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Recording of brain activity across spatial scales

CM Lewis[1,2], CA Bosman[2,3] and P Fries[1,2]

Brain activity reveals exquisite coordination across spatial scales, from local microcircuits to brain-wide networks. Understanding how the brain represents, transforms and communicates information requires simultaneous recordings from distributed nodes of whole brain networks with single-cell resolution. Realizing multi-site recordings from communicating populations is hampered by the need to isolate clusters of interacting cells, often on a day-to-day basis. Chronic implantation of multi-electrode arrays allows long-term tracking of activity. Lithography on thin films provides a means to produce arrays of variable resolution, a high degree of flexibility, and minimal tissue displacement. Sequential application of surface arrays to monitor activity across brain-wide networks and subsequent implantation of laminar arrays to target specific populations enables continual refinement of spatial scale while maintaining coverage.

Addresses
[1] Ernst Strüngmann Institute (ESI) for Neuroscience in Cooperation with Max Planck Society, 60528 Frankfurt, Germany
[2] Donders Institute for Brain, Cognition and Behaviour, Radboud University Nijmegen, 6525 EN Nijmegen, Netherlands
[3] Cognitive and Systems Neuroscience Group, Swammerdam Institute for Life Sciences, Center for Neuroscience, University of Amsterdam, 1098 XH Amsterdam, Netherlands

Corresponding author: Lewis, CM (chris.lewis@esi-frankfurt.de)

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Introduction

Scientific progress has repeatedly been catalyzed by the development of technologies that augment and enhance our senses. Although a given body of knowledge can often accommodate multiple perspectives, additional evidence, provided by new tools, is often required to adjudicate between competing theories. The intertwined evolution of scientific understanding and technical development is nowhere more evident than in the study of the brain. For the majority of human history, brain anatomy and physiology have remained obscure, hidden beneath the protective cladding of the cranium, and reachable only through clinical observation of subjects with brain lesions and studies of post-mortem anatomy [1–3]. By contrast, theories of brain function have flourished [4–7]. The development of new techniques and tools has gradually unveiled organizational and operational principles of the brain with increasing spatial resolution. This advancement has led to intense interest in and interrogation of nervous system function and a need to ground theories in detailed experimental exposition.

Anatomical techniques have revealed the intricate and prolific connectivity of brain cells and regions [8–10], while physiological methods have provided maps of sensory and motor responses [11,12] as well as the neural correlates of diverse cognitive functions [13•,14–17]. The majority of work in electrophysiology, the gold-standard in systems neuroscience, has attempted to understand localized brain regions through the piece-wise application of reductionist methods: analyzing single cells with well-controlled stimuli [18]. This tradition has provided a lens on the operational principles of brain cells and regions by quantifying brain responses parametrically as they relate to sensory and behavioral variables. At the same time, the individual study of isolated brain areas and cells has often reinforced the implicit perspective that local computations can be understood in isolation and that interactions between areas consist largely in the transfer of encapsulated bits of information through processing hierarchies [19]. However, evidence in support of an alternative perspective on brain function has emerged, thanks to the development of increasing computational power, high-density multichannel amplifiers and new recording technologies. This perspective suggests that localized populations integrate extrinsic and intrinsic signals, forming distributed patterns of coherent activity. Therefore, cognitive states may be irreducible to isolated components [20,21]. At the very least, activity in distributed regions influences the active processing of sensory and behavioral signals throughout the brain [22,23]. As such, the study of isolated areas and cells may provide a limited and potentially distorted perspective on integrated brain function.

The relatively recent advent of non-invasive neuroimaging methods has spurred a renewed appreciation for the widespread activation of distributed brain regions that occurs during behavioral tasks, as well as in uncontrolled states, such as passivity and sleep [24–26]. These methods — while useful to localize the anatomical areas involved in cognition — lack the temporal resolution needed to study the neuronal dynamics inherent in any brain operation. Yet, the perspective afforded by

whole brain imaging has influenced researchers using more traditional approaches to physiology. Simultaneously, new methods for constructing multi-electrode arrays (MEAs) [27], as well as cellular-resolution *in vivo* imaging techniques [28], have led to an appreciation for the intricate way in which extrinsic input is combined with recurrent activity in order to represent and operate on incoming signals in a coordinated manner [29•,30••,31,32•,33••]. However, a complete appreciation of the rich dynamics that engage local and distributed neural groups requires a transition from the focus on either isolated cells or isolated areas to a focus on the coordination between local populations and the integration of distributed functional networks. Although increased use of MEAs has improved our understanding of local cortical processing, future work should extend this initial scope, focusing on interactions across multiple spatial levels of brain activity. New studies must increasingly focus on the flow of information through laminar circuits, the role of identified cell-classes, and targeted recordings of interconnected populations in multiple areas. In order to understand the highly specific manner in which processing occurs, individual studies must attempt to record activity at each relevant scale. Here, we present a survey of recent work that turns in this direction, motivations for further development along these lines, and current technologies that enable an integrated approach to investigating distributed functional networks at a wide range of spatial scales.

