

Full-length review

Large-scale cortical networks and cognition

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Abstract

The well-known parcellation of the mammalian cerebral cortex into a large number of functionally distinct cytoarchitectonic areas presents a problem for understanding the complex cortical integrative functions that underlie cognition. How do cortical areas having unique individual functional properties cooperate to accomplish these complex operations? Do neurons distributed throughout the cerebral cortex act together in large-scale functional assemblages? This review examines the substantial body of evidence supporting the view that complex integrative functions are carried out by large-scale networks of cortical areas. Pathway tracing studies in non-human primates have revealed widely distributed networks of interconnected cortical areas, providing an anatomical substrate for large-scale parallel processing of information in the cerebral cortex. Functional coactivation of multiple cortical areas has been demonstrated by neurophysiological studies in non-human primates and several different cognitive functions have been shown to depend on multiple distributed areas by human neuropsychological studies. Electrophysiological studies on interareal synchronization have provided evidence that active neurons in different cortical areas may become not only coactive, but also functionally interdependent. The computational advantages of synchronization between cortical areas in large-scale networks have been elucidated by studies using artificial neural network models. Recent observations of time-varying multi-areal cortical synchronization suggest that the functional topology of a large-scale cortical network is dynamically reorganized during visuomotor behavior.

Keywords: Cerebral cortex; Cognition; Neural network; Temporal synchronization; Cross-correlation

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1. Introduction

One of the earliest and longest running debates in neuropsychology concerned the question of whether functions of the cerebral cortex are localized in circumscribed areas or are equally represented throughout the entire cortex. Resolution of this controversy, brilliantly detailed by Luria [122], slowly came about with the realization that cortical areas do perform unique elementary functions, but that complex functions require the integrated action of many areas distributed throughout both cerebral hemispheres. According to this view, a complex function is a system of interrelated processes directed toward the performance of a particular task, that is implemented neurally by a complementary system, or network, of functionally related cortical areas. Large-scale networks of cortical areas are seen as essential for high-level functions underlying cognition. Of course, since all cortical areas have extensive subcortical connections, large-scale cortical networks operate as part of even larger, whole brain systems.

A number of disciplines have contributed to the study of large-scale cortical networks [39–43,56,80–83, 86–89,130,134,151,161–163,183,184]. Neuroanatomical studies have established that large-scale networks consist of uniquely configured, interconnected sets of distributed cortical areas. Neurophysiological studies have demonstrated the functional coactivation of multiple areas in large-scale networks. And neuropsychological studies have confirmed that coordinated large-scale networks mediate several different complex cognitive functions.

Of critical concern to this review is evidence that cortical areas may not only become coactive during cognition, but may also become interdependent, or functionally connected. Thus, fragmentary sensory, motor and associative processes, occurring in individual cortical areas, may become integrated by the functional connection of those areas in large-scale networks. Evidence is presented that functional connections between cortical areas are manifested as interareal correlated activity. The recent controversy that has arisen over correlated cortical activity is examined and an explanation is provided which may reconcile the opposing views.

Several issues are considered which may be essential for an understanding of large-scale network operation. First, what determines the constellation of cortical

areas that participate in a large-scale network? Networks dedicated to particular cognitive functions are defined anatomically by unique sets of interconnecting pathways, but modulatory control processes are proposed to configure the networks for specific implementations of those functions. Second, what mechanisms can explain the functional connection of cortical areas in a large-scale network? Consideration is given to possible mechanisms, with a focus on the role of recursive, excitatory interactions. Finally, how does the network adapt to changing operational contingencies as implementation of a complex function evolves in time? It is suggested that the pattern of network interactions, already constrained by anatomical connectivity, is further constrained dynamically by the action of modulatory control processes and also by the outcomes of interareal informational transactions. Theoretical studies using software simulations of large-scale cortical interactions are reviewed in the treatment of these issues, as are recent observations of the real-time network dynamics during visuomotor task performance.

2. Parallel processing in large-scale cortical networks

2.1. Studies in non-human primates

Historically, the study of cortical information processing focussed on the idea of serial activation of neurons in one cortical area after another along a chain. This perspective derived from the stimulus-response paradigm of Sherringtonian reflex theory and early axonal tracing studies showing pathways connecting cortical areas in a progression from primary sensory areas, through higher-order sensory areas, prefrontal cortex, premotor cortex and terminating in primary motor cortex [105]. Hierarchical organization of sensory function [145] was explained as resulting from the sequential extraction of progressively more complex features by neurons along a chain [99] and hierarchical motor control was attributed to serial activation of a motor command chain [109].

The simple view of single serial chains has largely been superseded by a more comprehensive outlook on cortical function, which includes, but is not limited to, feedforward transmission. This change has come about as a result of anatomical evidence showing a larger number of cortical areas with sensory and motor functions, more complex patterns of connectivity among

them and a predominance of reciprocally arranged connections [6,67,128]. These findings suggest that cognitive information processing should be distributed in large-scale interconnected networks of cortical areas. Use of the term 'network', however, does not imply all-to-all connectivity of cortical areas, with direct accessibility of each area to any other. Cortical areas are not broadly interconnected in that way [106]: only 40% of all possible corticocortical connections are estimated to actually exist [67]. Each network has a unique set of connections related to its cognitive function.

The large-scale network description allows for hierarchical processing levels without the necessity of serial activation. Although cortical areas, particularly sensory areas, operate at different hierarchical levels based on various functional characteristics [67,180,182], hierarchical organization does not require that information processing be based on serial activation, with activity at one level terminating before beginning at the next hierarchically higher level. Instead, processing may proceed concurrently at multiple levels, with information shared across levels. Distributed processing may be an efficient way of allowing alternative communication routes and broad access to information in the face of changing operating requirements.

