り-116C→GによるXBP1ループの機能低下を代償させることにあるらしい（図3）。

おわりに

本研究は，躁うつ病の遺伝的リスクの1つおよびそのリスクを減少させる薬物のメカニズムを明らかにしたものである。躁うつ病は，このようなリスクがいくつも重なった結果発症するものと考えられる。現に，この多型におけるリスクアレルそのものは健常者にも多くみられるものであり，単純に発症に結びつくものではない。数あるリスクファクターの重ね合わさった結果，何らかの閾値を超えると発症に結びつくのではないか。したがって，この数を減らし，閾値以下になれば治療としては成功であると思われる。今回示したリスクは，*in vitro*においては3種類の気分安定薬のなかではバルプロ酸のみで解消されたことから，このリスクが発症に関与している患者ではバルプロ酸が効きやすい可能性がある。臨床的な薬物反応性と多型の関係を調べることで，将来的には*XBP1*の遺伝子型に応じた薬物選択すなわちテーラーメイド医療が可能になるかもしれない。

XBP1ループの機能低下は躁うつ病あるいは感情の制御にどのように関わっているのであろうか。うつ病による自殺者の脳において*HSPA5*の発現量が変化しているという報告もあり，ERシャペロンが何らかの関与をしているかもしれない[4]。HSPA5は，Ca^{2+}結合作用をもち，小胞体のCa^{2+}シグナリングに影響することが知られており，XBP1ループの障害によるCa^{2+}シグナリングの異常が関与している可能性も考えられる。また，神経伝達に必要なタンパクのfoldingに影響する可能性[5]，あるいは，XBP1に神経系特有の標的遺伝子がある可能性なども考えられる。XBP1はERストレス反応のみならず，多彩な働きをする転写因子であり，感情の制御に関わるような遺伝子がその下流にあるかもしれない。このカスケードの研究を突破口に感情制御の分子メカニズムが解明されることが期待される。

参考文献
1) Kato T : Neurosci Res 40, 105-113, 2001.
2) Kakiuchi C, et al : Nat Genet 35, 171-175, 2003.
3) Yoshida H, Matsui T, et al : Cell 107, 881-891, 2001.
4) Bown C, Wang JF, et al : Neuropsychopharmacology 22, 327-332, 2000.
5) Tate CG, Whiteley E, et al : J Biol Chem 274, 17551-17558, 1999.

著者プロフィール
垣内千尋：
1996年東京大学医学部卒。同年同大学院病理学講座に入学し、主にリンパ節病理の研究を行い，2000年学位取得。卒後同大学精神神経科に入局し，1年2ヵ月臨床研修を行った後，理化学研究所脳科学総合研究センター精神疾患動態研究チームへ。

著　書

Manuscript in press

Book: *Progress in Schizophrenia Research* (tentative)
Publisher: Nova Science Publishers, New York
Chapter: Using advanced neuroimaging techniques toward understanding schizophrenia
Authors: Hidenori Yamasue, Kiyoto Kasai, Kazuyuki Nakagome, Akira Iwanami, and Masato Fukuda
Section: Near-Infrared Spectroscopy, a Possible Clinically Available Laboratory Test
for Diagnosis and Treatment of Psychiatric Disorders

Abstract

In this paper, the author discusses the possible application of near-infrared spectroscopy (NIRS) as a clinical laboratory technique for the diagnosis and treatment of psychiatric disorders. NIRS has both advantages and disadvantages in the evaluation of cerebral blood volume (CBV) changes. Its advantages are as follows: 1) it enables complete noninvasive measurements at a low running cost and 2) it enables continuous CBV monitoring with high time resolution. Its disadvantages are as follows: 1) it measures CBV changes only with a low spatial resolution in limited brain regions, and 2) its obtained CBV values are expressed as hemoglobin concentrations relative to baseline levels. These features suggest that NIRS is an appropriate methodology for evaluating higher brain functions by monitoring CBV with utmost safety and ease. The number of NIRS studies of psychiatric disorders, such as depression, bipolar disorder, schizophrenia, post-traumatic stress disorder, and panic disorder, has increased in the past few years. The author has reviewed published NIRS studies on psychiatric disorders and presents recent findings of his research. The importance of establishing clinically available biological markers for the diagnosis and treatment of psychiatric disorders is emphasized.

Key Words:
Near-infrared spectroscopy, Depression, Bipolar disorders, Schizophrenia, Laboratory test

1. Medical application of near-infrared spectroscopy (NIRS)

Near-infrared spectroscopy (NIRS) is a novel technique for monitoring brain functions, and the number of studies on its medical applications has recently been increasing. The successful monitoring of hemoglobin concentrations using near-infrared light was first reported for human brain in 1977 (Jöbis 1977), four papers on NIRS application to human brain functions appeared in 1993 (Chance et al 1993, Hoshi and Tamura 1993, Kato et al 1993, Villringer et al 1993), the first paper on NIRS study in psychiatric disorders was published in 1994 (Okada et al. 1994), multichannel NIRS machines were developed in the late 1990s (Maki et al 1995, Tamura et al 1997), and medical application of

topographical NIRS data obtained using multichannel NIRS machines was reported in 1998 (Watanabe et al. 1998).

Increased attention to medical applications of NIRS has been represented in NIRS symposia held in Japanese medical conferences, e.g., "Clinical Applications of NIRS" at the 32nd meeting of the Japanese Society of Clinical Neurophysiology (November 2002), "Brain Function Mapping by Near-Infrared Spectroscopy" at the 5th meeting of Japan Human Brain Mapping Society (March 2003) and "Recent Developments in NIRS Studies" at the 6th meeting of Japan Human Brain Mapping Society (March 2004).

NIRS is employed not only for research purposes but also for medical practice. NIRS measurements were authorized by the Ministry of Health and Welfare of the Japanese government in 2002 as a clinically valid technique for both the determination of the dominant hemisphere and the identification of epilepsy foci before brain surgery. More rapid progress in basic and medical application research of NIRS is expected as NIRS apparatuses are increasingly employed.

