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Resting-State Functional Brain Connectivity: Lessons from Functional Near-Infrared Spectroscopy

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Abstract

Resting-state functional near-infrared spectroscopy (R-fNIRS) is an active area of interest and is currently attracting considerable attention as a new imaging tool for the study of resting-state brain function. Using variations in hemodynamic concentration signals, R-fNIRS measures the brain's low-frequency spontaneous neural activity, combining the advantages of portability, low-cost, high temporal sampling rate and less physical burden to participants. The temporal synchronization of spontaneous neuronal activity in anatomically separated regions is referred to as resting-state functional connectivity (RSFC). In the past several years, an increasing body of R-fNIRS RSFC studies has led to many important findings about functional integration among local or whole-brain regions by measuring inter-regional temporal synchronization. Here, we summarize recent advances made in the R-fNIRS RSFC methodologies, from the detection of RSFC (e.g., seed-based correlation analysis, independent component analysis, whole-brain correlation analysis, and graph-theoretical topological analysis), to the assessment of RSFC performance (e.g., reliability, repeatability, and validity), to the application of RSFC in studying normal development and brain disorders. The literature reviewed here suggests that RSFC analyses based on R-fNIRS data are valid and reliable for the study of brain function in healthy and diseased populations, thus providing a promising imaging tool for cognitive science and clinics.

Keywords

connectome, connectomics, small-world, graph theory, network, functional connectivity, fNIRS

Introduction

The human brain is a complex and dynamic system and is often represented as a structurally or functionally interconnected network that works to ensure both continuous processing and efficient information flow between interconnected units (He and Evans 2010; Sporns 2013). Examining neural connectivity patterns can provide valuable insight into how the human brain operates (Bassett and Gazzaniga 2011). Recent research has shown that modern neuroimaging and neurophysiological techniques (e.g., fMRI, electroencephalography/magnetoencephalography [EEG/MEG], and functional near-infrared spectroscopy [fNIRS]) are important tools for exploring functional integration among brain regions during different states, including the resting and task states in normal people and patients with neurological and psychiatric disorders (Bassett and Bullmore 2009; He and Evans 2010; Sporns 2013; Xia and He 2011; Yu and others 2012).

Functional near-infrared spectroscopy is a promising technology with a high temporal sampling rate, long period of continuous data acquisition, and low physical burden on the participants. As an emerging neuroimaging tool, fNIRS has been successfully used to localize brain activation during cognitive engagement (Gervain and others 2008; Nakano and others 2009; Niu and others 2010; Sugiura and others 2011; Taga and others 2003; Zeff and others 2007) and to identify functional connectivity during resting-state brain activity (Homae and others 2010; Lu and others 2010; Mesquita and others 2010; Niu and others 2012; Sasai and others 2011; White and others 2012; White and others 2009; H. Zhang and others 2010; Y.-J. Zhang and others 2010). To date, several typical approaches for the analysis of resting-state functional connectivity (RSFC) using other imaging modalities

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(e.g., fMRI and EEG/MEG) have also been applied to resting-state fNIRS (R-fNIRS) to characterize the local- or whole-brain functional connectivity. These approaches primarily include seed-based correlation analysis, independent component analysis (ICA), whole-brain correlation analysis, and graph-theoretical topological analysis (see the Resting-State Functional Connectivity Section under "Basic Concepts"). Here, we conducted a literature search on PubMed (www.ncbi.nlm.nih.gov/pubmed) using key words such as ((NIRS [All Fields] OR fNIRS [All Fields]) OR optical [All Fields]) AND ((resting-state [All Fields] AND functional connectivity [All Fields]) OR (resting-state [All Fields] AND functional networks [All Fields])), and 15 publications were identified in the human brain research field (Table 1).

