Brain structure and dynamics across scales: In search of rules

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Abstract

Louis Henry Sullivan, the father of skyscrapers, famously stated "Form ever follows function". In this short review, we will focus on the relationship between form (structure) and function (dynamics) in the brain. We summarize recent advances on the quantification of directed- and weighted-mesoscopic connectivity of mammalian cortex, the exponential distance rule for mesoscopic and microscopic circuit wiring, a spatially-embedded random model of inter-areal cortical networks, and a large-scale dynamical circuit model of money's cortex that gives rise to a hierarchy of timescales. These findings demonstrate that inter-areal cortical networks are dense (hence such concepts as "small-world" need to be refined when applied to the brain), spatially dependent (therefore purely topological approach of graph theory has limited applicability) and heterogeneous (consequently cortical areas cannot be treated as identical "nodes").

Keywords

Introduction

Recent years have witnessed a sea-change in our knowledge of the microscopic local cortical circuits and mesoscopic long-distance connectivity between cortical areas. We recently published a series of papers reporting a new dataset of quantitative- and weighted- inter-areal connectivity in the macaque monkey cortex [1••, 2, 3••]. Moreover, two separate teams reported datasets on the mouse whole-brain connectome [4••, 5••]. The findings revealed that the inter-areal connectivity at the mesoscopic level are dense (more than 50% of all possible connections are present) and dependent on spatial distances between cortical areas. These findings have highlighted limitations of theoretical analysis of brain circuits in terms of purely topological networks with sparse connectivity, and have led to the proposal of an

alternative class of spatially embedded random networks which could be more fruitful in Neuroscience [6••, 7]. In this review, we summarize recent advances and discuss to what extent those findings are valid across scales from micro- to mesoscopic cortical circuits, and between primate and rodent.

Whereas structural connectivity is essential for understanding the constraints of brain function, it alone is insufficient to predict the dynamical behavior of neural circuits. Consider two identical neurons interconnected by mutually inhibition. Given this connectome, can one predict the network's behavior? It turns out that experimentation and theory have uncovered multiple possibilities. First, both neurons may simply remain silent. Second, in response to inputs, the system may behave as a switch, causing only one neuron to be active at any one time. Third, if the neurons are endowed with a slow adaptation, each could take turns to be active leading to a "half-center" oscillator, which is the core of rhythmic central pattern generators. Finally, under certain conditions, the two neurons can be perfectly synchronized, spike by spike: the two neurons fire at the same time, leading to mutual inhibition after a brief delay, and when this inhibition has decayed they can fire again together [8]. This simple example illustrates that dynamical behavior often cannot be deduced from anatomy in a straightforward fashion; physiology and modeling are important for discovering the dynamical operations of neural circuits.

To tackle the brain-wide complex dynamics, which give rise to neuronal function and behavior, several groups have developed large-scale dynamical models [9••, 10, 11••]. In particular, combining monkey interareal connectivity with data on the areal differences in the number of spine counts per pyramidal neuron [12], a new model naturally exhibits a hierarchy of timescales [11••]. These findings exemplify a fruitful interplay between theory and experimentation in discovering general principles of how large-scale brain systems work. This progress has opened the door to tackle complex brain dynamical phenomena including neural avalanches [13] and lognormal distribution of firing rates [14••] in future research.

Spatially embedded microscopic and mesoscopic cortical connectivity

Local neuronal networks in the cortex exhibit non-random configurations with a wide range of synaptic strengths [15]. Because the connections within local areas account for about 80% of the total connections of the cortex [1••], the local circuits constitute a large part of the cortical machine. A recent investigation described the functional organization of synaptic strength in the local circuit thereby making a major contribution to our understanding of the cortex [16••]. In a first instance, these authors used natural images in vivo to look at the correlation of activity in neighboring neurons in the supragranular layers of the mouse visual cortex, before completing whole cell recordings of the same neurons in a slice preparation. These technically challenging experiments revealed the functional organization of the local circuit; the strong reciprocal connections are mostly found between pairs of neurons with high correlated responses whereas neurons with uncorrelated response are infrequently and weakly connected. These findings, extended to showing that cells with similar receptive fields were preferentially connected, are highly significant because they go some way to explaining how recurrent excitation of the supragranular layer neurons amplifies and

sharpens weak thalamic inputs [17], or produces self-sustained persistent activity in a number of cortical areas [18]. These results suggest that local circuit neurons may form subnetworks [19, 20, 21, 22], that could provide an important infrastructure supporting global and local integration.