The number of NIRS studies on psychiatric disorders is increasing. The reviews of such studies were first published in Japanese in 2000 (Kato 2000) and in English in 2002 (Strangman et al. 2002a). The author assumes that NIRS may be employed in psychiatry as a clinical laboratory test for the diagnosis and treatment of psychiatric disorders in the near future. He has published reviews on NIRS application in psychiatry in Japanese (Fukuda et al. 2001, 2003, 2004). The first international symposium focusing on the psychiatric application of NIRS was held in August, 2002 in Yokohama. Dr. Hideaki Koizumi (Hitachi Ltd., Advanced Research Laboratory), one of the pioneers in NIRS research, and the author co-organized the symposium entitled, "Near-Infrared Spectroscopy in Psychiatry" at the 12th World Congress of Psychiatry. The symposium included five presentations by basic researchers (Dr. Hideaki Koizumi and Dr. Shoko Nioka of Pennsylvania University) and three psychiatrists (Dr. Andreas J. Fallgatter of Wuerzburg University, Dr. Tadafumi Kato of RIKEN, and Dr. Makoto Ito of Gunma University). Dr. Fallgatter and the author will co-organize the second international NIRS symposium on psychiatry in June 2005 in Vienna entitled, "NIRS in Psychiatry: a Non-invasive Technology to Monitor Brain Function in Bedside Settings" at the 8th World Congress of Biological Psychiatry.

2. Characteristics of NIRS data and its possible application to psychiatric disorders

Hemoglobin concentration ([Hb]) data obtained using commercially available NIRS apparatuses theoretically have the following four characteristics: 1) represents [Hb] only near the brain surface, that is, cerebral cortex, with a low spatial resolution (2-3 cm), 2) is expressed only as values relative to its baseline levels, 3) can be monitored completely noninvasively at a low running cost, and 4) can also be monitored continuously with a high time resolution (0.1 second). These four characteristics of NIRS data and their implications for psychiatric application are described in detail below.

2.1. Measurement limited to brain surface with low-spatial resolution

Because the NIRS measurement of [Hb] is limited to the regions near the brain surface, the NIRS data primarily reflect cerebral blood volume (CBV) changes in the cerebral cortex. CBV changes in deep cerebral structures such as thalamus, limbic system, and basal ganglia cannot be measured directly. In addition, the spatial resolution of NIRS data is as low as 2-3 cm because NIRS detects near-infrared light scattered and reflected in the brain. The accurate identification and localization of the activated brain region, particularly of deep brain structures, are not possible as functional magnetic resonance imaging (fMRI) and magnetoencephalography (MEG). Therefore, the etiology and the pathophysiology of psychiatric disorders cannot be clarified only using NIRS.

In contrast, NIRS is a convenient technique suitable for analyzing brain activities over a large area of the cerebral cortices as a whole. For example, the technique may be inappropriate for the identification of precise functional localization within primary sensory areas, but is appropriate for the studies of association cortices and functional units in which activities in multiple brain regions are integrated. Hence, NIRS is considered to be suitable for brain function evaluation in psychiatric disorders because brain structures responsible for psychiatric disorders are assumed not to be confined to small regions in deep brain structures but to be widespread across association cortices or dispersed functional systems.

2.2. Relative nature of NIRS [Hb] data

CBV, cerebral blood flow, and cerebral glucose metabolism in psychiatric disorders are generally measured 1) during the resting state without any activation (baseline study) and 2) during the activated state when the subjects are exposed to any type of loading procedures (activation study). Data obtained from these two study designs are assumed to differ in their pathophysiological implications. For example, widespread decreases in cerebral glucose metabolism in depression revealed by positron emission tomography (PET) studies are obtained mostly in baseline studies, and are assumed to reflect decreased cerebral metabolism during the resting state; decrease in frontal lobe blood flow in schizophrenia observed in single-photon emission computed tomography (SPECT) studies are typically obtained during the frontal lobe activation tasks, and are assumed to reflect the insufficient activation of the frontal lobe during the activated state. It is possible that the abnormal findings in baseline studies are stable and nonspecific across brain regions and those in activation studies are more specific to certain brain regions responsible for the function. The clarification of abnormalities both in the resting and activated states is necessary for elucidating the etiologies and pathophysiologies of psychiatric disorders.

Conventional NIRS apparatuses measure [Hb] only as the changes from the baseline levels but they cannot determine absolute [Hb]. This means that NIRS data represent [Hb] changes caused by brain activation. NIRS data, therefore, should be interpreted together with the baseline findings obtained by other studies such as PET studies.

2.3. Noninvasive measurement at low running costs

The complete noninvasiveness and low running cost of NIRS measurements may lead NIRS to be a clinically available laboratory test for brain functions. Measurements can be easily repeated due to its noninvasiveness and low running costs, which enables NIRS data to be employed not only in the diagnosis of psychiatric disorders but also in the longitudinal monitoring of treatment courses. Therefore, NIRS may become a clinical laboratory method for the diagnosis of psychiatric disorders for which no reliable laboratory findings are currently available.

2.4. Continuous measurement with high-time resolution

The high time resolution of NIRS enables the application of NIRS in brain function analyses. Generally, functions of organs are reflected in the time courses of their activities, for example, electrocardiograms (ECG) for cardiac functions and respirograms for respiratory functions. Similarly, brain functions are well presented in the time courses of their activities, and data with high time resolutions are used as indices of brain function, such as electroencephalogram (EEG), magnetoencephalography (MEG), evoked potentials (EP), and event-related potentials (ERP). Among PET, SPECT, fMRI and NIRS for measuring brain metabolism and blood flow, , NIRS has the highest time resolution, and is therefore expected to be useful in elucidating brain dysfunctions.

From the four NIRS characteristics mentioned above, NIRS can be concluded to be a safe and easy technique for the examination of higher brain functions by globally monitoring relative changes in CBV.

3. NIRS findings in psychiatric disorders

NIRS studies of psychiatric disorders, such as depression, schizophrenia, posttraumatic stress disorder (PTSD) and panic disorder, have been published. Interestingly, all the NIRS studies reported a certain type of frontal lobe dysfunction in psychiatric disorders.

