Neocortical Circuits: Computation in 3-D

Definition

Connections between neurons within and between cerebro-cortical areas.

Characteristics

Cortical Architecture and Processing

Every thought, every idea, every memory, every decision, and every action we have to make, arise from the activity of neurons in our brains. The results of some of this activity surround us: household objects, books, technology and art. Of all brain structures, the neocortex, which forms over 80% of the volume of the human brain is, arguably, the most critical to what makes us human. This is a paradox, because the basic local architecture of the neocortex in all mammals, from mouse to man, appears to be very similar and is determined by the laminar distribution of relatively few types of excitatory and inhibitory neurons organized according to common principles of connectivity. These local circuits are organized in a framework of a six-layered columnar architecture, in which neurons with functional properties in common lie in discrete layers and in vertical slabs or columns [1] (Striate cortex functions).

The uniformity of its construction suggests that the neocortex provides circuits that are optimized for a class of cortical "algorithm" that can be implemented for the full range of demands of behavior, including perception, cognition, and action. A number of models indicate the forms of general computation that could be carried out in a uniform cortical architecture. Typically these models address a single principle of operation in a small group of neurons; in others a more detailed model is imposed on the columnar architecture of cortex. Experimental results in alert behaving primates and together with theoretical studies, suggest that cognitive operations proceed very rapidly across different cortical areas (Cerebro-cortical areas; Extrastriate visual cortex) by feedforward categorization and feedback modulation, with slower refinement by lateral local interactions. Specification of local and long-distance connections in the cortex will go some way to explaining the implementation of these processes.

Structural Specification of Cortical Connectivity: Integration of Intra- and Inter-Areal Connectivity

What is so special about the circuits of the neocortex? What makes them so efficient and so adaptable to different tasks? A major contribution to our understanding of the structure of the cortical circuit came with the model of a "canonical cortical microcircuit" [1]. This circuit expresses the functional relationships between the excitatory and inhibitory neurons in the different cortical layers and shows how the inputs to a local region of cortex from the sensory periphery via the thalamus, or from other cortical areas, are integrated by the cortical circuits. The most critical feature of the canonical circuit is that the neurons are connected in a series of nested positive and negative feedback loops called "recurrent circuits." Because the excitatory and inhibitory neurons are interconnected, excitation and inhibition remain in balance and so the positive feedback does not overexcite the circuit. This organization explains how it is that the relatively tiny numbers of neurons that provide the external inputs to this circuit are nevertheless effective, as they are amplified selectively by recurrent excitatory circuits [1]. Explorations of this model in the visual cortex (Visual cortex - neurons and local circuits), e.g. [2] have shown how this key notion of recurrent amplification explains the emergence of cortical properties, such as direction sensitivity and velocity sensitivity, orientation selectivity (Striate cortex functions), masking, and contrast adaptation.

The canonical model provides for a richer array of behaviors than the simple feedforward models that preceded it, and is readily applied across the cortex. For example, it is clear that the interlaminar connections have characteristic patterns across cortical areas and across species and thus may perform a generic computation [3]. What has been lacking until very recently is a quantitative model of the vertical (interlaminar) circuits. However, the studies by Binzegger et al. now clearly indicate that, in general, the contribution of the spiny neurons to interlaminar connections exceeds that of their intralaminar connections [4]. Hence, in the infragranular layers (layers 5 and 6), the majority of pyramidal cells connect outside their layer of origin. Layer 4 spiny neurons do connect within layer 4 (the "granular" layer), but their major projection is to layer 3. It is only in the supragranular layers (layer 1, 2 and 3) that the pyramidal cells make the majority of

their synaptic connections to the same layer. The consequence of this is that the monosynaptic recurrent connectivity of layer 2 and 3 pyramidal cells predominates more than recurrent connectivity in any other layer. The recurrent connectivity of layers 2/3 is intriguing in that the local axons of the pyramidal cells are not uniformly distributed, but form patches or clusters. This pattern of patchy connections, referred to as "lattice connections" by Rockland are embedded within inter-areal feedforward and feedback connections [5]. Because of its appearance when viewed from the surface of the cortex we refer to the local horizontal network formed by a small cluster of pyramidal neurons as a "Daisy" In the neocortex many pyramidal neurons serve a dual function: all of them form the major excitatory neurons in the local cortical circuit, but many of them also project outside their own cortical area to other cortical areas or subcortical structures. Thus many of the same neurons that form a Daisy could also project to other cortical areas.