Brain activity shows structure across spatial scales

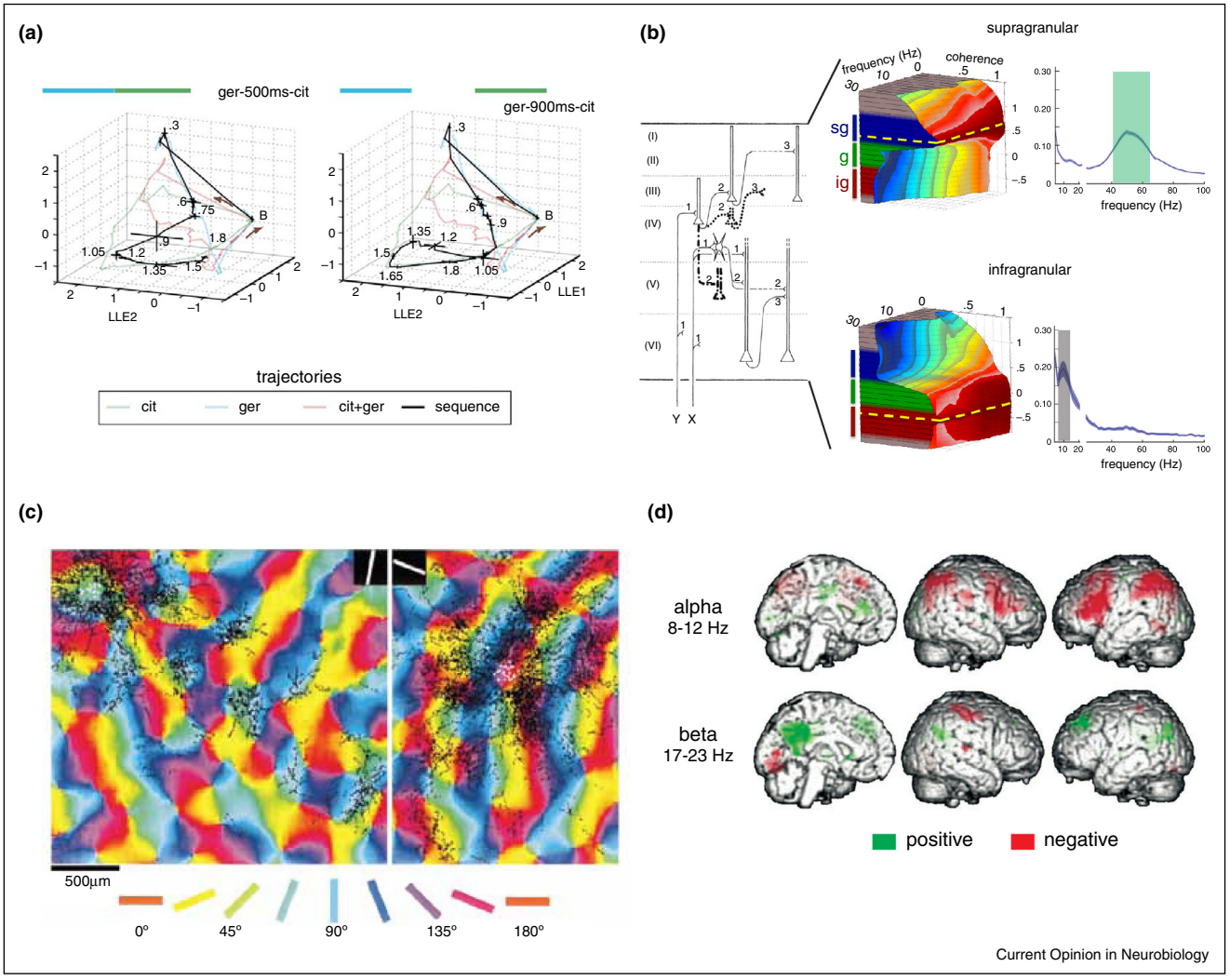
The need for studies that bridge spatial scales is evidenced by the intricate structure of neural activity patterns at multiple levels of spatial resolution. Across multiple orders of magnitude, from local populations in isolated patches [33••,34], interconnected laminar circuits [35,36], laterally connected mosaics of cortical areas [37], all the way to brain-wide networks [38,39], connectivity and activity patterns exhibit a high degree of spatial specificity.

