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Dynamic functional connectivity

Andreas A Ioannides

Recent studies show that anatomical and functional brain networks exhibit similar small-world properties. However, the networks that are compared often differ in what the nodes represent (e.g. sensors or brain areas), what kind of connectivity is measured, and what temporal and spatial scales are probed. Here, I review studies of large-scale connectivity and recent results from a variety of real-time recording techniques, which together suggest that an adequate description of brain organization requires a hierarchy of networks rather than the single, binary networks that are currently in vogue. Pattern analysis methods now offer a principled way for constructing such network hierarchies. As shown at the end of this review, a correspondence principle can be formulated to guide the interpretation across network levels and to relate nodes to well defined anatomical entities.

Addresses
Laboratory for Human Brain Dynamics, RIKEN Brain Science Institute, 2-1 Hirosawa, Wakoshi, Saitama, Japan 351-0198

Corresponding author: Ioannides, Andreas A (ioannides@postman.riken.jp)

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Introduction

Recent research in systems neuroscience has emphasized large-scale properties of the brain, establishing principles of its anatomical [1,2] and functional [3,4] organization. The study of complex networks has also matured over the past few years, thanks to well formulated concepts from graph theory and statistical physics [5,6], promoting applications in diverse fields, including neuroscience. In the early days of neuroimaging, Friston emphasized the need to distinguish between functional and effective connectivity [7]. 'Functional connectivity' refers to arbitrary relationships that might exist between the activations of distinct and often well separated neuronal populations, without any reference to physical connections or an underlying causal model. By contrast, 'effective connectivity' refers to causal effects that one neuronal population exerts on another, and it is based on an underlying model of the way the different neuronal populations are physically connected. The distinction between functional and effective connectivity has proven useful across diverse methodologies, such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), and electrophysiological recordings taken directly from multiple brain areas.

This review summarizes recent studies of functional brain connectivity, highlighting neuroimaging studies that use graph-theory-based tools for describing large-scale brain networks. Network models are attractive tools for studying brain organization: they provide a common framework for describing the connectivity of distinct brain areas at the level of anatomy and function, drawing from diverse data and measures of connectivity. Apparently, these large-scale networks reveal a common topology for anatomical and functional brain networks. I discuss these results in the light of recent results from multi-electrode recordings and transcranial magnetic stimulation (TMS), and data from functional connectivity analysis conducted in my own laboratory using magnetoencephalography (MEG). Finally, I propose a generalized network scheme that is more suitable than conventional binary networks for describing anatomical and functional connectivity data.

Graphs and their topology

Connectivity implies a network that consists of nodes, in which some form of processing takes place, and links between the nodes, which enable interactions and exchange of information. Graph theory is a branch of mathematics that describes such networks. This section provides some key definitions from graph theory to facilitate later discussion; knowledgeable readers can skip to the next section. More detailed descriptions of the underlying principles and ideas can be found in recent reviews of applications of graph theory to brain connectivity [8•,9].

A graph consists of a set of elements, called vertices or nodes, and a list of pairs of these elements. Graphs are defined as directed graphs (digraphs) or undirected graphs (graphs) according to whether their interconnections have directionality. The interconnections are given as a list of ordered or unordered pairs of their nodes, called arcs and edges, respectively. A 'subgraph' is a graph that contains a subset of the nodes and edges of the original graph.

The 'underlying graph' of a digraph is obtained by replacing each arc by an undirected edge. The arcs or edges can be binary (i.e. one when present and zero when

absent) or they can carry a signed or an unsigned weight. The weight of an edge can stand for measures such as physical distance, the strength of connection, or the timing of a connection between two nodes. The 'total weight' of a graph is defined as the sum of the weights of its edges. Real-world systems usually correspond to weighted graphs. For networks that have nodes in three-dimensional space and edge weights that represent the physical distance between pairs of nodes, one can define 'wiring cost' as the total weight of the graph. Binary undirected graphs are the easiest to analyze; a weighted graph can be reduced to a binary graph by applying a threshold. Hereafter, I refer to binary undirected graphs, unless otherwise stated.

A path between two vertices, i and j, is a succession of distinct edges. In the definition of edges that make up this path, vertices i and j appear only once (on the first and last edge), and every other vertex appears twice (once as the end of one edge and again as the beginning of the next). A cycle is a path that connects a node to itself — that is, a path with $i = j$. A graph is said to be 'connected' if a path exists between each and every pair of vertices, and 'disconnected' otherwise. The length k of a path equals the number of its edges.

