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# Spatiotemporal dynamics in large-scale cortical networks

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**Abstract**

Investigating links between nervous system function and behavior requires monitoring neuronal activity at a range of spatial and temporal scales. Here, we summarize recent progress in applying two distinct but complementary approaches to the study of network dynamics in the neocortex. Mesoscopic calcium imaging allows simultaneous monitoring of activity across most of the cortex at moderate spatiotemporal resolution. Electrophysiological recordings provide extremely high temporal resolution of neural signals at multiple targeted locations. A number of recent studies have used these tools to reveal novel patterns of activity across distributed cortical subnetworks. This growing body of work strongly supports the hypothesis that the dynamic coordination of spatially distinct regions is a fundamental aspect of cortical function that supports cognition and behavior.

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## Introduction

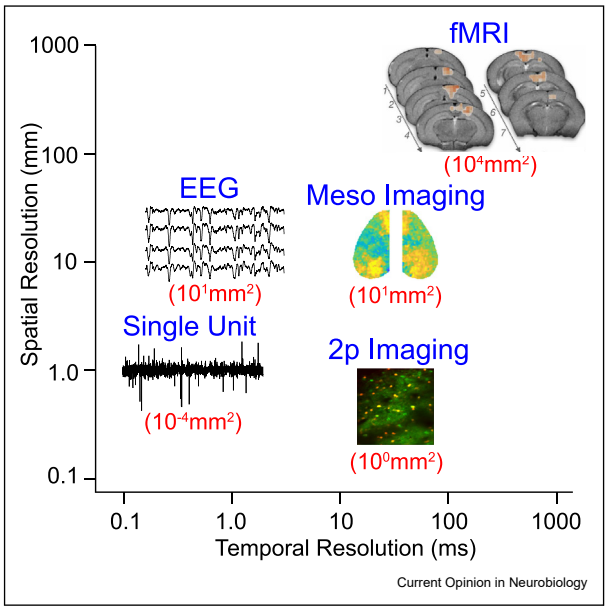
Cognitive functions, including perception, attention, and memory are critical for the generation of purposeful behavior and are thought to require interactions between neuronal networks distributed across the neocortex. However, robust characterization of coordinated activity at this scale requires measurements with both high spatial accuracy and temporal fidelity applied simultaneously to large areas of the cortex. Most commonly used methods for assessing cortical activity span a subset of possible spatial and temporal scales, meeting some but not all of these requirements (Figure 1). Here, we examine recent work using two highly complementary strategies—mesoscale imaging and electrophysiological recordings. These two approaches have generated exciting new insights into modes of communication present across large-scale cortical networks and links between network dynamics and behavior. Each technique provides powerful windows into neural activity, but also has distinct limitations that may be best overcome by making combined use of both approaches.

## Spatiotemporal heterogeneity in cortical network dynamics

Over the last twenty years, *in vivo* fluorescence microscopy has moved from a niche area of research to the dominant method for monitoring neuronal activity, particularly in model systems where genetically encoded indicators are readily applied [1–4]. In particular, protein-based calcium sensors provide a robust though indirect readout of neural firing that is applicable at a range of spatial scales, from single cells to large networks [1,5,6].