In the visual system, once thought to be serially arranged, parallel pathways project from the retina, through the lateral geniculate nucleus and primary visual cortex [120] and widespread divergence and convergence of projections exist among extrastriate areas [67]. Functionally distinct, parallel visual subsystems in the temporal and parietal regions receive projections from multiple extrastriate areas [180]. Moreover, neurons in multiple visual areas show temporally sustained and overlapping responses to patterned visual stimuli, indicating that visual processing proceeds in parallel in those areas [9,31,45,127]. These findings suggest that, taken as a whole, the visual cortex is best viewed as a large-scale network with parallel processing capability. The manifold possible pathways which exist for the distribution of information among visual areas may provide processing flexibility in visual scene analysis [18].

Non-visual areas are interconnected in large-scale networks as well. Subdivisions of the posterior parietal cortex do not simply relay sensory information to motor areas, but are extensively and uniquely interconnected with multiple areas of sensory, limbic and frontal cortex [29,30,104], comprising a network for the analysis of spatial information [88]. Both single-unit recording and 2-deoxyglucose metabolic mapping reveal coactivation of areas in this network during performance of spatial working-memory tasks [75,89].

The extensive anatomical interconnectedness of cortical motor areas [100], as well as the descending corticubral, corticopontine and even corticospinal projec-

tions of non-primary areas, imply that area M1 is not a final integration center for the cerebral control of movement [48,115,187,188] and that the multiple cortical areas function together as a distributed network. This interpretation is supported by neuronal population studies in M1 suggesting that the output of other motor areas bypasses M1 during certain types of movement [158]. Furthermore, simultaneous recordings of neuronal activity in multiple cortical motor areas show parallel processing in different areas during both preparation and execution of visually guided limb movements [4,5,38,107]. Parallel processing in distributed areas does not necessarily exclude sequential integration of movement parameters, which has been reported in premotor cortex [116].

2.2. *Human neuropsychological studies*

Human neuropsychological studies provide an important source of information on the distributed nature of large-scale cortical network operations. Behavioral studies of brain-lesioned patients reveal the cortical areas that cooperate in large-scale networks by demonstrating similar degradation of cognitive functions when those areas are lesioned. Positron emission tomography (PET) and electrophysiological investigations show the coactivation of multiple, distributed cortical (and subcortical) areas during the performance of sustained cognitive tasks.

In patients displaying neglect behavior, separate components of the orientation of directed attention to extrapersonal space are revealed by disruption of each of three crucial areas which interact as part of a large-scale network [129,130,133]. These three areas, dorsolateral posterior parietal, dorsolateral premotor-prefrontal, and cingulate cortices, are linked by extensive, reciprocal monosynaptic connections and may organize directed attention by providing distinct reference systems for interaction with the environment. Lesions in any of these areas or their interconnections can produce neglect behavior, implying that directed attention results from a distributed network minimally encompassing all three areas. PET studies of patients performing tasks with a strong attentional component also implicate widespread distributed networks of cortical and subcortical areas in the control of attention [150,151].

Current perspectives on linguistic processing suggest that it too is subserved by distributed networks rather than by strictly serially arranged pathways [79]. Recent clinical reviews [43,130,141,142] support the idea that linguistic processing in the cortex occurs in parallel at widely separate sites. Functional analysis of lesion-induced language impairments, language-activated PET scans and electrocorticographic and microelectrode recordings during language tasks all provide support

for distributed function. It is difficult to reconcile the classical view of unidirectional flow from Wernicke's area to Broca's area with new evidence that each area has both receptive and expressive properties and that they are activated simultaneously, not consecutively, during language tasks [74]. Distributed networks are implicated even in simple word-association tasks [147].

Human lesion evidence has been presented for large-scale distributed processing in perception and memory [39–43], suggesting that no single cortical area is responsible for the integration of perceptual phenomena. Bilateral lesions of anterior temporal or prefrontal cortices, areas traditionally considered to be 'integration' cortices, do not disrupt normal perception, whereas lesions of many different cortical sensory areas can impair basic perceptual integrative functions such as recognition and recall. Thus the cohesiveness of perceptual experience cannot be attributed to the functioning of any single cortical area, but involves integration of distributed processing in multiple areas.

3. Functional connections in large-scale cortical networks

Inherent in the concept of the large-scale cortical network is the premise that neurons in different areas become functionally connected while carrying out the complex operation of the network. The functional connection of two areas implies that they are coactive, and further, that their activity is interdependent. How is this interdependency manifested in cortical activity? Given the functional relevance that has been demonstrated for the temporal patterning of neuronal activity [114,123,171], a reasonable hypothesis is that interdependency is revealed by similarity of temporal pattern [45,103].

Measurement of the tendency of activity at two cortical locations to show similar temporal patterns (with possible delay) is most often accomplished with the cross-correlation function. Correlated activities [34,159,163] are those which are found to have a significant degree of similarity. When applied to continuous activity such as field potentials, as opposed to discrete activity such as spike trains, correlated activity is typically referred to as 'synchronization'. To conform to common usage, the term 'synchronization' will be used here, even though, in a strict sense, it refers to wave-shape identity (i.e., exact frequency and phase locking) rather than waveshape similarity.

The experimental observation of correlated activity in two cortical areas during execution of a complex function implies that the areas are functionally connected. Their functional connection requires that they be anatomically connected, but many pathways may be responsible for the anatomical connection [94], includ-

ing monosynaptic and polysynaptic pathways between the two areas, either unidirectional or reciprocal, as well as divergent feedforward pathways from other areas. As will be discussed below, the measurement of correlated activity in multiple distributed cortical areas, within an appropriate experimental framework, may provide a direct window onto the dynamic behavior of large-scale cortical networks in real time.

3.1. Single-neuron studies

A common strategy in the investigation of cortical correlation is to study the statistical relations between the activities of pairs of single neurons [11,131,186]. Since the dendritic activity of single cortical neurons is difficult to detect, requiring intracellular recording, correlated neuronal activity has been described almost exclusively in terms of spikes. The cross-correlation histogram is typically used to detect coincident spikes in simultaneously recorded spike trains [1,78,146]. Correlated neuronal firing has been observed in this way between neuron pairs in auditory, frontal, striate and inferotemporal cortices of the monkey [2,3,85,113,181], both neurons in the pair being located in the same area. It has also been observed between neurons located one each in areas 17 and 18 of the cat [140] and V1 and V2 of the monkey [25,153].