The distance d_{ij} between two nodes i and j is the length of the shortest path between these two nodes. The distance matrix D of a graph has as elements the distances d_{ij}. Entries that correspond to disconnected pairs of nodes take on values of infinity or are assigned a very large number (for computational purposes). The characteristic length of a graph L is the average value of the distances d_{ij}, excluding artificially large values that describe non-existent edges. A measure of local connectivity is provided by the 'clustering coefficient' of a node. Consider a node i and the set of nodes just one edge away, its immediate neighbors: the clustering coefficient of node i, C_i, is defined as the ratio of the number of edges of the immediate neighbors of node i divided by the possible maximum number of such edges. The global clustering coefficient C of the graph is obtained by averaging C_i over all the nodes of the graph. Graphs that have the same number of vertices and edges can have different topologies depending on how the edges are organized. Surprisingly, similar key properties — short characteristic length and relatively high clustering — can be seen in two different types of network: the 'random network' and the 'small-world network' [5].

A random network is obtained by randomly connecting pairs of nodes. Because edges of different physical length are equally probable, the wiring cost of these networks can be considerably high. A small-world network has many edges that connect nearby vertices and only a few edges that connect distant vertices. Most nodes connect to a few edges but a small number, the 'hubs', connect to considerably more edges. The long-range connections are too few to have an impact on the wiring cost, but there are enough of them for there to be short distances between any two nodes. Small-world networks can therefore achieve high connectivity, similar to that of random networks of the same number of nodes and edges but at much lower wiring cost.

A connected graph that has no cycles is called a tree. A 'spanning tree' of a graph G is a 'tree subgraph' of G that connects all of its nodes. The minimum spanning tree (MST) of a (weighted) graph is the one that has the minimum total weight. Graph theoretical methods such as MSTs, multidimensional scaling and similar methods are often referred to as 'pattern analysis'.

Graph theoretical tools and other methods for studying brain connectivity

Modern neuroimaging methods provide descriptions of activity in a circumscribed brain area in the form of time series. A network can be constructed by assigning a node for each brain area, and measures of the relatedness in activity can be computed from pairs of simultaneously recorded time series. If such measures of functional connectivity are available from all possible pairs in a group of n time series, then these can be represented by an $n \times n$ matrix using a corresponding weighted graph. A simpler network can then be constructed by 'pruning' and 'binarizing' the graph — that is, admitting only edges above a certain threshold. Sporns and colleagues have studied in some detail how properties of complex networks relate to the organization, development and function of complex brain networks. They have also considered the relationship between the structural substrate of neuroanatomy and the more dynamic functional and effective connectivity, and pointed out how network analysis offers a way forward [9].

Recent studies have demonstrated that many natural networks, including anatomical and binarized functional networks of brain connectivity, have a small-world topology: dense local connections and a few long-range connections. In addition to low wiring cost, small-world topology is well suited both to segregation of processing in specialized areas (thanks to its high local connectivity) and to efficient integration across distributed nodes (thanks to its short characteristic length) [10]. Multivariate methods offer an alternative way of identifying networks, or simply reducing the dimensionality of the data. They use the spatiotemporal information of the entire dataset to extract patterns that vary independently from each other. Among the many methods proposed recently, independent component analysis (ICA) has become popular for data from both electroencephalography (EEG) [11] and fMRI [12].

Nikolaos Laskaris and I have adapted pattern analysis techniques to identify structure in single-trial responses

by analyzing finite segments of time series (rather than single time points) [13]. These were later combined with nonlinear analysis [14] to make fuller use of the timing information in single-trial regional brain activations. My colleagues and I have applied pattern analysis methods to study variability in single trial responses to the same stimulus. In one study, single trials were ordered in an MST according to responses to median nerve stimulation in the secondary somatosensory area. Further analysis showed that the connectivity between primary and secondary somatosensory cortices was very different for well-separated clusters of homogeneous single trials (located at the antipodes of the MST) [15]. In another study, a data-driven spatial filter was used to extract the single-trial responses to pattern-onset visual stimuli. Pattern analysis of the single trial responses for the dominant dipolar pattern of the MEG signal at 70 ms demonstrated that the polymorphic response to the simple visual stimulus was generated by a coupling of polymodal areas and cooperative activity in striate and extrastriate areas. Although single trials were clustered using pattern definition that was typically only 20–40 ms long, the coherence in the single trial responses within some clusters survived much longer, usually showing up as 2–3 full periods of an alpha wave beginning well before stimulus onset [16].

The aforementioned data-driven approaches deal only with functional connectivity. These methods should be distinguished from model-driven methods [17] that deal with effective connectivity, in which data fitting is used to select one from among several hypothesized models.