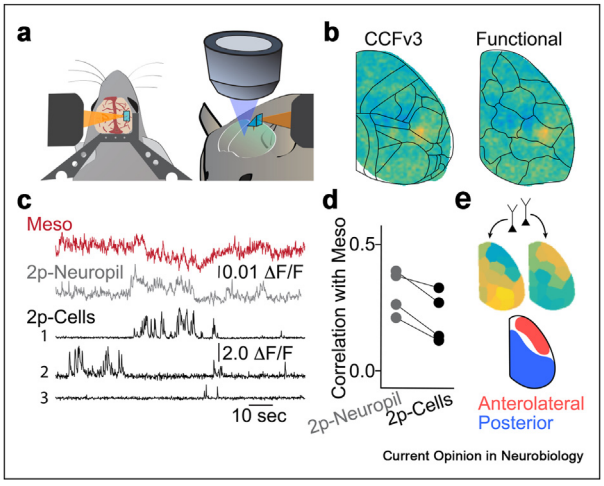
In the last few years, widefield ""mesoscopic" calcium imaging has been rapidly adopted by several laboratories due to its relative ease of application and ability to reveal novel aspects of functional network organization in awake, behaving animals [7]. Mesoscopic imaging represents a compromise among many desirable features, offering extremely large fields of view ($\sim$100 mm$^2$) [8] (Figure 1) with moderately high spatial resolution (single camera pixels correspond to a few tens of microns). To clarify the neuronal structures contributing to these signals, we carried out simultaneous widefield and 2-photon imaging using an implanted prism on the cortical surface (Figure 2). Our results showed that fluorescence from both cell bodies and neuropil (dendritic and axonal compartments) were correlated with mesoscopic dynamics, suggesting both contribute to the signal (Figure 2). Depending on the camera used, mesoscopic imaging also provides modest temporal resolution (10–100 ms per frame), ultimately resolving local circuit dynamics across the entire dorsal mouse neocortex [7]. Moreover, the availability of transgenic mouse lines and viral vectors for cell type- and circuit-specific expression of indicators enables even further dissection of functional network architecture [1–3,6,9].

**Figure 1**




Schematic illustrating the relative spatial and temporal resolution for several methods of monitoring brain dynamics including EEG (electroencephalography), single unit recording, widefield mesoscopic imaging, 2-photon imaging, and fMRI (functional magnetic resonance imaging. Numbers in red indicate approximate spatial scales sampled by each approach.

**Figure 2**




Insights from simultaneous mesoscopic and cellular resolution imaging. a, Schematic illustrating setup for carrying out dual widefield and 2-photon imaging through an implanted glass microprism on the cortical surface. b, Mesoscopic data can be parcellated using either fixed anatomical boundaries such as the Allen Institute Common Coordinate Framework (CCFv3, left) or correlation-based functional grouping of pixels unique to the individual data set (right). c, Example traces showing simultaneous mesoscopic and cellular recordings. d, Correlation between activity in either cell bodies or neuropil (via 2-photon imaging) with mesoscopic signals in the same area. e, Examples of the large-scale network patterns correlated with the activity of two individual cortical pyramidal neurons (upper). Schematic of anterolateral and posterior cortical divisions identified by dual mesoscopic and 2-photon imaging, corresponding to the dominant patterns of functional connectivity between single neurons and large-scale networks (lower). All panels adapted from the study by Barson et al. [8].

Indeed, the recent development of methods for driving widespread expression of genetically encoded indicators using systemic administration of viral vectors has opened the door to mesoscopic imaging in mice without the need for complex breeding strategies [8*,10,11]. For example, co-injection of two different high titer serotype 9 adeno-associated viral (AAV) vectors driving expression of the red fluorescent calcium sensor jRCaMP1b [12] and the green fluorescence acetylcholine sensor ACh3.0 [13*] enabled us to carry out simultaneous two-color imaging of these signals across the neocortex of awake, behaving mice [14**].

Using a two-color imaging strategy to measure local neuronal activity and cholinergic release across the cortex, we found a complex interrelationship between cholinergic modulation and cortical functional connectivity that varied across distinct subregions. Spontaneous variation in behavioral measures of arousal such as locomotion, whisking, and pupil dilation were correlated with broad, spatially patterned variation in the magnitude of cortical activity and cholinergic release. Indeed, moderate arousal occurred with elevated cholinergic signaling primarily in frontal regions, while stronger arousal was associated with global elevation in neuronal activity [14**]. Consistent with the heterogeneous pattern of cholinergic signaling, treatment with the muscarinic blocker scopolamine selectively decreased cortical activity in motor but not visual areas [14**]. This work is consistent with that of other labs showing widespread representation of spontaneous motor signals across the cortex [15,16]. Moreover, arousal was associated with an overall increase in large-scale network correlations in cortical activity, but non-monotonic changes in correlations of cholinergic release [14**]. Cholinergic release may thus have distinct impacts on correlations at different scales, potentially decreasing local correlations [17,18] and enhancing large−scale correlations [14**]. Looking forward, the rapid emergence of new genetically encoded reporters for a wide variety of neurotransmitter and neuromodulator signals presents a dizzying opportunity for new discoveries in the coming years using mesoscale imaging of large-scale networks [9,19].