3.1. Depression

The first NIRS paper on depression was published in 1996 (Okada et al. 1996). They recorded [Hb] from the forehead while the subjects were performing a mirror drawing task. Increases in oxygenated hemoglobin concentration ([oxy-Hb]) and decreases in deoxygenated hemoglobin concentration ([deoxy-Hb]), both indicating cerebral activation, were noted in the dominant frontal lobe in healthy volunteers, whereas those [Hb] changes were found in the nondominant or bilateral frontal lobes in depression. The authors interpreted these findings as indicating cerebral dominance abnormality in depression.

Subsequent NIRS studies on depression consistently demonstrated a reduction in [oxy-Hb] increases and [deoxy-Hb] decreases during frontal lobe activation tasks. Both [oxy-Hb] increases and [deoxy-Hb] decreases were smaller in unipolar depression and bipolar depression than in healthy volunteers during both a hyperventilation task and a word fluency task (Matsuo et al. 2000, 2002, 2004),

and [oxy-Hb] increases in depression were reduced in a rather large area of the frontal lobe as observed in a multichannel NIRS study (Suto et al. 2004). These findings suggest a decreased frontal lobe reactivity as the pathophysiology of depression and depressive states.

Some studies of depression focus on the relationship between NIRS findings and treatments such as electroconvulsive therapy (ECT) and repetitive transcranial magnetic stimulation (rTMS). [oxy-Hb] and total hemoglobin concentration ([total-Hb]; sum of [oxy-Hb] and [deoxy-Hb]) were reported to suddenly decrease immediately after ECT stimulation and to gradually recover afterwards (Saito et al. 1995); these changes were interpreted as indicative of a failure in the autoregulation mechanism of cerebral blood flow (CBF) (Saitoh et al. 1996). As for rTMS, increases in [oxy-Hb] recorded from the left frontal lobe during a mirror drawing task before treatment were reported to negatively correlate with the improvement of depressive symptoms by rTMS treatmentl This finding was interpreted as indicating that patients who performed the task without [oxy-Hb] increases had a preserved frontal lobe function (Elschweiler et al. 2000).

3.2. Schizophrenia

The first NIRS paper on schizophrenia was published in 1994 (Okada et al. 1994). [oxy-Hb] increases and [deoxy-Hb] decreases in the dominant hemisphere during a mirror drawing task were clearly observed in the healthy controls but they were not significant in the schizophrenic subjects. These findings were interpreted as indicating frontal lobe dysfunction in schizophrenia.

Subsequent NIRS studies on schizophrenia also demonstrated the findings consistent with frontal lobe dysfunction but with some inconsistencies. [deoxy-Hb] decreases in the right frontal lobe during a continuous performance test (CPT), a neuropsychological test for sustained attention, were attenuated in schizophrenic patients, suggesting deficits in attention function mediated by the right frontal lobe (Fallgatter and Strik 2000). [oxy-Hb] increases were definitely reduced in a random-number generation task but not in a sequential finger-to-thumb task, and were even reversed in a ruler-catching task (Shinba et al. 2004). [oxy-Hb] increases were attenuated in a verbal fluency test but unchanged in a letter number span test (Watanabe et al. 2004). [oxy-Hb] increases in a verbal fluency test were reduced during the task period but unchanged after the task period, suggesting inefficient frontal lobe activation (Suto et al. 2004).

3.3. Others

PTSD patients in the Tokyo Subway sarin attack were reported to demonstrate attenuated [oxy-Hb] increases and enhanced [deoxy-Hb] decreases in the frontal lobe during a verbal fluency task when compared with non-PTSD victims of the same attack (Matsuo et al. 2003a, b). The results were interpreted as representing the frontal lobe dysfunction for attention and concentration disturbances in PTSD patients.

Panic disorder patients were reported to demonstrate the underactivation of the left frontal lobe compared with healthy subjects during a frontal lobe task containing stimuli evoking anxiety and emotion (Akiyoshi et al. 2003).

Novelty seeking and persistence in the Temperament and Character Inventory were reported to correlate with the initial time segments of [oxy-Hb] changes during a finger tapping task in healthy subjects (Ito et al. 2002)

4. Multichannel NIRS study in Gunma University

Most of the previous NIRS studies on psychiatric disorders described in section 3 employed the NIRS apparatus with one or two channels. Considering the differentiated functions among the frontal lobe subregions, studies are required using multichannel NIRS apparatus that can cover a greater area of the frontal lobe to clarify the detailed frontal lobe dysfunction in psychiatric disorders. A brief introduction of a multichannel NIRS study on psychiatric disorders by the author and coresearchers in Gunma University is given below (Suto et al. 2004, Kameyama et al. 2004a).

4.1. NIRS examination settings

The authors employed two sets of 24-channel NIRS machines (ETG-100, Hitachi Medical Corporation, Japan) using near-infrared light of two wavelengths (760 and 840 nm) and measured [oxy-Hb] and [deoxy-Hb] every 0.1 second. The interprobe distance was set at 3.0 cm, which enabled the measurement of [Hb] at a depth of 2-3 cm from the scalp, that is, the surface of cerebral cortices. The probes of the NIRS machines were placed on the subjects' frontal and bilateral temporal regions (Fig. 1). The correspondence of 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: 24 channels in the frontal probe to the dorsolateral prefrontal cortex and each of the 12 channels in the temporal probes to inferior frontal, superior temporal, and anterior parietal cortices.

A verbal fluency task, a letter version, was selected for frontal lobe activation. The activation consisted of a 30-second pretask baseline, a 60-second verbal fluency task and a 60-second post-task baseline. In the verbal fluency task, the subjects were instructed to generate as many words as possible with an initial syllable of either /a/, /ka/ or /sa/. The three initial syllables changed in turn every 20 seconds during the 60-second task to reduce the time during which the subjects were silent. The number of words generated during the word 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 post-task baseline periods. A unilateral finger tapping task of 40-second duration was employed as the control task. Patients with major depressive disorder in their euthymic or subdepressive state, those with schizophrenia mainly in their residual state, those with bipolar disorder in their euthymic or subdepressive state comparable to the depression group, and their sex- and age-matched healthy volunteers participated in the present study. Most patients were under psychotropic medication at the time of the examination. This study was approved by the Institutional Review Board of Gunma University Graduate School of Medicine, and written informed consent was obtained from all the subjects prior to the study.

