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Spatiotemporal dynamics of low frequency BOLD fluctuations in rats and humans

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ABSTRACT

Most studies involving spontaneous fluctuations in the BOLD signal extract connectivity patterns that show relationships between brain areas that are maintained over the length of the scanning session. In this study, however, we examine the spatiotemporal dynamics of the BOLD fluctuations to identify common patterns of propagation within a scan. A novel pattern finding algorithm was developed for detecting repeated spatiotemporal patterns in BOLD fMRI data. The algorithm was applied to high temporal resolution T2*-weighted multislice images obtained from rats and humans in the absence of any task or stimulation. In rats, the primary pattern consisted of waves of high signal intensity, propagating in a lateral to medial direction across the cortex, replicating our previous findings (Majeed et al., 2009a). These waves were observed primarily in sensorimotor cortex, but also extended to visual and parietal association areas. A secondary pattern, confined to subcortical regions consisted of an initial increase and subsequent decrease in signal intensity in the caudate–putamen. In humans, the most common spatiotemporal pattern consisted of an alteration between activation of areas comprising the "default-mode" (e.g., posterior cingulate and anterior medial prefrontal cortices) and the "task-positive" (e.g., superior parietal and premotor cortices) networks. Signal propagation from focal starting points was also observed. The pattern finding algorithm was shown to be reasonably insensitive to the variation in user-defined parameters, and the results were consistent within and between subjects. This novel approach for probing the spontaneous network activity of the brain has implications for the interpretation of conventional functional connectivity studies, and may increase the amount of information that can be obtained from neuroimaging data.

Introduction

Spontaneous low frequency fluctuations (LFFs) in the blood oxygenation level dependent (BOLD) fMRI signal have become widely used for mapping the functional connectivity of the brain at rest (Biswal et al., 1995). Networks associated with different functional systems including visual, motor, auditory, memory and language have been detected in resting state fMRI studies (Cordes et al., 2000; Vincent et al., 2006). Researchers have also identified two widely-present networks, one containing areas (e.g. posterior cingulate and anterior medial prefrontal cortices) that are typically deactivated during the performance of a task (the "default mode" network) and another, "task-positive network" containing areas (e.g. superior parietal and premotor cortices) that are active during the performance of a wide variety of tasks and that may be related to attention (Fox et al., 2005).

Spontaneous fluctuations in the BOLD signal may contain a wealth of information not captured by most current analysis techniques, which focus on detecting correlations among different brain regions that are assumed to persist over several minutes (Biswal et al., 1995; Cordes et al., 2002; van de Ven et al., 2004). In a recent study using high temporal resolution data obtained from rats, we demonstrated that frame-by-frame visualization of band-pass filtered BOLD time-courses exhibits discrete spatiotemporal events, suggesting that detection of individual events in the data is possible (Majeed et al., 2009a). Waves of high signal intensity propagating from secondary somatosensory cortex (SII) to medial cortical areas were observed in α-chloralose anesthetized rats. These areas are not part of the same network when traditional seed-based cross-correlation techniques are used, indicating that the conventional methods may not extract all the information that can be obtained from functional connectivity data (Williams et al., 2010). This opens a new avenue for functional connectivity research. The detection of propagating waves of MRI signal fluctuations that may reflect slow changes in electrical activity

Abbreviations: cc, Correlation coefficient; CP, Caudate–putamen; CSF, Cerebrospinal fluid; LFFs, Low frequency fluctuations; SI, Primary somatosensory cortex; SII, Secondary somatosensory cortex; WL, Window length; WL′, Extended window length.

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naturally leads to speculation about whether other dynamic neural events can be detected with MRI in anesthetized rodents, and whether similar spatiotemporal patterns/events can be found in awake humans. An in-depth study of these patterns may help to elucidate the origin and significance of LFFs. For example, it has been proposed that LFFs in different brain regions may be caused by one or more subcortical sources or "drivers" (Drew et al., 2008). Identification of sources of the high intensity signal can identify possible drivers/regions receiving direct input from the drivers of the LFFs in BOLD. Also, if similar spatiotemporal patterns can be detected in humans, it may be possible to tie these events to behavioral performance data. The presence of such time-varying patterns would suggest that the coherence between the BOLD fluctuations from different areas may change over time. In support of that idea, a recent study reports variability in the coherence between posterior cingulate cortex and task-positive network over time (Chang and Glover, 2009). These studies highlight the need for novel analysis techniques that could capture time-varying features in spontaneous BOLD fluctuations.

Our preliminary exploration of the spatiotemporal patterns of spontaneous BOLD fluctuations was based purely on visual inspection (Majeed et al., 2009a). The amplitude of the low frequency BOLD fluctuations is small, typically ~1–2%, and visual detection of the patterns is limited by signal to noise ratio (SNR), and thus it is possible that patterns may be obscured in the presence of noise. Therefore, it is desirable to have an automatic method for the detection of such patterns. The previous study examined only single slice data, so that analysis was restricted to a single coronal plane. Three-dimensional data is necessary to characterize the true direction of propagation, which may contain significant through-plane components.

