**Key words:** functional connectivity, functional magnetic resonance imaging, Near-infrared spectroscopy

## Introduction

The human brain has approximately 50 functionally distinct cortical regions, which co-work with each other to conduct our cognitive and motor behaviors. An extensive network of fibers connects different cortical regions and disruptions in such cortico-cortical connectivity lead to cognitive and behavioral dysfunction.

Although measurement of functional connectivity of the human brain is essential in understanding both normal and pathological brain function, majority of brain mapping studies using functional neuroimaging technique has been directed toward assessing functional segregation rather than functional organization.

Notably, a few studies have explored functional connectivity using covariance analysis during cognitive tasks (1,2). The task-driven covariance analysis, such as eigenimage analysis (1) may not show actual anatomical connectivity, but rather concurrent neuronal activity resulting from the task itself (3).

An alternative to the task-driven method is connectivity inferred from data acquired during a resting state (4-9). During a resting state, there is spontaneous firing of neurons, which is always followed by rCBF increases with duration of -12 sec (10). Such rCBF increases change blood oxygen level, which in turn change the BOLD signal in fMRI time course (slow fluctuation). Neural firings in a specific brain region affect remotely located neurons in other brain areas through their efferent output (11). The

synchrony of the fluctuations in functionally related brain regions implies the existence of neuronal connection that facilitates coordinated activity. By calculating covariance of each voxel reference to the time course of a selected brain area, it is possible to detect the functional connection to the selected brain area.

The temporal and spatial resolutions of fMRI seem to have advantages to assess functional connectivity. Indeed, Biswal et al. observed that the low frequency (< 0.08Hz) MR signal fluctuations during resting state from single slice fMRI measurements are correlate between right and left motor cortices (4,5). While a few studies have demonstrated the possibility of functional connectivity MRI (fcMRI), methods are still under investigation and their reliability is controversial (4,5,6,8,9). Functional connectivity measurements during the rest status may be susceptible to subjects' artifacts resulting from motion and fluctuation or aliases in signal intensity due to physiological noise (12). Since a functional connectivity measurement requires high temporal resolution, Biswal et al. applied rapid sampled single slice EPI. If the functional connectivity measurement extends from single slice to a whole brain measurement at the expense of temporal resolution, MRI may become a useful tool for evaluating functional connectivity.

Near-infrared spectroscopy (NIRS) has higher temporal resolution than that of BOLD MRI and it provides a time course of more direct hemodynamic changes than those obtained by BOLD MRI. A simultaneous measurement of magnetic resonance imaging and NIRS allow us to employ a time course of hemodynamic changes obtained by NIRS as a reference time course for fcMRI. It would also provide some

physiological validity of the method of fcMRI.

In this study, we applied simultaneous measurements of magnetic resonance imaging and NIRS during the resting state in normal subjects. The aim of the present study is to compare a functional connectivity map of motor system based on the time course of NIRS signal over the primary motor cortex (M1) with that based on slow periodical fluctuation in signal intensity of BOLD MRI.

## Methods

### Subjects

Four right-handed male (range 31 - 42, mean age 34.8 year-old) without history of neurological and psychiatric disorders participated in the present study. Written informed consent was obtained from all subjects in accordance with ethical guidelines in place at local ethical committee.

### Paradigms

MR measurements were performed during two different paradigms: random finger tapping task sessions to be used to define representations of the right hand in the primary motor area (M1) in each subject and 'rest' sessions for functional connectivity maps. Subjects first performed the random finger tapping task and then the 'resting state' session. The interval of each session was 2min. Activation of brain regions related to random finger tapping was compared with that in a control condition alternating 5 cycles of 22.8-second epochs. In the random finger tapping condition, subjects were asked to oppose each right finger with the right thumb in random sequences at a frequency of 3Hz. The auditory stimuli of metronome (3Hz) were served by an air-

conducting headphone throughout scanning. Task performance was visually monitored during scanning. During control condition, the auditory stimuli were given but subjects were forbidden any movement and motor imagery and discouraged from thinking anything. Visual stimuli were presented by a PC and backprojected onto a screen, approximately 50-cm from the subject's head, using a 65536 -color liquid crystal display and an overhead projector. Subjects viewed the screen through a mirror attached to the head coil. They were asked to begin random finger tapping while screen was green and to stop random finger tapping and keep control condition while screen was red.