## Functional parcellation of cortical networks

The ability to readily image activity across the mouse cortex has brought front and center the goal of identifying spatial subregions, such as distinct cortical area, whose activity may provide insights into links between neural signaling and behavior. Fundamentally, this is a

question of reducing the high dimensionality of data generated by this modality (> 200,000 pixels per frame). There is a long history of assigning functional labels to cortical subregions (e.g., visual, somatosensory, association). Such divisions have traditionally derived from cytoarchitectonic and anatomical studies, an approach exemplified by the recent efforts of the Allen Institute to develop the Common Coordinate Framework (CCFv3 [20]). CCFv3 boundaries are easily mapped onto new, functional data sets, providing a standard, uniform parcellation scheme across individual mice and different laboratories and facilitating analysis and comparison of findings across studies (Figure 2).

However, a major drawback to structure-based parcellation is the lack of direct link to dynamic neuronal function. A number of recent studies using mesoscopic calcium imaging in awake, behaving mice have begun to develop strategies for subdividing cortical regions on the basis of activity. A new understanding of functional cortical architecture is emerging from these approaches. For example, Sexena et al. (2020) used localized nonnegative matrix factorization to decompose mesoscopic whole-cortex data into functional regions better representative of correlated neural dynamics in the individual animal [21]. However, this approach relied on the Allen CCFv3 as an initial seeding and adhered to corresponding parcel names. In contrast, other approaches have relied strictly on correlations between pixels, using graph-theory-based algorithms to group correlated pixels into functional parcels [8*,22,23**,24](Figure 2). These methods provide an entirely data-driven approach to the individual animal. However, the resulting parcellations typically do not align well across different individuals, raising challenges to statistical group analyses. Moreover, such functional parcellations do not appear to correspond easily to anatomical-based divisions. Another distinct approach to functional dimensionality reduction was highlighted by MacDowell and Buschman [25*], who used convolutional nonnegative matrix factorization to identify repeated spatiotemporal motifs. Unlike parcels, these motifs did not tile the cortex, but instead reflected potentially spatially overlapping but temporally dynamic patterns of activity. This method also produces individual, data-driven characterization of cortical networks but does not produce unique labels for discrete structural subdivisions.

## Dynamic correlations define cortical subnetworks

Analysis of mesoscopic imaging data has also produced novel insights into cortical network organization that were wholly unpredicted from anatomical divisions. Mesoscale imaging allows estimation of the continuous fluctuations in functional connectivity between distant cortical areas, which may carry unique information about behavioral output. For example, we developed a novel graph-based method to calculate the time-varying changes in pairwise correlations between cortical parcels. Surprisingly, spontaneous fluctuations in motor behaviors were better encoded by these dynamic correlations than by the time-varying changes in the magnitude of activity across parcels [23**]. We found that correlation dynamics were organized into two broad anterolateral and posterior subdivisions that did not map onto established anatomical borders [23**], suggesting distinct organizational principles for functional versus structural data sets. This dissociation was also observed by MacDowell and Buschman (2020), whose identified spatiotemporal motifs in mesoscopic imaging data also correspond poorly to atlas-based parcellation [25*]. Furthermore, our work combining mesoscopic and 2-photon imaging allowed us to identify the functional connectivity of single neurons with discrete large-scale networks [8*]. These analyses revealed that individual neurons were functionally connected with one of two regions that closely corresponded to the same anterolateral and posterior subdivisions derived from large-scale network correlations [8*] (Figure 2).

Carrying out similar imaging studies during task performance also has the potential for revealing network dynamics linked to goal-directed behavior. Mice carrying out a sensory discrimination task exhibit sensory- and strategy-specific activation of distinct regions throughout the cortex [15,26–29]. Overall, these studies reveal the power of mesoscopic imaging to detect coordinated spatial patterns of activity across large-scale networks.