The investigation of single cells during sensory and motor events has taught us a great deal about primary sensory and motor cortices and sub-cortical structures. However, despite the success of single unit studies in low-level brain areas, the ability to record populations of units has led to the conclusion that, even in very early brain areas, such as the retina, olfactory bulb or primary motor cortex, sensory and motor events are represented by the collective activity of large groups of cells (Figure 1a). Crucially, in these early areas, stimulus information conveyed in the joint activity of groups of cells does not simply reproduce the information contained in individual cells considered alone. Although the idea that joint activity conveys information remains contested, increasing evidence suggests that synchrony and coincident activity in populations can reveal aspects of stimulation missing from the responses of the same cells considered in isolation [40–43]. Further, synchronous activity is preferentially conveyed to downstream areas and may enhance plasticity [44–47]. The importance of population coding becomes even more evident in higher order areas, where single cell responses are often complex and exhibit an obscure relationship to external variables [30••,31]. These considerations have led to the suggestion that ensembles of cells may be involved in the dynamic representation of external and internal variables in the brain. It has therefore become important to study many elements in local circuits in order to shed light on the nature of local representation and computation as well as the functional organization of local circuits.

Activity within localized populations is also far from homogeneous. The cortex is organized into inter-mingled laminar circuits (Figure 1b) with distinct patterns of connectivity that varies by area. Although anatomy has long highlighted the intricate organization of laminae, electrophysiology has lagged behind, in part because of the lack of linear electrode arrays and the difficulty of unequivocally identifying the spatial location of recordings. Existing evidence suggests that, in visual cortex, activity is segregated into supra-granular and infra-granular compartments [48]. Stimulation leads to additional divergence, with both the generation of distinct rhythms in superficial and deep compartments, as well as, the selective locking of superficial and deep cells to the local rhythm [36,49]. The sequence of activity within laminar structures further demands careful measurement in order to determine how population activity is propagated through the local circuit and how activity in specific laminar compartments relates to both local and distant areas. Recent findings already suggest some potential ways in which differentiated information pathways may be realized by segregated laminar processing streams [50••,51••,52]. Further work is required in order to place local laminar circuits into the global context of distributed brain networks.

In addition to the intricate organization of laminar circuits along cortical depth, many areas are organized into topographical maps containing orderly representations of stimulus features [53]. In the visual domain, areas are organized along many feature dimensions, including: retinotopy, orientation, and ocular dominance (Figure 1c) [54]. These intermixed feature maps give rise to specific patterns of lateral connectivity with axons preferentially targeting areas of similar selectivity [11,55]. During the execution of visual tasks, this connectivity is likely to be responsible for the contextual effects, such as surround suppression, observed from the responses of single neurons [56]. However, the manner in which population activity is constrained and modulated by the lateral connectivity within and between

Figure 1



Brain activity shows intricate organization across spatial scales. **(a)** Population activity within the olfactory bulb distinguishes odorants through the coordinated activity of multiple cells [66]. **(b)** Analysis of current flow within cortical circuits has led to a canonical model of laminar organization (left column), suggesting that activity propagates sequentially through local networks [48,49,83]. Depth resolved recordings demonstrate laminar compartmentalization in macaque v1. Coherence between LFP on neighboring sites of a laminar array (middle column) obeys laminar boundaries [48]. Likewise, spike-field coherence computed from units in superficial and deep layers demonstrates distinct spectral profiles suggesting laminar activity is segregated into separable processing streams (right column) [49]. **(c)** The topographical organization of cortical areas reveals a high systematicity which reflects anatomical connectivity [11]. **(d)** The whole brain is organized into multiple distributed networks that are involved in distinct cognitive processes [39].

neighboring areas is still not well known. It is further likely that lateral activity within and between nearby cortical areas is tightly coordinated during natural vision, when the entire visual field is simultaneously activated by a coherent scene. Evidence of highly specific modulatory effects comes from experiments examining the impact of natural scenes on the response properties of single cells [57,58]. Simultaneous recordings at both the local and areal scale are necessary to begin to piece together a view on coordinated processing by populations within brain areas.

