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Review article

Biophysical and neural basis of resting state functional connectivity: Evidence from non-human primates

Li Min Chen [a,b,*], Pai-Feng Yang [a,b], Feng Wang [a,b], Arabinda Mishra [a,b], Zhaoyue Shi [a,c], Ruiqi Wu [a,b], Tung-Lin Wu [a,c], George H. Wilson III [a,b], Zhaohua Ding [a,c,d], John C. Gore [a,b,c,*]

[a] Vanderbilt University Institute of Imaging Science, Nashville, TN 37232, USA
[b] Department of Radiology and Radiological Sciences, Vanderbilt University Medical Center, Nashville, TN 37232, USA
[c] Department of Biomedical Engineering, Vanderbilt University, Nashville, TN 37232, USA
[d] Department of Electrical Engineering and Computer Science, Vanderbilt University, Nashville, TN 37232, USA

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ABSTRACT

Functional MRI (fMRI) has evolved from simple observations of regional changes in MRI signals caused by cortical activity induced by a task or stimulus, to task-free acquisitions of images in a resting state. Such resting state signals contain low frequency fluctuations which may be correlated between voxels, and strongly correlated regions are deemed to reflect functional connectivity within synchronized circuits. Resting state functional connectivity (rsFC) measures have been widely adopted by the neuroscience community, and are being used and interpreted as indicators of intrinsic neural circuits and their functional states in a broad range of applications, both basic and clinical. However, there has been relatively little work reported that validates whether inter-regional correlations in resting state fluctuations of fMRI (rsfMRI) signals actually measure functional connectivity between brain regions, or to establish how MRI data correlate with other metrics of functional connectivity. In this mini-review, we summarize recent studies of rsFC within mesoscopic scale cortical networks (100 μm–10 mm) within a well defined functional region of primary somatosensory cortex (S1), as well as spinal cord and brain white matter in non-human primates, in which we have measured spatial patterns of resting state correlations and validated their interpretation with electrophysiological signals and anatomic connections. Moreover, we emphasize that low frequency correlations are a general feature of neural systems, as evidenced by their presence in the spinal cord as well as white matter. These studies demonstrate the valuable role of high field MRI and invasive measurements in an animal model to inform the interpretation of human imaging studies.

Contents

* Corresponding authors at: Vanderbilt University Institute of Imaging Science, 1161 21st Avenue South, MCN AA-3109, Nashville, TN 37232, USA.
E-mail addresses: limin.chen@vanderbilt.edu (L.M. Chen), john.gore@vanderbilt.edu (J.C. Gore).

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1. Introduction

Correlations in low frequency blood oxygenation level-dependent (BOLD) signals from different parts of the brain in a resting state were first reported by Biswal et al. [1] and have subsequently become widely adopted as potential indicators of functional connectivity between regions [2,3]. These inter-regional correlations are measurable in the absence of any specific stimulus or task manipulation, though they may also change in the performance of a steady-state task or exercise [4–6] in a manner that can be related to behavioral measures. Correlations in BOLD signals between specific regions of the brain have been proposed to be a key signature of consciously driven mental activity (e.g. see [7–9]). Numerous applications of such measurements in various normal and disease conditions have led to observations of altered resting state networks, such as the so-called large scale 'default mode network', in conditions such as schizophrenia and chronic pain (e.g. [10–21]). These observations demonstrate that baseline brain activities are highly relevant for the execution and maintenance of normal brain functions. More importantly, the detection of similar phenomena in very different cortical networks (e.g. oculomotor, sensorimotor, and visual cortices) in anesthetized monkeys [22] has extended this view, suggesting that spontaneous BOLD fluctuations reflect intrinsic synchronous activities within anatomically connected and functionally engaged brain regions. However, despite this high level of interest and multiple potential applications, the validity of inferring direct functional connectivity from resting state fMRI (rsfMRI) data is largely unsubstantiated. Studies in non-human primates which combine fMRI and more invasive measurements have the potential to provide insights into the biophysical basis of resting state signals, and to validate their interpretation and significance. Here we review and summarize some of our recent studies performed at high field in monkeys that aim to better understand the nature and interpretation of resting state functional connectivity (rsFC). Together, they illustrate the value of high field fMRI and invasive studies of animals for informing the interpretation of human rsfMRI acquisitions.