Measures of functional connectivity

Advances in multi-electrode recording techniques [18] and two-photon optical imaging [19] have enabled the recording of large populations of neurons, simultaneously resolving the activity of each one in each trial. It therefore becomes possible to explore how the activity of each neuron correlates to the activity of other neurons as a single stimulus is processed or a specific response is prepared [20]. Relevant results can be summarized as follows: intracranial recordings have shown that the firing of neurons can be very precise [21] and synchronous across many cells [22]. Recent two-photon microscopy imaging of fairly large neuronal populations has demonstrated precise spatial organization [19] and recurrence of sequences in active neurons [23].

Large-scale organization of brain function has been investigated with fMRI using both network analysis and multivariate feature-extraction methods. Graph theoretical analysis of fMRI data has revealed small-world topology [24•] that has similar clustering patterns to that seen in anatomical connectivity [25]. Damoiseaux and colleagues [26] used a variant of ICA to identify independent and across-subject patterns of activations in the resting fMRI data of ten subjects. They identified ten such patterns, each presumably representing well interconnected areas; these included motor and sensory function, memory, executive function and the so-called default-mode network [27].

Increases in the number of sensors, along with the advent of digital technology, have established EEG and especially MEG as the methods of choice for non-invasive study of brain dynamics [11,28]. These methods have been used with averaged data [29] or long time series (from many seconds to minutes of continuous MEG data) [30] to study interactions between a small pairs of areas. More recently, correlations between the time series of individual EEG or MEG sensors have been used to derive measures of 'large-scale connectivity' based on graph theory [31•,32•,33]. These studies have emphasized the topology of the functional networks at different frequencies. Significantly, these studies claim to find small-world topology in some [33] or all [31•,32•] of the frequency ranges studied. Comparisons of such global networks for control subjects and patients have produced mixed results. For example, Stam and colleagues have reported differences in functional connectivity for many frequency bands with MEG [34]. For EEG, they have reported changes in the beta band, described as a loss of small-world properties in Alzheimer's patients compared with controls [35•]. The validity of these conclusions is pivotal to how function relates to structure.

Measures of effective connectivity

Electrical microstimulation [36,37] and TMS [38] go beyond correlation to demonstrate causal efficacy by interfering with activity in a given area before or during perception or action. Recent studies have combined microstimulation or TMS with other techniques to map the spread of activity following focal perturbations. The results are particularly relevant to connectivity studies. For example, an fMRI study [39] that followed electrical microstimulation of the macaque area V1 not only identified the activations in the expected projection sites in extrastriate areas but also showed that the activated area within V1 was larger than expected, possibly reflecting functional spread through horizontal connections. In another study [40••], high-density EEG and TMS reported a breakdown in effective connectivity during sleep compared with the awake state.

Limitations of large-scale connectivity studies with EEG and MEG: technical issues

Among the plethora of methods for studying brain connectivity, only analysis of neuroimaging data using graph theoretical tools provides a description of large-scale connectivity. Although the application of these methods to anatomical and fMRI data have produced networks that have similar topology, the claim that similar topologies also exist in both the EEG and the MEG data has

created considerable excitement [41]. In this and the next section, I critically examine the technical and theoretical basis of recent large-scale connectivity studies using EEG and MEG data.

Generators in the brain produce complex EEG and MEG maps. A focal generator produces a strong signal that always influences nearby sensors, especially in EEG. Tangential focal generators (i.e. generators that have current density direction perpendicular to the line joining the center of the head and the generator location) produce dipolar patterns rotated by 90° to each other when using EEG and MEG. The dipolar pattern has extrema with opposite polarity spaced at increasing distance between sensors as the depth of the single source increases. Comparisons between pairs of signals generated by the activation of a single, focal, tangential generator would therefore always show 'local clustering' (i.e. high similarity for pairs of sensors close to the peaks of signal intensity) and 'long-distance connections' (i.e. highly linked activity between remote sensors at the two extrema of the dipolar EEG or MEG patterns). The activation of few (or many) uncorrelated generators will therefore produce a small-world topology in a network computed from the raw signal topography. Signal transformations of the EEG and MEG signals can be used to reduce this 'small-world artifact' at the expense of low spatial frequencies and sensitivity for deep sources [42,43].

A second concern regarding recent EEG and MEG studies of functional connectivity is the use of raw sensor signals across runs and subjects. For EEG, the use of sensor-based summaries has some justification: the strongest contribution to the signal is from radial sources directly below the electrodes, which are fixed onto the head according to the standardized 10–20 system, which scales according to the shape and size of the head. For MEG, referring to the same sensor information across runs and subjects cannot be justified. First of all, the extrema of the signal can be far away from the generators, and their precise location depends on the head position relative to the sensors. Using the same sensors across different runs or repetitions of continuous recordings (that often last for many minutes) cannot be justified without first specifying stability of the head location within and across runs. Even if the size of the head and relative position could somehow be matched across subjects, generators that correspond to the same brain area would still produce different MEG signals on the same sensors because of differences in the local cortical geometry for each subject.