3.2. Relevance of the neuronal ensemble

Even though there have been reports of weak correlated firing between single neurons in different cortical areas, it has been argued that correlated activity between individual cortical neurons is not an effective means of establishing long-range functional interactions between cortical areas [50,64,144,172]. On the fraction-of-a-second time scale of cognitive events, single cortical neurons typically generate only a few spikes [1,73]. Since very few contacts exist between individual cortical neurons [12,47,76], the joint firing of tens of cells is minimally required to alter the firing probability of a single target neuron [1,172]. Thus only a small percentage of cortical spikes can be accounted for by the activity of any other single neuron [49,178]. Since correlated firing of single neurons is observed to be rare and weak even for neurons in the same cortical area [49,50], significant functional interactions may not occur between single neurons in widely separated areas.

Numerous alternatives to the single neuron have been proposed as the basis for understanding integrative functions of the cortex [56,69,97,134,170]. Although differing in many aspects, they all emphasize that cooperative effects occur in ensembles of neurons in local neighborhoods due to synaptic interactions [47,57]. Studies of regional cerebral metabolism and

blood flow support the hypothesis that the cortical implementation of high-level function involves neurons acting in ensembles rather than individually [154]. From this perspective, local neuronal ensemble activity reflects the level of integration necessary to establish synchronization between cortical areas [172,173]. Since local interactions involve both axonal action potentials and postsynaptic dendritic potentials, local ensemble activity is manifested both as the summed firing of action potentials, measured by the local multi-unit spike density [70] and the sum of dendritic currents, measured by the local field potential (LFP) [165].

Interareal correlation may be most robust for the LFP, which is an instantaneous spatial average of ensemble activity [73], since spatial averaging is an important characteristic of the communication between cortical areas. The spatial averaging manifested in the LFP may approximate that which occurs in the interactions between areas as a result of axonal divergence and dendritic integration. Since the LFP, unlike single-cell dendritic activity, is readily obtainable by extracellular recording, due to the summation of currents from large numbers of neurons in the local neighborhood, it may provide an advantageous signal for measuring the synchronization of local ensemble activity from different cortical areas.

3.3. Neuronal ensemble studies

A large number of studies have examined correlated cortical activity at the ensemble level. They have focussed primarily on multi-unit spike and field potential activity in the γ -frequency (20–90 Hz) range [16]. Near-periodic γ -frequency oscillations [23,90,92,93,102] have been shown to be correlated between sites within areas of the visual cortex of the cat [60,62–64,91,111] and monkey [72,112,119]. γ -Frequency oscillations in the visual system are similar to those previously reported in the rabbit olfactory system [13,19].

Interareal synchronization of γ -frequency oscillations has been reported in several cortical systems. In the cat visual cortex, it has been observed between LFPs from areas 17–19 [49–53] and between multi-unit activity from areas 17 and posteromedial lateral suprasylvian sulcus [63]. In the monkey, it has been seen between LFPs from visual areas V1 and V2 [54], and, in relation to behavior, between LFPs from somatosensory and primary motor areas [138] and from primary and non-primary motor areas [157]. In the rabbit olfactory system, it has been observed during inspiration between LFPs from the olfactory bulb and cortex [14,15]. Finally, it has also been reported to occur interhemispherically between left and right primary visual cortices [61] and hippocampi [27].

These findings have led to proposals that synchronization of γ -frequency oscillations may be a general

cortical phenomenon, representing the functional connection of different cortical areas [16,37,161,162]. This hypothesis has been criticized, however, on the basis of other evidence suggesting that pronounced oscillations at γ -range frequencies are *not* a robust phenomenon in visual cortical areas in relation to various types of visual stimulation [10,77,84,174,175,190].

In attempting to reconcile these two points of view, it is important to recognize that the definition of ‘oscillation’ encompasses aperiodic as well as periodic variations [108]. Therefore, the absence of stimulus-induced oscillations at specific frequencies in the γ -range is not inconsistent with a possible functional role for synchronization [65,163], since synchronization may occur widely in the cortex based on aperiodic oscillations [21,174]. In support of this explanation is evidence suggesting that aperiodicity may be important in visual cortical function of the monkey: the power spectrum of the population response (LFP) in V1 has a broad-band, approximately $1/f$ -distribution [72], characteristic of aperiodic oscillations; stimulus-attribute information is present in the LFP dynamics in V1 across a broad frequency band [185]; light-bar stimulation induces a broad-band increase in LFP power in areas V1 and MT [190] and also induces aperiodic synchronization of multi-unit activity between sites in the superior temporal sulcus [112]. (Further evidence for broad-band processing is discussed in Section 6). These findings suggest that aperiodic signals may play a significant role in cortical function and that aperiodic synchronization may be a general phenomenon, of which near-periodic synchronization is a special case under certain conditions or in certain species.

4. Control of large-scale cortical networks

A crucial issue that proceeds from the idea of parallel processing in large-scale cortical networks is how the network is controlled for the efficient coordination of information transactions. This coordination has been postulated to depend on dynamic control processes [143,184] of both cortical and subcortical origin. Even within the constraints imposed by the anatomical connectivity of a distributed network, a multiplicity of combinations of functionally connected areas are possible. It is hypothesized that control processes are necessary to modulate the network by dynamically selecting an effective subset of areas to implement each step of processing in a complex function. The constellation of functionally connected areas which comprise this subset may be termed the *functional topology* of the network [55,69]. Control processes include regulation of the inputs to an area (input gating), regulation of the operation performed by the area and regulation of the targets to which the area transmits (output gating)

[183]. Different mechanisms, usually based on particular aspects of anatomical connectivity, have been suggested as control processes.