4.2. NIRS findings in psychiatric disorders

Figure 2 shows the grand averaged waveforms of [oxy-Hb], [deoxy-Hb], and [total-Hb] during the verbal fluency task in the control group recorded from the frontal (center) and the bilateral temporal probes (left and right). Two vertical bars in each graph indicate the start and the end of the 60-second period of the task. As shown in three representative channels magnified below, distinct [oxy-Hb] increases were observed during the task period: [oxy-Hb] rapidly increased immediately after the start of the task period, was maintained at the activated level during the task period, and decreased gradually after the task was finished particularly in the frontal channels. The superimposed individual waveforms of [oxy-Hb] changes shown below confirmed that the grand averaged waveforms essentially represent the data of most individuals in each group.

The grand averaged waveforms of [oxy-Hb], [deoxy-Hb], and [total-Hb] during the verbal fluency task are shown in Fig. 3 and 4 for the patients with depression and schizophrenia, respectively, with three representative channels magnified below and their superimposed individual waveforms of [oxy-Hb], as in Fig. 2. In the depression group (Fig. 3), small [oxy-Hb] increases during the initial time segment of the task period were followed by reduced [oxy-Hb] increases across the remaining task period compared with those in the control group for both the frontal and temporal channels. In the schizophrenia group (Fig. 4), blunted [oxy-Hb] increases during the initial time segment of the task period were followed by sustained moderate [oxy-Hb] increases across the remaining task period, and [oxy-Hb] decreases immediately after the task period were followed by [oxy-Hb] reincreases during the post-task period, particularly in the left lower frontal channels. In the bipolar disorder group (data not shown), [oxy-Hb] increased more slowly than that in the control group during the former half of the task period, but peaked in its latter half with increases comparable to those of the control group.

The multichannel NIRS machine employed can also visualize these CBV changes as topographical maps moving at 0.1 second intervals, and [oxy-Hb] topographs at three time points during and three time points after the task period are shown in Fig. 5. The topographs show that [oxy-Hb] increases, which were clearly observed during the task period in the lower frontal and anterior lower temporal channels in the control group, were reduced during the task period in the depression group, and were paradoxically maintained during the post-task period in the schizophrenia group. The channel positions with significant [oxy-Hb] differences between the depression and control groups are superimposed on a reconstructed brain image, showing that the depression patients had reduced CBV reactivity in the prefrontal area and bilateral posterior perisylvian regions (Fig. 6).

The differences between the psychiatric and control groups were not observed in the finger tapping task, suggesting that the above findings are somewhat specific for frontal lobe activation as in the case of the verbal fluency task. Schematic illustrations of [oxy-Hb] changes during the verbal fluency task are presented for the control, depression, bipolar disorder, and schizophrenia groups in Fig. 7

4.3. Clinical correlates of NIRS findings

The state and trait dependencies of and medication effects on the NIRS findings described above in subsection 4.2. cannot be concluded at present because of the small number of subjects studied. The following preliminary findings in the depression group suggest that NIRS findings can be either state-and trait-dependent according to channel position: the reduction in [oxy-Hb] increases was commonly observed in the patients with euthymic and subdepressive states in the frontal channels, but correlated with depression severity in some temporal channels. Also, the effects of psychotropic medication on NIRS data can be excluded if similarity of NIRS findings in on-drug patients and some medication-free patients in the present study are replicated.

The NIRS findings described above may represent different aspects of pathophysiology in psychiatric disorders from CBF and cerebral metabolism findings in PET and SPECT studies. For example, decreased brain activities in depression were reported in many PET and SPECT studies of subjects in their resting state; that is, the findings reflect the brain activity without any activational demand. Hence, the decreased activities reported are assumed to correspond to depressed mood and loss of energy in depression. On the other hand, NIRS data represent activational CBV changes in response to task demands; reduced [oxy-Hb] changes represent a decreased reactivity of the brain function in depression. Such decreased reactivities are assumed to correspond to clinical symptoms such as loss of mood reactivity, markedly diminished pleasure, and psychomotor retardation.

4.4. Neural mechanism of NIRS findings

Altered [oxy-Hb] change patterns in psychiatric disorders in the present study cannot be attributed to nonspecific general factors such as differences in vascular responsiveness to neuronal activities, because [oxy-Hb] change patterns differed between the verbal fluency and finger tapping tasks. Neural mechanisms underlying the obtained NIRS findings are little understood because no previous studies using other methodologies have examined brain functions with a time resolution as high as that of NIRS. We presume the NIRS findings as reflecting the characteristics of their frontal lobe functions as follows: smaller [oxy-Hb] changes in depression are interpreted as representing reduced reactivity, delayed but unaltered [oxy-Hb] increases in bipolar disorder as delayed but unaltered reactivity, and reduced [oxy-Hb] increases during the task period with sustained [oxy-Hb] increases during the post-task period in schizophrenia as inefficient reactivity in frontal lobe functions.

5. Relationship between NIRS and fMRI data

Both NIRS and fMRI are techniques for monitoring brain activities by measuring the degrees of hemoglobin oxygenation; however, they use different principles and parameters. The results obtained using NIRS and fMRI mostly agree with each other, but with some disagreements because of the difference in their objects of measurement.

5.1. Simultaneous measurements by NIRS and fMRI

Five studies of simultaneous measurements by NIRS and fMRI in humans have been

published thus far. Three studies emphasize the close relationship between [deoxy-Hb] decreases in NIRS and blood-oxygenation-level-dependent (BOLD) signals in fMRI, and the remaining two studies show a stronger relationship between [oxy-Hb] increases and BOLD signals.

The following three studies emphasized the relationship between [deoxy-Hb] decreases in NIRS and BOLD signals in fMRI on the basis of the concept that BOLD signals reflect deoxy-Hb in small vessels. [Deoxy-Hb] decreases and [oxy-Hb] increases were observed in the motor area contralateral to the finger tapping with a lower localization accuracy than BOLD signals in fMRI (Kleinschmidt et al. 1996). [deoxy-Hb] decreases strongly correlated with the changes in BOLD signals in the motor area contralateral to the hand grasping (Toronov et al. 2001). BOLD signal intensities in the activation of the motor area contralateral to the finger tapping correlated with [deoxy-Hb] decreases ($r=-0.79$) and [total-Hb] increases ($r=0.74$) (Mehagnoul-Schipper et al. 2002).