A third concern about recent studies of functional connectivity is the use of connectivity measures that ignore the fine temporal detail of the signal and the directionality of connectivity. The aforementioned results from multi-electrode, microstimulation and TMS, and MEG research from my own group [15,44], all show that activity elicited by a stimulus arrives early in the primary sensory cortex and spreads within a few milliseconds to near and distant areas. In the next 100–200 ms, these areas are reactivated many times, presumably through mutual interactions and continuing input from the thalamus, cerebellum and brainstem. Connectivity patterns that correspond to fast interchanges of activity will not survive hemodynamic smoothing, and might also be eliminated in measures of similarity for which zero lag is computed over long time periods.

Limitations of large-scale connectivity studies using EEG and MEG: theoretical issues

Much of the current excitement over network models is based on their promise of a unified representation of brain connectivity. However, ascribing all types of brain connectivity to the network structures that have been theoretically well studied might be counterproductive. Even at the level of anatomical connections, the use of a single network that has undirected edges might be limited, for at least three reasons. First, our knowledge of connectivity in the macaque remains fragmentary at best, and is even more limited for the human brain. Second, the network studies reported so far are based on conspicuous connections, and largely ignore weaker connections and results from single axon tracings that show much richer laminar and inter-area connections [45]. Third, the anatomical networks are not static: they change rapidly over development, and also as a result of learning in adult life. Whether the latter occurs through the development of new connections or by the unmasking of silent synapses is still under debate. The use of binary graphs can nevertheless be broadly justified for anatomical connectivity, because at least the presence or absence of a strong connection can be unambiguously defined.

Functional connectivity poses a more challenging problem. The first challenge is to define what nodes and edges should really be. The sensors are obviously poor choices for nodes. It is also difficult to define unambiguously the boundaries of generators. Ignoring for the moment the aforementioned concerns, the results of network analysis suggest that the small-world topology is plausible for low-frequency functional connectivity, as derived from fMRI and electrophysiological data below the alpha rhythm. The evidence available so far about functional connectivity at higher frequencies is inconclusive, so it is prudent to consider a richer set of networks than the ones used to describe anatomy.

Measures of fast activity

My colleagues and I have previously demonstrated that magnetic field tomography (MFT) [46] can extract robust tomographic estimates of brain activity from each

snapshot of minimally processed MEG data [47]. Measures of functional connectivity between areas can then be obtained by computing the mutual information between time-delayed segments of the resulting regional activations [48]. Ideally, a network analysis should be based on mutual information estimates obtained from single-trial MFT solutions using a large number of nodes throughout the brain, which is a computationally demanding task. I have often used the less demanding computation of mutual information using the MFT solutions derived from the average MEG signal. This analysis is particularly effective in identifying influences in early responses and it has already demonstrated that the connectivity pattern depends on the properties of the stimulus [49] and where it is presented in the visual field (Figure 1) [50]. These results show that functional connectivity patterns are highly sensitive to task demands, and they agree with the expectation that the way a brain area responds depends on the status of other connected areas [51].

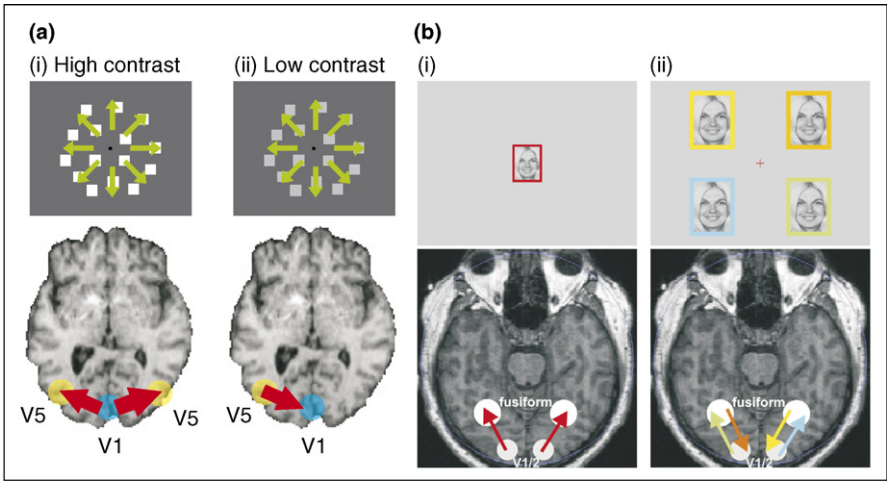
Mutual information analysis of single-trial MFT solutions has shown that brain function proceeds in stages, with each stage organized around one or more hubs — that is, brain areas that show not only high activity but also increased connectivity with other brain areas. Transitions between stages are often brought about by links from the hub of one stage to the hub of the next. Figure 2 shows an example of such transitions during the processing of facial emotional expression in the right hemisphere of normal subjects, and the absence of such organization in schizophrenic subjects [52,53].

