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Previews

Topographic Dynamics in the Resting Brain

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In this issue of *Neuron*, Wang et al. (2013) demonstrate that spontaneous neural activity measured using functional neuroimaging is strongly related to millisecond-scale neuronal interactions and topographically precise anatomical connections in the primate somatosensory cortex.

Spontaneous or endogenously driven neural activity has been a focus of investigation in electrophysiology for many decades (Buzsáki, 2009). In recent years, researchers have focused on fluctuations in blood oxygenation level-dependent (BOLD) activity acquired during a "task-free" or "resting" state, as the spatiotemporal structure of these signals has proven richly informative about the functional organization of the human brain (Raichle, 2011).

Resting-state dynamics are commonly characterized via "functional connectivity," which describes the statistical dependence of activity at different locations in the brain. Resting-state functional connectivity is often computed via a Pearson correlation of fMRI BOLD signal time series recorded from different voxels. Despite the unconstrained mental state in resting-state fMRI experiments, patterns of functional connectivity across the brain are quite reproducible within individuals and across large cohorts of participants (Biswal et al., 2010). This observation suggests that functional connectivity may be shaped by the underlying anatomical connectivity. This notion has gained support from direct comparisons of anatomical and functional connectivity in the monkey (Vincent et al., 2007) and human (Honey et al., 2009) brain, as well as from interventional studies demonstrating changes in functional connectivity after manipulations of the anatomical substrate (Johnston et al., 2008). In addition, computational models combining cellular biophysics and networks of synaptic connections can generate realistic functional connectivity patterns (Deco et al., 2011).

Despite the growing promise of BOLD functional connectivity, important questions remain concerning the optimal data acquisition and analysis methods (Cole et al., 2010) and the spatiotemporal scales at which dynamical correlations usefully indicate functional properties of the brain. Does functional connectivity recorded with fMRI (a slow and indirect neural observation) relate to functional connectivity recorded more directly with invasive electrophysiological methods? Does anatomical connectivity predict resting-state BOLD functional connectivity at spatial scales finer than a cubic millimeter? Can patterns of correlation in the BOLD signal reveal intra-areal functional topographies?

In this issue of *Neuron*, Wang et al. (2013) make significant progress toward addressing these questions. Their focus is on connectivity within area 3b and area 1 of the squirrel monkey somatosensory cortex. Both of these areas contain complete representations of the monkey's body surface. Wang et al. (2013) focus on the subregions of area 3b and area 1 that represent the tips of the digits of the hand, which can be precisely localized by tactile stimulation. A key feature of the study is that it employs three different techniques for recording brain connectivity, and each kind of connectivity is registered against functionally mapped intra-areal topography.

First, using high field-strength fMRI, resting-state functional connectivity is recorded among seed voxels placed in different parts of the somatosensory cortex. Functional connectivity between area 3b and area 1 was observed between voxels that responded to tactile stimulation of the same digits, indicating that the interregional connectivity is spatially precise and functionally meaningful. In addition, seeds placed in a third somatotopic region (area 3a) exhibited correlations with area 1 but not area 3b, consistent with the known anatomical connectivity between area 3a and area 1. Additionally, different digits appeared functionally connected to each other within area 3b. These patterns were consistently observed across multiple animals.

Second, injections of the anatomical tracer BDA into physiologically identified digit representations allowed the reconstruction of intra- and interareal anatomical projections. Area 3b was shown to receive interareal inputs from topographically matched locations in area 1, as well as intra-areal inputs from other digit representations within area 3b. These anatomical results suggest two main directions of signal flow: one characterized by cross-digit connections within area 3b, and the other by digit-selective connections between area 3b and area 1.