However, the following two studies found stronger correlations between [oxy-Hb] in NIRS and BOLD signals in fMRI. Correlations with BOLD signal intensities were stronger for [oxy-Hb] and [total-Hb] than for [deoxy-Hb] (Haida et al. 2000). Another study also revealed stronger correlations with $1/\Delta$BOLD for Δ[oxy-Hb] (approximately $r=0.9$) and Δ[total-Hb] ($r=0.8$) than for Δ[deoxy-Hb] in NIRS (Strangman et al. 2002b).

Combining the findings described above, the significance of three [Hb] indices in NIRS measurements are assumed as follows (Tamura 2002): 1) [oxy-Hb] is the most sensitive and reliable parameter in near-infrared measurements; 2) [total-Hb] changes also approximately correspond to blood flow changes if their magnitudes are sufficiently large; 3) [deoxy-Hb] changes are highly complex for precise interpretation.

5.2. Two differences between NIRS and fMRI data

The relationships between [Hb] data in NIRS and BOLD signals in fMRI are rather complex as described in section 5.1. Commonly encountered in several NIRS laboratories are two differences between NIRS and fMRI data: 1) the activated brain regions indicated by [oxy-Hb] increases in NIRS are not so clearly localized as those indicated by BOLD signals in fMRI (localization problem); 2) spatial and temporal correspondences with assumed brain activation are observed in NIRS often more clearly for [oxy-Hb] and [total-Hb] than for [deoxy-Hb], which is considered to be closely related to BOLD signals in fMRI (correspondence problem). These two issues are discussed in the following subsections.

5.2.1. Localization problem

The first problem regarding the relationships between [Hb] data in NIRS and BOLD signals in fMRI is the localization problem; the activated brain regions indicated by [oxy-Hb] increases in NIRS are not so clearly localized as those indicated by BOLD signals in fMRI. Two explanations for the localization problem are possible. First, the difference in spatial resolution between NIRS and fMRI is considered to affect their localization accuracy of activated brain regions. The lower spatial resolution of NIRS than that of fMRI can result in more blurred vague identification of activated brain regions; that

is, brain regions defined as activated using NIRS tend to be broader than those defined using fMRI.

Second, standard procedures for fMRI data analyses can identify activated brain regions rather narrower than the real-activation regions. Statistical parametric mapping (SPM) generally employed in fMRI data analyses adopt hypothesized models of CBF changes in response to task loads, and the brain regions are identified as activated if their BOLD signal intensity changes show a high temporal correlation with the models. The response models generally assume that CBF increases and decreases several seconds after the start and the end of the task, respectively.

The above-mentioned procedures for data analyses will result in the precise estimation of the significance levels of activation in brain regions where CBF changes occur in the same time course as that in the proposed models, but in the underestimation of the activation in brain regions where CBF changes really occur but in a time course different from those of the assumed models. For example, the primary sensory cortex in a sensory stimulation task and the primary motor cortex in a simple motor task are preferentially identified as activated, but the association cortices, for example, tend to be identified as not activated because their activation time courses differ from those of the assumed models.

On the other hand, NIRS measures CBV changes without any assumptions on their time courses because of its high time resolution; hence, it can detect activated brain regions regardless of their time courses. That is, brain regions indirectly as well as directly activated by a task demand are recognized as activated. Such differences in data analysis between NIRS and fMRI could be the second reason for the broader identification of activated brain regions in NIRS than those in fMRI.

5.2.2. Correspondence problem

The second problem regarding the relationships between [Hb] data in NIRS and BOLD signals in fMRI is the correspondence problem; spatial and temporal correspondences with assumed brain activation are often observed in NIRS more clearly for [oxy-Hb] and [total-Hb] than for [deoxy-Hb], which is considered to be closely related to BOLD signals in fMRI. This problem can be explained on the basis of the assumed differences between the measurement objects of NIRS and fMRI: NIRS mainly measures hemoglobin in capillaries whereas fMRI mainly measures hemoglobin in small vessels.

The conventional BOLD signal theory hypothesizes that fMRI measures hemoglobin changes in small vessels, particularlly in venules. According to the theory, brain activation causes [deoxy-Hb] increases due to oxygen consumption in the activated regions, followed by [deoxy-Hb] decreases due to overcompensatory increases in CBF; these [deoxy-Hb] changes in small veins are considered to be reflected in changes in the BOLD signal intensity. If the contribution of capillaries as well as small vessels to hemoglobin signals is taken into consideration, however, the assumption mentioned above must be modified to obtain a revised theory, as has been suggested recently (Yamamoto and Kato 2002).

The revised theory claims that brain activation induces blood flow changes in both terms of velocity and bed areas. The changes in blood flow velocity and flow bed areas are detected as CBF and CBV, respectively, and the ratio of velocity to bed area changes in blood flow differs between small vessels and capillaries; bed area changes are smaller than velocity changes in small vessels, but are larger in capillaries (Table 1). These differences result in the differences in the [oxy-Hb] and

[deoxy-Hb] changes between small vessels and capillaries in the overcompensatory hemodynamic phase; [oxy-Hb] increases and [deoxy-Hb] decreases in small vessels, and [oxy-Hb] increases and variable [deoxy-Hb] changes occur in capillaries. Considering that fMRI and NIRS preferentially detect hemoglobin signals in small vessels and capillaries, respectively, the hemodynamic changes due to brain activation are expressed as [deoxy-Hb] decreases in small vessels (namely, BOLD signal changes) in fMRI and [oxy-Hb] increases in NIRS.

The explanation for the correspondence problem mentioned above is only speculative at present, and awaits more decisive evidences from experimental studies.

6. Establishing laboratory tests for the diagnosis and treatment of psychiatric disorders

NIRS has already been presented as a possible laboratory test for psychiatric disorders in a psychiatry textbook for medical students (Okuma "*Modern Clinical Psychiatry, 9th ed*", 2002) and in a medical handbook for the general population (Nomura, Higuchi "*Encyclopedia of the Mind and its Disorders*", 2003) in Japan. This may represent a strong desire of patients and families with psychiatric disorders for the establishment of laboratory tests which are clinically available for the diagnosis and treatment of their illnesses.