The recent findings from multi-electrode recordings and two-photon imaging, as summarized in [18–23], and the identification of high-frequency oscillatory activity in response to strong stimulation of the median nerve [54] provide candidate physiological activity that can generate a measurable high-frequency MEG signal. MEG data from experiments that used visual cues to define planning, preparation and execution or inhibition of saccades were analyzed in my laboratory using high sampling and wide-band filters to include ubiquitous sharp transients in the raw signal [55]. Tomographic analysis of the data identified transient focal brain activations or 'MEG spikes'; these were widely distributed across the cortex, cerebellum and brainstem during cue presentations and saccades, and they showed sensitivity to task demands. The MEG spikes were organized into feedforward and corollary discharge sequences that could, when combined with the slower activity-linked processing in discrete brain areas over long periods, last hundreds of milliseconds. In new experiments [47], MEG-spike-triggered averaging was used to demonstrate that the MEG spikes correlate with background alpha oscillations that couple polymodal and primary sensory areas in the awake state. Figure 3 shows examples of this coupling and how it is reduced during sleep. MEG spikes might provide an ultra-fast communication channel in the brain that probably works below the conscious level but might underpin normal brain function.

Generalized networks and a correspondence principle

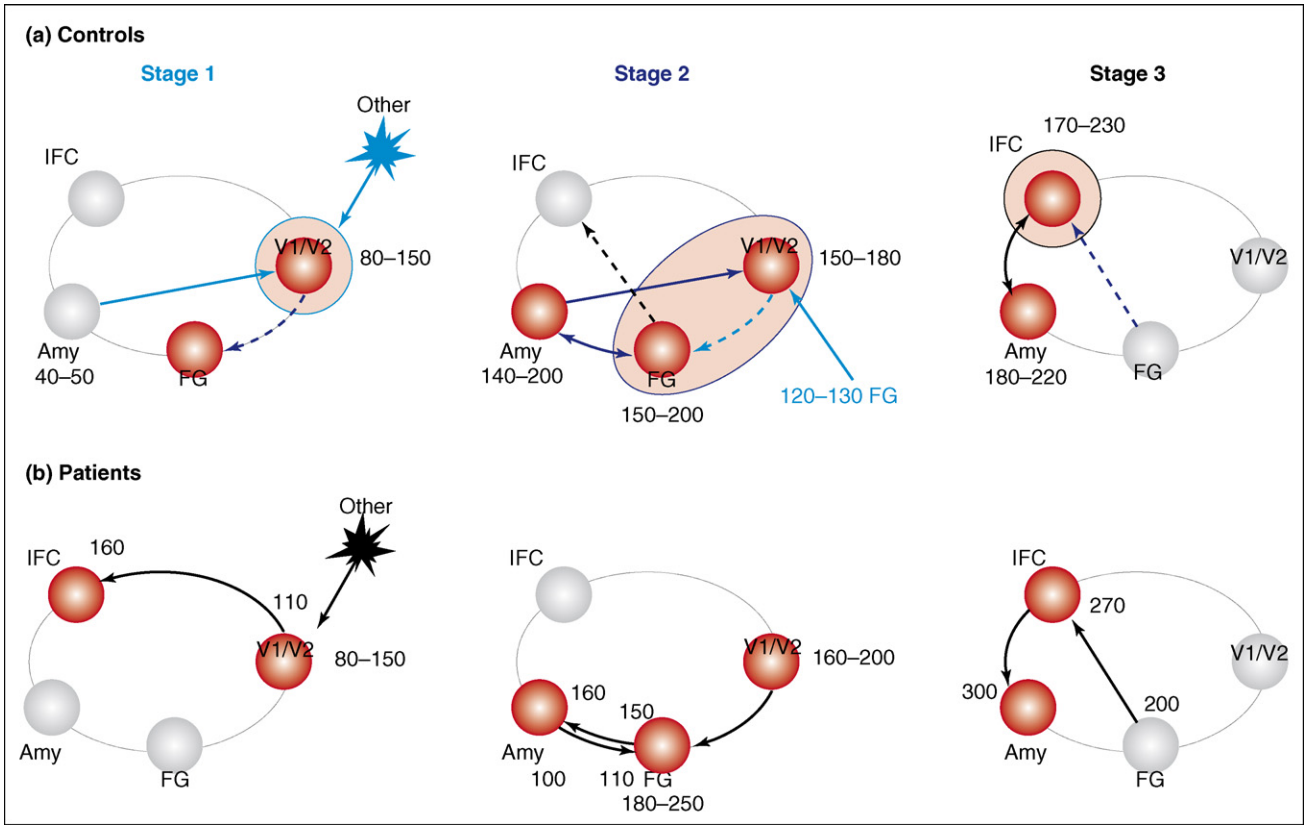
Area specificity and connectivity between areas are not static properties. Brain activity should be viewed in terms

