating that 5-HT_{1A} receptor agonists and 5-HT_{2A} receptor antagonists produce similar neurochemical and behavioral effects on a variety of measures [26]. Chronic buspirone treatment to rodents has been found to differentially and reciprocally regulate 5-HT_{1A} and 5-HT_{2A} receptor mRNA and binding sites in the CA1 and CA2 regions of the rat hippocampus, whereas both upregulated 5-HT_{1A} and 5-HT_{2A} receptors in the dentate gyrus and CA3 and CA4 regions of the hippocampus [27]. Meneses and Hong [28] have suggested that stimulation of presynaptic 5-HT_{1A} receptors is the likely basis for improvement in cognition from 5-HT_{1A} agonists. This work is discussed elsewhere in this volume.

2.1. Postmortem studies

Postmortem studies have reported 5-HT_{1A} receptor density is increased in frontal and temporal cortices in schizophrenia [29–34]. Subsequent PET studies [35,36] confirmed an increase in cortical 5-HT_{1A} receptor binding in schizophrenia. We identified the high-affinity [^3H]8-OH-DPAT binding sites which correspond to the 5-HT_{1A} receptor component coupled to G-proteins in human postmortem prefrontal cortex, and found an 80% elevation of the high-affinity sites in subjects with schizophrenia [34]. These studies could find no evidence that this was due to antipsychotic drug treatment. The increased density of 5-HT_{1A} receptors may represent upregulation secondary to diminished 5-HT_{1A} receptor stimulation [32,34]. Whether this presumptive decrease in stimulation of 5-HT_{1A} receptors and subsequent increase in 5-HT_{1A} receptor density is related to the cognitive impairment in patients with schizophrenia remains to be determined.

2.2. Effect of augmentation with 5-HT_{1A} agonists on cognition in schizophrenia

Sumiyoshi and colleagues conducted a series of pilot studies of the effects of the addition of tandospirone, a 5-HT_{1A} partial agonist and azapirone derivative [37,38], to ongoing treatment with small to moderate doses of typical antipsychotic drugs (mainly haloperidol), on cognitive function in patients with schizophrenia [39–41]. The addition of tandospirone (30 mg/day), but not placebo, to typical antipsychotic drugs for 4–6 weeks, was found to improve executive function in one study [39,40] and verbal learning and memory in another[39–41].

Buspirone, 30 mg, neither improved or impaired cognition in healthy human subjects [42]. On the other hand, Yasuno et al.

[43], reported that acute (60 min) administration of a relatively high dose of tandospirone (60 mg/day), impaired verbal memory in healthy volunteers. They also found a lower dose (30 mg/day) of tandospirone slightly impaired memory performance in normals [43]. This discrepancy between the findings of Yasuno et al. [43] and ours may be due to differences in the treatment regimen (acute vs. chronic), subjects studied (normal controls vs. patients with schizophrenia), or a combination of the above [44].

Switching patients with schizophrenia to ziprasidone [45] or perospirone [46], two atypical antipsychotic drugs which are 5-HT_{1A} partial agonists, from typical antipsychotics, improved some aspects of verbal memory in subjects with schizophrenia. Adjunctive use of tandospirone with perospirone produced additional enhancement of verbal learning and memory in a single subject [47].

We have recently reported additional evidence for the beneficial effect of augmentation therapy with 5-HT_{1A} agonists in schizophrenia by conducting a randomly assigned placebo-controlled double-blind study to determine if the addition of buspirone would enhance cognitive function in subjects with schizophrenia treated with atypical antipsychotic drugs [48]. Patients with schizophrenia, who had been treated with an atypical antipsychotic drug for at least 3 months, were randomly assigned to receive either buspirone, 30 mg/day (a small to moderate dose), or matching placebo for 6 months. Several cognitive domains, including attention, verbal learning and memory, and executive function, as well as psychopathology, were assessed. Buspirone outperformed placebo in improving the performance on the Digit Symbol Substitution Test, a measure of attention/speeded motor performance as well as an index of general cognitive function [49]. It is noteworthy that none of the cognitive domains assessed showed deterioration after augmentation with buspirone. Scores on the Brief Psychiatric Rating Scale (total, positive subscale) were improved during treatment with buspirone but not placebo, but the effects did not reach statistical significance.

