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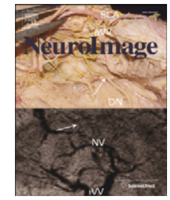

Does the resting state connectivity have hemispheric asymmetry? A near-infrared spectroscopy study

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ABSTRACT

Near-infrared spectroscopy (NIRS) is a novel technology for low-cost noninvasive brain imaging suitable for use in virtually all subject and patient populations. Numerous studies of brain functional connectivity using fMRI, and recently NIRS, suggest new tools for the assessment of cognitive functions during task performance and the resting state (RS). We analyzed functional connectivity and its possible hemispheric asymmetry measuring coherence of optical signals at low frequencies (0.01–0.1 Hz) in the prefrontal cortex in 13 right-handed (RH) and 2 left-handed (LH) healthy subjects at rest (4–8 min) using a continuous-wave NIRS instrument CW5 (TechEn, Milford, MA). Two optical probes were placed bilaterally over the inferior frontal gyrus (IFG) and the middle frontal gyrus (MFG) using anatomical landmarks of the 10–20 system. As a result, 28 optical channels (14 for each hemisphere) were recorded for changes in oxygenated (HbO) and de-oxygenated (HbR) hemoglobin. Global physiological signals (respiratory and cardiac) were removed using Principal and Independent Component Analyses. Inter-channel coherences for HbO and HbR signals were calculated using Morlet wavelets along with correlation coefficients. Connectivity matrices showed specific patterns of connectivity which was higher within each anatomical region (IFG and MFG) and between hemispheres (e.g., left IFG < — > right IFG) than between IFG and MFG in the same hemisphere. Laterality indexes were calculated as t-values for the 'left > right' comparisons of intrinsic connectivity within each regional group of channels in each subject. Regardless of handedness, the group average laterality indexes were negative thus revealing significantly higher connectivity in the right hemisphere in the majority of RH subjects and in both LH subjects. The analysis of Granger causality between hemispheres has also shown a greater flow of information from the right to the left hemisphere which may point to an important role of the right hemisphere in the resting state. These data encourage further exploration of the NIRS connectivity and its application for the analysis of hemispheric relationships within the functional architecture of the brain.

Introduction

Near-infrared spectroscopy (NIRS) is a novel and promising technology for cost effective and noninvasive brain imaging in research and clinical practice. It has several unique features whose capabilities have not yet been fully explored. Using this technique, one can measure local changes in hemoglobin concentrations within cortical layers and, provided multiple channels are used, proceed to spatial image reconstruction for both oxygenated (HbO) and de-oxygenated forms of hemoglobin (Diffuse Optical Tomography). Thus, NIRS detects hemodynamic modulations as an indirect measure of neuronal activity conceptually similar to the blood oxygen level dependent (BOLD) functional magnetic resonance imaging (fMRI) signal. In addition to low cost and portability, NIRS provides an imaging method with reasonable spatial and excellent temporal resolution (as found in electrophysiological methods such as EEG and MEG) complementary to other imaging methods based on the hemodynamic response (fMRI and positron emission tomography, PET). With the advent of multi-channel and high density optical instruments, it also becomes possible to measure dynamic interactions between brain areas through temporal correlations of NIRS signals and therefore deriving a NIRS-based 'functional connectivity' similar to the functional connectivity measured by the fMRI BOLD signal (Friston et al., 1993).

Recent advances in brain functional network analysis provide new tools to study functional architecture of the brain. Evidence is emerging that this architecture is relatively stable during various cognitive tasks as well as the resting state. Numerous fMRI studies have confirmed that resting state networks (RSN) (De Luca et al., 2006) reflect interactions in cognitively relevant functional networks. Recent studies have also demonstrated that NIRS can be used to detect spontaneous hemodynamic fluctuations (Hoshi et al., 1998; Obrig et al., 2000; Toronov et al., 2000) and to assess regional connectivity through functionally relevant correlations within those fluctuations

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(Lu et al., 2010; White et al., 2009). Here, we explore the feasibility of analyzing RSNs within the left and right prefrontal cortex in the temporal and spectral domains measuring correlation of hemodynamic NIRS signals along with their coherence at low frequencies (0.01–0.1 Hz) in the resting state. In this report, we present preliminary data with the major goal to assess the applicability of noninvasive optical imaging as a tool for hemispheric lateralization of functional connectivity. In this study, we focused on temporal modulations of optical signals measuring correlation and coherence of those modulations within and between the investigated areas to study local and bilateral functional connectivity in the resting state.

Materials and methods

Participants

Thirteen right-handed and two left-handed young adults (six females, age 18–30, mean age 23) took part in the study after signing a consent form approved by the Georgetown University Institutional Review Board. All subjects reported as being in good health, having normal (or corrected to normal) vision and without medications. Before experiments, they undertook a battery of behavioral tests which included measures of IQ (Weschler Abbreviated Scale of Intelligence; the average IQ score 121.7) and handedness. During one or two separate experimental sessions lasting up to 40 min, they performed a rapid target detection task with simultaneous optical and EEG recording of brain activity as described earlier (Medvedev et al., 2010, 2011). Before and after the task, two minute segments of brain activity were recorded during the resting state when subjects were asked to sit in the dental chair quietly and relaxed avoiding thinking about anything specifically. For each 2-min segment, first half was recorded when subjects were asked to focus their gaze on the crosshair presented in the middle of a computer monitor (viewing distance of 75 cm) thus minimizing eye movements and the second half was recorded with their eyes closed. As a result, 4 or 8 min of the resting state from each subject were taken into further analysis. The results related to task performance have been published elsewhere (Medvedev et al., 2010, 2011) and here we present the data related to the resting state.

