Network Analysis, Complexity, and Brain Function

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Throughout the early history of neurology and neuroscience, most theoretical accounts of brain function have emphasized either aspects of localization or distributed properties [1]. Instead, modern views focus extensively on the structure and dynamics of large-scale neuronal networks, especially those of the cerebral cortex and associated thalamocortical circuits whose activation underlies human perception and cognition [2,3]. Both, localized and distributed aspects of brain function naturally emerge from this network perspective. This essay highlights several unique characteristics of brain networks and explores how a computational analysis of these networks (see also [4]) may impact on our understanding of human brain function.

With a few notable exceptions (such as diffusible messengers), all communication between nerve cells is carried out along physical connections, often linking cells that are separated by large distances. Signals within these connections consist of series of action potentials (spikes) of unit magnitude and duration. The arrival of an action potential at a synaptic junction triggers numerous biochemical and biophysical processes, ultimately resulting in transmission of electrical signals to the postsynaptic (receiving) cell, which may in turn generate an output spike transmitted along the neuron's axon. Neurons in the cerebral cortex maintain thousands of input and output connections with other neurons, forming a dense network of connectivity spanning the entire thalamocortical system. According to a detailed quantitative study [5], the human cerebral cortex contains approximately 8.3×10^9 neurons and 6.7×10^{13} connections. The length of all connections within a single human brain is estimated between 100,000 and 10,000,000 km [5]. Despite this massive connectivity, cortical networks are exceedingly sparse, with an overall connectivity factor (number of connections present out of all possible) of around 10^{-6}. Brain networks are not random, but form highly specific patterns. A predominant feature of brain networks is that neurons tend to connect predominantly with other neurons in local groups. Thus, local connectivity ratios can be significantly higher than those suggested by random topology.

Networks in the brain can be analyzed at multiple levels of scale. Within small and localized region of the brain, neurons form characteristic sets of connections, so-called local circuits [6]. For example, neurons forming cortical columns show specific patterns of connectivity between morphologically and pharmacologically distinct classes of cells in different layers. At a higher level of scale, such columns communicate through "tangential" or "horizontal" connections, forming networks of columns within single cortical areas. Connection patterns formed by these local, intra-areal networks are thought to be responsible for the specific processing requirements

of each area (e.g., [7]). In visual cortex, for example, intra-areal connections within and across columns preferentially link neurons that share similar response properties. Considering the entire brain, the large-scale organization of the cortex is characterized by patterns of interconnections linking brain areas within and between specific sensory and motor systems (e.g., [8]). These connection pathways form networks that are species-characteristic, reflecting specific evolutionary adaptations.

Neural connections are formed through developmental processes that at least in part are dependent upon neural activity [9]. Many brain networks remain plastic throughout the lifetime of the organism, exhibiting specific modifications of synaptic efficacy at multiple time scales as well as continuous morphological change. Thus, the detailed structural organization of brain networks will to some extent reflect the developmental and experiential history of the individual organism [10–12]. This point deserves special emphasis. Although it is possible (and perhaps desirable) to analyze brain networks as static entities, without reference to how they were generated, it is nonetheless essential to realize that their fine structure and morphology is the result of continuous interaction between neural substrate, ongoing neuronal activity and embodied action of an *individual* organism within an environment.

ANATOMICAL AND FUNCTIONAL CONNECTIVITY

Because of the close relationship between neural connectivity and neural activity throughout the brain, it is important to consider structural connection patterns within the context of the specific patterns of dynamic ("functional") interactions they support. The closeness and intricacy of this relationship is perhaps unique among natural and artificial networks. Thus, our first distinction is that between anatomical (structural) and functional connectivity.

Anatomical connectivity simply refers to the set of physical or structural connections linking neuronal units at a given time. In any structural analysis of neural connection patterns, a choice has to be made on the level of the spatial scale at which the analysis is to be performed. Analyses carried out at the local circuit level would most likely focus on the pattern of synaptic connections between individual neurons. Analyses of intra-areal patterns of connections would involve "connection bundles" or "synaptic patches" linking local neuronal populations (neuronal groups or columns). Analyses of large-scale connection patterns would focus on connection pathways linking segregated areas of the brain. Such pathways would comprise many thousands or millions of individual fibers.