Finally, Wang et al. (2013) obtained electrophysiological recordings of single units isolated in specific locations within area 3b and area 1. Functional connectivity between neurons was identified by computing cross-correlograms between the spike trains of different units. If the correlogram for a given pair of spike trains exhibited a significant peak, then the two recording sites were considered synchronized, and thus functionally connected. The analysis of neuronal recordings from numerous sites within area 3b and area 1 revealed that correlations among matched digits in the two areas were stronger than those between nonmatched digits. In addition, significant correlations were identified between recording sites in area 3b corresponding to different digits. Closer examination of the peak latency of the spike correlograms

suggested that feedforward interareal interactions from area 3b to area 1 were stronger than the corresponding feedback connections. Within area 3b, it was not possible to define which interactions were feedforward and which were feedback, but the intra-areal interactions between digits were nevertheless asymmetric, so that some digits seemed to be driving responses in others.

Thus, in mapping the functional architecture of the primate somatosensory cortex, Wang et al. (2013) successfully combined the strengths of their three measurement tools. They measured correlations in spontaneous BOLD signals, which do not always reflect direct neuronal interactions, but which provide a noninvasive indicator of connectivity that can be applied at a whole-brain scale. They employed fiber tract tracing, which is an invasive measure, but which provides a spatially precise picture of axonal connectivity. Finally, they measured interregional correlations in the firing rates of isolated neurons, an invasive technique with a limited field of view, but which directly captures neuronal interactivity with millisecond resolution.

The convergent findings across methods validate the overall approach and present a largely consistent picture of connectivity within the squirrel monkey somatosensory cortex. Anatomical and functional connections, the latter extracted from neurophysiological recordings and resting-state fMRI, appear to be organized into two main "axes of information flow." One axis predominantly links representations of matched digits in area 3b to area 1, while the other axis links representations of different digits within area 3b. Moreover, this study demonstrates that BOLD correlations are diagnostic of neuronal interactions both with and across areas, even in voxels smaller than 0.7 mm^3.

The topographic order revealed within spontaneous somatosensory dynamics is consistent with studies of the feline visual system (Kenet et al., 2003). There, using optical imaging, spontaneous and stimulus-evoked dynamics were shown to exhibit similar patterns of intra-areal correlation, and the spatial profile of this connectivity reflected the topography of orientation selectivity. In this new study, it is the inter-areal correlations that reflect an underlying topography, this time the body surface representations in areas 3b and area 1. Based on a combination of invasive and noninvasive recordings from multiple somatosensory regions, Wang et al. (2013) proposed a functional principle for somatosensory cortex: diffuse integration of information within areas and more targeted digit-specific information flow between regions.

Wang et al. (2013) show that correlations in resting-state BOLD signals measured noninvasively at submillimetric scale can be reliably registered against maps of functional topography. This work is part of an emerging trend in which large-scale BOLD connectivity analyses are combined with fine-grained functional mapping (Haak et al., 2012; Donner et al., 2013; Jbabdi et al., 2013). These topographically targeted approaches contextualize the correlations in BOLD signal and in neuronal spike trains in terms of cytoarchitectonic boundaries. In addition, they provide a more precise connection between spontaneous and task-elicited behavior, constraining the meaning of the "function" in functional connectivity.

There are three clear directions for future development of this work. First, Wang et al. (2013) examined connectivity in an anesthetized animal in the absence of behavior and so studies are needed to show how these spatially precise patterns of functional connectivity are altered across goal states, attentional states, and levels of arousal. Second, there were no interventional measures of interactivity, which leaves open the possibility that correlations were driven by common sources. Electrical and optogenetic stimulation are a growing trend for causal mapping (e.g., Keller et al., 2011). Finally, Wang et al. (2013) restricted their field of view to a subset of peri-Rolandic regions. Future work should investigate how these precise patterns of somatotopic BOLD connectivity relate to motor and prefrontal cortical dynamics, and how they change in the wider neural context (McIntosh, 1999).

In summary, Wang et al. (2013) have precisely examined the relationship between anatomical connectivity, BOLD signal correlations, and neuronal spiking correlations within primate somatosensory cortex. Their work presents a coherent picture of the interareal connectivity and dynamics at the fine scale of topographically mapped body surface representations, enriching our understanding of functional connectivity and its anatomical underpinning.

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