In this review, we summarize these recent advances made in the study of RSFC derived from R-fNIRS data, focusing mainly on areas of ongoing research and application. This study will hopefully generate more excitement about the emerging R-fNIRS RSFC field. This article is organized into three main sections. First, we introduce several basic principles and concepts regarding fNIRS and brain connectivity. Then, we review a series of R-fNIRS studies from three perspectives: RSFC detection methods (e.g., seed-based correlation analysis, ICA, whole-brain correlation analysis, and graph-theoretical topological analysis), RSFC performance assessment (e.g., reliability, reproducibility, and validity) and its relevant applications. Finally, we highlight future directions and challenging issues within the R-fNIRS RSFC research field.

Basic Concepts

R-fNIRS Imaging Systems

Multiple optical instruments have been applied to R-fNIRS studies for the measurement of the hemodynamic response in human brain tissue, which include the CW5/CW6 system (TechEn, Milford, MA; Mesquita and others 2010; Niu and others 2011; Niu and others 2012, 2013), the DYNOT system (NIRx Medical Technologies, New York, NY) (Niu and others 2011), a customized high-density diffuse optical tomography (DOT) system (White and others 2009; White and others 2012), and the ETG100/4000/ETG7000 systems (Hitachi Medical Co., Tokyo, Japan) (Duan and others 2012; Homae and others 2010; Lu and others 2010; Sasai and others 2012; Zhang and others 2011; H Zhang and others 2010; Y-J Zhang and others 2010). All of these are continuous wave (CW) instruments and are currently considered to be more readily commercially available than other imaging-domain systems, such as those based on frequency or time domains. In CW systems, light sources emit light continuously, either at a constant intensity or are modulated at a low (a few kilohertz) frequency, and the absorption changes in tissue are determined by measuring the attenuation of the incident light.

General Principles of R-fNIRS Detection

Human brain tissue is a turbid media in which near-infrared (NIR) light (650-1000 nm) is diffused by tissue cells and is absorbed mainly by oxygenated hemoglobin (HbO_2) and deoxygenated hemoglobin (HbR) (Ferrari and Quaresima 2012; Jobsis 1977; Wray and others 1988). Given that the two chromophores have distinct absorption spectra in the NIR range, neural activity–based changes in HbO_2 and HbR concentrations in the cerebral cortex can be quantified using two or more wavelengths (Boas and others 2004; Jobsis 1977; Zhang and others 2012). During image collection, sources are fixed into a custom holder and are then placed adjacent to the scalp, allowing the NIR light to penetrate the scalp, skull, and cerebrospinal fluid to reach the cortical layers of the brain (Jobsis 1977). The reflected light from the cortical tissue is then received by detectors that are positioned a few centimeters away from the sources. Typically, a source–detector pair with a separation of approximately 3 cm is considered to be able to effectively record cortical brain tissue activation (Niu and others 2010; Tian and others 2011).

The concentration calculation of HbO_2 and HbR in the continuous wave systems is mainly based on the Beer–Lambert law (Cope and Delpy 1988). When light of a certain wavelength λ_1 passes through a nonscattering homogeneous medium, the incremental optical density (ΔOD) from the reference is expressed as

$$\Delta OD = -\log I / I_0 = \varepsilon \cdot \Delta C \cdot L \quad (1)$$

where I and I_0 are the intensities of the detected and illuminated light, respectively, ε is the molar absorption coefficient, C is concentration, and L is the length that light travels through the medium (optical pathlength) (Arridge and others 1992; Delpy and others 1988). For a light-scattering system such as brain tissue, the change of optical density is modified according to the Beer–Lambert law (Cope and Delpy 1988; Delpy and others 1988):

$$\Delta OD_{\lambda_1} = (\varepsilon^{\lambda_1}_{HbO_2} \cdot \Delta C_{HbO_2} + \varepsilon^{\lambda_1}_{HbR} \cdot \Delta C_{HbR}) \cdot L^{\lambda_1} + S_{\lambda_1} \quad (2)$$

where $S_{\lambda 1}$ refers to the optical attenuation mainly due to scattering, ε is the molar absorption coefficient of HbO_2 or HbR, ΔC represents the concentration changes of HbO_2 or HbR (unit: μmol/L or μM). To minimize the effect of $S_{\lambda 1}$, a dual-wavelength method is often used (Cope and Delpy 1988; Delpy and others 1988). For λ_2, the optical density is written as

Table 1. Overview of R-fNIRS RSFC Studies.