At the level of the whole brain, cognitive neuroimaging has revealed a number of distributed networks (Figure 1d) [24,39,59,60]. A great deal of work has been devoted to delineating functional networks, relating them to known anatomy and ascribing specific operations to localized areas within these networks. Additionally, the increased emphasis on functional networks has precipitated the confrontation of competing theoretical accounts of how distributed populations communicate, represent task variables and realize flexible and robust task sets and contexts. Crudely, the two dominant views differ in

one key aspect: whether or not the brain can be conceived of as a feed-forward system, sequentially processing incoming signals through increasingly specific and abstract nodes of a hierarchy [61,62]. The first view, long dominant in electrophysiology, can be related to the reflex-arc of Sherington and was succinctly espoused by Horace Barlow [63,64]. The other view, which suggests that processing of incoming signals is a dynamic, active process involving intrinsically generated activity in equal measure to extrinsic signals, suggests that brain computations and information cannot be understood in isolation. This perspective can be traced back to Helmholtz and William James who both suggested that incoming, sensory activity is combined with internal signals related to goals and expectations [4,5]. However, despite the growing interest in how brain function is realized by distributed networks, the vast majority of electrophysiology studies have confined their measurements to small groups of local populations in circumscribed areas. In order to understand how local and distributed ensembles are coordinated across brain-wide networks during active behavior, it is necessary to simultaneously monitor neural activity at both scales.

Targeted study of dynamics at specific spatial scales

Recent work has begun to bridge spatial scales by dense local or inter-areal recordings with the use of multiple electrodes or imaging techniques. Multi-electrode arrays have provided exciting new perspectives on sensory and motor physiology by recording from dense populations of cells. From these recordings, it is possible to correlate the activity within clusters of locally connected cells in order to infer novel features of ensemble coding and computation. In the retina and olfactory bulb, these results have suggested a high degree of computation and coordination even at early stages of the sensory hierarchy (Figures 1a, 2a) [65,66]. Further, these studies allow the determination of local circuit structure and connectivity from the functional response profiles of individual cells. By constructing putative circuits from observed dynamics and relating them to anatomy, local computations can be inferred and the information available to downstream areas can be estimated. Similar methods can be applied sequentially along sensory hierarchies in order to determine how local computations influence downstream populations.

Likewise, work using MEAs that span the laminae enables the inference of sequential processing in local circuits, and distinct patterns of activity to be associated with different contexts [51••,67]. Extra-cellular recordings from laminar circuits allow the identification of putative cell types from both the spike waveform, as well as from the cross-correlation function in short time intervals (Figure 2b) [68•]. In the hippocampus and primary sensory cortices, laminar circuits have been determined from the pattern of extracellular current flow and from the correlation of single unit spike times [36,48,68•]. These same methods, applied in the lateral dimension, have begun to integrate single unit responses into the local dynamics of neighboring patches of cortex. For example, cortical areas often exhibit coherent patterns of activity in the form of traveling waves that affect single unit responses and conform to areal boundaries in a consistent manner (Figure 2c) [69]. Future work should investigate lateral dynamics during natural vision and complex behaviors in order to correlate both laminar and lateral activity profiles with specific cognitive or sensory contexts.