2.3. Further consideration of mechanism of action of 5-HT_{1A} agonists to improve cognition in schizophrenia

The possible mechanisms underlying the cognitive benefits of 5-HT_{1A} agonists, besides the ability of these agents to enhance the release of DA and acetylcholine in the prefrontal cortex and hippocampus, can be mentioned here. First, the ability of 5-HT_{1A} receptors to alter the release of glutamate and GABA provides a basis for the role of 5-HT in controlling cognitive process subserved by the prefrontal cortex [50]. Diminished GABA release in response to activation of inhibitory 5-HT_{1A} (or 5-HT_{1B}) heteroreceptors on GABAergic interneurons may facilitate hippocampal ACh and striatal DA release, respectively, which could compensate for possible deficiencies of these neurotransmitters in these brain areas [62]. Second, the 5-HT_{1A} agonist F13714, or the antipsychotics, clozapine, ziprasidone and aripiprazole, that are partial agonists at 5-HT_{1A} receptors, has been shown to protect against excitotoxin-induced striatal lesions in the rat [51]. This finding suggests that 5-HT_{1A} agonism may have a neuroprotective effects against pathological processes which may contribute to some of the cognitive impairment in schizophrenia. Third, a recent study [52] suggests the facilitative influence of the 5-HT_{1A} agonist tandospirone on anaerobic metabolism in the prefrontal cortex, suggesting a novel mechanism by which 5-HT_{1A} receptor agonism ameliorate deficits in some key domains of cognition in subjects with schizophrenia. The ability of systemic administration of risperidone at doses of 1 and 2 mg/kg to increased ACh release in the prefrontal cortex is antagonized by systemic administration of high doses (WAY100635) but not by a low dose (0.1 mg/kg) of the antagonist

which antagonizes preferentially presynaptic 5-HT_{1A} autoreceptors. Furthermore, local application of WAY100635 into the prefrontal cortex also attenuated risperidone-induced increases in ACh efflux. WAY100635 alone did not affect acetylcholine release in the prefrontal cortex. These results suggest that risperidone increases ACh release in the prefrontal cortex by stimulation of postsynaptic 5-HT_{1A} receptors. We also demonstrated an important influence of 5-HT_{1A} receptors on muscarinic mechanisms that may be of importance to cognitive impairment in schizophrenia [53]. The ability of the M1 receptor agonist, 4-[3-(4-butylpiperidin-1-yl)-propyl]-7-fluoro-4H-benzo[1,4]oxazin-3-one (AC260584), to increase the release of acetylcholine and dopamine in the rat medial prefrontal cortex and hippocampus was attenuated by the muscarinic M1 receptor antagonist telenzepine (3 mg/kg, s.c.) but not by the 5-HT_{1A} receptor antagonist N-[2-(4-2-methoxyphenyl)-1-piperazinyl]-N-(2-pyridyl) cyclohexanecarboxamide (WAY100635, 0.2 mg/kg, s.c.). However, the increase in dopamine release produced by 10 mg/kg AC260584 was blocked by both telenzepine and WAY100635.