Study	Subjects	Instrument	Sources/Detectors	Wavelengths (nm)	Brain Regions	Analytical Methods
White and others (2009)	5 adults	Custom-built DOT	24S/28D 24S/18D	750/850	Sensorimotor, visual cortex	Seed-based correlation analysis
Lu and others (2010)	29 adults	ETG-4000	17S/16D	695/830	Sensorimotor, auditory	Seed-based correlation analysis
H. Zhang and others (2010)[a]	21, 19 adults	ETG-4000	17S/16D	695/830	Sensorimotor, visual	ICA
Homae and others (2010)	52 infants	ETG-7000	30S/30D	785/830	Whole-head	Whole-brain correlation analysis
Y-J Zhang and others (2010)	30 adults	ETG-4000	8S/7D	695/830	Frontal, temporal	Seed-based correlation analysis
Mesquita and others (2010)	11 adults	CW5	16S/32D	690/830	Whole-head	Seed-based correlation analysis
H. Zhang and others (2010)	16 adults	ETG-4000	17S/16D	695/830	Sensorimotor	ICA
Sasai and others (2011)	21 adults	ETG-100	10S/8D	695/830	Whole-head	Whole-brain correlation analysis
Niu and others (2011)[b]	8, 9 adults	CW5, DYNOT	10S/16D, 32S/32D	695/830, 760/830	Sensorimotor	Seed-based correlation analysis
Zhang and others (2011)	21 adults	ETG-4000	17S/16D	695/830	Sensorimotor	Seed-based correlation analysis
White and others (2012)	8 infants	Custom-built DOT	18S/16D	750/850	Visual	Seed-based correlation analysis, ICA
Duan and others (2012)	21 adults	ETG-4000	8S/8D	695/830	Sensorimotor	Seed-based correlation analysis, graph-theory analysis
Sasai and others (2012)	28 adults	ETG-4000	8S/8D	695/830	Whole-head	Seed-based correlation analysis
Niu and others (2012)	15 adults	CW6	12S/24D	690/830	Whole-head	Graph-theory analysis
Zhang and others (2012)	21 adults	ETG-4000	17S/16D	695/830	Sensorimotor	Whole-brain correlation analysis
Niu and others (2013)	18 adults	CW6	12S/24D	690/830	Whole-head	Graph-theory analysis

R-fNIRS = resting-state functional near-infrared spectroscopy; RSFC = resting-state functional connectivity; DOT = diffuse optical tomography; ICA = independent component analysis.
[a]For this study, 21 subjects were scanned at the sensorimotor areas and 19 at the visual regions.
[b]For this study, 8 subjects were scanned using the CW5 system and 9 using the DYNOT system.

$$\Delta OD_{\lambda_2} = (\varepsilon_{HbO_2}^{\lambda_2} \cdot \Delta C_{HbO_2} + \varepsilon_{HbR}^{\lambda_2} \cdot \Delta C_{HbR}) \cdot L^{\lambda_2} + S_{\lambda_2} \quad (3)$$

Therefore, by measuring the changes in the optical densities at two wavelengths, the concentration changes of HbO_2 and HbR in tissue can be calculated as

$$\Delta C_{HbR} = \frac{\varepsilon_{HbO_2}^{\lambda_1} \cdot (\Delta OD_{\lambda_2} / L^{\lambda_2}) + \varepsilon_{HbO_2}^{\lambda_2} \cdot (\Delta OD_{\lambda_1} / L^{\lambda_1})}{\varepsilon_{HbO_2}^{\lambda_1} \cdot \varepsilon_{HbR}^{\lambda_2} - \varepsilon_{HbO_2}^{\lambda_2} \cdot \varepsilon_{HbR}^{\lambda_1}} \quad (4)$$

$$\Delta C_{HbO_2} = \frac{\varepsilon_{HbR}^{\lambda_1} \cdot (\Delta OD_{\lambda_2} / L^{\lambda_2}) + \varepsilon_{HbR}^{\lambda_2} \cdot (\Delta OD_{\lambda_1} / L^{\lambda_1})}{\varepsilon_{HbR}^{\lambda_1} \cdot \varepsilon_{HbO_2}^{\lambda_2} - \varepsilon_{HbR}^{\lambda_2} \cdot \varepsilon_{HbO_2}^{\lambda_1}} \quad (5)$$