Optical data collection

Optical signals were recorded using a continuous-wave NIRS instrument CW5 (TechEn, Milford, MA) with two 14 × 8-cm probes, each accommodating 11 optodes with three dual-wavelength (690 and 830 nm) laser sources and eight detectors for each hemisphere. The light sources and detectors of the CW5 instrument were connected to the subject's head by flexible optical fiber bundles. Their front ends (optodes) were arranged on a supporting plastic base ('optical probe') which was placed on the head using anatomical landmarks provided by the international 10–20 system. Two such optical probes were placed bilaterally over the prefrontal areas between locations F3/4-F7/8-C3/4 thus covering the inferior frontal gyrus (IFG) and the middle frontal gyrus (MFG) (Fig. 1). As a result, 28 optical channels (14 for each hemisphere) were recorded. During data preprocessing, respiratory and cardiac oscillations were removed using Independent Component Analysis and signals were pass band filtered between 0.01 and 0.1 Hz to target slow oscillations of the resting state networks.

Optical data analysis

After offline frequency demodulation, optical data were filtered <1 Hz, downsampled to 20 samples per second and stored on the acquisition computer for further analysis. The cutoff frequency of 1 Hz was used to reduce cardiac oscillations present in the optical signal. Independent Component Analysis (ICA) was performed and artifactual components generated by superficial layers (scalp and skull) as well as cardiac and respiratory signals were removed using the approach as described previously (Medvedev et al., 2008). After the ICA procedure, optical signals from all resting periods were combined and used to calculate relative changes in concentration of oxygenated (HbO) and deoxygenated (Hb) hemoglobin using the open-source software HOMer (Photon Migration Laboratory, Massachusetts General Hospital, MA; http://www.nmr.mgh.harvard.edu/PMI/resources/homer/home.htm). Hemodynamic activity for each source-detector pair is referred to as an 'optical channel' throughout.

Anatomical localization of optode positions has been described previously (Medvedev et al., 2011) and is briefly reviewed here. The standard locations Cz, C3, F3, F7 and T3 in the left hemisphere (and the corresponding locations in the right hemisphere) from the 10–20 system were determined for each individual subject by taking head measurements before experiments. Then a 128-channel EGI electrode sensor net was placed on subject's head and the placement of the corresponding electrodes at the 10–20 locations was verified. Optical probes were positioned on top of the electrode net using electrodes C3/4, F3/4, F7/8 and T3/4 as reference points (Fig. 1). F3/F4 electrodes have been shown to be located on left/right middle frontal gyrus, between posterior 1/3 and 1/2; while F7/F8 electrodes are located on pars triangularis of left/right inferior frontal gyrus (Kim et al., 2007). Taking this information into account and relating positions of optical fibers to the reference electrode positions, we assumed that source-detector pairs from the lower half of the left probe (i.e., s1-d2, s1-d4, s1-d6, s2-d4, s2-d6, s3-d6, s3-d8) reflect the activity of the left inferior frontal gyrus (IFG) while source-detector pairs from the upper half (i.e., s1-d1, s1-d3, s1-d5, s2-d3, s3-d5, s2-d7, s3-d7) reflect the activity of the left middle frontal gyrus (MFG) (Fig. 1). Accordingly, the corresponding source-detector pairs from the lower/upper halves of the right probe were taken as reflecting the activities of the right IFG/MFG, respectively.

The typical frequency band used in the fMRI field to assess functional connectivity is 0.01–0.1 Hz because other bands are contaminated by noise and physiological artifacts such as respiratory- and cardiac-related fluctuations in oxygen supply (Glerean et al., 2012). We therefore bandpass filtered our signals within 0.01–0.1 Hz. We utilized a 'seed-based' approach to calculate functional connectivity which is commonly used in the fMRI field and based on correlations between the signal in the 'seed' voxel (or over a relatively small group of voxels) and all other voxels (Friston et al., 1993). However, we did not use a specific 'seed' channel and calculated correlations between all optical channels pairwise. First, pairwise correlation coefficients were calculated using the preprocessed raw data and the 'corrcoef' Matlab function (The Mathworks Inc., Natick, MA). Coefficients of correlation (here referred to as 'correlations') were calculated separately for oxy- and deoxygenated hemoglobin thus giving two separate measures of connectivity. Second, time-frequency decomposition of HbO and HbR signals was performed with the Morlet wavelets and power/coherence were also calculated for all pairwise channel combinations. Using original Matlab scripts, we calculated pairwise correlations/coherences between all optical channels in each subject and divided them into the following four groups: 1)–2) unilateral relationships (all pairwise correlations/coherences between channels within the IFG and channels within the MFG, separately for the left (1) and the right (2) hemispheres); and 3)–4) bilateral relationships (between all homologous channels within the left/right IFG (3) and the left/right MFG (4)). All correlations/coherences were subjected to Fisher's z-transform (making their statistical distributions close to normal distributions).

We also analyzed functional connectivity by Granger causality (GC) applied to the whole time courses of activities in brain structures. Granger causality as a measure of connectivity has important