The evidence from both preclinical and clinical studies, reviewed above, indicates 5-HT_{1A} receptors are an interesting, if not entirely convincing, target for the management of cognitive disturbances of schizophrenia. It must be noted that there is some evidence that 5-HT_{1A} receptor blockade is more likely to be of benefit in alleviating cognitive impairment than 5-HT_{1A} receptor stimulation ([54,55,56]). WAY-101405 is a silent 5-HT_{1A} antagonist which was recently reported to be effective in multiple rodent models of learning and memory, including novel object recognition and reversing the memory deficits induced by scopolamine [57]. In vivo microdialysis studies in the dorsal hippocampus of freely moving adult rats demonstrated that acute administration of WAY-101405 increased extracellular ACh levels [57]. Novel antipsychotic compounds with efficacy at 5-HT_{1A} receptors, e.g. F156063, SLV313, SSR181507, and bifeprunox [58–61] which are in development as treatments for schizophrenia, will provide further tests of whether 5-HT_{1A} agonism is useful or possibly harmful for cognitive function. The ability of these newer agents to enhance cognitive function appears to be promising but further study is needed [62,63]. While there are other 5-HT receptors, e.g. 5-HT_{2C}, 5-HT_6 which hold promise for improving cognition in patients with schizophrenia and perhaps other disorders with cognitive impairment as well, [64,65,66] the 5-HT_{1A} receptor is clearly one that has the most evidence to support its potential as a target for schizophrenia at the current time.

In conclusion, there are several clinical studies which indicate that 5-HT_{1A} agonism may be beneficial to improve cognition in some patients with schizophrenia. There is, in fact, no evidence that the authors are aware of that 5-HT_{1A} agonism can impair cognition in schizophrenia. This is consistent with some but not all preclinical studies of the ability of 5-HT_{1A} agonists and antagonists to modulate memory and learning in various animal paradigms.

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Gender difference in right lateral prefrontal hemodynamic response while viewing fearful faces: A multi-channel near-infrared spectroscopy study

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ARTICLE INFO

ABSTRACT

Near-infrared spectroscopy (NIRS) has been widely used to non-invasively assess brain function in various psychiatric disorders. Previous NIRS studies have extensively investigated prefrontal activation associated with cognitive tasks; in contrast, NIRS signals from prefrontal cortex in response to emotional stimuli have received little attention. We investigated spatiotemporal characteristics of hemodynamic response during an emotional activation task using fearful facial expression stimuli. We also evaluated gender difference and the relationship with anxiety-related personality traits. Subjects were 10 women and 10 men, all right-handed and matched for age, education and IQ estimated from the adult reading test. NIRS signals that are assumed to reflect regional cerebral blood volume were monitored over prefrontal regions by 52-channel NIRS. Women showed significantly increased [oxy-Hb] change relative to men in the right ventrolateral prefrontal cortex during the latter half of the task period. Frontopolar [deoxy-Hb] response correlated significantly with trait anxiety scores in the whole sample. These results suggest that gender and trait anxiety have an effect on individual variability of NIRS signals in response to emotional stimuli. This observation may help to establish NIRS as a clinical tool for monitoring prefrontal function on an individual basis.

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1. Introduction

Near-infrared spectroscopy (NIRS), a relatively new functional neuroimaging technology, enables the non-invasive measurement of spatiotemporal characteristics of brain function, which are assumed to reflect regional cerebral blood volume (rCBV). NIRS has been developed to be non-invasive, easy-to-use, portable, restraint-free and replicable (Kono et al., 2007). Consequently NIRS is relatively psychologically and physically undemanding, which makes it advantageous for clinical applications and translational approach. To date, NIRS has been used to assess brain function in many neurological and psychiatric clinical conditions such as stroke (Strangman et al., 2006), schizophrenia (Suto et al., 2004) and mood disorder (Kameyama et al., 2006).

NIRS has made advances in cognitive activation research, because it can readily detect cortical activation in fronto-temporal cortical surface areas. However, the characteristics of NIRS signal change associated with emotional processing are not well understood. Knowledge of the spatiotemporal pattern of NIRS-recorded

hemodynamic response to emotional tasks may be important to assist NIRS assessment of emotion-related psychiatric disorders such as mood disorders, anxiety disorders and post-traumatic stress disorder.

