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Evaluating the effects of systemic low frequency oscillations measured in the periphery on the independent component analysis results of resting state networks

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ABSTRACT

Independent component analysis (ICA) is widely used in resting state functional connectivity studies. ICA is a data-driven method, which uses no a priori anatomical or functional assumptions. However, as a result, it still relies on the user to distinguish the independent components (ICs) corresponding to neuronal activation, peripherally originating signals (without directly attributable neuronal origin, such as respiration, cardiac pulsation and Mayer wave), and acquisition artifacts. In this concurrent near infrared spectroscopy (NIRS)/functional MRI (fMRI) resting state study, we developed a method to systematically and quantitatively identify the ICs that show strong contributions from signals originating in the periphery. We applied group ICA (MELODIC from FSL) to the resting state data of 10 healthy participants. The systemic low frequency oscillation (LFO) detected simultaneously at each participant's fingertip by NIRS was used as a regressor to correlate with every subject-specific IC time course. The ICs that had high correlation with the systemic LFO were those closely associated with previously described sensorimotor, visual, and auditory networks. The ICs associated with the default mode and frontoparietal networks were less affected by the peripheral signals. The consistency and reproducibility of the results were evaluated using bootstrapping. This result demonstrates that systemic, low frequency oscillations in hemodynamic properties overlay the time courses of many spatial patterns identified in ICA analyses, which complicates the detection and interpretation of connectivity in these regions of the brain.

Introduction

Functional connectivity is commonly defined as the coordination of activity across brain regions. It has been widely investigated using functional MRI (fMRI), by detecting temporal correlations of the BOLD signal between brain regions during task activations and in resting state conditions (Friston et al., 1996). Resting state functional connectivity studies provide information regarding spontaneous activity that is generated intrinsically and naturally within the brain (Biswal et al., 1995; Fox and Raichle, 2007), and as it requires little participation, it is the preferred approach for studying functional brain activity among certain populations of individuals, including cognitively impaired patients who may not be able to perform tasks.

There are two widely used methods for analysis of functional connectivity in fMRI data (Rosazza et al., 2012). The first method is seed-based analysis (Biswal et al., 1995; Fox et al., 2006; Raichle et al., 2001; Vincent et al., 2008), in which a region of interest (ROI) or seed voxel is selected based on an a priori hypothesis of anatomical and/or functional relationships in the brain. The time course obtained from the ROI is correlated with that of other voxels in the brain. The second method is independent component analysis (ICA), a completely data-driven approach to separate the signals into statistically independent components (Beckmann et al., 2005; Calhoun et al., 2005; Damoiseaux et al., 2006; Kiviniemi et al., 2003; McKeown and Sejnowski, 1998). A number of studies have shown that these two methods yield results with significant similarities (Rosazza et al., 2012; Van Dijk et al., 2010). One benefit of ICA is that it does not require a priori anatomical assumptions or subjective selection of seed areas. Another benefit is that it can, to some extent, isolate sources of noise. In spite of these advantages, a major concern with ICA is that it requires the user to make a subjective determination whether a component represents a neuronal signal, another type of signal, or an artifact (Cole et al., 2010).

Many attempts have been made to develop methods to categorize ICA components accurately and objectively, but they have not been adopted as standard practice (Perlbarg et al., 2007; Sui et al., 2009; Tohka et al., 2008). Instead, visual inspection is the most commonly used method for component selection (Kelly et al., 2010). In order to improve this method and help reduce the false negative rate, criteria for identifying those independent components (ICs) representing artifactual noise were recently outlined and include irregular spotted patterns,

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extra-cerebral locations, and motion-related ring patterns (Kelly et al., 2010; Tohka et al., 2008). In addition, the time courses corresponding to these components have easily recognizable features, such as temporal spikes, dominance in the high frequency region (>0.1 Hz), and high repeatability in a fixed pattern. However, beyond these easily identifiable "noise" ICs, there are many other ICs (especially from ICA group analysis), which have symmetrical patterns, reside mostly in the cortex, and have smooth time courses that are dominated by energy in the low frequencies (≤0.1 Hz). Many of these ICs are commonly regarded as resting state networks (RSNs). Therefore, it is necessary and critical to understand the peripheral physiological contributions to these ICs.

Birn et al. (2008a) studied the effects of respiration-related low frequency oscillations (LFOs) on the RSNs derived from ICA of resting state data (Birn et al., 2008a). They found that ICA frequently confused the respiration-related IC with the default mode network (DMN), a widely accepted RSN. In most cases, the time course associated with DMN was significantly correlated with changes in the respiration volume per time. This work demonstrated that even the most accepted RSNs might have significant peripheral physiological contributions. Our recent work confirmed this idea with a concurrent near infrared spectroscopy (NIRS)/fMRI resting state study, which demonstrated that the BOLD fMRI signal obtained from many brain voxels is highly correlated with the LFOs (0.01 Hz–0.15 Hz) that were measured simultaneously at peripheral sites (e.g. fingertip) by NIRS (Tong et al., 2012a). Moreover, by using cross correlation between these two signals, we showed that the LFO is not static, but instead, travels with the blood circulation and arrives at different brain voxels at different times. Interestingly, the areas affected by this dynamic systemic blood fluctuation were shown to overlap significantly with many well-known RSNs. Since this systemic LFO corresponded to variations in parameters that directly affect the BOLD fMRI signal (e.g., blood flow, oxygenation, and volume), and these variations are in the same low frequency band as the RSN fluctuations, we postulated that many RSNs are likely to be influenced by this peripheral physiology.