One interpretation of the strongly interconnected neighboring neurons in the supragranular layers is that they constitute cell assemblies. In a sensory area, these cell assemblies not only encode sensory input but also integrate contextual information such as reward, attention and expectation [21]. These contextual interactions are derived largely from the network of long-range inter-areal connections (see Figure 1). The inter-areal graph in macaque has a density of 67%, with individual target areas receiving inputs from between 30 to 80 source areas suggesting high levels of global interactions [2]. The specificity of the inter-areal network is derived from connection weights being highly heterogeneous and conforming to a distance rule, namely the weight of connection between two areas decays exponentially with their wiring distance (Figure 1) [1••]. These findings make it possible to propose a statistical algorithm that predicts many of the observed anatomical features of the inter-areal cortical network including the existence of a network core, the distribution of cliques, global and local weight based communication efficiencies and overall wire-length minimization [3••]. The spatially embedded properties of the interareal network reflect morphological constraints such as folding and the spatial clustering of sensory, motor and cognitive areas. The interareal and local networks share a number of features including lognormal distribution of weights and an exponential decline in connection weight [2, 1••, 15, 23], suggesting that binary connectivity in the brain is rooted in physical and geometrical properties, opening the possibility for a general model of cortical connectivity including local connectivity.

The exponential distance rule stands out from network models applied to the brain connectivity that typically are purely topological and do not take spatial organization into consideration [24•]. Motivated by the recent anatomical findings, Song et al. recently proposed a spatially embedded cortical network model [6••]. In this model the cortex is described as a continuum in space, which is partitioned into a discrete number of areas. Connections are established, point-to-point, using a simple "axonal growth rule" inspired by developmental neurobiology. The model captures the salient quantitative statistics of the monkey data, including the inter-areal connection probability as a function of wiring distance or functional similarity distance between two cortical areas, the five-order of magnitude range of connection weights. Furthermore, the model also reproduces key network properties such as sequence of in- or out-degree, and distribution of three-node motifs (Figure 2). This work suggests a novel class of spatially embedded random networks that are generative and of potential importance for understanding the brain connectomics.

Similarity and differences between primate and rodent

Much recent work on the functional connectivity of local circuits has been carried out in mice, which is warranted given the high selectivity of cortical receptive fields in this species. Last year two groups reported directed- and weighted-connection data of the mouse brain [4••,5••]. The inter-areal weights of the whole brain span 10^4 fold, whereas intra-cortical

connection weights vary over two orders of magnitude [4••]. While the inter-areal cortical connection weight distribution is well fit by a lognormal distribution in both species, the range of weight values seem to be significantly narrower (10^2 fold) in mouse compared to monkey (10^5 fold). Presently it is unclear whether this discrepancy is due to differences in brain size or to rodent primate differences in scaling, as the connection strength measured by both groups depends on neuron number), or technique (intensity of EGFP signals labeled by a anterograde tracer versus count of neurons labeled by a retrograde tracer) used for weight quantification. Regardless, neither technique directly measured the physiological synaptic strengths. While we lack functional data at this level, the synaptic ultrastructure of inter-areal connections show a skewed distribution with a wide range of values [25], suggesting that inter-areal synapses could show a similar range in weight or strength values as do local synapses. Physiological studies [26, 15, 23, 16] revealed synaptic strengths in the microcircuit spanning two orders of magnitude. Note that, at least for nearby pairs of neurons (within a couple of hundreds of microns), the probability of connection decreases with distance but the synaptic strength (measured by the amplitude of excitatory postsynaptic potential) remains constant [15, 23]. It remains to be seen whether the range of physiologically defined synaptic weights are similar for local versus long-distance connections, and across species.

Other important differences between rodent and primate cortical biology need to be considered. First, the scaling rules for rodents and primates are very different [27••], allowing considerable increases in neuron number via increased brain size and neuronal density in primates compared to rodents. Secondly, human and non-human primate corticogenesis shows unique features that could have important structural as well as functional consequences [28•]. A specialized germinal zone named the OSVZ largely generates the supragranular layers of the primate cortex. The precursors of the OSVZ show very different lineage relationships to those observed during mouse corticogenesis. During evolution there is an increase in the number of neurons in the supragranular layers [29], due to the primate-specific high incidence of proliferative divisions of OSVZ precursors.