Functional imaging research with functional magnetic resonance imaging (MRI) and positron emission tomography (PET) has investigated the neural substrates of emotional activity and amygdala response to fearful facial expressions has been a consistent finding (Blair et al., 1999). In fearful facial expression tasks, activation was also evident in the right inferior frontal, premortor cortex and left insula in Japanese individuals (Moriguchi et al., 2005). Canli et al. (2002) reported that activations associated with unpleasant memories involved the bilateral superior frontal gyrus (Brodmann's area (BA)6), right middle (BA46), bilateral inferior frontal gyri (BA44, 45), left lateralized anterior cingulate (BA32), right precentral gyrus (BA4), left thalamus, and left insulae. However, the involvement of prefrontal cortical function with fearful emotional tasks remains to be elucidated. To this end, we developed a fearful facial expression task with the use of standard fearful faces for use with NIRS measurement.

To our knowledge only two NIRS studies have investigated emotion-evoked hemodynamic responses in healthy subjects. Herrmann et al. (2003) reported that a task with higher self-

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monitoring requirements induced prefrontal cortical activation, while this activation was not observed during emotional induction with lower self-monitoring requirements. Hongyu et al. (2007) reported a gender difference in [oxy-Hb] response to emotional stress such as viewing pictures stimulating negative emotion. However, these two studies did not utilize high temporal resolution (typically 0.1 s) for analysis of temporal characteristics, which is an advantage of NIRS.

To establish NIRS signals as a useful clinical tool for estimating individual prefrontal cortical function, sources of inter-individual difference have to be determined before investigation can begin into the application of NIRS to diagnostic evaluation. For this issue, we need to clarify the effect of gender and trait anxiety on inter-individual difference in NIRS signals, and this was the main purpose of the current study. Improving our knowledge about gender difference will enhance our ability to develop gender-specific evaluation and treatments for neuropsychiatric brain disorders (Cosgrove et al., 2007). Most studies on gender difference in emotion-related brain activity have suggested that women show stronger brain activation for affectively negative pictures than do men (George et al., 1996; Hall et al., 2004; McClure et al., 2004). Lee et al. (2002) reported greater left hemisphere activation for women and greater right hemisphere activation for men while viewing faces depicting sad emotions. However, the gender difference in prefrontal hemodynamic response to fearful stimuli has not been clarified.

In order to address these outstanding questions, the present multi-channel NIRS study measured prefrontal hemodynamic change in participants while they viewed emotional facial expressions, and investigated gender difference and the relationship with trait anxiety. The ultimate aim was to determine the suitability of NIRS assessment as a useful clinical tool for emotion-involved psychiatric disorders.

2. Methods

2.1. Subjects

Twenty healthy Japanese adults, 10 women and 10 men, matched for age, education, and estimated-IQ, participated in the study (Table 1). Subjects were screened using the Structured Clinical Interview for DSM-IV Axis I Disorder, Non-patient Edition (SCID-NP) (First et al., 1997; Japanese version, Kitamura and Okano 2003) by a trained psychiatrist (K.M., or R.T.), to confirm that the subjects had no history of major mental illness. Other exclusion criteria were neurological illness, traumatic brain injury with any known cognitive consequences or loss of consciousness for more than 5 min, a history of substance abuse or addiction in themselves or a family history of axis I disorder in their first-degree relatives. All were right-handed based on the Edinburgh Inventory (Oldfield, 1971). The subjects were asked to fill out the State-Trait Anxiety Inventory (STAI) (Spielberger et al., 1970) before the NIRS measurements. Their estimated-IQ was evaluated as the score of the Japanese version of National Adult Reading Test (JART) (Matsuoka et al., 2006). Their subjective sleepiness was evaluated as the score of the Stanford Sleepiness Scale (SSS) (Hoddes et al., 1971) immediately after the task. Written informed consent was obtained from all subjects before participation following the guidelines approved by the Ethics Committee of Medicine, The University of Tokyo.

Table 1
Demographic characteristics.