In the 'resting state' session for functional connectivity map, subjects were instructed to view black screen, be as motionless as possible, and perform no specific cognitive exercise during MR measurement. The subject's eyes were visually monitored by near-infrared camera attached to the head coil to confirm whether they were awake during scanning. All subjects were awake during all scanning sessions.

**fMRI procedure**

Blood oxygen level-dependent contrast EPI was acquired twice in each subject (13). After automatic shimming, a time course series of 110 (for random finger tapping task) or 210 volumes (for resting state) were obtained using single-shot gradient-refocused echo-planar imaging (TR = 2000 msec, TE = 60 msec, Flip angle = 90 degree, in-plane resolution 3.44 x 3.44 mm, FOV = 22 cm, contiguous 7-mm slices to cover the entire brain with a 1.5T MAGNETOM Vision plus MR scanner (Siemens, Erlangen, Germany) using the standard head coil. Head motion was minimized by placing tight but comfortable foam padding around the subject's head.

**NIRS procedure**

We used a near infrared spectroscopy (NIRS) system (OMM-2000; Shimadzu, Japan) to detect changes in oxygenated hemoglobin (oxyHb), deoxygenated hemoglobin (deoxyHb), and total hemoglobin (totalHb), included in the cerebral cortex a few centimeters below the skull surface. 8 source fibers were attached at the probe pad fixed on the head of the subject and each source fiber transmitted light from three laser diodes of 780, 805 and 830nm. The location of left M1 in each subject was determined by transcranial magnetic stimulation (fig.1a). Diffusely reflected light fluxes from the brain was caught by another 8 fibers and respectively guided to photomultipliers for final detection. Inter-optode distance was set at 30mm to ensure the NIR light to reach the cerebral cortex. From the possible combination of 64 (8 X 8) source-detector signals, absorbance signals (Abs) coming from 23 neighboring source-detector pairs were picked up according to an operator-definable table. Changes in hemoglobin values, oxyHb, deoxyHb and totalHb were obtained from the absorbance values of respective wavelength by the next equation. Absorbance values of respective wavelength by the next equation.

$$\begin{pmatrix} \Delta oxyHb \\ \Delta deoxyHb \\ \Delta totalHb \end{pmatrix} = \begin{pmatrix} -1.4887x & 0.597 & 1.4847 \\ 1.854 & -0.2394 & -1.0947 \\ 0.3653 & 0.3576 & 0.39 \end{pmatrix} \cdot \begin{pmatrix} \Delta Abs(780nm) \\ \Delta Abs(805nm) \\ \Delta Abs(830nm) \end{pmatrix}$$

Thus obtained values of oxyHb, deoxyHb and totalHb at 23 respective positions on the cerebral cortex were used for imaging after adapting the liner interpolation. One of laser diodes lit for 5 milliseconds one by one. And minimum time for acquisition of a full image data was 100 milliseconds. Time integration of images was carried out for final

presentation depending on the required S/N ratio and the required response time.

**Data analysis**

**1) Data analysis of task-related change**

Data were analyzed with Statistical Parametric Mapping software (SPM99, http//:www.fil.ion.ucl.ac.uk/spm). The first ten volumes of each fMRI scan were discarded because of non-steady condition of magnetization, and remaining 100 volumes were used for analysis. Scans were realigned and spatially normalized to the standard stereotactic space of Talairach using EPI template. The parameter for affine and quadratic transformation to the EPI template that was already fit for Talairach space was estimated by least-squares means (14). Data were then smoothed in a spatial domain (full width at half-maxim = 8 x 8 x 12 mm) to improve the signal to noise ratio. After specifying the appropriate design matrix, delayed box-car function as a reference waveform, the condition, slow hemodynamic fluctuation unrelated to the task, and subject effects were estimated according to the general linear model and temporal smoothness into account. Global normalization was performed using proportional scaling. To test hypotheses about regionally specific condition effects, the estimates were compared by means of linear contrasts of each rest and task period. We applied a conjunction analysis to search commonly activated areas from multi-subject fMRI data (15). The resulting set of voxel values for each contrast constituted a statistical parametric map of the t statistic SPM{t}. Any clusters with $p < 0.001$ were considered significant.