Functional connectivity refers to the pattern of temporal correlations (or, more generally, deviations from statistical independence) that exists between distinct neuronal units [13,14]. Such temporal correlations are often the result of neuronal interactions along anatomical or structural connections; in some cases observed correlations may be due to common input from an external neuronal or stimulus source. Deviations from statistical independence between neuronal elements are commonly captured in a covariance matrix (or a correlation matrix), which, under certain statistical assumptions, may be viewed as a representation of the system's functional connectivity. Although temporal correlations are perhaps most often used to represent statistical patterns in neuronal networks, other measures such as spectral coherence or consistency in relative phase relationships [15] may also serve as indicators of functional connectivity.

The relationship between structural and functional dimensions of brain connectivity is mutual and reciprocal. It is easy to see that structural connectivity is a major constraint on the kinds of patterns of functional connectivity that

can be generated. In the other direction, functional interactions can contribute to the shaping of the underlying anatomical substrate. This is accomplished either directly through activity (covariance)-dependent synaptic modification, or, over longer time scales, through effects of functional connectivity on an organism's perceptual, cognitive or behavioral capabilities, which in turn affect adaptation and survival. The reciprocity between anatomical and functional networks deserves emphasis as it captures some of the unique aspects of brain networks.

SEGREGATION AND INTEGRATION IN THE BRAIN

The networks of the cerebral cortex exhibit two main principles of structural and functional organization, *segregation* and *integration* [16–18]. Anatomical and functional segregation refers to the existence of specialized neurons and brain areas, often organized into distinct neuronal populations (groups or columns) or cortical areas. These specialized and segregated sets of neurons selectively respond to specific input features (such as orientation, spatial frequency, or wavelength), or conjunctions of features (such as faces). They reside in cortical areas that process separate feature dimensions (such as color and motion) or sensory modalities.

However, segregated and specialized neuronal units do not operate in isolation. There is abundant evidence that coherent perceptual and cognitive states require the coordinated activation, that is, the functional integration, of very large numbers of neurons within the distributed system of the cerebral cortex [19,20]. Electrophysiological studies have shown that perceptual or cognitive states are associated with specific and highly dynamic (short-lasting) patterns of temporal correlations (functional connectivity) between different regions of the thalamocortical system [21]. Human neuroimaging experiments have revealed that virtually all perceptual or cognitive tasks, for exam-

ple, object recognition, memory encoding and retrieval, reading, working memory, attentional processing, motor planning, and awareness, are the result of activity within large-scale and distributed brain networks [2,22].

BRAIN NETWORKS AND COMPLEXITY

Integration and segregation may be viewed, in some sense, as antagonistic principles. Functional segregation is consistent with the information-theoretical idea that neurons attempt to extract specialized information from their inputs, eliminating redundancy and maximizing information transfer [23]. Segregation tends to favor the analysis of inputs into (orthogonal and independent) principal components, ultimately represented in the activation of dedicated sets of neurons. Functional integration, on the other hand, establishes statistical relationships (temporal correlations) between different and distant cell populations and cortical areas, leading to the generation of mutual information between brain regions. By creating these mutual dependencies, local neuronal specialization may be degraded. Both, functional segregation and integration (principally manifesting themselves in rate coding and temporal coding strategies, respectively) can have causal efficacy within the brain, in that the integrated action of specialized neurons can exert specific causal effects on other neurons.

The interplay between segregation and integration within a given neural system is captured by the global structure of the system's covariance matrix. This global structure can be quantified using statistical measures based on mutual information between subsets of elements within the system (reviewed in [16]). Most important among these measures is complexity [17], which captures the degree to which a neural system integrates specialized information. Defined as the ensemble average of mutual information across all bipartitions of a neural system, complexity is high for systems that contain specialized elements that are capable of global (system-wide) interactions. On the other hand, complexity is low for random sys-

tems, or for systems that are highly uniform (or, in other words, systems that lack either global integration or local specialization).

Complexity, as defined above, refers to a pattern of functional interactions produced by a structural network. Are the structural networks of the cerebral cortex capable of generating complex patterns of interactions? And if so, are there specific structural motifs that give rise to high levels of complexity? Answering these questions requires a computational analysis of structural connectivity patterns found in the brain.

BRAIN NETWORKS AS DIRECTED GRAPHS

Neuronal networks consist of units connected by directed links (synapses).