One potential control process is the gating of specific thalamic input to the cortex [35,164]. Because it is uniquely situated to project to all the thalamic nuclei topographically, the thalamic reticular nucleus has been postulated to serve as a gate on the activity of thalamocortical relay neurons. The exact mechanism by which this occurs is not known, but, since thalamic reticular neurons are believed to be inhibitory, increased activity in thalamocortical neurons has been proposed to occur by disinhibition through imposed inhibition on the thalamic reticular neurons [164] or by rebound spike bursting [121]. Spatial patterns of activity in the thalamic reticular nucleus that result from influences imposed on it from other sources may selectively gate input to specific sets of cortical areas.

Another control process may be the regulation of cortical excitability [117]. The so-called ‘non-specific’ thalamocortical afferents have been proposed to control cortical excitability by depolarizing the apical dendrites of cortical pyramidal cells to lower their firing thresholds [59]. If the excitability of a specific set of cortical areas were raised in this way, those areas would be ‘primed’ to be more responsive to inputs and interactions between them would be facilitated. It has also been suggested that chandelier cells, which inhibit the initial segments of pyramidal cell axons, may contribute to threshold adjustment [143]. The output of an area could thus be gated by enhancing the transmission from certain of its pyramidal cells and diminishing that from others. The selective regulation of cortical excitability is suggested by the increased blood flow in specific cortical areas that is associated with selective attention [150,151], although, in general, the regulation need not be related to consciousness [110].

Control processes have also been proposed to play a role in perception and memory [39–43]. Control neurons may retain information about the combinational relations of cortical areas that are functionally connected during perception and later use that information to reassociate the same areas during memory recall. Acting at both subcortical and cortical levels, control neurons may serve to coordinate activity over a range of organizational levels. The consequent integration of distributed processing in large-scale networks is proposed to be responsible for the cohesiveness of perceptuomotor behavior.

Neuroanatomical evidence in support of the proposition that control processes coordinate the activities of multiple distributed cortical areas is provided by the identification of large-scale divergent projection pathways. Single sites in non-specific thalamic nuclei have been found to project to multiple widespread cortical target areas [86–89]. Cell clusters in the medial pulv-

inar, for example, project to distributed sets of cortical target areas that are themselves linked by corticocortical connections [8]. This suggests that the pulvinar may prime particular sets of cortical areas, thereby facilitating their interaction [143,177,184]. Non-thalamic subcortical sources, such as the amygdala [7] and hippocampal region [139,155,168], may also contribute to the regulation of cortical networks by way of divergent projection pathways to multiple cortical target areas. Cortical source areas, such as dorsolateral prefrontal, posterior parietal and extrastriate visual areas, also project widely to multiple cortical target areas, and may play a coordinating role [67,86–89,160]. In short, thalamic, non-thalamic subcortical, and cortical sources may all cooperate in the dynamic organization of information processing within large-scale cortical networks [154].

5. Recursive interactions in large-scale cortical networks

A major effect of the coordination by control processes of distributed activity in large-scale networks is likely to be the promotion of direct, recursive interactions between local networks in interconnected cortical areas. Since cortical areas are almost exclusively connected by excitatory synapses between pyramidal cells [12,46] and since most connected areas are reciprocally coupled, bidirectional excitatory interactions between areas presumably are an important feature of cortical network dynamics. Recursive interactions between cortical areas may allow multiple local networks to temporarily combine into larger processing units in order to accomplish information transactions that require contributions from them all [124]. This would suggest that activity in each local network evolves under the continuing influence of activity occurring simultaneously in other local networks to which it is connected [89,191] and that, in the words of Goldman-Rakic et al. [89], “a single pattern of activity arises at virtually a single stroke over a number of interconnected cortical areas”.

A number of groups have studied the functional properties that result from recursive cortical interactions. Damasio and colleagues [39–43] have proposed that perceptual function depends on recursive interactions among multiple cortical areas in large-scale distributed networks. In addition to sensory and motor areas, perceptual networks are proposed to include association areas that retain information about the functional topology of the network. During recall from memory, the association areas direct the recreation of the same functional topology. Thus an act of perception and its recall depend on recursive interactions among the same cortical areas.

Other groups have attempted to determine the functional properties resulting from recursive interactions by using computational techniques. For example, Edelman and colleagues [56,68,166,167,172,173] have constructed a reentrant cortical integration (RCI) model that emphasizes the importance of recursive signalling (reentry) among multiple cortical areas by way of reciprocal connections. The sharing of information among distributed local networks by reentry allows each local network to use discriminations made by other local networks for its own processing. Episodes of correlated activity coincide with short-term changes in synaptic efficacy [172,173]. Advantages of the RCI model are that there is no need for a 'teacher' [36], since local networks are constrained and directed by feedback from other local networks in the large-scale network; the local network has access to information from many other local networks, not just from one as in serial processing schemes; conflicting responses among multiple local networks are competitively eliminated; and because outputs from a local network return to it by reentry, the local network can iteratively synthesize responses to complex, ongoing stimuli.

Other studies have considered the computational implications of reciprocal corticocortical pathways in terms of pattern analysis [28,44,136,137,156,179]. Although differing in their implementation and degree of sophistication, these proposals essentially envision the backprojection from one (higher) area as providing an instructive function to another (lower) area. Features of the activity pattern in the lower area are enhanced when they match a template backprojected from the higher area.

Freeman [71] has emphasized the dynamic properties that result from recursive interactions among local networks. A major feature of his KIII model of reciprocally coupled local networks, representing three olfactory cortical areas, is the emergence of aperiodic or 'chaotic', activity directly as a result of coupling. This type of activity may provide for diversity in the output of the system, as well as the rapid and flexible selection of optimal responses under constraints imposed by the interaction of the system with its environment [33].