**2) Analysis of functional connectivity using fMRI during rest state**

Fig.1a and 1b show schemes of analysis of functional connectivity using fMRI during rest state. Data of rest state were also analyzed with SPM99. The first ten volumes of each fMRI scan were discarded because of non-steady condition of magnetization, and remaining 200 volumes were used for analysis. Scans were realigned and spatially normalized to the standard stereotactic space of Talairach and then smoothed in a spatial domain. A VOI of primary motor cortex (seed voxels) defined by the data of previous fMRI session (fig.1a). The VOI includes 45 voxels (6 mm x 6mm x 10 mm) surrounding the most activated voxel during motor fMRI. Global normalization was performed using proportional scaling and time course was taken as the arithmetic average of the normalized signal intensity in the VOI. Because, hemodynamic change associated with spontaneous firing during rest should be slow fluctuation (4,5,6,8,10) and we also found low frequency spectrum below 0.08 Hz in MR and NIRS time series after Fourier transformation (fig.1a and 1b). Therefore, the resting state data from each pixel was passed through a finite-impulse response (FIR) filter to remove all frequencies above 0.08Hz using signal processing tool of Matlab 5.3. The reference time courses of the VOI and intrinsic signal change in the left M1 obtained by NIRS were also passed through a FIR filter to remove all frequencies above 0.08Hz (fig.1a and 1b). The filtered fMRI time course of the left M1 or filtered NIRS time course of reversed deoxyHb and oxyHb in the left M1 as a reference waveform, 6 motion parameters (translation X, Y, Z, and rotation X, Y, Z), and subject effects were estimated according to the general linear model (fig.1a and b). Global normalization was performed using proportional scaling and parameters of head motion were treated

as confounding covariates. We applied a conjunction analysis to search commonly areas from multi-subject fMRI data (15). The resulting set of voxel values for each contrast constituted a statistical parametric map of the t statistic SPM{t}. Any clusters with p <0.001 were considered significant.

## Results

Fig.2 shows for results of group studies the significant activations for the right random finger tapping (Fig.2a, 2b) and the significant interregional correlations during rest status using MR signal (Fig.3a, 3b) and NIRS signal (Fig.4a, 4b).

Activation related to random finger tapping was identified in the left sensorimotor area, dorsal premotor area (PMdr), supplementary motor area (SMA), dorsal cingulate motor area (CMAd), parietal association areas, and cerebellum (Fig.2a, 2b). On the other hand, functional connectivity maps obtained by using BOLD signals fluctuation and NIRS signal fluctuation demonstrated essentially the same interregional correlations during rest status. The functional connectivity MR mapping using BOLD signal revealed significant (p <0.001) correlation between left M1 (seed voxels) and the contralateral and ipsilateral primary sensorimotor areas, PMdr, SMA, CMAd, and the posterior parietal association area (PSAAp) (Fig.3a, 3b). For the time course of oxy-hemoglobin the left M1, significantly (p <0.001) correlated voxels were found in the contralateral and ipsilateral primary sensorimotor areas, PMdr, SMA, CMAd, the PSAAp and the cerebellum (Fig.5a, 5b). Using the time course of deoxyHb-hemoglobin

as the reference curve for functional connectivity MR mapping, significantly correlated voxels were not found in any region. While we applied less rigorous statistical threshold ($p < 0.05$), significantly correlated voxels were found in the similar areas.

Table 1 shows the number of subjects correlating with left M1 to each region. The percentage of correlating in each brain region was 89% by using BOLD signal fluctuation and 85 % by using NIRS signal (oxyHb) fluctuation, respectively. Therefore connectivity MR maps are quite consistent among subjects and regressors (BOLD signal and NIRS signal). Fig.5 shows typical fMRI map during random finger tapping map (fig.5a) and functional connectivity map (fig.5b, 5c) obtained from a single subject. Significant correlation ($p < 0.001$) between left M1 (seed voxels) and the contralateral and ipsilateral primary sensorimotor areas, PMdr, SMA, CMAd, cerebellum, inferior parietal lobule and the PSAAp was detected by using BOLD signal time course as a reference curve (Fig.5b). Functional connectivity MR map using NIRS signal also demonstrated similar connectivity map (Fig.5c).

## Discussion

In this study, we found that the functional connectivity MR mapping during resting state can reveal functionally connected areas with the primary motor area. Furthermore, such functional connectivity MR maps were similar to the connectivity established by non-neuroimaging methods (16,17). In addition to previous functional

MR connectivity mapping, we performed simultaneous measurement of BOLD MRI and NIRS. The data indicated that as well as NIRS signal which can measure intrinsic hemodynamic time course, functional MR connectivity mapping using MR signal fluctuation could detect functionally connected distant areas. Inter-subject variability and inter-modality variability were quite good.