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Such networks can be described using methods derived from the theory of directed graphs [24,25]. The structure of a given network is captured by its adjacency matrix, with binary elements a_{ij} that represent the presence or absence of a directed edge between vertices j (source) and i (target). If such an edge exists, vertex j can directly communicate signals (spikes) to vertex i. Such direct connections are not the only way in which neuronal elements can influence each other. Indirect interactions can proceed along paths, defined as ordered sequences of distinct vertices and edges. If there is neither a direct connection nor a path between vertices j and i, then j cannot functionally influence i in any way.

The analysis of structural connections and paths within networks allow

the quantification of a broad range of network characteristics [4,26]. For example, the adjacency matrix of a network allows the derivation of the reachability matrix and the distance matrix. The reachability matrix indicates, for each ordered pair of vertices j and i, whether a path (of any length) exists from j to i. If all entries of the reachability matrix are ones, the network consists of only one component and is strongly connected. Partitioning of the reachability matrix into nonoverlapping subsets of vertices with no paths between them indicates the existence of multiple components. The entries of the distance matrix give the length of the shortest (directed) path between the two vertices j and i. The global maximum of the distance matrix is also called the diameter. The average of all the entries of the distance matrix has been called the "characteristic path length" [27].

These methods and measures can be applied to connectivity matrices of the cerebral cortex, which have been assembled from hundreds of neuroanatomical studies conducted in a variety of species, including cat [28] and nonhuman primates [8,29]. Results indicate that the cerebral cortex is comprised of clusters of densely and reciprocally coupled cortical areas that are globally interconnected [4,30–32]. Dynamically, these structural motifs give rise to functional connectivity with high complexity [4,30,31]. Cortical networks share some attributes of so-called "small world architectures," including high values for cluster indices and short characteristic path lengths [30]. In addition, cortical networks can be "wired up" using very little wiring length, a key constraint given the limited amount of volume available in real three-dimensional brains.

These network characteristics of real cortical connection matrices are strongly associated with the capacity of the cortex to combine functional segregation and integration. As discussed earlier, complexity (as a measure of functional connectivity) captures the extent to which a system combines segregation and integration. Complexity (and other measures, such as entropy or integration) can be

used as cost functions in simulations designed to optimize network architectures. Networks optimized for high complexity show structural motifs that are very similar to those observed in real cortical connection matrices [4,30], in particular a tendency to form clusters, short characteristic path lengths, and short wiring lengths. Other measures produce networks with strikingly different structural characteristics.

These results open up an interesting new perspective on the role of complexity in evolution. Although it is unrealistic to assume that complexity could be directly used as a cost function during natural selection, it is possible that an increased ability of neuronal networks to combine functional segregation (generation of specialized neural circuits maximizing information transfer) together with their functional integration (generation of temporal correlations across feature domains and modalities) was favored. Thus, the concomitant increase in complexity could have driven morphological change in a direction that is consistent with the patterns of cortical connectivity we actually observe.

FROM NETWORKS TO COGNITION

The structure of brain networks is a result of the combined forces of natural selection and neural activity during evolution and development. From a computational and information theoretical perspective, two of the major problems brains have to solve are the extraction of information (statistical regularities) from inputs and the generation of coherent states that allow coordinated perception and action in real time. Solutions to these problems are

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reflected in the dual organizational principles of functional segregation and functional integration found throughout the cerebral cortex. The requirement to achieve segregation and integration simultaneously imposes severe constraints on the set of possible cortical connection patterns. Much more empirical and computational work is needed to elucidate the functional principles shaping structural connection patterns in the cortex. Our own computer simulations (reviewed in more detail in [4,30]) suggest that networks that optimally combine segregation and integration have structural motifs that are very similar to the ones present in large-scale cortical systems.

Very likely there are many more ways in which structural properties of brain networks impact upon the dynamical and informational patterns neurons can generate and maintain. There is mounting evidence that dynamical patterns generated by brain networks underlie all of cognition and perception (see e.g. [2,15,21,22]. At least some aspects of vision seem to be embedded in the structural connectivity of parts of the thalamocortical system [33,34], and disruptions of the wiring of these networks result in severe and specific alterations of mental and perceptual function. The nature of awareness and consciousness itself may be rooted in the rapid integration of information [35,36], requiring a structural network capable of sustaining this process. Network analysis may be the key to understanding and harnessing the remarkable computational and informational power of the brain.

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