	Male (n = 10)		Female (n = 10)		Comparison	
	Mean	S.D.	Mean	S.D.	t[18]	p
Age	33.5	9.0	31.8	9.0	0.422	0.678
Education	16.2	0.6	16.3	1.9	−0.159	0.877
Estimated-IQ[a]	108.7	7.4	104.1	9.8	1.474	0.158
State anxiety[b]	40.1	7.7	38.4	6.3	−0.563	0.580
Trait anxiety[b]	36.7	9.7	39.2	10.2	0.541	0.595
Sleepiness[c]	2.7	1.2	2.5	1.1	0.200	0.844

[a] Assessed using the Japanese version of National Adult Reading Test (JART).
[b] Assessed using the State-Trait Anxiety Inventory (STAI).
[c] Assessed using the Stanford Sleepiness Scale.

2.2. Emotional activation task

Each participant sat on a comfortable chair and [oxy-Hb], [total-Hb], and [deoxy-Hb] changes were measured during an emotional activation task. The task consisted of a 30-s pre-task baseline, a 60-s activation period and a 70-s post-task baseline (Fig. 1). For the pre-task and post-task baseline periods, neutral faces were presented every 2 s. For the activation period (60 s), fearful faces were presented every 2 s on 17 in. display placed on a desk 70 cm front of the subject. Pictures from the Facial Action Coding System (Ekman and Friesen, 1978) were used as emotional stress materials. Fearful pictures were slides E25–E32. Neutral pictures were slides N1–N56. The subjects were instructed to, as quickly as possible, indicate vocally whether the presented face was male or female. Therefore, the subjects answered male or female 15 times in pre-task, 30 times in task, and 35 times in post-task. This was intended to make the subjects concentrate on watching the faces and covertly evaluate the facial expression.

2.3. NIRS measurement

Change in [oxy-Hb], [deoxy-Hb] and [total-Hb] were measured with an ETG-4000 (HITACHI Medical Cooperation, Japan) monitored with 52 channels. The machine measures relative [oxy-Hb], [deoxy-Hb] and [total-Hb] using two wavelengths of infrared light (695 nm and 830 nm) based on the modified Beer-Lambert law. In this system, [oxy-Hb], [total-Hb], and [deoxy-Hb] values include a differential pathlength factor (DPF). The distance between pairs of detector probes was set at 3.0 cm and we defined each measuring area between pairs of source-detector probes as a 'channel'. As described in the previous literature (Takizawa et al., 2008), the probes of the NIRS machine were fixed with thermoplastic 3 × 11 shells and placed at 52 measuring points, with the lowest probes positioned along Fp1–Fp2 line according to the international 10–20 system used in electroencephalography. These measuring points are labeled as ch1–ch52 from right-posterior to left-anterior probes (Fig. 2). This arrangement of the probes can measure [oxy-Hb], [total-Hb], and [deoxy-Hb] from bilateral prefrontal (approximately dorsolateral [Brodmann's area (BA) 9, 46], ventrolateral [BA 44, 45, 47], and frontopolar [BA 10]) and superior temporal cortical surface regions.

The time resolution of the NIRS machine was set at 0.1 s. [oxy-Hb], [total-Hb], and [deoxy-Hb] changes were analyzed using first-order correction to exclude task-unrelated changes during the fearful facial expression task. To acquire a stable baseline activation, a 20-s non-measured period was given in the 30-s pre-task period, and the NIRS measurement was started from the last 10 s of the pre-task period. The pre-task baseline was determined as the mean across the last 10 s of the pre-task period and the post-task baseline was determined as the mean across the last 5 s of the post-task period, and a linear fitting was performed on the data between the two baselines. Moving average methods were applied to remove short-term motion artifacts in the analyzed data (moving average window: 5 s). Grand mean waveforms averaged across subjects were created separately for type of [Hb] and for each group.

Subject's whose data displayed artifacts were excluded from averaging using a fully automated procedure separately for each channel.