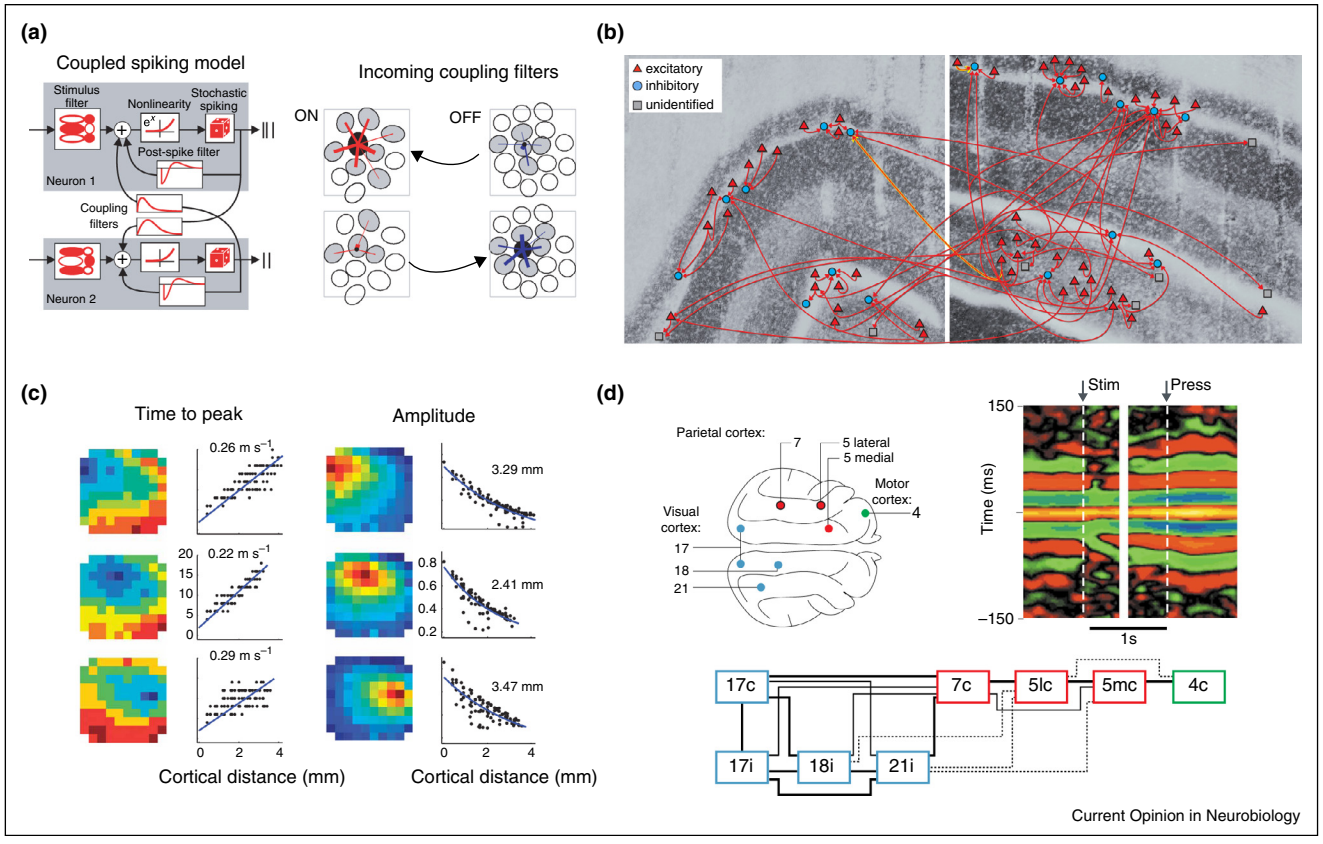
Finally, interest in how brain-wide networks realize distributed processing during cognition has resulted in a number of studies investigating the functional relationship between different nodes of sensory-motor pathways (Figure 2d). Early work in awake, behaving cats indicated the presence of networks of synchronized pathways which were structured in a task specific manner [70–72]. Further work in non-human primates has extended these findings to correlate information flow with task state and performance [13•,14,16,17,50••,73–78]. Effort must now be made to bridge these spatial scales studied in isolation in order to determine how fine-scale and large-scale interactions are orchestrated by cognitive demands and determine behavior and sensory processing.

Novel methods to bridge spatial scales

The focus on specific spatial scales and on limited areas and recording sites has been the result of a number of practical factors: (1) the amount of physical space and invasiveness necessary to investigate multiple areas or record with high numbers of channels has limited the scale and scope of experiments; (2) determining areas that interact and the communicating populations within them is difficult, especially on a day-to-day basis and without exhaustive mapping; and (3) the analysis of recordings from many channels is both computationally and statistically demanding. However, current technologies allow future work to reduce these difficulties.

Future work can take advantage of highly specifiable lithography-based micro-electro-mechanical system (MEMS) construction to design arrays configured specifically to target multiple areas across spatial scales. One approach that we are enthusiastically pursuing is to use a combination of recording methods in order to sample both the widespread activity patterns across multiple brain areas, as well as refined mapping of specific regions of interest and targeted recording of identified populations. The use of electrocorticography allows mapping of the distributed set of areas engaged in a task (Figure 3a,b). Once areas of interest are identified, dense surface recordings with higher resolution can be used to further map local activity (Figure 3c) and find specific populations of interest.