Recent studies of corticogenesis suggest that members of local assemblies are clonally related [30]. This suggests that the intricate lineages of the primate OSVZ precursors will lead to larger and perhaps more complex interconnected assemblies in the supragranular layers of the primate compared to the rodent. The supra- and infragranular layers differ in their coding strategies; whereas supragranular layers exhibit sparse coding, infragranular layers exhibit dense coding [31]. Sparse coding leads to greater efficiency but at the cost of increased numbers of neurons in agreement with the expansion of the primate supragranular layers. Hence, in the primate, the expanded supragranular layer could argue for an increased role of sparse coding.

Recently it has been suggested that feedback connections could serve to stabilize reliable propagation of information coding in spike times through the cortex [32]. The hierarchical organization of interareal connections and their interaction with the local circuit is thought to implement predictive coding, according to which predictions (i.e. expectations) descend the cortical hierarchy and prediction errors ascend the hierarchy [33]. Would the precision of feedback connections be sufficient to allow the cortical network to learn the statistical

regularities of the sensory input? Indeed in the primate this might be relatively more feasible than in the rodent because there is a high precision feedback pathway in the upper part of the primate supragranular layers [2]. In the primate there are two feedback streams, one in the supragranular layers that contains uniquely cortical projecting neurons, and one in the infragranular layer which houses the subcortical projecting neurons [34]. The feedback stream in the supragranular layers is point-to-point, contrasting with the diffuse feedback stream in the infragranular layers. Hence the primate counterstream organization would have a fine grain supragranular feedback system conveying predictions in a sparse coding system and a more classical infragranular course grain feedback system conveying predictions in a dense coding system.

From structure to dynamics: a hierarchy of timescales

The advance of the diffusion tensor imaging (DTI) technique has led to the perspective of non-invasive and quantitatively mapping of connections of the human brain, making it possible to study the structure-dynamics relationship using dynamical "whole-brain" modeling [35•, 9••, 10]. However, DTI has some inherent limitations compared to axonal tracer method [36, 37], and it does not provide directional or hierarchical information about interareal connectivity.

Recently, we developed a dynamical model of the primate cortical system, with inter-areal connections constrained by the recently published weighted- and directed- connectivity data for monkeys [11••]. We assumed that all local areas share an excitatory-inhibitory recurrent architecture described by the same mathematical model. However, certain network properties exhibit heterogeneity quantitatively. In particular, the strength of synaptic excitation varies from area to area, which was calibrated by the anatomical data on the number spines per pyramidal neuron [12]. Interestingly, a hierarchy of timescales emerges in this model system: early sensory areas show brief, transient responses to input (appropriate for sensory processing), whereas higher association areas such as the prefrontal cortex integrate inputs over time and exhibit persistent activity (suitable for decision-making and working memory). Such a hierarchy of "temporal response windows" is supported by fMRI and MEG observations [38,39,40•], our model suggests a large-scale circuit mechanism for this important characteristic of large-scale cortical organizations. It is well known that, in an isolated local circuit, the time constant of dynamics could be larger with strong recurrent excitation [18]. However, the pattern of the timescale hierarchy in the large-scale model has been shown to critically depend on interareal connection loops. For instance, an area with relatively weak local connections may display slow reverberatory dynamics as a result of being part of a large feedback system. This explains why the dominant timescale of a cortical area is not a monotonic function of its position along the brain's hierarchy (Figure 3D). A theoretical work mathematically identified classes of network architecture that give rise to a hierarchy of disparate timescales differentially localized in different regions of a network [41].

A segregation of timescales, that are heterogeneously distributed in different parts of the cortical system has a least two conceptual consequences that need to be considered. Spatial differences in neuron response led to a reappraisal of the concept of receptive field by

indicating that there are responses beyond the classical receptive field. Similarly, we need to elucidate what is the integration of a signal from a higher area with a long time constant on a neuron with a short time constant in a lower area. Differences in time scales should be contrasted to the idea of scale-free neural dynamics [42,43•,44,45]. Insofar as scale-free dynamics is defined by the lack of a characteristic timescale, does it imply a homogeneity of (however complex) neural dynamics regardless of the cortical location? Future experiments will determine more precisely to what extent neural dynamics differ across cortical areas. At the same time, this question can be investigated in computational modeling constrained by new anatomical data.