To date, the majority of resting state fMRI studies have examined relatively large-scale networks, involving relatively large volumes of cortex, and much less is known about the characteristics of resting state MRI signals at finer scales. For example, the default mode network has been the focus of numerous studies in which large volumes of cortex have been shown to exhibit variations in their average BOLD signals with other regions that are several centimeters distant. While these larger scale features may be important, the basic processing, functionally homogeneous units of the brain are organized on a much finer, columnar scale. Moreover, execution and maintenance of many brain functions require coordinated activity of brain structures across different scales of brain networks, ranging from macro-scale global networks (in cm to tens of cm, e.g. the default mode network), local meso-scale networks (in hundreds of μm to a few mms, e.g. functionally specific digit modules within the primary somatosensory cortex, S1), to micro-scale networks (in μm to tens of μm, at cellular level). At the meso-scale level, modules or columns are believed to be the fundamental building blocks of cortical specialization, and these often are composed of functionally similar neurons. Individual digit regions in sub-regions of S1 cortex (i.e., areas 3a, 3b, 1 and 2) are classical examples of such modular structures (for reviews, see [23,24]) and have been the focus of our studies. Such clustered populations of neurons are thought to permit more efficient information processing and functional segregation. In contrast to the many rsfMRI studies of the macro-scale whole brain networks, no reports have focused on the functional organization and connectivity networks at this meso-scale level, partly because of spatial resolution limits imposed on human fMRI studies. As a further step, to validate the idea that rsFC is a more general and intrinsic phenomenon within the central nervous system, we have extended our studies from the brain to the grey matter of the spinal cord. By taking advantage of higher signal and contrast to noise ratios at high field (i.e., 9.4 T), which in turn allows higher spatial resolution, we have shown that individual digit sub-regions in somatosensory areas exhibit strong rsFC in monkeys [25–28] and this region provides an ideal model for examining basic issues relevant to the interpretation and validation of resting state connectivity. Similarly, as shown below, the sensory and motor horns of spinal cord grey matter also exhibit strong and functionally relevant resting state connectivity, so studies of monkey spine may also shed light on the origins and significance of rsfMRI signals.

Understanding how BOLD signals, which originate from hemodynamic changes, are related to underlying electrical activity is essential for the quantitative interpretation of fMRI data. To date, the majority of studies have focused on understanding the relationships between evoked fMRI signals and underlying electrophysiological changes during the processing of the responses to tasks or stimulations. A number of simultaneous fMRI and single-site micro-electrode recording studies have suggested a direct link between increases in neuronal activity (as quantified by multi-unit activities and local field potentials (LFPs)) and localized increases in cerebral blood flow and BOLD signals in conventional stimulus conditions (e.g. [29–32]), but the precise spatiotemporal correspondence between neural activity and fMRI signals remains rather poorly understood, and there have been very few similar investigations of resting state signals. Our own studies suggest strongly that the spatial extents of rsfMRI and LFP correlations are similar and co-localize, and specific frequency components of spontaneous LFPs underlie correlated rsfMRI signals between regions [33]. Studies in monkeys allow the use of invasive multi-channel micro-electrode arrays to record electrophysiological signals from the brain and thus provide unique opportunities for examining quantitatively the relationships between rsfMRI and underlying neural activities.

Distinct from previous work in cats and rodents, the functional regions of the non-human primate brain and spinal cord share considerable homology with humans [34–36]. Studies of monkeys provide a crucial linkage between a large existing literature of animal data obtained with invasive methods and human fMRI data involving higher mental functions. The ability to combine very high resolution fMRI, invasive microelectrode array recordings and histology would be impossible in human subjects. For example, the primary somatosensory cortex S1 provides a unique model for investigating rsfMRI within well defined neural circuits. Nearly all previous sub-millimeter fMRI studies have investigated the visual system, and it is unclear how well the findings can be generalized. The primary somatosensory cortex of squirrel monkey is an alternative experimental model for studies of functional connectivity, with several advantages. First, the orderly topographic map of S1 serves as an anchor for our understanding of cortical organization. This orderly map is especially reflected in the hand region which is characterized by a lateral to medial representation of individual digits in each of four subregions of areas 3a, 3b, 1 and 2. This has been well established by studies of neuronal receptive field properties and of the effects of preferred stimuli and histological characterizations. Each area has distinct stimulus preferences, suggesting their different roles in specific somatosensory functions. In contrast to the visual system, stimulus evoked activations in the hand region can easily be detected and quantified in 'single condition' maps e.g. vibrotactile stimulation of a single digit, a classical example of the columnar structure of cortex. This eliminates unnecessary ambiguities in designing orthogonal stimuli that are commonly used to reveal modular structures in the visual system. Secondly, we have demonstrated how the functional organization of this region may be mapped at sub-millimeter scale [25–28] for touch processing. Our data have demonstrated that single digit fMRI (both BOLD and CBV) activations can be reliably mapped and their responses scale with different magnitudes of vibrotactile stimuli. In addition, these maps correspond very well with results from ultra-high resolution optical imaging of intrinsic signals, which confirm that digit activations are organized in a somatotropin manner. Moreover, more recent work has shown that the distinct subregions of S1 show both short-range correlations to other sub-regions within S1 as well as longer range thalamo-cortical connections that can be mapped simultaneously. Additionally the immediately neighboring face area serves as a control region that allows the extent of spatial correlations to be