Since the first report of resting functional connectivity maps using functional connectivity MR imaging were reported over 6 years ago (4), this method has been used in relatively small number of reports as compared to the exponential growth in fMRI research in general. This small growth is probably due to a skepticism of functional connectivity MR mapping whether it is fact or artifact (12). One reason for skepticism is that the exact physiological mechanisms behind the BOLD signal are still to be clarified. A weakness of functional connectivity MR mapping with BOLD signal fluctuation is the selection of bias in choosing a seed voxel. If the seed voxels overlap with CSF or vessels, results can vary substantially between voxels selected from within a VOI. The present study indicated that hemodynamic changes in the left M1 obtained by NIRS were well correlated to other distant motor areas. As well as fMRI signal, NIRS signal is also modulated by motion and physiological noises, however NIRS can measure hemodynamic changes of brain directly. Furthermore, physiological noises (0.3Hz for respiration, 1 Hz for cardiac pulsation) have higher frequencies than that of resting-state hemodynamic fluctuation (below 0.1Hz) (4,5,8). Because of these arguments, we conclude that functional MR connectivity mapping must reflect a real functional connectivity in the brain, not detecting correlation of artifacts. Our simultaneous

measurement of fMRI and NIRS should confirm some physiological validity of functional MR connectivity mapping. Furthermore, connectivity maps showed good inter-subject variability. These facts indicated that functional MR connectivity mapping using hemodynamic fluctuation during rest status is a reliable method.

Unlike previous fcMR studies (4,5,9), we performed whole brain measurement for functional connectivity with relatively low temporal resolution (2sec). One would concern whether such low frequency sampling data can detect synchrony of neural activities. However, several studies have clarified that only low frequency components of spectrum (below 0.1Hz) contribute significantly to correlation coefficient for interregional connectivity (6,8). We also found low frequency spectrum below 0.08 Hz in NIRS data having high temporal resolution (200 msec) after Fourier transformation. In terms of sampling rate, TR 2 sec seems to be sufficient to detect such a slow hemodynamic phenomenon. We consider that whole brain measurements even with low temporal resolution should be essential to explore functional connectivity without a prior hypothesis.

Unexpectedly, functional connectivity MR mapping using oxyHb time course showed more significant correlation between motor areas than those obtained using reversed deoxyHb time course. The positive BOLD signal is caused by deoxyHb washout from activated areas (13). A previous report of simultaneous measurement of NIRS and fMRI demonstrated high temporal correlation between BOLD signal and reversed deoxyHb concentration obtained by NIRS (18). In this context, we expected that reversed deoxyHb time course should be suitable for a reference curve for

functional connectivity MR mapping. This discrepancy could be explained by small signal changes of deoxyHb obtained by NIRS. However, the precise physiological mechanisms of underlying the BOLD signal are still under investigation. Recently, Hess et al. reported that hemodynamic basis of fMRI signal is not necessarily a washout of deoxyHb (19). Instead, they suggested that a positive BOLD signal could also be caused by a local increase of blood volume regardless of deoxyHb levels (19). Their observations may partly explain our unexpected results. Further study will clarify whether deoxyHb is suitable for a reference curve of BOLD MRI.

The functional connectivity MR mapping technique during resting state has been so far proven to show similar connectivity to that established by other non-neuroimaging techniques (16,17). However, our results demonstrated that indirect connection, such as betweenM1 and PSAAp, could be detected by this method. Similar results were shown in a previous study reported by Xiong (9). It is not clear whether functional connectivity MR mapping can evaluate the degree of directness of a connection. This is one possible limitation or confounds of functional MR connectivity mapping. Furthermore, it is also unclear whether functional MR connectivity mapping can reveal the direction of projection.

Finally, during the rest status, it is likely that a wide variety of cognitive and sensory processes should be activated in a chaotic manner. It is not clear whether hemodynamic fluctuations during resting are modulated by levels of consciousness. Simultaneous measurement of EEG (and event-related potential) and functional connectivity mapping may clarify these issues.

Although functional connectivity MR mapping has limitations and issues to be clarified as we mentioned above, this method may provide in vivo non-invasive measurements of functional connectivity in human brain and it should improve interpretation and modeling of brain activations obtained by task driven brain mapping methods. As well as understanding of normal brain functions, functional connectivity MR mapping have a potential to become a useful tool to understand physiology of normal development and aging of human brain, pathophysiology underlying demyelinating disease, and psychiatric disorders such as schizophrenia.