Inter-Areal Projections

The inter-areal connections come in three flavors: feedforward, feedback, and lateral connections [5,6] (Visual cortex - neurons and local circuits). Feedforward connections originate principally from the supragranular layers, target layer 4 and connect lower to higher visual areas (Extrastriate visual cortex) in a sequence tending to show increases in receptive field (Visual cortical and subcortical receptive fields) size and response latency. Feedback connections originate from principally infragranular layers, and connect higher to lower visual areas in a sequence suggesting decreases in receptive field size and response latency. It has been suggested that feedforward neurons have a "driving" and feedback neurons a "modulatory" influence. This is why the feedforward and feedback pyramidal cells located in the supragranular layers could also participate in the local Daisy circuits. The feedback neurons located in the infragranular layers likewise may participate in the local Daisy circuit via the local vertical connections with the supragranular layer pyramidal cells [3]. The infragranular feedback neurons probably provide an input to the Daisy, because one of the principal targets of the feedback projections are the supragranular layers (particularly layer 1).

Thus far, most of our knowledge concerning the local horizontal network is derived from studies of the primary visual cortex (Visual cortex - neurons and local circuits) of cats and monkeys, where it has been claimed that the horizontal clusters link columns of cortex with representations of like-orientation (Striate cortex functions). In other cortical areas, including areas of prefrontal cortex in the monkey, such as area 46, horizontal clusters are equally apparent, but the representations they link have yet to be defined. At a structural level there are important regularities, whose functionality has yet to be divined. Across all areas and species examined (which include the major divisions of neocortex), there is a linear relationship between the size of the clusters and their spacing [3]. The size of the patches also correlates with the diameter of the lateral spread of the dendrites of pyramidal cells, which increases from occipital cortex to prefrontal cortex. It is not known what determines the constancy in the relations of these dimensions.

Inter-Areal Hierarchies

Van Essen and colleagues have gone a long way in exploring the particular hierarchy to be found in the visual system and beyond. They showed that pair-wise comparison of the laminar organization and connections linking cortical areas made it possible to define all inter-areal pathways as either feedforward, feedback or lateral (linking areas on the same hierarchical level) (Extrastriate visual cortex). While the Felleman and Van Essen model has continued to exert a powerful influence on concepts of neorcortical function and brain organization, it has been questioned by the group of Malcolm Young that showed that there are 150,000 equally plausible solutions to the Felleman and Van Essen model [7].

In order to obtain a determinate model, it is necessary to define the hierarchical distance between stations. Precise quantification of the laminar organization of inter-areal connectivity provides a useful measure of hierarchical distance [5,6]. Injections of retrograde tracers in a mid-level target area show that afferent areas contain both labeled supra- and infragranular layer neurons. Feedforward projections originate predominantly from supragranular layers, and the exact proportion of supragranular neurons labeled relative to all labeled neurons in the same area depends on the hierarchical distance from the target area. Feedforward projections to far-distant areas originate almost exclusively from supragranular layer neurons, and as one approaches the target area, there is a smooth increase in the contribution from the infragranular layers. Likewise in the case of feedback projections, as the hierarchical distance increases there is a steady increase in the proportion of infragranular layers so that far-distant feedback projections are almost uniquely from infragranular layers. This regularity has been encapsulated in a "distance rule" that has the power to define the hierarchical organization of a cortical network from the analysis of the projections to only a small number of key areas [6]. Tracing experiments reveal that around 90% of the projections are local (within 1-2 mm), that is, most of the projections

onto a cell are from neurons within the same area. Of the remaining 10%, about two thirds come from neighboring areas and are lateral, so that information flow across the hierarchy is assured by a truly minute proportion of feedforward and feedback neurons. The observation of dense local connections coupled with sparse long-range connections conforms to the idea of a "Small-World" network and goes along with a model of areas as functionally specialized modules, with the long-distance connections serving to communicate the information processed locally within areas rapidly across the cortex.

Physiological Integration of the Daisy Architecture with the Connections between Cortical Areas

How long-range connections influence local circuit functions is an important step in understanding the computational function of the neocortex. One approach is to temporarily inactivate the area by cooling and study what effect the inactivation as on a target area the projecting regions. Cortical areas V2 (Cerebro-cortical area V2) and MT (Cerebro-cortical area MT) have feedback connections to the primary visual cortex (area V1 (Cerebro-cortical area V1)), and cooling area V2 or area MT reduces the receptive-field center response of area V1 neurons. This suggests that there may be a summing of feedback activity with feedforward input from the thalamic lateral geniculate nucleus (LGN), which relays retinal activity to area V1. Integration is further suggested by the evidence that feedback projections from extra-striate cortex overlap with clusters of area V1 cortical output neurons [8].

One way to investigate the dynamics of the interaction of inter- and intra-connectivity is to examine the visuo-topic scales of both systems and compare them to the receptive field response of neuronal aggregates in area V1 [8]. In these studies the representation of the visual field (Vision) is determined for the extent of the local Daisy connection as well as for the inter-areal connections. These studies suggest that Daisy connections have the appropriate spatial extent to mediate a restricted portion of the visual response of area V1 neurons, which corresponds to the spatial summation zone within the receptive field. The extent of the Daisy connections was however insufficient in extent to account for the full surround response from beyond the classical receptive field (Vision). This makes sense because the relatively long delays of the suppressive orientation-selective effects of surround stimulation are similar to those reported for the slow propagation of excitatory activation mediated by horizontal connections.