Concluding remarks

The quest for the principles of cortical function have to explain the "skeleton of strong connections in a sea of weak connections at the level of the local circuit [15, 46] and the highly skewed distribution of inter-areal connection weights linking areas across different sensory, motor and cognitive modalities [2]. The insight from the recent work [16••] points to an experimental approach to tackle the local aspects of the cortical network, and a similar approach is now becoming technically feasible for the inter-areal cortical network. This work raises many conceptual questions such as the relationship between large-scale population codes and circuit connectivity and the topology of interconnected subnetworks [21]. However, while work in the rodent is in many ways cutting edge, benefitting as it does from numerous technological advantages, we need to keep in mind the important qualitative differences in the rodent and primate brain. The advent of genetic engineering in the primate promises to greatly facilitate future research in this direction. Establishing a firm link from structure to function is essential to understand complex neural dynamics.

Acknowledgments

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- We review recent work on mesoscopic, directed- and weighted-connectivity of monkey and rodent.

- New data led to the proposal of a spatially-embedded random network model for the mammalian cortex.

- Several important differences between primate and rodent are highlighted.

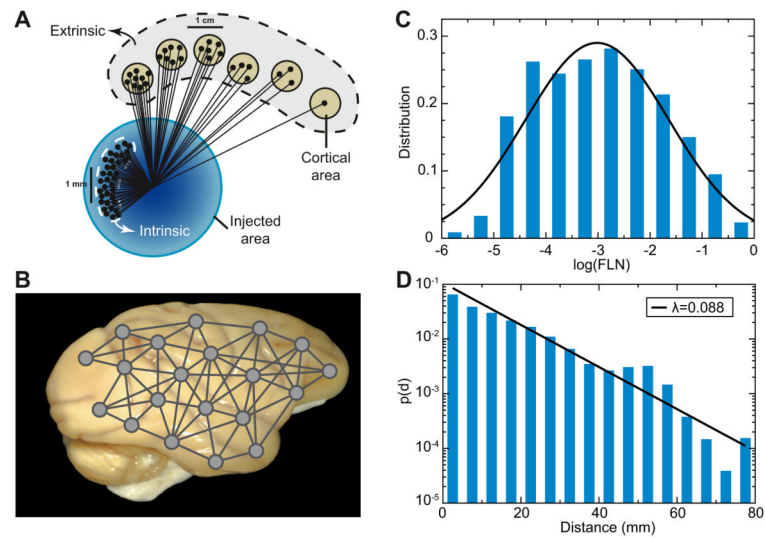- A large-scale dynamical model of the primate cortex gives rise to a hierarchy of timescales.

Figure 1.
Inter-areal connections of macaque monkey cortex. (A) A retrograde tracer is injected in a (target) area, and relative weight of connection between a source area and the target area is quantified by the fraction of labelled neurons (FLN), which is the number of labelled neurons in the source area divided by the total number of labelled neurons. (B) The analysis is carried out with a number of cortical areas, leading to a weighted- and directed- inter-areal network connectivity. (C) FLNs span five order of magnitudes and are fit by a lognormal distribution. (D) FLN between a pair of cortical areas is an exponential function of their distance, with the characteristic distance length of ~ 11 mm. Adapted with permission from [1••].
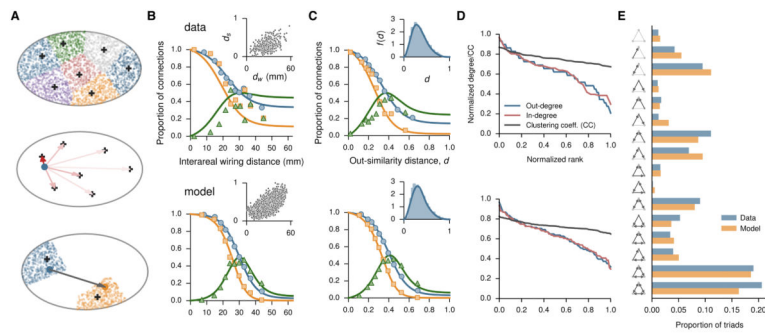
Figure 2.