The summation of the changes in HbO_2 and HbR provide variations in the total hemoglobin (HbT), which reflects the variable blood flow within the tissue. Of note, the optical pathlength (L) in the tissue is longer than the physical one (the distance between the sources and detectors) due to the scattering effect, such that (Arridge and others 1992; Delpy and others 1988)

$$L = DPF \cdot d \quad (6)$$

where d is the distance between the light source and the detector and DPF is the differential pathlength factor that indicates the lengthening of the average optical pathlength due to light scattering in tissue. DPF has been measured in participants with a range of ages (Strangman and others 2003).

Resting-State Functional Connectivity

The resting state is a natural condition in which there is neither overt perceptual input nor behavioral output. Because this state is convenient to achieve, comparable across different studies, and reflects spontaneous or intrinsic brain activity, the resting state is a vital experimental

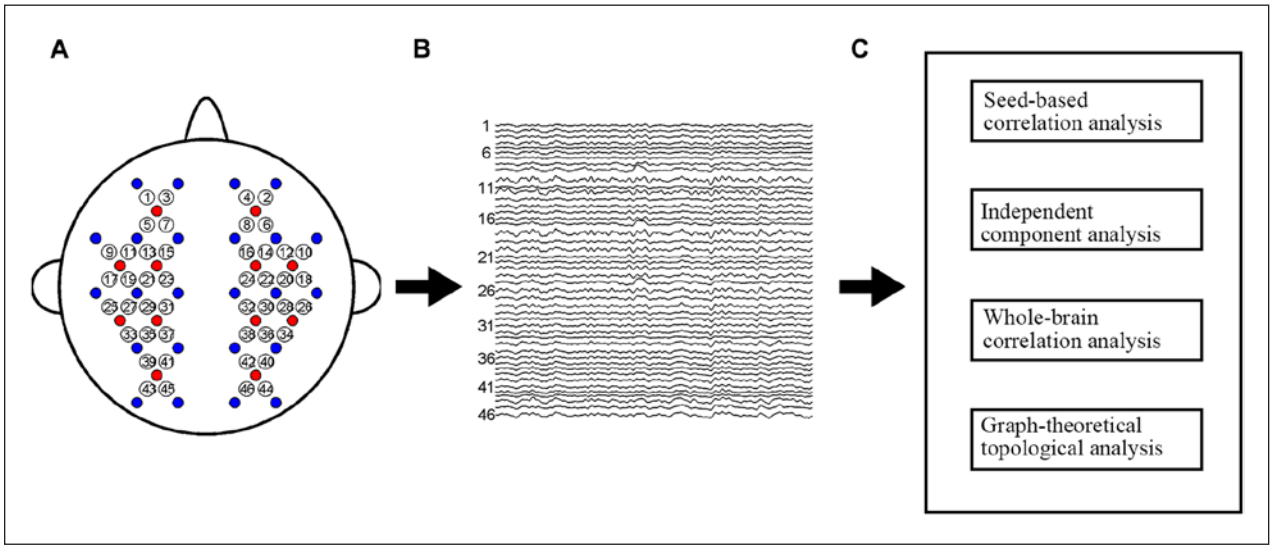

Figure 1. Diagram for R-fNIRS RSFC analysis. The charts represent the (A) R-fNIRS data collection, in which sources (red) and detectors (blue) were symmetrically placed on the left and right hemispheres and the adjacent source and detector constitute one measurement channel (46 channels for this probe arrangement), (B) calculation of hemoglobin concentration signal at each channel, and (C) RSFC analysis approaches based on the concentration signals. R-fNIRS = resting-state functional near-infrared spectroscopy; RSFC = resting-state functional connectivity.

