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Review Article

Clustered Organization of Cortical Connectivity

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Abstract

Long-range corticocortical connectivity in mammalian brains possesses an intricate, nonrandom organization. Specifically, projections are arranged in 'small-world' networks, forming clusters of cortical areas, which are closely linked among each other, but less frequently with areas in other clusters. In order to delineate the structure of cortical clusters and identify their members, we developed a computational approach based on evolutionary optimization. In different compilations of connectivity data for the cat

and macaque monkey brain, the algorithm identified a small number of clusters that broadly agreed with functional cortical subdivisions. We propose a simple spatial growth model for evolving clustered connectivity, and discuss structural and functional implications of the clustered, small-world organization of cortical networks.

Index Entries: Rhesus macaque monkey; cat; cluster analysis; neural networks; cortical development; robustness; vulnerability; network function; small-world networks; scale-free networks; spatial growth.

Investigations of the global structural organization of neural systems connectivity are a fundamental starting point for understanding structure–function relationships in the brain. Previous work has demonstrated that cerebral cortical areas in mammalian brains, for instance that of the cat or the rhesus macaque monkey, are neither completely connected nor randomly interlinked. Instead, they show an intricate

specific organization, and various features of the cortical network arrangements have been described. For example, 'streams' of visual cortical areas are segregated functionally (Ungerleider and Mishkin, 1982) as well as in terms of their input, output, and mutual connections (Young, 1992). Topological sequences of areas indicate potential signaling pathways across the cortical networks (Petroni et al.,

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2001), and sensory cortical networks may also possess elements of a serial organization (Young et al., 1995). Alternatively, hierarchies of cortices can be constructed based on the laminar origin and termination patterns of the areas' interconnections (Felleman and Van Essen, 1991; Hilgetag et al., 1996; Hilgetag et al., 2000b). Moreover, cortical connectivity may be characterized by various structural network indices, such as symmetry, which describes the proportion of reciprocal connections of an area, and transmission, that is, the ratio of the number of local inputs to outputs (Kötter and Stephan, 2003). Also, a matching index can be computed that assesses the pairwise similarity of areas in terms of their specific afferents and efferents (Hilgetag et al., 2002). These indices are complemented by functional (entropic) measures such as 'segregation' and 'integration' that can be employed to evaluate distributed system performance (Sporns et al., 2000a).

In recent years, the field of network analyses has attracted considerable interest. This is based on the realization that many complex social, technical, or biological networks share characteristic features of their general organization. In particular, two main characteristic types of systems were identified, scale-free (SF) and small-world (SW) networks. SF networks (Barabasi and Albert, 1999) possess more highly connected nodes, or hubs, than randomly rewired networks with the same number of nodes and edges, leading to a power-law degree (edges per node) distribution. SW networks (Watts and Strogatz, 1998), on the other hand, are characterized by clustering of local neighborhoods (described by the clustering coefficient C , indicating the average fraction of the neighbors of a node that are *directly* connected), which is substantially higher than that in randomly wired networks of the same size. In addition, SW networks possess shorter average shortest path lengths (ASPs) than seen in strictly regular networks (e.g., lattices), but similar ASPs as in same-size random networks.

In the following investigations, we focus on corticocortical connectivity at the systems level, that is, long-range projections among cortical areas. There have been pioneering studies about the interconnections of different types of neurons at the level of intrinsic neuronal circuits, for instance, Gupta et al. (2000), and Kalisman et al. (2003). However, detailed information about connectivity at the cellular level, based on systematic sampling, is still largely missing. Nonetheless, long-range connections at the systems level may provide the structural scaffold for functional and effective connectivity (Friston, 1994) and be partly responsible for the neural activation patterns observed in studies of perception and cognition, for example, Büchel and Friston (1997).

While the moderate size of known corticocortical networks makes it difficult to decide directly if their node degrees follow a SF distribution, the existence of SW attributes in such networks can be more clearly tested. Indeed, the analysis of structural as well as functional connection data for mammalian cortical networks has shown that these systems can be described as SW networks (Hilgetag et al., 2000a; Sporns et al., 2000b; Stephan et al., 2000) (*see* Fig. 1). The SW organization implies the existence of local clusters, which are infrequently linked with each other. In fact, Watts and Strogatz originally derived the topology of SW networks from same-size networks with completely connected neighborhoods, by redistributing some of the links randomly within the network (Watts and Strogatz, 1998). Even with the knowledge that cortical connectivity is highly clustered (Fig. 1B), however, the actual structure of these clusters is still unknown. In the following two sections, we present an evolutionary optimization approach that addresses the problem of identifying the number and composition of cortical clusters. Subsequently, we propose a simple biological model for the generation of cortical network clusters, and in the last two sections of the paper