The visuotopic representation of feedback projections from extra-striate cortex to area VI are commensurate with the full center-surround response of the area V1 neurons (Visual cortical and subcortical receptive fields). The influence of extra-striate cortex on Daisy connectivity is coherent with the temporal constraints: the timing of the visual responses of higher visual areas largely overlap with area V1 responses, the conduction velocities of the large-caliber fibers projecting from extra-striate cortex to area V1 are considerably faster than those of the horizontal intrinsic fibers, and the inactivation of extra-striate cortex influences the early part of the area V1 neuron visual response. Hence, it would seem that the physiology and the visuo-spatial correspondence between the intra- and inter-areal connection systems provides the basis for the integration of local and global signals in the primary visual cortex [8].

Conclusions

One fundamental question about feedback and feedforward pathways is whether they constitute distinct functional systems, as implied by the terminology used. Taking the geniculo-cortical pathway (geniculo-striate pathway) as a model, cortical feedforward pathways supposedly mediate driving influences and feedback mediate modulatory influences. Physiological studies support this general view, e.g. cooling area V1 in the monkey leads to silencing of area V2 neurons, whereas cooling area V2 has only marginal effects on the activity of area V1 neurons. However, if a small driving projection was contained in the feedback pathway that remains dominated by a modulatory function, the driving function might not show up in the cooling experiments. The distance rule suggests that the physiology of feedforward and feedback pathways linking cortical areas is determined by the composition of the parent neurons in terms of supra- and infra-granular layers [6]. The differences in the physiology of feedforward and feedback pathways could be the consequence of (i) differences in the cellular targets and/or (ii) differences in the intrinsic properties of the parent neurons. The idea that a cortical area is homogenous both in function and structure has been floating for over a century. In a seminal paper, Daniel and Whitteridge [9] showed that while the amount of cortex devoted to a degree of the visual field (the "magnification factor") (Striate cortex functions) does change across the cortex, there appears to be a constant ratio between the numbers of peripheral receptors and the number of visual degrees represented in the cortex. In the 1970s, Hubel and Wiesel took this a step forward in suggesting that the entire apparatus for representing a point of the retinal image is contained in a small region of cortex a few millimeter in area, which they called a "hypercolumn." The primary

visual cortex thus consists of many such hypercolumns. However, the dynamic properties of neuron response have been shown to change dramatically within a visual cortical area at different eccentricities, and a recent paper shows marked differences in the inputs to the central and peripheral representation of area V1 [10]. The dominance of inter-areal projections by nearby areas could lead to such a specialization because the layout of the visual areas results in different sets of areas being closer to central than peripheral visual field representations. This in turn leads to the prediction that the central representation of early visual areas will be preferentially connected to the ventral processing stream and peripheral to the dorsal processing stream (Extrastriate visual cortex). Thus while a given cortical area may be formed by multiple copies of a canonical circuit, each region of the area could be modulated independently by its nearest neighbors. Eccentricity-dependent differences in organization would be consistent with the anatomical specializations in the retina (fovea vs. periphery) as well as the behavioral evidence of eccentricity dependence of different tasks (for example, object recognition in central vision vs. global spatial localization in the periphery). Such observations raise questions about how a cortical area should be defined, since it cannot be done by assuming that one area behaves as a single functional entity.

Our approach to investigating cortical hierarchy is based on Graph Theory, in which the distribution of connections between areas is analyzed over the whole network to infer the connectional distances between areas [7]. Such an analysis shows that the distribution of areas bears a close resemblance to their spatial layout in the cortex suggesting organizational principles linking connectivity, adjacency and cortical folding. This study, however, is based only on the presence or absence of a connection between two areas and does not take into account the strength of connections. Because strong connections are very short-range, integrating the strength of neural connections in these models will strongly emphasize the importance of adjacency. Given that the strength of connectivity is eccentricity-dependent, comparing graphs across the cortex will allow us to explore structural features of contextual processing. The challenge will then be to extract the rules allowing integration of Daisy architecture in the contextual process. Significant efforts are now being made to understand how graphical processing can be instantiated in networks of uniform processing elements, how this can be done using asynchronous event-based methods, which are the essence of neuronal computations, and whether graphical processing can be promoted from simple uniform propagation between nodes (whether defined as neurons, clusters of neurons, or cortical areas) to a dynamic "intelligent" selective propagation. The solution to such problems will be an important step to understanding the principles by which biological brains achieve their intelligence.

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