In this paper, we describe a method for the detection of repetitive spatiotemporal patterns in fMRI data, validate it using appropriate controls and test it for robustness. The method is applied to multislice data obtained from humans and rats to characterize reproducible spatiotemporal patterns. The results suggest that BOLD fluctuations propagate temporally over brain areas, and conventional functional connectivity analysis may not reveal such interactions. These findings not only push the limits of information that can be obtained from functional connectivity data, but also open new directions for future research.

Materials and methods

Animal preparation

All experiments were performed in compliance with guidelines set by the Emory University Institutional Animal Care and Use Committee (IACUC). Eight rats were initially anesthetized with 5% isoflurane and maintained at 2% isoflurane during preparation for imaging. Optical ointment was applied to the eyes of the animal. Two needle electrodes were inserted just under the skin of each forepaw, one between digits 1 and 2, and the other between digits 2 and 3. The rat was given a bolus of medetomidine (0.5 mg/kg) and isoflurane was discontinued. Anesthesia was maintained with a constant medetomidine infusion rate (0.1 mg/kg/h). The rat was placed on a heated water pad while in the magnet to maintain rectal temperature at 37 °C. Each animal was secured in a head holder with ear bars and a bite bar to prevent head motion and was strapped to a plastic cradle. Heart rate and blood oxygen level were continuously monitored during the experiment using a pulse oximeter, clipped to the left forepaw. A pressure-sensitive respiratory pad placed under the chest was used to continuously monitor breathing. All animals were carefully monitored for any sign of inadequate anesthesia (motion in the MR images, an abrupt rise in heart rate, or uneven respiration), but none were observed in the course of this study.

Animal imaging

All images were acquired with a 9.4 T/20 cm horizontal bore BRUKER magnet, interfaced to an AVANCE console (Bruker, Billerica, MA) and equipped with a gradient set capable of providing 20 G/cm with a rise time of 120 μs. A two-coil actively decoupled imaging setup was used (2 cm diameter surface coil for reception and 7 cm diameter volume coil for transmission; Bruker, Billerica, MA) to achieve maximal SNR over the cortical areas of interest. Scout images were acquired in three planes with a FLASH sequence to determine appropriate positioning for the fMRI study. A gradient-echo EPI sequence (64×64 matrix, echo time (TE) 15–20 ms, repetition time (TR) 1.5 s, field of view 2.56 cm×2.56 cm) was used to acquire a series of images during forepaw stimulation in order to locate the slice containing forepaw region of the primary somatosensory cortex (SI). A block design stimulation paradigm was used, consisting of alternating rest and stimulation blocks (4 mA current, 300 μs pulses repeated at 9 Hz, 30 TRs on, and 30 TRs off). The slice containing forepaw region of SI was used as a reference for slice placement for functional connectivity scans. Functional connectivity data were acquired with gradient-echo EPI with the following parameters: TR 500 ms, TE 20 ms, field of view 1.92 cm×1.92 cm or 2.56 cm×2.56 cm, four 2 mm thick slices, and 1200 repetitions. No stimulation was given during functional connectivity scans.

Human imaging

Two groups of human subjects were scanned for this study. The data from the first group was acquired with short TR (300 ms) to minimize the effects of aliasing and achieve better temporal resolution, while the data from the second group was acquired with long TR (1.5 s) to allow whole-brain coverage and inter-subject registration. Imaging was performed on a 3 T Siemens scanner using a birdcage head coil. Experiments were conducted according to the Georgia Institute of Technology/Emory University Institutional Review Board (IRB) guidelines. The subjects were asked to lie quietly in the scanner with their eyes closed. Anatomical scout scans were acquired in the three orthogonal planes and were used for placement of the slices for the functional scans.

Group 1 — six healthy volunteers (19–22 years old; 3 males, 3 females)

Two runs of EPI image series were acquired with the following parameters: 300 ms TR, 30 ms TE, 3.44 mm×3.44 mm in-plane resolution, 1600 repetitions, and four 5 mm thick horizontal slices (parallel to the line joining anterior and posterior commissures).

Group 2 — 14 healthy volunteers (32–66 years old, 3 males, 11 females)

A single run of EPI image series was acquired with whole-brain coverage, using the following parameters: 1500 ms TR, 30 ms TE, 3 mm×3 mm in-plane resolution, 276 repetitions, and 28 horizontal slices with 4 mm thickness.

Preprocessing

All analyses were performed using Matlab (MathWorks, Natick, MA) unless otherwise noted. The processing steps described below were performed on all the datasets (humans and rats) unless specified otherwise. Slice-timing correction and motion correction were performed on all the datasets using AFNI (Cox, 1996). For the rat data, the area comprising the brain was segmented using an intensity threshold and manual removal of remaining voxels outside the brain. Gray matter, white matter and cerebrospinal fluid (CSF) masks were obtained for the human data using Statistical Parametric Mapping (SPM8) software (Wellcome Department of Cognitive Neurology, London, UK). Group 2 human datasets (TR = 1.5 s, whole-brain coverage) were spatially normalized to match the MNI template and