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Detection of resting state functional connectivity using partial correlation analysis: A study using multi-distance and whole-head probe near-infrared spectroscopy

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ABSTRACT

Multichannel near-infrared spectroscopy (NIRS) is a functional neuroimaging modality that enables easy-to-use and noninvasive measurement of changes in blood oxygenation levels. We developed a clinically-applicable method for estimating resting state functional connectivity (RSFC) with NIRS using a partial correlation analysis to reduce the influence of extraneural components. Using a multi-distance probe arrangement NIRS, we measured resting state brain activity for 8 min in 17 healthy participants. Independent component analysis was used to extract shallow and deep signals from the original NIRS data. Pearson's correlation calculated from original signals was significantly higher than that calculated from deep signals, while partial correlation calculated from original signals was comparable to that calculated from deep (cerebral-tissue) signals alone. To further test the validity of our method, we also measured 8 min of resting state brain activity using a whole-head NIRS arrangement consisting of 17 cortical regions in 80 healthy participants. Significant RSFC between neighboring, interhemispheric homologous, and some distant ipsilateral brain region pairs was revealed. Additionally, females exhibited higher RSFC between interhemispheric occipital region-pairs, in addition to higher connectivity between some ipsilateral pairs in the left hemisphere, when compared to males. The combined results of the two component experiments indicate that partial correlation analysis is effective in reducing the influence of extracerebral signals, and that NIRS is able to detect well-described resting state networks and sex-related differences in RSFC.

1. Introduction

The human brain is a complex network comprised of multiple regions with divergent functions, yet these regions work in concert to perform, coordinate, and regulate many higher-order processes by sharing information with one another. Functional magnetic resonance imaging (fMRI) studies have demonstrated that blood oxygenation level-

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dependent (BOLD) signals contain low frequency (<0.1 Hz) components that are strongly correlated between brain regions during a resting state (Biswal et al., 1995). This correlation, usually referred to as resting state functional connectivity (RSFC), is thought to provide information regarding the neuronal integration of the human brain and the neural underpinnings of neuropsychiatric disorders (Greicius, 2008; van den Heuvel and Hulshoff Pol, 2010).

Several constellations of RSFC among anatomically separated brain regions have been observed and reproduced–termed resting-state networks–with each network consisting of brain regions involved in carrying out similar functions, such as motor function, visual processing, auditory processing, and executive function (Damoiseaux et al., 2006; De Luca et al., 2006; van den Heuvel and Hulshoff Pol, 2010). Each resting state network contains bilateral homologous brain regions. Previous research suggests that informational interchange between hemispheres occurs via the corpus callosum, as dramatic decreases in interhemispheric RSFC are observed following complete section of the corpus callosum (Johnston et al., 2008). In addition, the posterior cingulate cortex, medial frontal cortex, and inferior parietal regions are consistently observed to decrease their activity in a variety of cognitive activation tasks (Raichle et al., 2001). These areas are found to exhibit synchronized oscillation, and comprise what is known as the "default mode network" (Greicius et al., 2003).

Near-infrared spectroscopy (NIRS) is a functional neuroimaging technique that enables the noninvasive detection of relative changes in oxyhemoglobin (oxy-Hb) and deoxyhemoglobin (deoxy-Hb) concentrations in the cortical surfaces (Toronov et al., 2000). Measuring RSFC with NIRS has some advantages with respect to clinical applications. First, NIRS has relatively high temporal resolution (10 Hz) in comparison with that of fMRI (about 0.5 Hz), preventing the aliasing of higher frequency cardiac or respiratory signals (Mesquita et al., 2010). Second, NIRS is relatively inexpensive, easy to set up, and tolerant of motion artifacts in comparison with fMRI, and measurements can be obtained while the participant is sitting in a natural, upright position (Takizawa et al., 2008). In addition, because RSFC can essentially be measured without the imposition of activation tasks on the participant, the assessment of RSFC using NIRS is as facile as performing a bedside electroencephalogram (Medvedev, 2014; Mesquita et al., 2010; Niu et al., 2012; Sasai et al., 2011). NIRS studies have successfully detected bilateral homologous RSFC in frontal regions (Medvedev, 2014), sensorimotor regions (Lu et al., 2010; White et al., 2009), visual areas (Zhang et al., 2010a, b), and auditory areas (Lu et al., 2010). Interhemispheric RSFC between homologous regions was also observed in infants (Homae et al., 2010; Imai et al., 2014; White et al., 2012). Studies that simultaneously recorded NIRS and fMRI revealed that both oxy-Hb and deoxy-Hb low-frequency oscillations are well correlated with BOLD oscillations (Sasai et al., 2012).