Figure 2

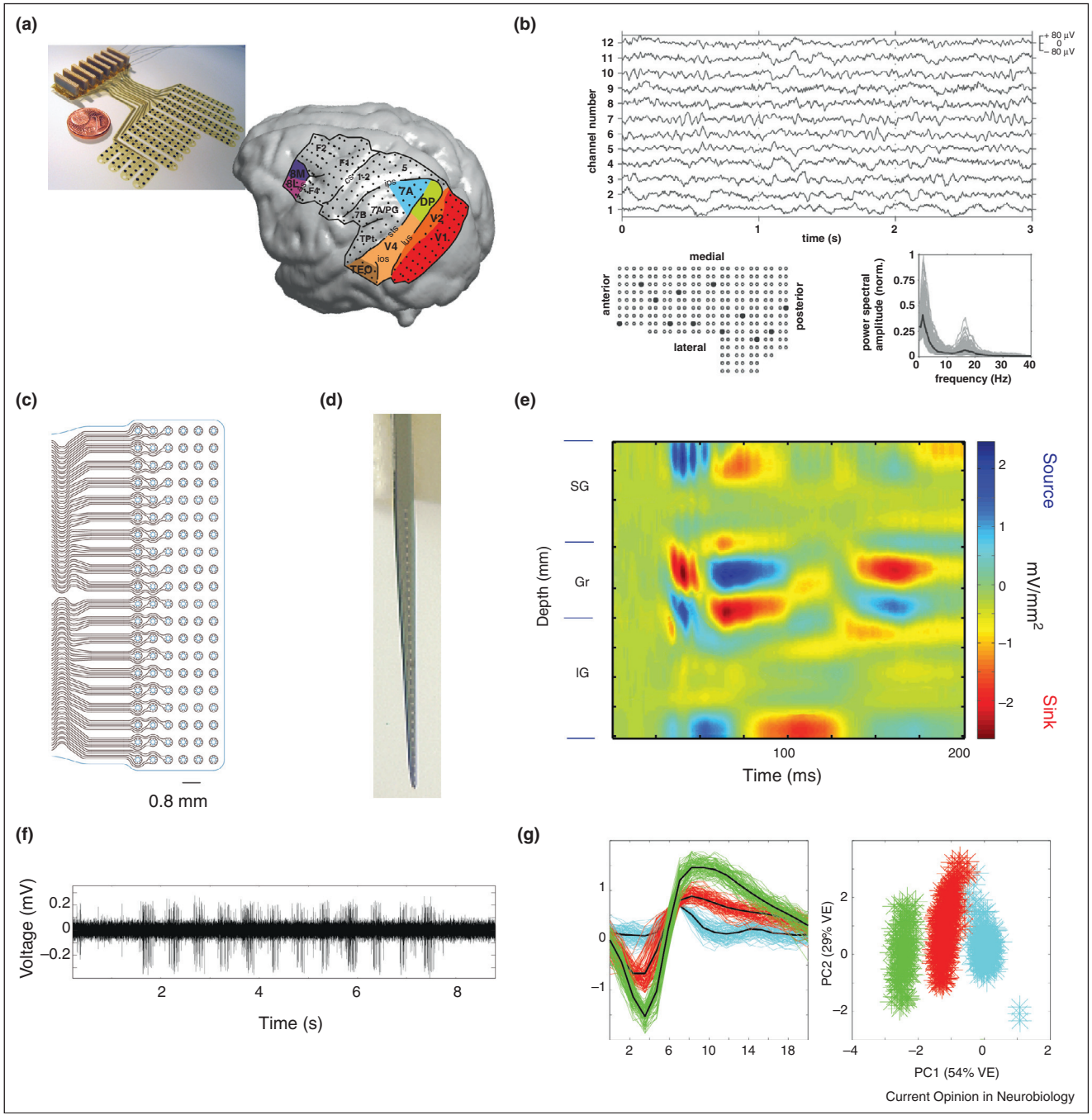


Targeted recordings recover organizational principles across spatial scales. **(a)** Multi-electrode recordings from a population of retinal ganglion cells can recover anatomical connectivity. A dense sample of isolated ganglion cells was recorded and statistical methods were used to derive the functional characteristics of single-units and the coupling parameters of the population [65]. **(b)** MEA recording from the hippocampus can determine putative cell type and construct patterns of laminar connectivity. Multiple single units were recorded in awake behaving rats across the hippocampal laminae. The cross-correlation of spiking activity and waveform characteristics enabled the derivation of a putative laminar network [68•]. **(c)** MEA recording from macaque primary visual cortex exhibits coordinated activity across lateral networks. Many sites spanning a small portion of visual cortex were recorded and spiking activity at single sites was used to trigger the local field potential across the array. Single spikes gave rise to coordinated waves of LFP that traveled across the lateral extent of the array [69]. **(d)** Many sites in visual, parietal and motor cortex of awake behaving cats were recorded during the execution of a perceptual task. Distributed areas showed coordinated activity that was synchronized in a specific manner during task execution. Above right shows synchronization between parietal areas during discrete portions of the task. Lower schematic summarizes connectivity across task periods. Line weight indicates the strength of synchronization [70].