Figure 1



Connectivity changes depending on stimulus properties and visual field presentation. **(a)** Using data from [49], the direction of dominant information flow between V1 and V5, derived from the patterns of evoked activity in these two areas, at high contrast (i) and low contrast (ii). **(b)** Functional connectivity (mutual information estimates of linked activity) between V1/V2 and the face fusiform area (FFA) for face stimuli presented either to the center (i) or to one of the four quadrants (ii) of the visual field. The dominant first-linked activity (arrow) is from V1/V2 to the FFA for stimuli in the center or the lower quadrants of the visual field, but from the FFA to V1/V2 for stimuli in the upper quadrants. The color of the frame for each stimulus corresponds to the color of the relevant linked-activity arrow. For more details, see [50].

Figure 2

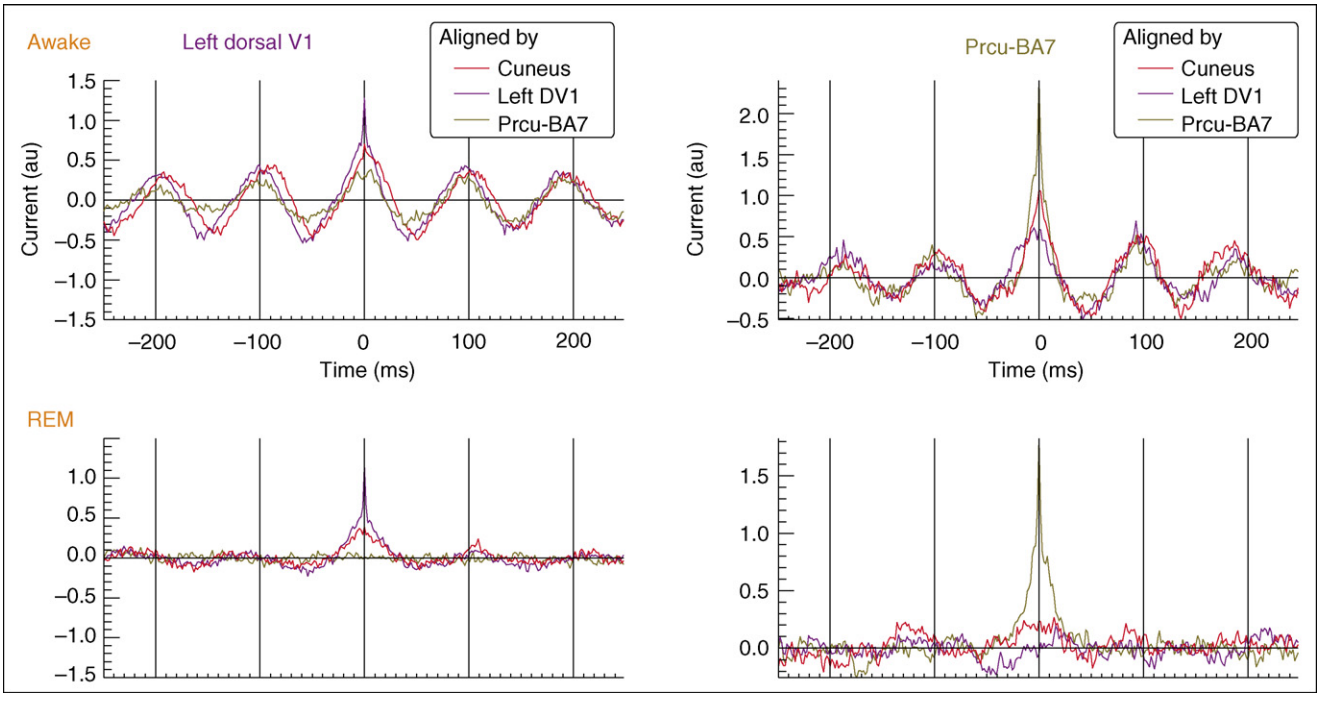


Bottom-up construction of time-dependent network activity. The single-trial activations are computed from the full magnetic field tomography (MFT) solutions, millisecond by millisecond, in four right-hemisphere areas known to be involved in the processing of faces or facial expressions of emotion: V1/V2, the fusiform gyrus (FG), the inferior frontal cortex (IFC) and the amygdalae (Amy). The mutual information is computed between all possible pairs of areas, using a 40 ms window from each time series and shifting it by a 4 ms window across the time axis of each time series in turn. The resulting two-dimensional map of linked activity has a threshold applied to it, leaving islands that describe links of finite duration between the two areas. Superimposing the 'thresholded' maps for different subjects produces a mutual information map of common links across subjects. A network (with directed edges) can then be defined by joining together all links that fall within a given latency window. The mutual information obtained from the analysis of the data of normal subjects shows three well defined stages of processing, with hubs as indicated here by highlighting and pale red shading: first V1/V2, then V1/V2 and the FG, and later still the IFC. To distinguish the stages, labels and arcs are in light blue for stage 1, deep blue for stage 2 and black for stage 3. The nodes (areas) participating in the links of the displayed stage are in red and others are in gray. Within-stage links are represented by solid arrows and links between hubs marking the transition between stages are represented by dashed arrows. Light undirected links between nodes are included as a reminder that links between these areas might be present but, if they exist, they are below the cut-off threshold. The numbers in the figure mark latencies from stimulus onset in milliseconds. For nodes, the period of activation is given by the