## Electrophysiology reveals fast long-range network dynamics

In comparison to mesoscopic imaging, analysis of electrophysiological brain signals offers several complementary advantages for investigating communication across large-scale cortical networks. Electrical recordings provide sub-millisecond resolution, offering a degree of temporal fidelity not possible via commonly used imaging approaches (Figure 1). The most frequently used electrophysiological technique is extracellular recording, where a single electrode site can measure both local field potentials (LFPs), which largely arise from synchronous synaptic events, and spiking, which arises from the action potentials of individual nearby neurons. A common measure of communication between cortical areas is the coherence between the local field potentials in each area in a specific frequency band such as theta (3–8 Hz), beta (16–35 Hz) or gamma (30–80 Hz). Functional connectivity, which may reflect both direct and indirect influences of one area on another, has also been estimated from measures of coherence and Grainger causality [30-32**]. However, recent work has highlighted the complexity of the relationship between connectivity, power, and coherence. Indeed, coherence may arise from

inter-areal communication in accordance with connectivity patterns, and changes in coherence may reflect changes in oscillatory power in synaptic inputs from sender to receiver areas rather than a more direct measure of functional connectivity [32**]. These findings underscore the necessity for laminar recordings and current source density (CSD) measurements in addition to more traditional single-site measurements of field potentials and spiking [33].

Simultaneous recordings across multiple cortical areas have highlighted the potentially distinct roles of specific frequencies of neural activity in inter-areal communication [31,34–36]. Interareal coherence in distinct frequency bands of the LFP during task performance may vary across pairs of visual cortical areas according to relative position in the cortical hierarchy [36], suggesting a selective frequency-based mode of interareal communication. Long-range, frequency-specific interactions have likewise been observed between the hippocampus and prefrontal cortex, with theta and beta frequencies associated with errors and correct responses, respectively [37]. Recent work suggests that functional connectivity supported by these distinct LFP frequency bands may also play a role in predictive coding, with predictable and unpredictable stimuli associated with distinct temporal patterns of activity and changes in functional connectivity among higher-order cortical areas [38].

## Dynamic interareal communication

Sampling of signals across the cortical hierarchy reveals functional connectivity, as measured by coherence and Grainger causality, across distinct frequency bands among cortical modules. The overall pattern of this functional connectivity may be related to anatomical connectivity [30,36] and exhibits bidirectional interactions among areas that follow known reciprocal anatomical connections. Functional interactions among large-scale cortical networks exhibit selective feedforward and feedback routing of communication via specific subsets of activity patterns. Feedforward and feedback connectivity, as identified by Grainger causality, may occur in distinct frequency bands [30,36] and rely on distinct patterns of population activity on different timescales [39]. However, frequency-specific interactions are unlikely to represent the sole mechanism for interareal communication. Indeed, fluctuations in activity in higher-order visual areas V2 and V4 are not driven by the largest amplitude fluctuations in their afferent, primary visual cortex (V1), but rather are related to a subset of V1 activity patterns that can be described as a low-dimensional communication subspace [40*].

Fine temporal modulation of coherence or changes in functional connectivity may further organize information transfer among cortical areas. Electrophysiological data suggest that functional connectivity across large-scale cortical networks may undergo rapid dynamic changes during behavior. Recent work using a spatial attention task found that the frontal eye field and the lateral intraparietal area exhibited evolving functional interactions characterized by two rhythmically alternating states coordinated by theta phase [41]. Computational modeling suggests that even short bursts of patterned activity can selectively route input signals and shape interareal communication [42]. Indeed, frequency-specific transient synchronization between two cortical areas has been associated with trial-by-trial variations in task performance [43,44*]. Brief epochs of rhythmic functional interaction may thus enhance information transmission and contribute to perceptual performance.

Local extracellular recording electrodes often provide both local field and spike signals from the same electrical contact site in the brain. In addition to rhythmic coordination of local field potential signals, fine timescale coordination of spiking events is likewise associated with enhanced perceptual performance. Coordinated spiking between neurons in areas along the cortical hierarchy may be predictive of behavioral performance. In recent work, Shahidi et al. (2019) found that coordinated spiking between V1 and V4 neurons increased in a short epoch following stimulus presentation and was predictive of behavioral performance [45]. Frequency-specific and temporally precise relationships in spiking activity between areas may further enhance encoding and transmission of information in a phase-dependent manner [46]. Similarly, highly dynamic patterns of local and long-range coupling between spike timing and oscillatory phase across frontal cortical areas FEF and LIP were associated with different behavioral outcomes in an attention task [44*].