6. Dynamic reorganization of large-scale cortical networks

It has often been noted in contemporary studies of human cognition that a central role is played by sequential, time-consuming processes [32,118,148,149]. Sequentiality, such as that observed as scanning in certain visual attention tasks [176], may in fact be a necessary computational requirement of some high-level processes [101,132]. That is, the processes may have to be carried out in stages, with one sub-process

following after another. However, sequential high-level processing need not be implemented by a serial cascade of cortical areas, with each sub-process processed by a single and separate region [45]. From a computational viewpoint, serial cascade models are inefficient because they suffer from a computational explosion when faced with a large number of processing constraints [66,125,126].

Alternatively, complex, high-level functions may be implemented by parallel processing in large-scale cortical networks. According to this view, sequentiality of function results from dynamic network reorganization. Each sequential sub-process in high-level function corresponds to a change in the functional topology of the network, which is adaptively reconfigured under the influence of control processes implementing constraints imposed by the evolving processing contingencies of the high-level function [24,183]. Thus, as an animal performs a complex process composed of sequential functional steps, the areas engaged at each step depend on the particular sub-process that is executed. This same principle of reconfiguration of a distributed network has also been recently proposed as the basis for adaptive behavior in an invertebrate nervous system [189].

6.1. Mapping functional connections

Correlation studies, reviewed in Section 3, support the idea that transient functional connections between different cortical areas are observable as temporal synchronization of their activities. However, most of these studies have not directly addressed the issue of large-scale integration in relation to complex function. It has been argued [17] that to characterize the operation of large-scale cortical networks in high-level functions requires at least three basic procedural steps for the mapping of functional connections among cortical areas.

First, to test for functional connections among widely distributed cortical areas minimally requires simultaneous sampling of the activity from sites in each of those areas, as well as computation of the degree of synchronization for all possible site pairs. Because most synchronization studies have only dealt with single site pairs, they lack sufficient spatial sampling to address questions about large-scale function. Second, synchronization studies should be carried out within the context of a well-controlled behavioral task. Functional connections between cortical areas may only appear when the subject is engaged in task-related processing. Finally, for reasons discussed in Section 3, the measurement of synchronization should allow for the possibility of aperiodic synchronization. It should also have sufficient temporal precision to be sensitive to changes in functional state that occur during task performance.

6.2. Multi-areal synchronization studies

These considerations motivated recent studies [17,20–22] in monkeys to test whether LFP synchronization exists among sites in widely distributed cortical areas. The coherence spectrum, a statistical measure of broad-band synchronization in an ensemble of trial repetitions, was computed between LFPs for all pairwise combinations of up to 16 widely distributed recording sites in one cerebral hemisphere of macaque monkeys performing a visual pattern discrimination task. (The field potential was localized at each site by differential recording from a transcortical bipolar electrode.) Coherence was computed in a sliding 80-ms window in order to track changes in stimulus- and response-related information processing.

Following presentation of the static visual stimulus, significant increases in coherence (indicating synchronization) were observed among LFPs from sites in striate, prestriate, inferotemporal, superotemporal, posterior parietal, somatosensory, motor and frontal cortices. Spatial patterns of task-related synchronization were complex, selectively involving roughly 40% of the sampled site pairs (Fig. 1). Synchronization was spatially selective: two sites could become synchronized without involving other intervening sites. It occurred over both short distances, e.g., occurring between sites in posterior visual areas or between frontal sites, and long distances, e.g., between posterior and frontal sites. Synchronization involving frontal or motor sites did not necessarily occur later than that involving visual sites, as would be expected for serial cascade processing, but rather could occur just as soon after stimulus presentation. The variance of phase over trials was always

non-zero, indicating that synchronization did not simply result from imposed common external driving.

Synchronization appeared in episodes of significant coherence lasting on the order of 50–200 ms (Fig. 2A,C,E), a time scale similar to that proposed for the transient conjunctions of neuronal assemblies from different cortical areas involved in visual attention [35]. It was observed as waveform alignment of single-trial LFPs (Fig. 2B,D,F) from the same sites, during the same time intervals that showed significant coherence for the ensemble of trials. Synchronization episodes involved a broad frequency range between 0 and 100 Hz, including but not limited to the γ -band. Although the level of coherence declined with increasing frequency, the temporal patterning of the episodes was similar at all observable frequencies. The LFP amplitude at one or both of the sites in a synchronized pair tended to increase over this broad band, consistent with the report [190] that the cortical response in the monkey to visual stimuli is a broad-band increase in power.

In this visual pattern discrimination task, the monkey signified the recognition of one pattern type by making a motor response and the other type by withholding that response. Many site pairs, primarily involving at least one non-visual site, showed episodes of synchronization continuing through the time of the response. For those pairs, the level of coherence just before and during the response significantly differed from the same period when the response was withheld, indicating a functional role for broad-band synchronization in task performance.

Functionally related, large-scale correlated activity has also been observed in relation to visuomotor pro-