However, as is well known among psychiatric professionals, no laboratory findings can be used to conclusively establish diagnoses, to assess severity, or to monitor responses to treatment of psychiatric disorders. Pioneering and promising techniques reported in research papers suffer from the following weaknesses with respect to their possible employment as laboratory tests in clinical settings: they are often too elaborate, too time consuming, or too expensive; the data distributions are, in fact, significantly different between patient and control groups, but are not sufficiently segregated to allow delineation of a single case data between groups; certain characteristics are commonly observed in both patients and their relatives, i.e., as trait markers, and hence they are useful for the identification of vulnerability to psychiatric disorders, but not for confirming the presence of psychiatric disorders. Therefore, the establishment of laboratory tests that are useful for disease diagnosis, severity assessment, treatment selection, recovery monitoring, recurrence prediction, and even onset prevention of psychiatric disorders is currently one of the most urgent problems in psychiatric practice. If established, such laboratory tests would not only be useful for psychiatric professionals, but also helpful in enabling patients and their families to play a central role in their psychiatric treatment and thus to empower themselves.

The importance of establishing laboratory tests for the diagnosis and treatment of medical problems has already been well documented for physical illnesses such as hypertension and diabetes mellitus. For example, patients with hypertension can monitor their hypertension status by checking their blood pressure levels using a sphygmomanometer in their home at any time without seeing their doctors. The ability to obtain blood pressure data by themselves motivates patients to exercise regularly, restrict their salt intake, and adhere to their antihypertensive medication regime. That is, the ability to monitor their own hypertension status enables them to play a central role in its treatment.

Among structural and functional brain imaging techniques such as MRI, SPECT, PET, EEG, and MEG, NIRS is one of the most promising candidates for a laboratory test for the diagnosis and treatment of psychiatric disorders in clinical practices, because of the small size of the apparatus, the complete noninvasiveness of the measurement, the least necessity for the constraint of the subjects' heads and bodies, and the smallest expenses for the apparatus and running costs. Such laboratory tests will help to make psychiatric diagnosis more objective, psychiatric treatment more efficient, and prognosis prediction more accurate. As the first step to be established as a clinical test, results of efforts to standardize NIRS data for age and sex have already been reported (Kameyama et al. 2004b).

In addition, if NIRS devices can be downscaled to be as small as sphygmomanometers for home use, psychiatric patients will be able to use them in order to monitor their psychiatric condition and psychological stress levels on a daily basis at home, and to evaluate by themselves the efficacy of their psychological treatments, such as cognitive therapy. If such domestic scale NIRS machines become widespread in the future, they can be employed for stress management in the general population, and thus would serve to promote psychological health and to prevent the development of psychiatric disorders.

The author expects that the findings of various psychiatric studies including NIRS will lead to the availability of laboratory tests for the clinical diagnosis and treatment of psychiatric disorders in the near future.

Acknowledgements

The NIRS data presented in section 4 were obtained and analyzed in collaboration with the following researchers in the Department of Psychiatry and Behavioral Science, Graduate School of Medicine, Gunma University: Profs. Masahiko Mikuni, Itsuro Ida, Toru Uehara, Drs. Makoto Itoh, Tomohiro Suto, Masaki Kameyama and Yutaka Yamagishi, and also with the assistance of medical school students at Gunma University: Mr. Ryu Takizawa and Ms. Ayako Kawakami.

References

[1] Akiyoshi J, Hieda K, Aoki Y, Nagayama H. Frontal brain hypoactivity as a biological substrate of anxiety in patients with panic disorders. *Neuropsychobiology* 2003; 47:165-170.

[2] Chance B, Zhuang Z, UnAh C, Alter C, Lipton L. Cognition-activated low-frequency modulation to light absorption in human brain. *Proc Natl Acad Sci* 1993; 90:3770-3774.

[3] Eschweiler GW, Wegerer C, Schlotter W, Spandl C, Stevens A, Bartels W, Buchkremer G. Left prefrontal activation predicts therapeutic effects of repetitive transcranial magnetic stimulation (rTMS) in major depression. *Psychiatry Res: Neuroimaging* 2000; 99:161-172.

[4] Fallgatter AJ, Strik WK. Reduced frontal functional asymmetry in schizophrenia during a cued continuous performance test assessed with near-infrared spectroscopy. *Schizophr Bull* 2000; 26:913-919.

[5] Fukuda M, Uehara T, Ito M, Suto T, Kameyama M, Mikuni M. Functional brain imaging in psychiatry using multi-channel near-infrared spectroscopy. *Jpn J Clin Psychiatry* 2001; 30:937-951 (in Japanese).

[6] Fukuda M, Ito M, Suto T, Kameyama M, Yamagishi Y, Uehara T, Ida I, Mikuni M. Near-infrared spectroscopy as a laboratory test for diagnosis and treatment of psychiatric disorders in clinical practice. *Brain Sci Ment Disord* 2003; 14:155-171 (in Japanese).

[7] Fukuda M, Kameyama M, Yamagishi Y, Uehara T, Ito M, Suto T, Ida I, Mikuni M. Near-infrared spectroscopy in pathophysiological studies of psychiatric disorders. *Jpn J Clin Psychiatry* 2004; 3:787-798 (in Japanese).

[8] Haida M, Kurita T, Shinohara Y, Kawaguchi F, Koizumi H. Simultaneous measurement of optical topography and functionalMRI. *Cereb Blood Flow Metabol (Tokyo)* 2000; 12:227-8 (in Japanese).

[9] Hoshi Y, Tamura M. Detection of dynamic changes in cerebral oxygenation coupled to neuronal function during mental work in human. *Neurosci Lett* 1993; 150:5-8.

[10] Ito M, Suto T, Uehara T, Ida I, Fukuda M, Mikuni M. Cerebral blood volume activation pattern as biological substrate of personality: multichannel near-infrared spectroscopy study in healthy subjects. *In*: Hirata K et al. eds. "*Recent Advances in Human Brain Mapping*", Elsevier Science, 2002; 71-75.