paradigm for the study of brain function (Fox and Raichle 2007; Zhang and Raichle 2010). Functional connectivity derived from resting-state brain activity (i.e., RSFC) measures the temporal synchronization of spontaneous neuronal activation patterns of anatomically separated brain regions (Fox and Raichle 2007). In the past several years, an increasing body of research from different modalities has begun to explore RSFC between brain regions, and significant progress has been made. While the study of RSFC is an emerging topic in the R-fNIRS field, it is attracting increasing attention. Currently, four different types of R-fNIRS RSFC approaches have been used (Fig. 1): (1) the seed-based correlation analysis, which computes temporal correlations between a predefined channel of interest and other channels; (2) the independent component analysis or ICA, which uses the whole data set (i.e., all channels) to divide the brain into several statistically independent functional systems; (3) whole-brain correlation analysis, which examines the temporal correlation of time series between any two measurement channels in the whole brain; and (4) graph-theoretical topological analysis, which describes the topological organization patterns of brain networks.

Resting-State Functional Connectivity Studies Using R-fNIRS

R-fNIRS RSFC studies have been attracting increasing attention. To date, interesting progress has been made in three categories: RSFC detection methodologies, RSFC performance assessment, and the relevant applications of RSFC (Table 1).

Methodologies of RSFC Detection

Seed-based correlation analysis. The basic idea behind seed-based RSFC detection is the estimation of the strength of pairwise relationships between the seed regions (usually defined in terms of anatomical location or stimulus-induced activation foci) and all other regions in the brain. Using this method, several R-fNIRS studies have identified intrinsic functional connectivity in different brain systems (Fig. 2), such as the sensorimotor (Lu and others 2010; White and others 2009; White and others 2012), visual (White and others 2009), auditory (Lu and others 2010), and language systems (Y-J Zhang and others 2010). For example, White and others (2009) investigated RSFC in bilateral motor and visual regions of five participants. They found that the functional connectivity maps in each subject identified regions of the motor and visual cortices that highly resembled well-known functional networks that had been measured by fMRI. The functional connectivity maps were reproducible across sessions and subjects, demonstrating the feasibility and usefulness of the R-fNIRS technique for resting-state brain network detection. Using the seed-correlation approach, Lu and others (2010) examined the RSFC in the auditory systems of a group of 29 subjects. Unlike in White and others' work, Lu and others analyzed the group-level RSFC and found a high degree of functional connectivity in the bilateral auditory systems. This connectivity was