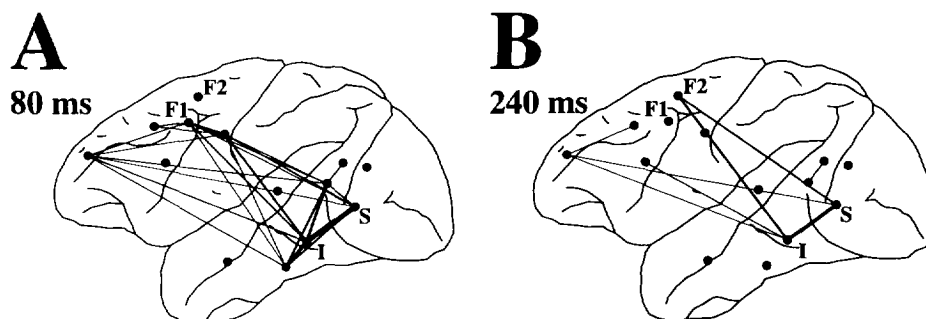


Fig. 1. Local field potential (LFP) synchronization was measured with the coherence spectrum, which provides a statistically reliable index of correlated activity as a function of frequency. To track the change in coherence with time, an 80-ms long analysis window was progressively stepped across the length of the trial. At each step, coherence spectra were computed for all pairwise combinations of cortical recording sites. The value of significant coherence between two sites is represented by the thickness of the line connecting the sites. Patterns were derived from a total of 493 trials from one monkey performing a visual pattern discrimination task, with a hand response, in a session lasting about 45 min. (For further experimental details see [20,21]). A: coherence values that were significantly above baseline ($P < 0.01$) are displayed for the 50-Hz frequency component when the analysis window was centered at 80 ms after stimulus onset. Significant coherence, representing the statistically reliable occurrence of synchronization, was found between posterior visual sites, between frontal sites and between visual and frontal sites. B: when the analysis window was centered at 240 ms post-stimulus, the pattern of significant coherence had changed. As one example of this change, note that the frontal site marked F2, which was not involved in the pattern at 80 ms, did have significant coherence with inferotemporal and striate sites at 240 ms.

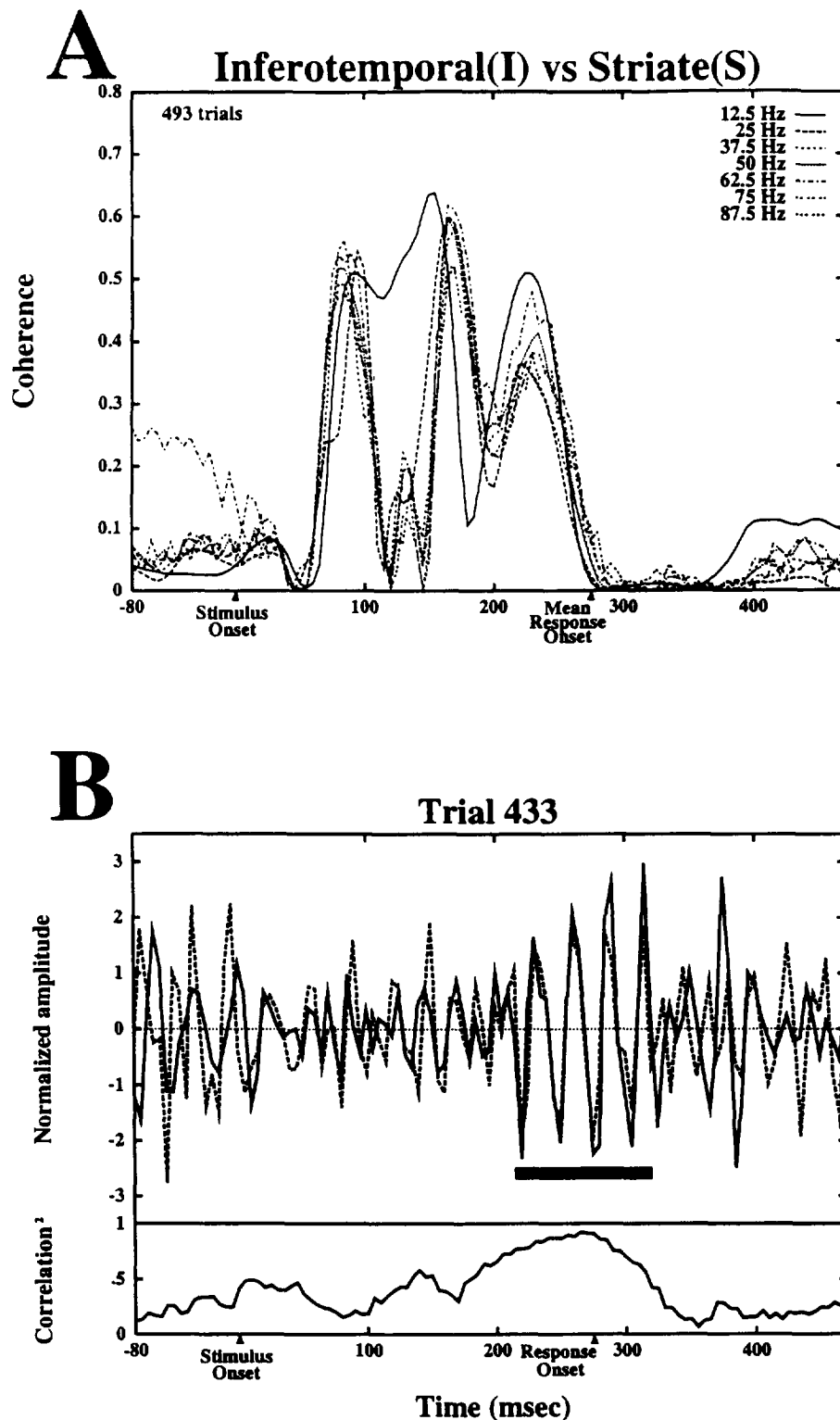


Fig. 2. Task-related episodes of elevated coherence, lasting on the order of 50–200 ms, followed stimulus onset, the change in coherence with time being similar at all available frequencies. The frequency resolution of the coherence spectra was 12.5 Hz (1 cycle per 0.08 s). Synchronization was observed among single-trial LFPs from the same sites and in the same time intervals that showed elevated coherence for the ensemble of trials. Three examples are shown of pairs having significant task-related coherence. A, C and E show the coherence time-series for all frequencies superimposed; B, D and F show the corresponding LFPs from single trials, digitally filtered from 30 to 80 Hz, along with the corresponding moving squared correlation. A: an inferotemporal site and a striate site, marked I and S in Fig. 1, had significantly elevated coherence in multiple episodes from about 80 to 280 ms post-stimulus. B: an interval of highly synchronized activity occurred in the single-trial LFPs prior to response onset, as indicated by a peak in the squared correlation, corresponding to a coherence episode roughly at the same time.

cessing in humans [80–83]. The correlation measure in those studies is derived from scalp-recorded, averaged event-related potentials, and thus has a coarser spatial resolution than that in the monkey. Also, since γ -

frequency components are degraded by volume conduction through the skull and by the averaging procedure performed prior to computation of the correlation measure, waveform alignment in the human studies has