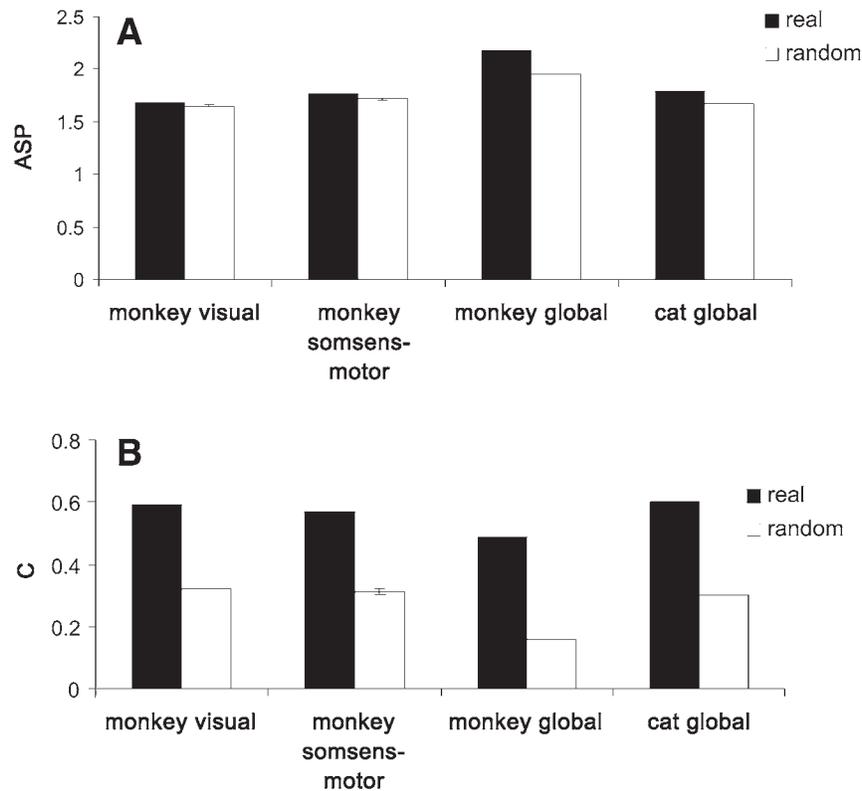


Fig. 1. Small-world characteristics of cortical networks in rhesus monkey and cat. Clustering and shortest path length indices were computed for data sets of monkey visual cortices (32 areas, 319 connections), monkey somatosensory and motor cortices (15 areas, 66 connections), as well as global compilations of monkey and cat cortical areas (73 areas, 834 links, and 55 areas, 891 connections, respectively). See Hilgetag et al. (2000a) for details. The same indices were calculated for data sets in which the connections were randomly redistributed among the areas ($n = 20$ for each network type). **(A)** All-pairs shortest paths (ASP) were similar in the biological and randomized networks. **(B)** Average local clustering (clustering coefficient C ; Watts and Strogatz, 1998) was much greater in cortical compared with randomized networks. Taken together, the two measures imply small-world features (Watts and Strogatz, 1998) in cortical systems networks.

discuss the structural and functional implications of clustered cortical connectivity.

Identifying Network Clusters

In order to identify the putative clusters in cortical network data, a computational approach based on an evolutionary optimization algorithm was proposed (Hilgetag et al., 2000a). This stochastic clustering approach appeared as a useful strategy, since the data available in the anatomical literature were high-dimensional, incomplete, and of an ordinal or

binary nature (listing only existence or absence of a connection), excluding alternative analytical approaches.

The approach was based on the rationale that in clustered network arrangements, areas should be more frequently connected within their respective clusters than with areas in other clusters. Consequently, a cost function was designed that consisted of two components whose sum was minimized. The components were defined as: $C1$ (attraction component)—the integer number of connections existing

between all different clusters, and $C2$ (repulsion component)—the integer number of absent connections *within* all clusters. The first component can be considered as an attraction force, since it is zero in the limit case in which only one global cluster, and no inter-cluster connections, exist. Minimizing the second component, on the other hand, tends to break up clusters, as it can be reduced to zero by an arrangement that consists of completely separate areas. By minimizing both components simultaneously, their opposing forces produce a global cluster arrangement, consisting of the most densely intra-linked groups of areas with comparatively fewer links to other clusters in the network. In addition, the cost components could be weighted to emphasize one or the other component of the cluster definition, and to influence the number of resulting clusters.