[11] Jöbis FF. Noninvasive infrared monitoring of cerebral and myocardial oxygen sufficiency and circulatory parameters. *Science* 1977; 198:1264-1267.

[12] Kameyama M, Suto T, Yamagishi Y, Ito M, Toru U, Fukuda M, Mikuni M. Cerebral blood volume changes during cognitive and motor activation in bipolar disorder: a multichannel near-infrared spectroscopy study. *Biol Psychiatry* 2004a; 55:135S (abstract for the 59th annual meeting of Society of Biological Psychiatry).

[13] Kameyama M, Fukuda M, Uehara T, Mikuni M. Sex and age dependencies of cerebral blood volume changes during cognitive activation: a multichannel near-infrared spectroscopy study. *NeuroImage* 2004b; 22:1715-1721.

[14] Kato T, Kamei A, Takashima S, Ozaki T. Human visual cortical function during photic stimulation monitoring by means of near-infrared spectroscopy. *J Cereb Blood Flow Metab* 1993; 13:516-520.

[15] Kato T. MRS and NIRS. *In*: Kurachi M, Matsuda H, Eds. *Neuroimaging in Clinical Practice of Psychiatry (Encyclopedia of Clinical Psychiatry Vol. S10)*, Nakayama Shoten, Tokyo, 2000; 498-510 (in Japanese).

[16] Kleinschmidt A, Obrig H, Requardt M, Merboldt K-D, Dirnagl U, Villringer A, Frahm J. Simultaneous recording of cerebral blood oxygenation changes during human brain activation by magnetic resonance imaging and near-infrared spectroscopy. *J Cereb Blood Flow Metab* 1996; 16:817-826.

[17] Maki A, Yamashita Y, Ito Y, Watanabe E, Mayanagi Y, Koizumi H. Spatial and temporal analysis of human motor activity using noninvasive NIR topography. *Med Phys* 1995; 22:1997-2005.

[18] Matsuo K, Kato T, Fukuda M, Kato N. Alteration of hemoglobin oxygenation in the frontal region in elderly depressed patients as measured by near-infrared spectroscopy. *J Neuropsychiatry Clin Neurosci* 2000; 12:465-471

[19] Matsuo K, Kato N, Kato T. Decreased cerebral haemodynamic response to cognitive and physiological tasks in mood disorders as shown by near-infrared spectroscopy. *Psychol Med* 2002; 32:1029-1037

[20] Matsuo K, Kato T, Taneichi K, Matsumoto A, Ohtani T, Hamamoto T, Yamasue H, Sakano Y, Sasaki T, Sadamatsu M, Iwanami A, Asukai N, Kato N. Activation of the prefrontal cortex to trauma-related stimuli measured by near-infrared spectroscopy in posttraumatic stress disorder due to terrorism. *Psychophysiology* 2003a; 40:492-500.

[21] Matsuo K, Taneichi K, Matsumoto A, Ohtani T, Yamasue H, Sakano Y, Sasaki T, Sadamatsu M, Iwanami A, Asukai N, Kato N, Kato T. Hypoactivation of the prefrontal cortex during verbal fluency test in PTSD: a near-infrared spectroscopy study. *Psychiatry Res: Neuroimaging* 2003b; 124:1-10.

[22] Matsuo K, Watanabe A, Onodera Y. Prefrontal hemodynamic response to verbal-fluency task and hyperventilation in bipolar disorder measured by multi-channel near-infrared spectroscopy. *J Affect Disord* 2004; in press.

[23] Mehagnoul-Schipper DJ, van der Kallen BFW Colier WNJM, van der Sluijs MC, van Erning LJTO, Thijssen HOM, Oeseburg B, Hoefnagels WHL, Jansen RWMM. Simultanous 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 Mapping* 2002; 16:14-23.

[24] Okada F, Tokumitsu Y, Hoshi Y, Tamura M. Impaired interhemispheric integration in brain oxygenation and hemodynamics in schizophrenia. *Eur Arch Psychiatry Clin Neurosci* 1994; 244:17-25.

[25] Okada F, Takahashi N, Tokumitsu Y. Dominance of the 'nondominant' hemisphere in depression. *J Affect Disord* 1996; 37:13-21.

[26] Saito S, Yoshikawa D, Nishihara F, Morita T, Kitani Y, Amaya T, Fujita T. The cerebral hemodynamic response to electrically induced seizures in man. *Brain Res* 1995; 673:93-100.

[27] Saito S, Miyoshi S, Yoshikawa D, Shimada H, Morita T, Kitani Y. Regional cerebral oxygen saturation during electroconvulsive therapy: monitoring by near-infrared spectrophotometry. *Anesth Analg* 1996; 83:726-30.

[28] Shinba T, Nagano M, Kariya N, Ogawa K, Shinozaki T, Shimosato S, Hoshi Y. Near-infrared spectroscopy analysis of frontal lobe dysfunction in schizophrenia. *Biol Psychiatry* 2004; 55:154-164.

[29] Strangman G, Boas DA, Sutton JP. Non-invasive neuroimaging using near-infrared light. *Biol Psychiatry* 2002a; 52:679-693.

[30] Strangman G, Culver JP, Thompson JH, Boas DA. A quantitative comparison of simultaneous BOLD fMRI and NIRS recordings during functional brain activation. *NeuroImage* 2002b; 17:719-731.

[31] Suto T, Fukuda M, Ito M, Uehara T, Mikuni M. Multichannel near-infrared spectroscopy in depression and schizophrenia: cognitive brain activation study. *Biol Psychiatry* 2004; 55:501-511.

[32] Tamura M, Hoshi Y, Okada F. Localized near-infrared spectroscopy and functional imaging of brain activity. *Phil Trans Soc Lond B* 1997; 352:737-742.

[33] Tamura M. Functional brain imaging using light (1). *Clin Encephalogr (Osaka)* 2002; 44:389-397 (in Japanese).

[34] Toronov V, Webb A, Choi JH. Investigation of human brain hemodynamics by simultaneous near-infrared spectroscopy and functional magnetic resonance imaging. *Med Phys* 2001; 28:521-527.