Dense mapping enables the subsequent implantation of single electrodes, laminar arrays (Figure 3d) or injections targeting local neuronal groups that cooperate across long distances. Recording with penetrating arrays allows further determination of laminar current flow (Figure 3e), as well as the monitoring of extracellular action potentials with the possibility to determine putative cell class (Figure 3f,g). Figure 4 illustrates the sequential process described above for an example study investigating inter-areal laminar interactions between well-characterized local populations while simultaneously monitoring widespread activity across the brain. Such studies will enable the relation of single cells to local population activity, areal dynamics and inter-areal communication across brain-wide networks. Finding interacting populations without these tools requires exhaustive searching and has limited the number of distributed areas that can be simultaneously monitored during behavior. The use of surface arrays that permit the placement of penetrating sharp electrodes *in situ*, allow targeting of specific ensembles and further refine the population to local circuits, ideally with a laminar resolution. By iteratively refining the spatial scale, while continuing to monitor distributed activity widely, studies can begin to integrate local populations into distributed networks.

Some studies have already made progress in this direction by multi-modal approaches, such as simultaneous imaging and electrophysiology [79–82]. These approaches allow activity at multiple scales to be monitored, but still require sacrifices to be made, either in terms of temporal resolution or the spatial extent of global sampling. Multi-scale recording with electrophysiology is particularly appealing

Figure 3



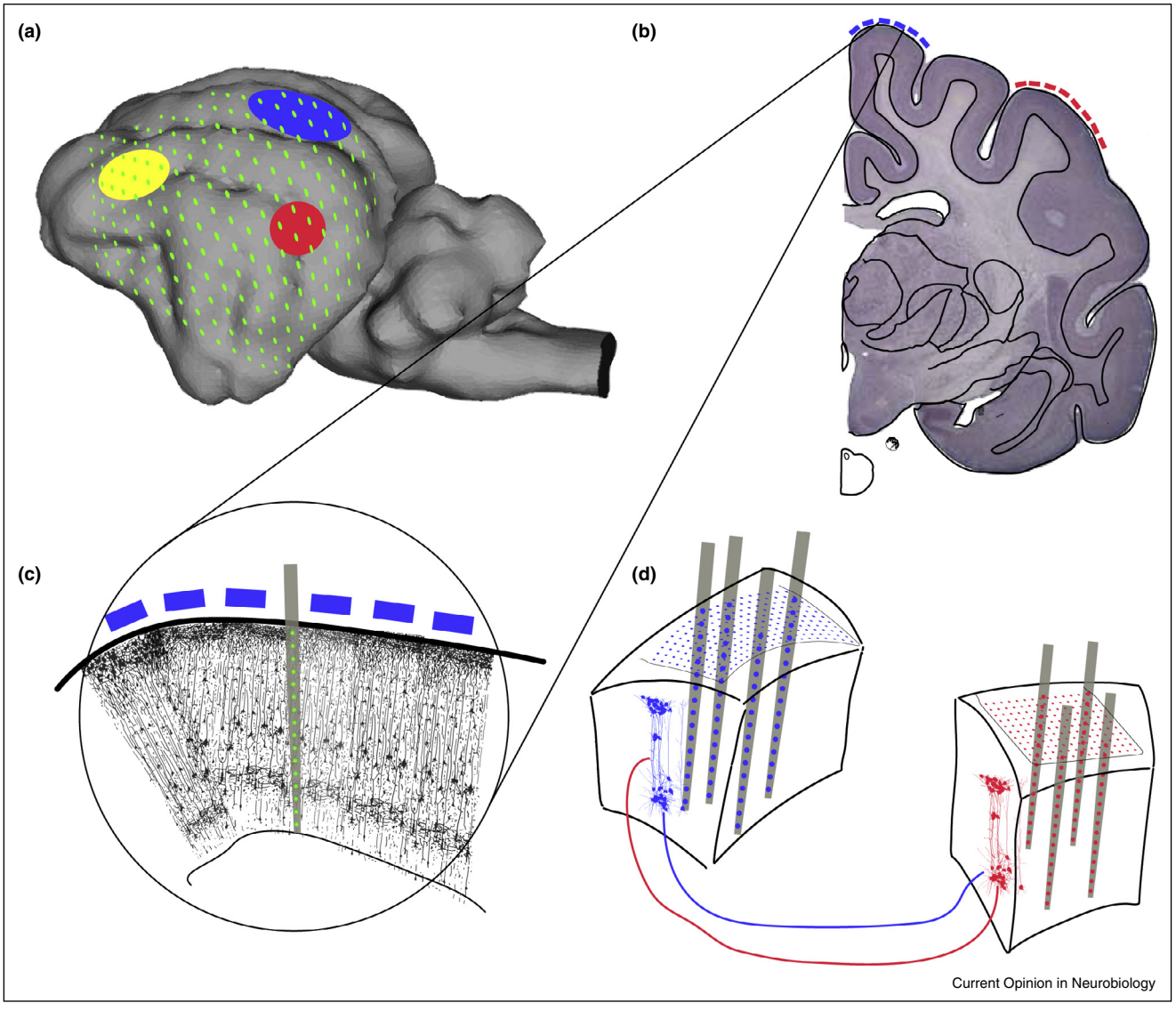
Multi-scale recording achieved with custom multi-electrode arrays. **(a)** Electrocorticography array that allows simultaneous monitoring of 252 sites across one hemisphere in the awake, behaving macaque monkey. This technique allows regions of distributed networks to be identified and the analysis of interactions based on task and behavioral state. The schematic illustrates the position of the array over the cortex of one monkey with anatomical landmarks and putative areas annotated based on anatomical registration to an atlas [13•,50••,84–86]. **(b)** Example traces from distributed sites on the array recorded from an awake monkey during execution of a selective attention task. Sites showing example LFP traces and the power spectrum from those sites, showing a distinct oscillatory peak in spectral power [84]. **(c)** A dense ECoG array enabling mapping of local activity with high spatial resolution. Schematic courtesy of Colin Bierbrauer, CorTec GmbH, Freiburg, Germany. **(d)** Silicon laminar array for monitoring of LFP and extracellular spiking activity within a local population. Image courtesy of Arno Aarts, ATLAS Neuroengineering, Leuven, Belgium. **(e)** Example of the current source density derived from a 32 contact laminar array, allowing the determination of laminar structure. **(f)** Example of the high frequency activity on one channel from such an array implanted in area 17. The recording shows activity over a period of 9 seconds, during visual stimulation with a grating from 1.5 to 8.5 seconds. The activity of single isolated units is visible. **(g)** Example of the sorted single units identified from the example trace. Recordings such as these allow the putative identification of cell-class and allow local and inter-areal processing to be localized to specific laminar compartments.