The component cost function was employed in an optimization algorithm that started with random cluster arrangements and gradually lowered the cost of candidate solutions through simple ‘mutations’ (alternatively: placing an area in a newly created cluster; merging an isolated area with a cluster; swapping two areas between their respective clusters). These mutations also served to increase or decrease the number of clusters in the global arrangement. As a result, an arrangement was obtained that simultaneously represented an optimal number of clusters as well as their optimal configuration. For further details of the approach, which may be flexibly employed in a variety of clustering problems, *see* Hilgetag et al. (2000a).

Structure of Cortical Clusters

The analyses delineated a small number of distinctive clusters in all cortical systems studied (primate visual, global primate cortical, global cat cortical, Hilgetag et al., 2000a); clusters could also be identified in the primate prefrontal cortex (Hilgetag and Barbas, 2003). By sufficiently increasing the weight of the

repulsion cost component during the optimization routine, the algorithm could also be steered to generate clusters that no longer contained any identified absent connections. These clusters, which consisted of three to ten areas were, therefore, maximally dense, and potentially completely connected, depending on the existence or absence of currently unknown links. Since they cannot be further decomposed into smaller clusters, such maximally connected sub-networks may be considered network ‘building blocks’ of cortical systems (Hilgetag et al., 2000a); cf., Milo et al. (2002) for an alternative concept of network building blocks, based on significant circuit patterns.

The identified area groupings largely agreed with functional cortical subdivisions (Fig. 2A). For instance, clusters found in the analysis of global cortical data consisted predominantly of visual, auditory, somatosensory-motor, or frontolimbic areas, respectively (Hilgetag et al., 2000a). More specifically, the clusters identified in the primate visual system closely followed the previously proposed visual streams. In agreement with the idea that structural connectivity clusters also correspond to functional cortical subdivisions, cluster analyses of semi-functional (neuronographic) connection data demonstrated the existence of functional processing clusters with broadly similar subdivisions (Stephan et al., 2000).

Development of Clustered Connectivity

Is the organization and formation of clustered structural and functional connections in cortical systems shaped by experience-dependent neural activity? Recent findings suggest that this may be unlikely, as the basic architectonic and connectional layout of the brain can be produced in the absence of neurotransmitter action (Verhage et al., 2000). Moreover, it would be expected that different individual experiences lead to the formation of specific

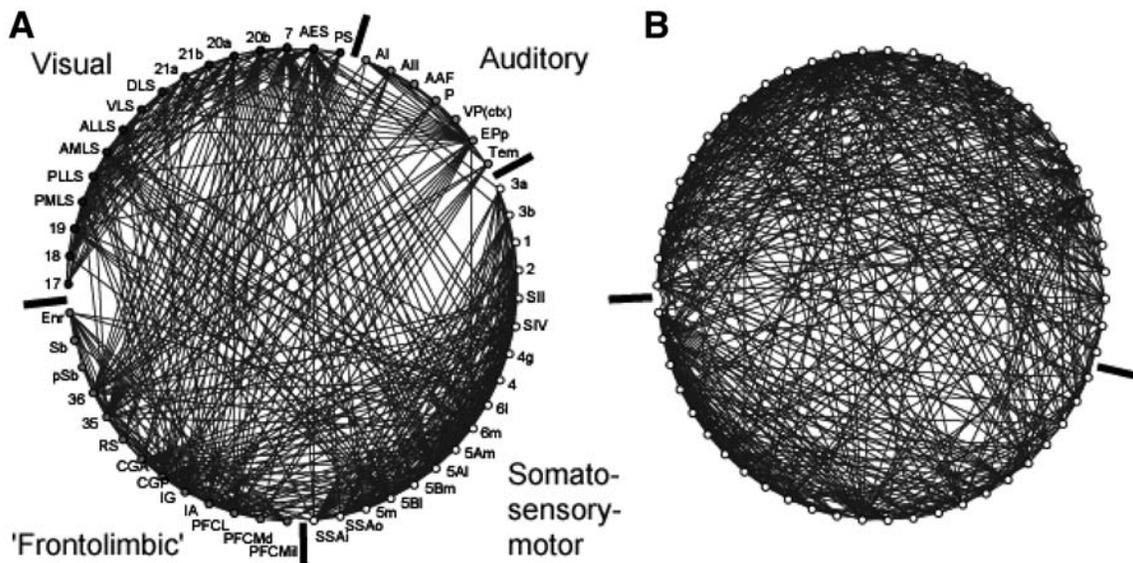


Fig. 2. Clustered structure of biological and simulated networks of cat corticocortical connectivity, based on Hilgetag et al. (2000a) and visualized by the Pajek program (<http://vlado.fmf.uni-lj.si/pub/networks/pajek/>). Bars indicate borders between nodes in separate clusters. **(A)** Cortical areas were arranged around a circle by evolutionary optimization, so that highly inter-linked areas were placed close to each other. The ordering agrees with the functional and anatomical similarity of visual, auditory, somatosensory-motor, and frontolimbic cortices. **(B)** A network of 55 areas generated by simulated cortical growth (Kaiser and Hilgetag, 2004b). Areas with similar connectivity were placed adjacently using the method of Non-Metric Multidimensional Scaling (NMDS) (Kruskal and Wish, 1978). In the upper and lower part of the diagram, highly connected, clustered regions can be identified.

patterns of connections in individual brains. However, the labeling of projections to the same cortical region in different subjects showed no instances where links (of substantial density) existed in some individual animals but not others, even though the density of corresponding corticocortical connections appeared to be highly variable (Hilgetag and Grant, 2000).