[35] Villringer A, Plank J, Hock C, Schleinkofer L, Dirnagl U. Near-infrared spectroscopy (NIRS): a new tool to study hemodynamic changes during activation of brain function in human adults. *Neurosci Lett* 1993; 154:101-104.

[36] Watanabe E, Maki A, Kawaguchi F, Takashiro K, Yamashita Y, Koizumi H, Mayanagi Y. Non-invasive assessment of language dominance with near-infrared spectroscopic mapping. *Neurosci Lett* 1998; 256:49-52.

[37] Watanabe A, Kato T. Cerebrovascular response to cognitive tasks in patients with schizophrenia measured by near-infrared spectroscopy. *Schizophr Bull* 2004; in press.

[38] Yamamoto T, Kato T. Paradoxical correlation between signal in functional magnetic resonance imaging and deoxygenated haemoglobin content in capillaries: a new theoretical explanation. *Phys Med Biol* 2002; 47:1121-1141.

Figure Legends

Fig. 1 NIRS examination.

One of the researchers is undertaking multichannel NIRS examination with temporal probes on his head, and its results are displayed as a [oxy-Hb] topograph on the CRT (Gunma University, Optical Topography System ETG-100 by Hitachi Medical Corp.).

Fig. 2 Grand averaged waveforms of hemoglobin concentration changes during cognitive activation in the control group (Suto et al. 2004).

Grand averaged waveforms of [oxy-Hb] (red line), [deoxy-Hb] (blue line), and [total-Hb] (yellow line) changes during cognitive activation (between two vertical light-blue lines) in the frontal channels (center), and the left (right) and right temporal channels (left) in the control group. Three sets of grand average waveforms and superimposed individual waveforms of [oxy-Hb] changes in representative channels (circled in orange) are enlarged below.

Fig. 3 Grand averaged waveforms of hemoglobin concentration changes during cognitive activation in the depression group (Suto et al. 2004).

Data for the depression group are shown as in Fig. 2.

Fig. 4 Grand averaged waveforms of hemoglobin concentration changes during cognitive activation in the schizophrenia group (Suto et al. 2004).

Data for the schizophrenia group are shown as in Fig. 2.

Fig. 5 Topographical presentation of [oxy-Hb] changes during cognitive activation in the three groups (Suto et al. 2004).

The [oxy-Hb] changes in the control (Con., left), depression (Dep., center), and schizophrenia groups (Sch., right) are presented as topographical maps along the time course of the task (from top to bottom). Each set of topographical maps is composed of three maps corresponding to the results in the frontal and bilateral temporal channels. The time from the start of the task is indicated in seconds on the left-hand side. The red, green, and blue areas in the topographs indicate increase, no change, and decrease in [oxy-Hb], respectively.

Fig. 6 NIRS channels with significant differences in [oxy-Hb] changes between the depression and the control groups in the verbal fluency task superimposed on the 3D reconstructed brain image.

Fig. 7 Schematic illustrations of [oxy-Hb] changes during the verbal fluency task for the control, the depression, the bipolar disorder, and the schizophrenia groups.

Table

The relationship between BOLD in fMRI and [Hb] data in NIRS

	small vessels	capillaries
blood flow velocity	↑ ↑	↑
blood flow bed area	↑	↑ ↑
oxy-Hb	↑	↑ ↑ **
deoxy-Hb	↓ ↓ *	↑ ~ ↓ **

* : reflected as BOLD signals in fMRI

** : reflected as [Hb] changes in NIRS

1章 統合失調症の遺伝学

岡崎祐士　峯田 聖　谷井久志

要 旨

統合失調症は遺伝が関与しているが（遺伝率 0.7 以上）メンデル遺伝形式は特定されておらず，環境因子も関与する多因子疾患と考えられている．1980 年代後半から遺伝子マッピング研究が開始された．遺伝形式や従って浸透率の仮定を要しない罹患同胞対法の採用，DNA マーカーの進歩（マイクロサテライトマーカー，SNPs），ハイスループットシステムの開発，ハプロタイプ解析の採用，メタ分析可能な数の所見蓄積などによって，21 世紀に入って統合失調症感受性遺伝子マッピングはようやく実りつつある．有望な候補遺伝子として *COMT*（22q11），*DTNBP1*（*Dysbindin*，6p24-21），*NRG1*（8p12-p21），*RGS4*（1q21-q22），*GRM3*（7q21-q22），*DISC1*（1q42），*G72*（13q32-q34），*DAAO*（12q24），*PPP3CC*（8p21），*CHRNA7*（15q13-q14），*PRODH2*（22q11），*Akt1*（14q22-q32）などが挙げられている．しかし，これらの表現型への寄与度は小さく，表現型が核内遺伝子配列変異や多型のみで説明できるかには疑問が呈されており，遺伝子の塩基配列だけでは規定できないメカニズム（エピジェネティクスなど）の関与への顧慮が必要と考えられる．

キーワード　罹患同胞対法　連鎖不平衡解析　エピジェネティクス

1-1・はじめに

ある疾患が遺伝子・ゲノム解析研究の対象になるには，当然のことながらその疾患の成立のいずれかの側面に遺伝因が関与していることが前提である．疾患が遺伝するとは，疾患が遺伝子型の表現型（遺伝形質）であり，遺伝子型と表現型が関連して上流世代から下流世代に伝達される現象を呈するものである．セントラルドグマの強い影響から免れずに分子遺伝学が発展したために，タンパク質はすべて核内遺伝子の直接の発現によるものであり，遺伝子マッピングによって得られる結果はすべて，核内遺伝子の変異や多型，つまり塩基配列変異として見いだされるはずだという暗黙の仮定が存在した．メンデル遺伝形式の伝達を示す疾患はこの仮定で間違いないが，非メンデル遺伝形式疾患が存在し，その場合には，いったん保留して考えなければならない．世代間伝達を示すようにみえる疾患でも，核内遺伝子配列多型や変異によるもののみとは限らないからである．スプライシング異常を原因とする疾患などセントラルドグマの例外は今日当たり前になっている．たとえばタンパク質をコードしない mRNA もタンパク質発現にかかわる[1]．また，下流世代に伝達もされるが核