because it is unconstrained with respect to these considerations, and MEMS techniques allow an unprecedented combination of spatial and temporal resolution with coverage and configuration.

Looking forward

The brain achieves adaptive behavior through the coordinated activity of distributed populations of neurons. In order to map behaviors and cognitive variables onto physiology, it is necessary to sample the brain's activity at each relevant scale (Figure 4). Studies that utilize measurements across spatial scales promise to increase our understanding of brain function by tracking sensory, motor and cognitive variables as they evolve through local populations and across brain-wide networks. New studies employing these methods will allow us to determine both local and global constraints on neuronal activity and will elucidate how recurrent activity is dynamically modified and shaped by task and behavioral context. By monitoring distributed activity across scales, we will be able to better

Figure 4



Recording of brain activity across spatial scales. **(a)** Wide sampling of cortical activity by electrocorticography allows the mapping of cortical networks engaged in a behavior. Identified regions can then be targeted for higher-resolution recording. Green dots represent sites on an ECoG array; colored areas represent regions engaged in a functional network, identified by ECoG. **(b)** High resolution ECoG mapping of two areas involved in an identified network. Dense mapping of the areas allows the identification of local populations within the areas that are interconnected or share selectivity. **(c)** Targeted ensemble recording across laminar circuits from identified, coupled populations. Laminar arrays can be inserted at specific points in the cortical area that correspond to interacting populations. **(d)** Dense mapping of interacting populations through laminar arrays to monitor the propagation of information through local and distributed circuits.

estimate the intrinsic state of the brain, a crucial step as neuroscience moves towards understanding the active role of intrinsic brain dynamics and cognition in shaping brain responses. Although compelling theories of brain function that take into account the brain's recurrent activity have been formulated, the restricted nature of experimental data has so far limited the adjudication between competing theories. Likewise, the lack of experimental data on how local dynamics are integrated between communicating populations and orchestrated into distributed activity patterns across the whole brain, limits our understanding of brain function and disorders. We strongly advocate the application of these diverse tools in order to unify our understanding of the brain's coordinated patterns of activity across spatial scales.

Conflict of interest statement

Nothing declared.

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