A spatially embedded random network model of large-scale cortical system. (A) The model cortex is a continuous volume in a 3D Euclidean space in the shape of a spheroid, here represented in 2D as an ellipse for illustration purposes. Top: N areal centers are chosen randomly from the spheroid (plus symbols), and the configuration of the areal centers defines the parcellation of the model cortex into N areas (various colors) through a Voronoi partition of the spheroid, i.e., each area is the set of points closer to a given center than to any other center. Middle: The source of an axon (blue dot) is sampled uniformly from within the spheroid, and the direction of the axon is determined by the sum of the forces which attract the axon to the areal centers. The individual forces decay with the distance to the areal centers (arrows) according to an inverse power law, with the strengths represented here by the red intensity from light (weak) to dark (strong) red. Bottom: With the direction fixed, the axon extends from the source (blue dot) to the target (orange dot); the length is determined by sampling from an exponential distribution. The areas corresponding to the source and target of the axon are assigned according to the parcellation shown at the top. (B) Proportion of directed connections and occurrence of reciprocal and unidirectional pairs as a function of interareal (center-to-center) wiring distance in data (top) and model (bottom). The occurrence of reciprocal (squares) and unidirectional (triangles) connections are compared with p^2 (orange line) and $2p(1-p)$ (green line), respectively, where p is the maximum-likelihood estimate of the proportion of directed connections (blue line). (Insets) Relationship between similarity and wiring distances in the edge-complete subnetwork. (C) Same as B but as a function of output similarity distance. (Insets) Distribution of similarity distances. (D) Normalized in- and out-degree sequences and clustering coefficients (for areas in the edge-complete subnetwork). In-degree represents input from all 91 source areas, for the 29 injected areas; out-degree represents output to the 29 injected areas, from all 91 source areas. (E) Comparison of the triad motif distribution in model and data. Reproduced with permission from [6••].
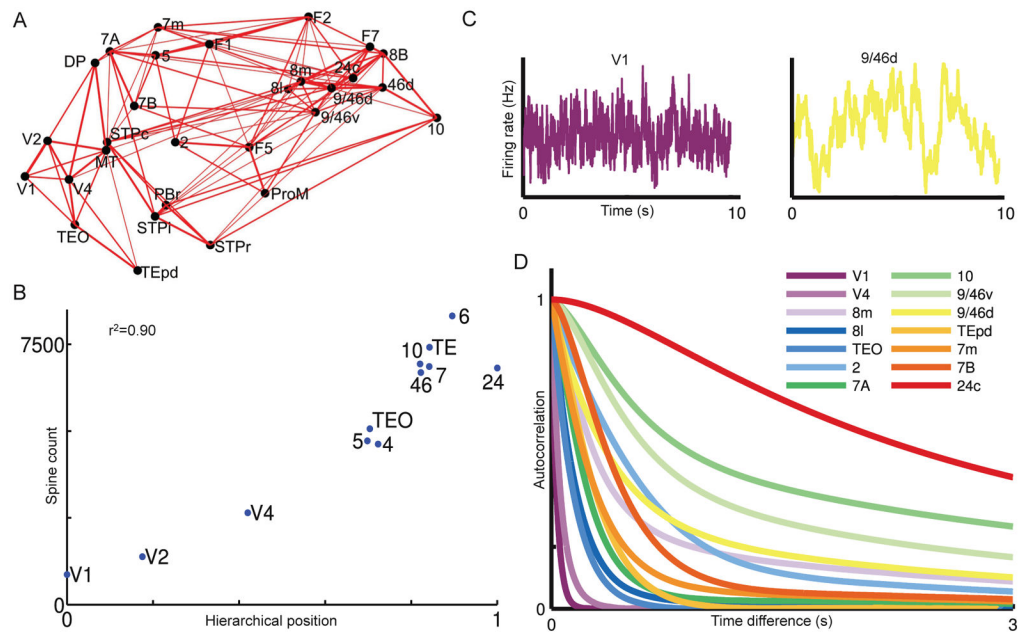
Figure 3.
Hierarchy of timescales in an anatomically-constrained dynamical model of macaque cortex.
(A) Connections between 29 areas in the macaque cortex. Strong connections are indicated
by lines, with line thickness determined by connection strength. (B) The number of spines
on the basal dendrites of pyramidal cells in an area is strongly correlated with the area's
hierarchical position determined by the pattern of laminar projections. This is incorporated
into the model, in which the excitation input strength is larger in areas higher in the
hierarchy. (C) Stochastic activity fluctuations are fast in Area V1 but much slower in
dorsolateral prefrontal cortex area 9/64d. (D) Autocorrelation functions in response to white-
noise input to area V1, from which a dominant time constant was extracted for each cortical
area. The model shows a hierarchy of timescales, with sensory areas and association areas
characterized by short versus long timescales, respectively. Reproduced with permission
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