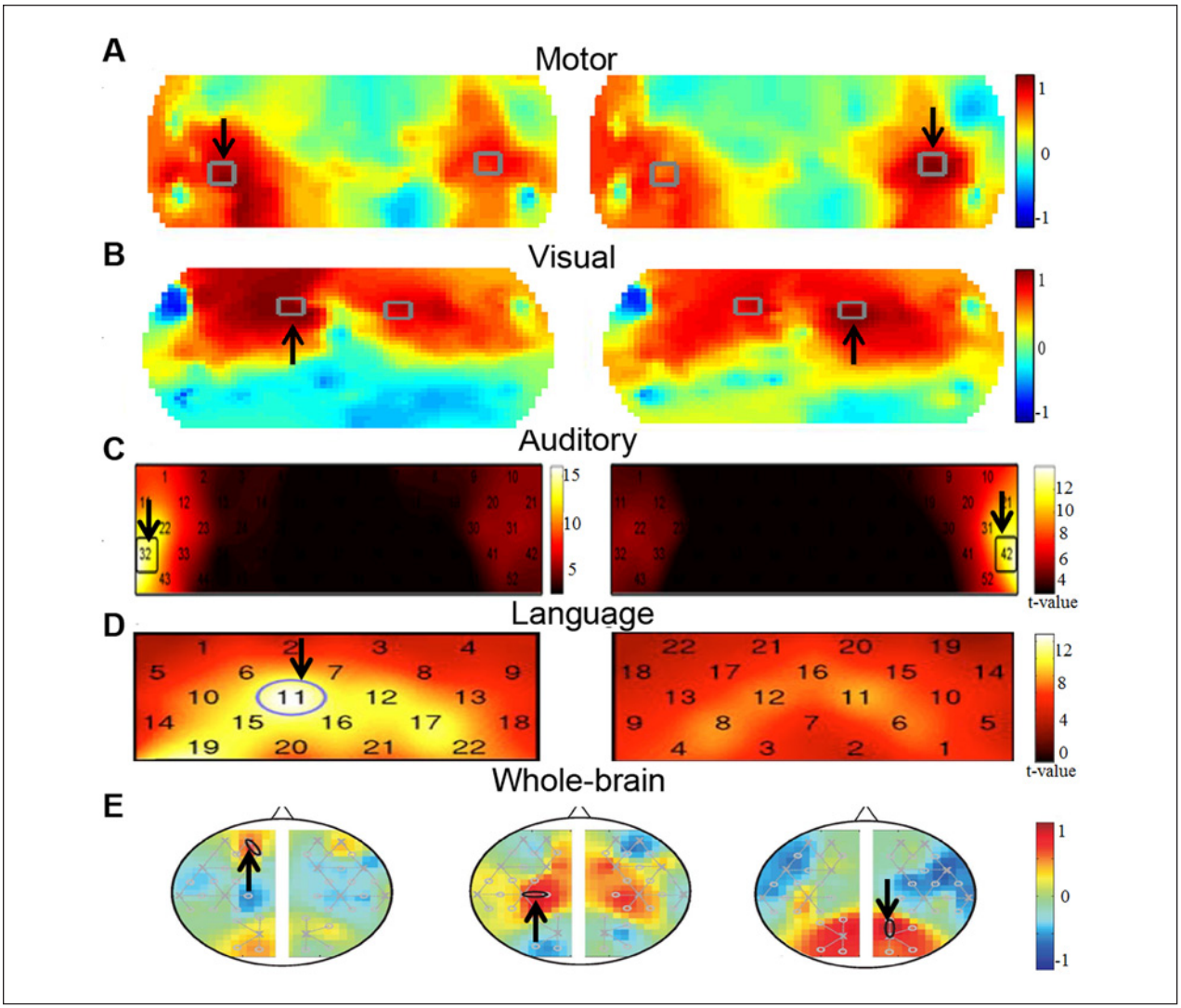

Figure 2. Seed-based correlation analysis. The resting-state functional connectivity (RSFC) map was produced separately from the (A) motor regions (White and others 2009), (B) visual regions (White and others 2009), (C) auditory regions (Lu and others 2010), (D) language systems (Y-J Zhang and others 2010), and (E) entire brain (Mesquita and others 2010). The RSFC maps in (A-C) represent the correlation calculated from left and right hemispheric seeds (black arrows), respectively. The RSFC maps in (D, E) represented the correlation from the given seeds (black arrows), respectively. Note that the numbers in (C) and (D) represent the indices of the measurement channels in the probe and the color bar represents the statistical values such as correlation coefficient or *t* values.

consistent with that determined from both a data-driven cluster analysis and a predefined template in the auditory regions. Also using the seed-correlation analysis strategy, this research group found strong functional connectivity within the bilateral language system (Y-J Zhang and others 2010), further confirming the feasibility of using R-fNIRS to detect RSFC in high-level functional brain systems. In whole-head functional network studies, the seed-correlation approach was also shown to be capable of identifying multiple functional brain networks from the whole-brain data set. The corresponding study was performed by Mesquita and others (2010), who simultaneously recorded brain signal in regions of the frontal, parietal, temporal and occipital cortices of each participant. The seed point in each functional brain system was separately localized and then used as the correlation analysis of the whole-brain data. Each identified functional system corresponded to a functional connectivity network, more often evidently for the sensorimotor and visual networks, further highlighting the feasibility of using functional connectivity and optical methods to investigate cortical interactions within the entire brain system.