There are three kinds of noise artifacts (high-frequency noise, low-frequency noise and no signal) and that body-movement artifacts show sharp signal changes compared with those of normal hemodynamics.

High-frequency noise is caused by insufficient intensity of the detection light in the OT system, and the digital and analog gains are taken to their maximum values. Therefore, the channels in this maximum value gain state are determined as artifact channels.

Low-frequency noise has excessive fast Fourier transform (FFT) power in the 0.1–1 [Hz] spectra of the oxy-Hb and the deoxy-Hb (OT system sampling rate is 10[Hz]). In such cases we applied the FFT to the oxy-Hb($x_{oxy}(t)$) and the deoxy-Hb($x_{deoxy}(t)$).
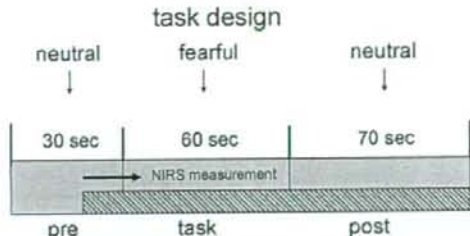

task design

Fig. 1. Task design. At the pre-task (30 s) and post-task (70 s) period, neutral faces were presented every 2 s. At the task period (60 s), fearful faces were presented every 2 s. Therefore, the whole task included 15 stimuli in the pre-task, 30 stimuli in the activation task, and 35 stimuli in the post-task. At the pre-task period, we started the NIRS measurement from the last 10 s of the pre-task period.
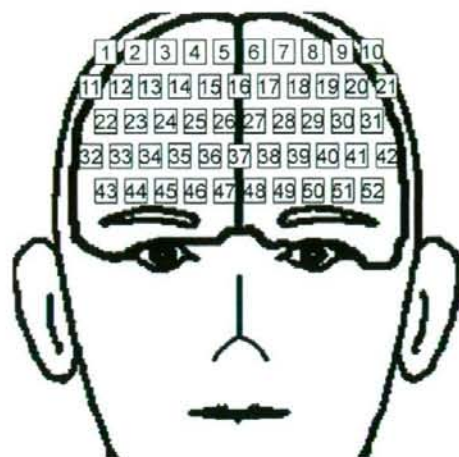
Fig. 2. Schematic representation diagram of 52 channels over the prefrontal cortex.

and the FFT power is calculated using ($P_{oxy}(t)$ and $P_{deoxy}(t)$).

$$P_{oxy}(t) = \sqrt{ real\left(\sum_{j=1}^{N} x_{oxy}(t)e^{-j\omega t} \right)^2 + imag\left(\sum_{j=1}^{N} x_{oxy}(t)e^{-j\omega t} \right)^2 } \qquad (1)$$

$$P_{deoxy}(t) = \sqrt{ real\left(\sum_{j=1}^{N} x_{deoxy}(t)e^{-j\omega t} \right)^2 + imag\left(\sum_{j=1}^{N} x_{deoxy}(t)e^{-j\omega t} \right)^2 } \qquad (2)$$

We calculated the maximum value of the 0.1–1 [Hz] spectra from the $P_{oxy}(t)$ and $P_{deoxy}(t)$, the channels above this threshold are determined as an artifact channels.

$$max(P_{oxy}(N/100 : N/10)) > 5 \qquad (3)$$

$$max(P_{deoxy}(N/100 : N/10)) > 6 \qquad (4)$$

Here, N is the number of OT measurement points.

The no signal has no change in oxy-Hb and deoxy-Hb concentration in all measurement time-points. Therefore, the channels in which the standard deviation value of all the measurement points is 0 are determined as an artifact channels.

Body-movement artifacts are sharp changes. Therefore, channels that have body-movement artifacts with oxy-Hb and total-Hb changes over 0.15 [mM mm] in over 20 successive samples (during 2 [s]) are determined as an artifact channels.