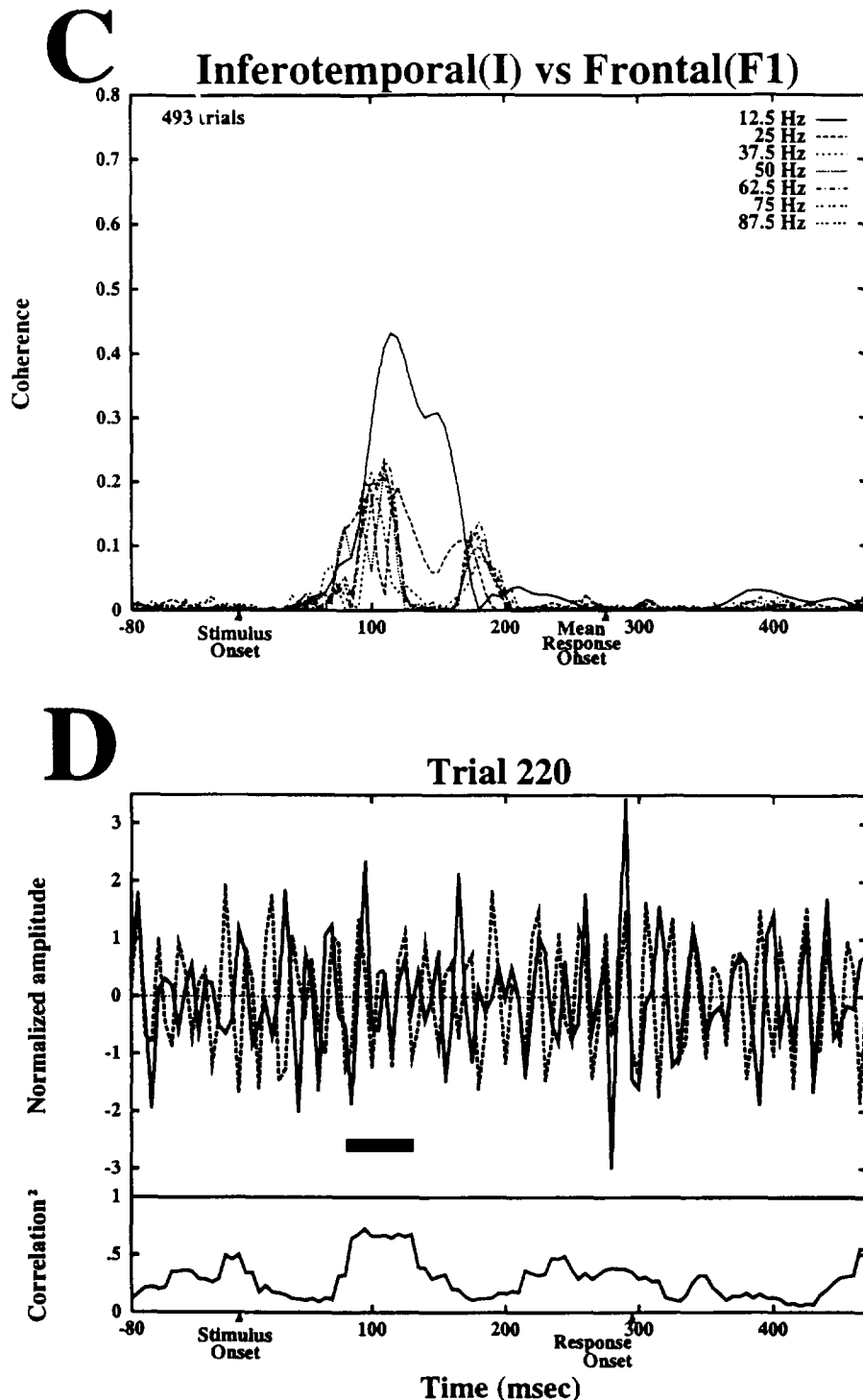


Fig. 2 (continued). C: the same inferotemporal site I also was engaged in episodes of elevated coherence with a frontal site F1 from about 80 to 200 ms post-stimulus. The episodes were finished by 240 ms, the time of the pattern in Fig. 1B. D: the single-trial LFPs were briefly synchronized at about the time of the first coherence episode. E: inferotemporal site I was also coherent with a second frontal site F2, but the episodes followed a different time course. They were not significantly coherent at the time of the early pattern of Fig. 1A, but were coherent during the later pattern of Fig. 1B. F: synchronization during this later coherence episode is illustrated for a single trial.