NIRS signals are, however, potentially influenced by both cerebral and extracerebral blood oxygenation changes (Sasai et al., 2012). It has been reported, for example, that changes in skin blood flow can exert significant influences on NIRS measurements in prefrontal regions (Takahashi et al., 2011). The observed correlation between two NIRS signals appears larger than the actual correlation of the cortical activities when the signals contain common components derived from extracerebral signals.

In this study, we utilized partial correlation as the index of RSFC. Partial correlation analysis was used to calculate the correlation between any two brain regions after subtracting mutual dependencies on common influences from other brain areas. In comparison to Pearson product-moment correlation (henceforth Pearson's correlation), partial correlation is thought to more precisely reflect direct relationships between brain regions (Marrelec et al., 2006).

An fMRI study that calculated partial correlation coefficients between resting state BOLD signals from 90 brain regions found that, among 4005 possible region-pairs, 76 showed significant positive correlation, of which 29 were interhemispheric homologous region-pairs, 44 were intrahemispheric region-pairs, and only three were asymmetric interhemispheric pairs (Salvador et al., 2005).

For NIRS studies, partial correlation analysis is expected to reduce the influence of extracerebral signals because the nonspecific correlation between NIRS signals due to their shared extracerebral components are factored out by partial correlation analysis.

The objective of this study is to establish a protocol for measurement and analysis using NIRS that is easily applicable to the investigation of RSFC architecture, and to test its validity with data from healthy participants. We performed two experiments to test the following hypotheses. Experiment 1 used a multi-distance arrangement NIRS, which has the ability to separate the original NIRS data into signals derived from deep (cerebral-tissue) and shallow (extracerebral-tissue) components of the head. First, we hypothesized that low frequency bands would not contain major systemic signals, and that the coherence between deep signals would exhibit more variation than that observed between shallow signals since deep signals reflect blood oxygenation oscillations specific to each brain region. Second, we hypothesized that, as compared with Pearson's correlation, partial correlation would effectively remove the influence of extracerebral signals, and that RSFC estimated from original NIRS signals would be comparable to that estimated from deep signals. Experiment 2 used a whole-head NIRS arrangement. We hypothesized that RSFC between interhemispheric homologous and intrahemispheric brain region-pairs constituting previously reported resting state networks would be detected using partial correlation analysis. We additionally hypothesized that partial correlation analysis would allow us to detect the sex- and age-related differences in RSFC observed in previous fMRI studies (Biswal et al., 2010; Lenroot et al., 2007; Tomasi and Volkow, 2012a, b), with specific focus on interhemispheric homologous region-pairs and age-related decreases in RSFC.

2. Materials and methods

2.1. Experiment 1

2.1.1. Participants

Seventeen healthy adults (9 male, 8 female; age = 34.0 ± 3.9 years) participated in the study. Following a thorough explanation of the study requirements and procedures, all participants provided written informed consent, in accordance with the Declaration of Helsinki. The existence of psychiatric disorders was ruled out using the Mini-International Neuropsychiatric Interview (Otsubo et al., 2005; Sheehan et al., 1998). This study was approved by the Research Ethics Committee of the University of Tokyo Hospital (approval No. 630-11, 3361).

2.1.2. Data acquisition

Participants were seated upright in a comfortable chair in a quiet, dimly lit room. The measurement protocol consisted of an (1) eight-minute resting period, (2) a 1 min interval period, and (3) a four-minute period of intentional motion. Participants were instructed to close their eyes, minimize body movement, clear their minds, and stay awake as signals were collected during the eight-minute resting period. Data were collected at a sampling rate of 0.1 s. A total of 4801 time points from resting period was used for analysis. Upon completion of the resting period, sleepiness was evaluated using the Stanford Sleepiness Scale (SSS) (Hoddes et al., 1973).

Fluctuations in relative concentrations of oxy-Hb and deoxy-Hb were measured using a multi-distance NIRS arrangement (composed of two ETG-4000 machines, Hitachi Medical Co. Ltd., Tokyo, Japan). The system comprised of two thermoplastic shells containing eight sources and 15 detectors with adjacent source–detector (S-D) pairs (henceforth referred to as "channels" [Ch]) separated by either 30 mm or 15 mm (Fig. 1A). 44 long distance (30 mm) channels were used to record a combination of signals derived from both deep and shallow tissue, whereas 16 short distance (15 mm) channels were used to record