## Embedded cortical subnetworks

Although previous work has largely used single electrodes or large fixed arrays to record field potentials and spiking activity, the development of high-density recording arrays and novel strategies for analysis provide new opportunities to examine fast interactions within and among cortical areas. Recent work using multisite high-density recordings across the mouse brain revealed shared spontaneous movement and state representation across areas with cellular resolution [16,47]. Multiple simultaneous high-density recordings from distinct cortical visual areas in mouse cortex further revealed a cortical network of modules of neurons based on functional connectivity [48**]. One module of neurons embedded within the cortical hierarchy may serve feedforward sensory processing, whereas the other may function in recurrent integration of sensory information [48**]. Together, these findings suggest that subnetworks of functionally connected neurons across areas may participate in distinct motor and sensory

computations. There is thus a critical need for further high-density recordings with high spatial and temporal resolution to examine how interactions across embedded subnetworks of neurons support functional connectivity and interareal communication.

## Complementary strengths across modalities

Comparing the data derived from both widefield imaging and electrophysiology reveals strikingly complementary strengths and weaknesses. Mesoscopic imaging provides the ability to monitor activity contiguously across much of the dorsal neocortex. In addition, genetic encoding of indicators allows specific targeting of neuronal subpopulations and longitudinal imaging is straightforward, enabling studies of plasticity across development and learning [3,8,49]. Finally, new imaging systems are being developed for carrying out mesoscopic imaging in freely moving animals [50]. However, the origins of the signals in typical experiments are somewhat ambiguous, arising from both cell bodies and neuropil at unspecified cortical depth (see Figure 2). Moreover, single cells are not spatially resolved (given the various tradeoffs between field of view, pixel density, and optical resolution).

In contrast, the temporal resolution of electrophysiology is unmatched, providing the ability to measure spike timing in single cells whose physical location can be determined precisely. In addition, combining single unit recording with LFPs on the same channel gives information about the relationship between synaptic currents and spike output. Moreover, electrophysiological recordings are not limited to the cortex, linking activity to structures throughout the nervous system. However, genetic identification of the recorded cells is difficult, though optogenetic manipulation can provide this information in some cases [51]. Also, dense coverage across the cortex is not possible given the physical limitations of electrode implantation, and chronic recordings of the same neurons can be challenging.

Given these well-matched strengths, combining these two modalities can yield a highly synergistic experimental paradigm. Simultaneous mesoscopic imaging and electrophysiological recordings of either the visual cortex [52] or striatum [53] has given investigators critical new insights into the organization of largescale functional connectivity and network organization in the brains of behaving animals. Further work examining patterned activity such as traveling waves [54–56] may provide opportunities to more precisely relate electrophysiological measurements like oscillations to the spatiotemporal pattern of mesoscale activity.

## General conclusion

The burgeoning array of methodological approaches suitable for monitoring activity with high spatial and temporal resolution across the cortex is driving rapid progress in our understanding of large-scale coordinated neural activity and its relationship to behavior. Both mesoscopic imaging and electrophysiological recordings provide strengths and weaknesses in this regard. The application of genetically encoded indicators targeting specific subsets of cell types opens up the study of functionally distinct circuits that are physically interspersed throughout cortical networks [57–59]. In parallel, novel electrophysiological probes create opportunities for simultaneous recordings of single neurons communicating across distant areas [48**].

In addition, recent studies are beginning to combine different recording modalities, effectively merging the strengths of each approach across diverse spatial and temporal scales. For example, multiple groups have combined 2-photon imaging or electrophysiological recordings of single neurons with simultaneous mesoscopic imaging to investigate the functional connectivity across cells and networks [8,52,53**]. Indeed, a central open question in cortical physiology is the relative role of local versus long-range synaptic connections in linking activity across distant circuits. In the future, such synergistic approaches are likely to reveal critical new avenues of exploration and understanding, promoting further discovery of the neural basis of cognition and behavior.

## Conflict of interest statement

Nothing declared.

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