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**Legend for figures**

Fig.1 A scheme of analysis of functional connectivity MR mapping during rest state using BOLD signal fluctuations. The VOI surrounding the most activated voxel during motor fMRI. Global normalization was performed using proportional scaling and time course was taken as the arithmetic average of the normalized signal intensity in the VOI. Fourier transformation was done to evaluate characteristics of time courses of MR signal during resting status. All subjects showed low frequency spectrum below 0.08 Hz in MR time series after Fourier transformation. Therefore, the resting state data from each pixel was passed through a finite-impulse response (FIR) filter to remove all frequencies above 0.08Hz. The reference time courses of the VOI were also passed through a FIR filter to remove all frequencies above 0.08Hz. The filtered fMRI time course of the left M1 as a reference waveform (first column in the design matrix) , 6 motion parameters (translation X, Y, Z, and rotation X, Y, Z: from second to seventh column in the design matrix), and subject effects were estimated according to the general linear model (the last column in the design matrix).

Fig.1b A scheme of analysis of functional connectivity MR mapping during rest state using NIRS signal fluctuations. NIRS signals also demonstrated low frequency spectrum below 0.08 Hz after Fourier transformation. The reference time courses of the intrinsic signal change in the left M1 obtained by NIRS were also passed through a FIR filter to remove all frequencies above 0.08Hz. The filtered NIRS signal time course of reversed deoxy-Hb and oxy-Hb in the left M1 as a

reference waveform, 6 motion parameters (translation X, Y, Z, and rotation X, Y, Z), and subject effects were estimated according to the general linear model.

Fig.2 Results of group studies the significant activations for the right random finger tapping.

Fig.2a Statistical Parametric Map of the t statistics. The SPM is displayed in a standard format as a maximum intensity projection viewed from the right-hand side, the back and the top of the brain. The anatomical space corresponds to the atlas of Talairach (14). The SPM demonstrated significant activation in the left primary sensorimotor area, left dorsal premotor area (PMdr), bilateral, supplementary motor area (SMA), dorsal cingulate motor area (CMAd) and parietal association areas and cerebellum.

Fig.2b Transaxial slice images of activation map during random finger mapping.

Fig.3 The functional connectivity map using BOLD signal fluctuation during the rest status.

Fig3a. The SPM MIP image showed significant correlation between left M1 and other motor-related areas, such as contralateral primary sensorimotor areas, PMdr, SMA, CMAd, posterior parietal association area (PSAAp) and the cerebellum.

Fig3b. Transaxial slice images of functional connectivity map using BOLD signal fluctuation during the rest status.

Fig.4 the functional connectivity map using NIRS signal (oxy-Hb) fluctuation during the rest status.

Fig.4a The SPM MIP image showed significant correlation between left M1 and other

motor-related areas, such as contralateral primary sensorimotor areas, PMdr, SMA, CMAd, posterior parietal association area (PSAAp) and the cerebellum. Furthermore, fig.3 and fig.4 showed essentially the same pattern.

Fig4b. Transaxial slice images of functional connectivity map using NIRS signal (oxy-Hb) fluctuation during the rest status.

Fig.4c Functional connectivity MR map using NIRS signal fluctuation (time course of oxyHb change) (fig.3) also revealed significant correlation between left M1 and other motor-related areas.

Fig. 5 Representative functional MR maps of an individual subject.

Fig.5a The SPM demonstrated significant activation in the left primary sensorimotor area, left dorsal premotor area (PMdr), dorsal cingulate motor area (CMAd) and parietal association areas and cerebellum.

Fig.5b Significant correlation between left M1 and the contralateral and ipsilateral primary sensorimotor areas, PMdr, SMA, CMAd, bilateral cerebellum, and the PSAAp was detected by using BOLD signal time course as a reference curve.

Fig.5c Functional connectivity MR map using NIRS signal (time course of oxyHb change) also demonstrated similar connectivity map.

Table 1 No of subjects correlating with M1 in each region

| Region | M1 | S1 | PMdr | CMAd | SMA | PSAAp | Cerebellum |
|---|---|---|---|---|---|---|---|
| BOLD signal | 4 | 4 | 3 | 4 | 4 | 3 | 3 |
| NIRS signal | 4 | 4 | 2 | 4 | 4 | 3 | 3 |