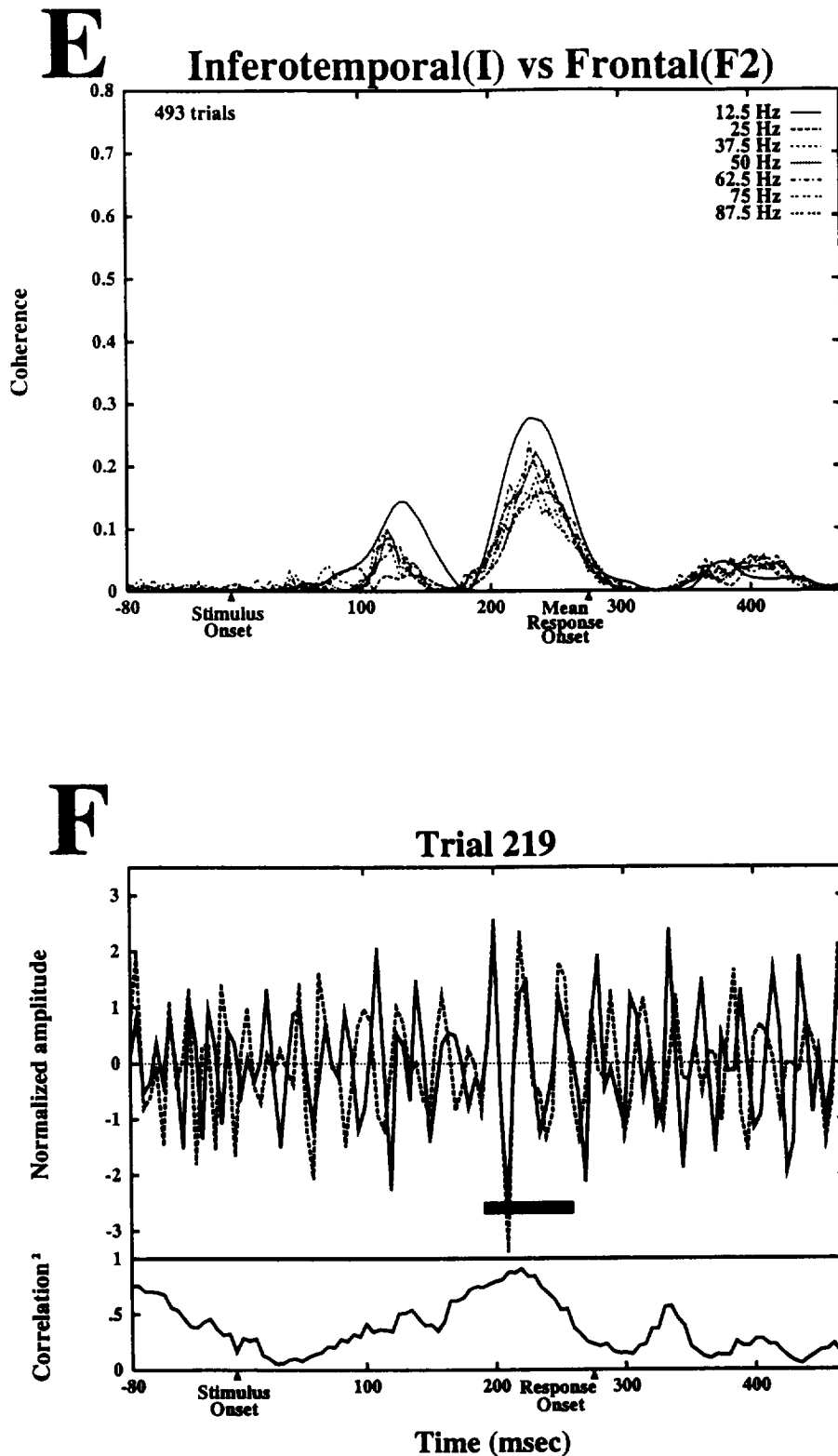


Fig. 2 (continued).

thus far only been observed in the δ - θ -frequency range. In spite of these differences, the human correlation results essentially agree with those from the monkey in corroborating the dynamic reorganization of large-scale

cortical networks during visuomotor performance. In addition, they suggest that networks may be configured *prior* to task performance, in anticipation of sensory input and in preparation for action [81,83].

7. Summary and conclusions

The concept of large-scale cortical networks provides a reasonable framework for integrating results from neuroanatomical, neuropsychological and neurophysiological studies on distributed functioning of the cerebral cortex. According to this description, elementary functions are localized in discrete cortical areas, whereas complex functions are processed in parallel in widespread cortical networks. Control processes, operating at cortical and subcortical levels by a variety of mechanisms, dynamically organize and regulate large-scale cortical networks. Cortical areas in the network become functionally connected through direct recursive interaction or through intermediary cortical or subcortical structures.

An important contribution to the investigation of large-scale cortical networks has come from electrophysiological studies of cortical synchronization. Evidence has been reviewed that functional connections between cortical areas are manifested in the form of interareal synchronization. Although synchronous activity may turn out simply to reflect underlying network operations, it might also play an important functional role in determining cortical output, as described in the following scenario.

A distinctive feature of cortical activity, which is likely to have important functional significance, is its temporal variability [73,103,114,135]. As an animal interacts with its environment, the cortex must process time-varying sensory patterns and generate time-varying motor patterns on time scales of milliseconds to seconds. Successful behavioral adaptation may depend on the ability of the cortex to flexibly process a wide range of complex temporal patterns. That such flexibility exists is suggested by the aperiodicity of cortical ensemble activity. Aperiodic processes, characterized by broad-band, $1/f$ -like power spectra, typically depend on mechanisms operating at many time scales and thus have an inherent flexibility in the time domain [26,96]. A diversity of temporal patterning is thus available in the output of cortical ensembles.

In order for this diversity to be useful for information processing, a mechanism must exist for the selection of specific, functionally relevant cortical activity patterns. It is this selective function that may be provided by multi-areal synchronization in large-scale cortical networks. The synchronization of a temporal activity pattern in multiple cortical areas may signify the consensual resolution of processing by those areas. If that activity pattern is transmitted from those areas over projection pathways which converge on common cortical or subcortical target neurons, then synchronization may allow the pattern to be reproduced in the target structure. Reinforcement of a temporal pattern by synchronous excitation at multiple synapses on a

target neuron's dendritic tree may be necessary for the reliable retransmission of that pattern by the target neuron [1,35,152,162,169,172]. Therefore, synchronized mutual reinforcement of converging outputs from multiple cortical areas, at other cortical or subcortical target areas, may accomplish the rapid selection of specific, functionally relevant patterns by causing those patterns to be retransmitted by the target areas. This process may underlie the coordinated transfer of multimodal cortical information which has been postulated to occur both to the hippocampal region [58] and to the basal ganglia [95].

The importance of large-scale cortical network operations has been emphasized by a recent study in which computer simulations of interactions in a large-scale network mimicked certain aspects of schizophrenic behavior [98]. Pathological outputs resulted from a reduction in connectivity between network nodes, suggesting that schizophrenia reflects a breakdown of interactions between cortical areas. This work underscores the need for intensive investigation into the operation of large-scale cortical networks, which may yield unique insights into the neural implementation of cognitive function.

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