start and end latencies. For arcs, the latency of the source node initiating the linked activity is placed at the tail and the latency of the target node at the head of the arrow. Part **(a)** shows the networks for each stage in normal subjects (controls); **(b)** shows that the links between areas for patients whose responses to faces and facial expressions show no such organization into stages. For more details about the timing, see [53].

of malleable processes across trials and even within a trial across time. Adequate description of connectivity might need a hierarchy of networks, rather than the relatively static networks that are used to describe anatomy and fMRI and PET data. Above the base level, virtual nodes and edges can form networks that have very different topologies. Networks at the same horizontal level might correspond to different tasks [56] or simply to different responses to identical stimuli.

In physics, the continuity of descriptions between the classical and quantum domains demands that quantum theory must approach classical theory in the limit of large quantum numbers. The fulfillment of this condition establishes a correspondence principle, namely the existence of a formal analogy between quantum and classical theories that can guide interpretation of the results from the new theory. I propose a similar correspondence principle as a guide for the interpretation of connectivity across levels. A continuity of descriptions should be possible between levels, so that (virtual) nodes and edges at a higher level can be related to nodes and edges at the next lower level, and thus eventually to well-defined anatomical areas and connections (Figure 4). For

Figure 3



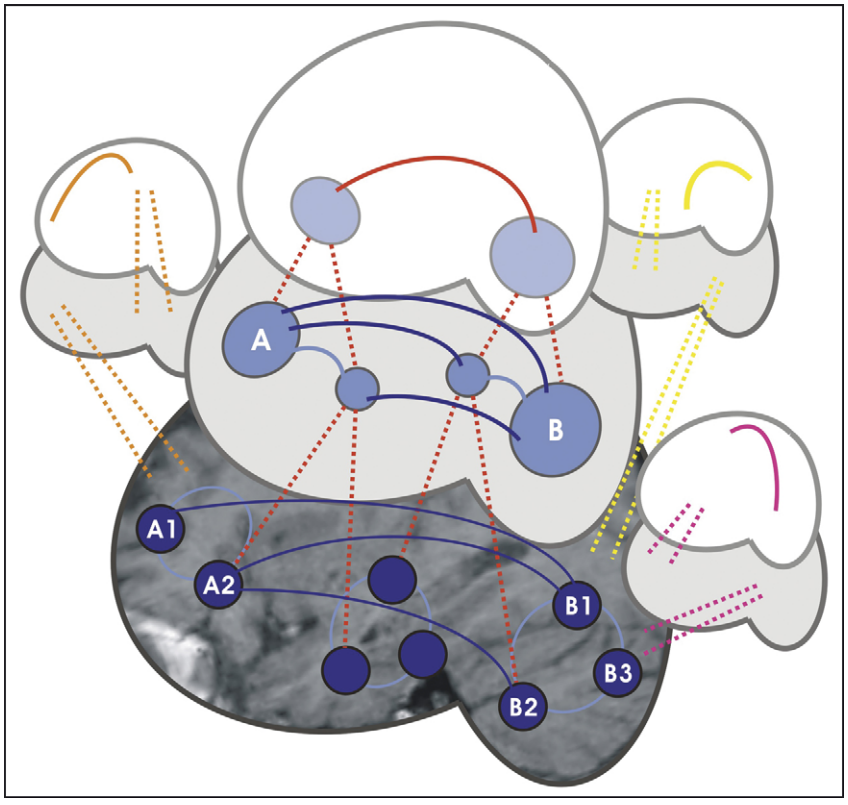
Magnetoencephalography (MEG) spike-triggered averaging reveals oscillatory dependence and coupling between areas. MEG spikes were identified in the cuneus, left dorsal V1 (Left DV1) and precuneus (Broadman's area 7; Prcu-BA7) from continuous real-time magnetic field tomography (MFT) estimates of activity of subjects during quiet wakefulness with eyes closed and during rapid eye movement (REM) sleep. For this analysis, data from the experiment described in [57•] were used. Averages in arbitrary units (au) were then constructed for the activity in the left dorsal V1 and precuneus after aligning the MEG spikes from each of the three areas. The MEG spikes are clearly identified at zero (time of alignment) in the area of alignment in both the awake condition and REM sleep. In addition, oscillatory activity in the alpha band is identified in left dorsal V1 and precuneus in the awake state and for all alignments. No oscillations are evident during REM sleep. The activity of the left dorsal V1 is still correlated with activity in the cuneus but not with activity in the precuneus.