Thus the number of averaged subjects varied across channels (N = 39–52 [mean, 50.5; SD, 3.0]).

2.4. Statistical analysis

Firstly, potential confounding factors such as age, education, estimated-IQ, trait anxiety, and sleepiness were compared between the two groups (male and female) by Student's t-test and these demographic characteristics are given in Table 1.

Next, [oxy-Hb], [total-Hb], and [deoxy-Hb] changes of the grand averaged waveforms were compared every 0.1 s between the two groups (male versus female) at each channel by Student's t-test. This analysis enabled a more detailed comparison of [oxy-Hb], [total-Hb], and [deoxy-Hb] changes along the time-course of the activation task. The differences were interpreted as meaningful if 200 consecutive comparison points reached a significance level of 5% among 1300 points during the task and post-task period, to avoid multiple comparison errors (Kameyama et al., 2006).

Additionally, Pearson's correlation coefficients were calculated for the relationship between the mean [oxy-Hb], [total-Hb], and [deoxy-Hb] changes during the task period and potential confounding factors such as age, education, estimated-IQ, trait anxiety, and sleepiness. Statistical analysis was performed using SPSS 10.1.3J software (Tokyo, Japan).

3. Results

3.1. Potential confounding factors

The two groups (males and females) did not differ significantly on age, education, estimated-IQ, scores of state and trait anxiety, and index of sleepiness (Table 1).

3.2. Group comparison

The results of the t-test for the between-group comparison of the [oxy-Hb] and [deoxy-Hb] changes during the tasks are shown in Figs. 3–5. Female subjects were associated with significantly greater [oxy-Hb] increase than male subjects in 5 channels (ch12, 22, 23, 33 and 34). All subjects' superimposed figures about [oxy-Hb] in the significant channel (ch23) are shown in Figs. 6 and 7. The [deoxy-Hb] decrease in the female subjects was significantly greater than that of male subjects in 3 channels (ch33, 41 and 45). Those channels with greater [oxy-Hb] change in female subjects compared to male subjects were situated approximately in the right ventrolateral prefrontal cortex (PFC) and right premotor cortex. There is no significant between-group difference in [total-Hb] changes.

3.3. Correlational analysis

Mean [oxy-Hb], [total-Hb], and [deoxy-Hb] changes during the task period showed no significant correlation with age, education, estimated-IQ, or sleepiness in the whole sample.

As for the task period, mean [oxy-Hb] and [total-Hb] changes were not significantly correlated with trait anxiety score in the whole sample. A significant negative correlation was found between mean [deoxy-Hb] change and trait anxiety score in the frontopolar prefrontal region (ch38; $r = -0.54$, $p = 0.0016$) in the whole sample.

However, when we performed correlational analysis separately for males and females, mean [oxy-Hb], [total-Hb], and [deoxy-Hb] change during the task period had no correlation with age, education, estimated-IQ or sleepiness in either group.

4. Discussion

Using multi-channel NIRS with wide coverage of the PFC, we identified gender differences and a relationship with anxiety traits in the hemodynamic changes in lateral PFC associated with covert evaluation of emotional expression of faces. Females maintained greater right ventrolateral and premotor cortical activations during the latter half of the task than did males. Additionally, frontopolar [deoxy-Hb] response had a significant correlation with trait anxiety scores in all the subjects. Potential confounding factors such as age, education, estimated-IQ, trait anxiety and sleepiness did not account for the gender difference in brain activation due to the fearful stimuli. The observation of activation in right ventrolateral and premotor PFC was consistent with previous findings (Moriguchi et al., 2005). These results suggest that multi-channel NIRS can detect gender differences in prefrontal hemodynamic response associated with emotional tasks.

4.1. Gender difference in brain activation

Several previous studies reported that females displayed more brain activity in association with fear than did males (George et al., 1996; Hall et al., 2004; McClure et al., 2004). In the present study, we found the same gender difference in right ventrolateral PFC and