Using the systemic LFO measured in the periphery (fingertip) by NIRS to identify the physiological component in RSNs (based on BOLD fMRI) offers several advantages: 1) Both the NIRS and the BOLD fMRI signals are blood-related, and therefore sensitive to changes in blood flow, volume and oxygenation; 2) The systemic LFO measured at the fingertip is a direct measurement of the physiological hemodynamic fluctuations within the same frequency band as BOLD fMRI (0.01–0.15 Hz), but without any mathematical assumption or modeling; and 3) The systemic LFO identified by NIRS has no aliased contribution from respiratory or cardiac pulsation (i.e., due to the high temporal resolution of NIRS, we can filter out all the high frequency signals >0.2 Hz). Therefore, the effects arising only from this systemic LFO, which has been shown to have significant impact on BOLD fMRI, can be singled out and identified easily. Recently, functional connectivity has been investigated using functional NIRS (fNIRS) only (Lu et al., 2010; Mesquita et al., 2010; Sasai et al., 2011; Zhang et al., 2010b). Consistent RSNs have been found by both seed-based (Lu et al., 2010) and independent component (Zhang et al., 2010a) analyses. Due to the fact that fNIRS can only probe the networks on the surface of the cortex and is sensitive to the extracerebral systemic physiological fluctuations, the potential impact of our results on RSN studies using fNIRS alone may be even greater.

In the present concurrent NIRS/fMRI resting state study, we extended our previous research, in which we performed the resting state fMRI on healthy participants while using NIRS to measure the physiological signals at the fingertip, and combined it with a novel method to quantify the contribution of systemic LFO to a full set of RSNs identified by ICA in the resting state data. We also used a bootstrapping method to test the consistency and reproducibility of these physiologically correlated ICs and to assess the effects of dimensionality in the ICA process. To the best of our knowledge, the method we used is the first attempt to assess which RSNs are most affected by physiological signals originating in the periphery in an objective and systematic manner. Importantly, our results are not limited by the analytical method we used in this study (i.e., ICA) because the physiologically correlated RSNs we identified are consistent with well-established RSNs (Beckmann et al., 2005; Damoiseaux et al., 2006; Smith et al., 2009).

Materials and methods

Protocols and instrumentation

Concurrent NIRS and fMRI resting state studies were conducted in 10 healthy volunteers participating in an ongoing protocol (4M, 6F, average age ± SD, 30 ± 7 years). Participants were asked to lie quietly in the scanner and view a gray screen with a fixation point in the center. The Institutional Review Board at McLean Hospital approved the protocol and volunteers were compensated for their participation.

All MR data were acquired on a Siemens TIM Trio 3T scanner (Siemens Medical Systems, Malvern, PA) using a 32-channel phased array head matrix coil (200 time points, TR/TE = 3000/30 ms, flip angle 90°, matrix = 64 × 64 on a 224 × 224 mm FOV, 50 2.5 mm slices with 0.625 mm gap parallel to the AC–PC line extending down from the top of the brain). Physiological waveforms (pulse oximetry, and respiratory depth) were recorded using the scanner's built-in wireless fingertip pulse oximeter and respiratory belt.

MRI-compatible NIRS optical probes, each with one collection fiber and one pair of illumination fibers (1.5 cm separation between collection and illumination fibers), were used to record NIRS signals. One probe was placed over the tip of the left middle finger (the other hand was holding the "squeeze ball" to signal the MR technician), one probe was placed on the left big toe, and in 7 participants, an additional probe was placed on the right big toe, as shown in Figs. 1a and b. NIRS data were recorded using an ISS Imagent instrument (ISS, Inc., Champaign, IL) at 690 and 830 nm. The sampling rate of the NIRS data acquisition ranged from 6.25 to 12.5 Hz (in all cases the cardiac waveform was fully sampled). FMRI data were collected for 10 min; NIRS data were recorded continuously during this time, and before and after the resting state fMRI acquisition.

Data preprocessing was conducted on both NIRS and fMRI data. For the NIRS data, each pair of raw NIRS time courses (690 and 830 nm data) was converted into three time courses representing temporal changes of the oxy-, deoxy and total hemoglobin concentration (Δ[HbO], Δ[Hb] and Δ[tHb], respectively) using the Modified Beer–Lambert law (Delpy et al., 1988; Kocsis et al., 2006) in Matlab (The Mathworks, Natick, MA). For the BOLD fMRI data, regular preprocessing steps in FSL (Smith et al., 2004), including motion correction, slice timing correction, and spatial smoothing (5 mm) were performed.

Systemic low frequency oscillation analyses

Previously we have established that LFOs measured at the fingertip by NIRS are systemic blood signals that travel to different body parts (including the brain) with different time delays (Tong and Frederick, 2010; Tong et al., 2012a). As a first step, we conducted the same analyses on these 10 participants. The detailed analytical procedure can be found in the previous work (Tong et al., 2012a). In short, a bandpass filter was used to isolate LFO signals (0.01–0.15 Hz) spectrally from simultaneously recorded NIRS data (i.e., Δ[tHb]) from the fingertip and the toe. In the studies of LFOs (including ours), the range of the low frequencies is commonly set to be 0.01–0.1 Hz. However, recent studies indicated that BOLD resting state signals are more broadband than previously thought (Niazy et al., 2011). Since this work is to understand the impact of the LFOs on the RSNs, we expanded the frequency band to 0.01–0.15 Hz. In our analyses we use Δ[tHb] because the LFO is closely associated with changes in blood flow and volume, which have been