example, virtual nodes at a higher level might combine areas that are anatomically distant in the cortex but that functionally are brought together by activity in structures such as the cerebellum [57•]. It might not always be possible to find such correspondences, either because of the underlying complexity or because current knowledge is inadequate.

The pattern analysis methods that Nikolaos Laskaris and I have described previously [13,14] can be used to guide construction and navigation across levels. Linked activity can be computed between all pairs of areas and all single trials, and used to construct the network at the base level. This would be a very difficult network to interpret, partly because of its complexity and especially because of the high trial-to-trial variability of each node. The overall organization becomes more apparent as separate networks are constructed above the base level, each corresponding to one of the homogeneous clusters identified by pattern analysis of the activity in one or more nodes. My colleagues and I have used pattern analysis methods to describe hidden regularities in the activity of nodes and to study connectivity in the auditory [58], somatosensory [15], visual [16] and oculomotor [55,59] systems.

To use this correspondence principle, it is necessary to aim consistently for localization accuracy that would enable fMRI and MEG foci of activity to be matched to anatomical areas that are well defined by distinct architecture and receptor signatures [60]. Recent results on MEG localization capability [44,47,61] from my team suggest that such a program is indeed within reach, and efforts to relate functionally delineated areas to cytoarchitectonic maps have already been made [62]. If a precise correspondence between functionally and anatomically defined areas could be established, it would become possible to test whether there is an anatomical connection that corroborates a functional connectivity link. The first such tests would probably use group comparisons of functional and anatomical connectivity measures. Eventually, comparisons must be made for individual subjects, possibly using a combination of MEG with new tracking techniques from diffusion tensor imaging [63].

Figure 4



The organization of structure and function of the brain might require a hierarchy of levels. The network at the base of the hierarchy can be related to anatomy and it is appropriate not only for anatomical networks but also for networks describing slow processes as measured by PET and fMRI, and possibly relevant for networks derived from slow EEG and MEG components below the alpha rhythm. As processes at faster scales are included, new virtual networks emerge. Virtual networks at the same level might correspond to responses to slightly different stimuli, or even a range of responses to the same stimulus depending on the state of the brain at the time. In the example, node A in the second level of the hierarchy emerges from the activity of nodes A1 and A2 and links between them. A similar relationship holds for node B in the second level and nodes and connections of nodes B1, B2 and B3 at the base level. The dotted lines between levels show the emergence of similar nodes and emphasize that a node at one level can contribute to the emergence of more than one node in the next level. The different colors in the dotted lines between levels help trace the virtual nodes and edges across different levels. Elements of networks high in the hierarchy should be related as much as possible to recognizable anatomical areas and connections by tracing their origin back to the base level of the hierarchy.

Conclusions

Recent advances mean that brain connectivity can be studied in detail using diverse methods. Some provide precise measures of activity of single neurons or populations of neurons, and also of how these activities correlate to each other. Others enable us to interfere with processing, and hence probe causal links between activity in a given area and function. Yet others provide us with measures of mass activity from which large-scale networks can be derived. Graph theory has shown that the small-world topology that has been demonstrated for anatomical networks is shared by large-scale networks derived from fMRI and PET data, and possibly from slow electrophysiological data. In interpreting the results, it is important to remember that in all cases, even for anatomy, the network descriptions are only approximations of the real systems. We suggest that a nested hierarchy of networks might be more suitable for capturing the rich connectivity of the brain than is the current generation of single binary graphs, especially for functional networks derived from EEG and MEG data, where some early conclusions might have to be revised.

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- •• of outstanding interest

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