To explore alternative developmental mechanisms, we created a computational model for spatial network growth (Kaiser and Hilgetag, 2004c). In order to generate networks with distributed clusters, and SW properties as found in mammalian cortical connectivity (Fig. 1), the growth algorithm imposed limits for network growth (reflecting internal factors such as apoptosis factors or external borders such as the skull) and set the probability for forming new

connections such that it depended inversely on the metric distance between areas. Under these conditions, distant nodes with long-range connections to the existing network could still occur, though not frequently. These nodes were pioneers in so far sparsely populated regions, and areas placed nearby were likely to establish a connection to the pioneer nodes. Thus, the model was able to yield new clusters distant to the previously existing network (Fig. 2B). Both the clustering coefficient (Watts and Strogatz, 1998) and the average shortest path of generated networks were similar to those found in cortical networks in the monkey and cat. Interestingly, it was unnecessary to include chemical gradients or neural activity to generate these structural features in the model. However, such factors may be necessary for the functional differentiation

of cortical networks (Sur and Leamey, 2001). While our model demonstrated principal mechanisms by which the clustering of cortical networks may be explained, it did not replicate the specific cortical connectivity patterns found in mammalian brains. Future work will need to establish the exact factors that result in the specific cortical projection systems.

Structural Implications

Various technical and biological networks, such as a protein-protein interaction network (Jeong et al., 2001) were found to be robust towards random elimination of areas or connections (Barabasi and Albert, 1999). The presented cortical connectivity networks shared this feature (Martin et al., 2001) owing to the availability of many alternative pathways within clusters.

In networks composed of multiple distributed clusters, inter-cluster connections take on an important role. It can be demonstrated that these are the connections that occur most frequently in all shortest paths linking areas with one another (Kaiser and Hilgetag, 2004a). Such projections therefore may be of particular importance for the structural stability and efficient working of cortical networks, and we suggest that the modeling of essential network links (e.g., with the help of structural equation modeling, McIntosh et al., 1994) should focus on inter-cluster connections.

More generally, the frequency of a particular connection in all pairs shortest paths across a network is a useful measure for the impact of the connection's removal on network stability and efficiency. This correlation was much greater in cortical networks than in other biological networks (Kaiser and Hilgetag, 2004a). When connections used frequently in the shortest paths were removed from the network, a large impact on the average shortest path arose, indicating that no alternative paths with lower, or the same, length existed. This was owing to

both the existence of inter-cluster connections as well as the arrangement of connectivity within clusters.

Such an optimal connection placement ensures a low average shortest path length despite the existence of separate clusters. Also, a preliminary analysis of wiring length in the macaque cortex (Kaiser and Hilgetag, 2004b) suggested that the cortical network is optimized for low ASPs, rather than for other factors such as minimal wiring length.

In the absence of reliable structural connection data for the human brain, studies of monkey and other mammalian connectivity can help to extract essential features which may apply to both the animal models and human cortical connectivity. Such analyses may also help to identify determinants of structural connectivity, depending, for instance, on spatial proximity (Young, 1992) or architectonic type (Barbas, 2000; Hilgetag and Barbas, 2003) of the potentially linked cortical areas.

Functional Implications

Can clusters also be seen as a useful level of description for analyzing and modeling functional connectivity? Since the connectivity clusters found in several cortical systems tend to follow functional subdivisions of these systems, and as they are, moreover, broadly similar to clusters of semi-functional, neuronographic interactions (Stephan et al., 2000), it appears that structural clustering may underlie at least some cortical activation patterns. However, given the already very short path lengths between any two areas (typically, cortical areas are connected directly or via just one intermediate area, e.g., Hilgetag et al., 2000a), one wonders what additional benefit the connectional aggregation within clusters might bring. Sporns and colleagues (2000a) suggested that the distributed cluster structure of cortical systems is ideal for achieving high functional complexity, that is, an optimal balance between functional

integration and independence or specialization of different cortical areas. Alternatively, the close association of areas within clusters offers itself to efficient recurrent processing. Closed feedback loops between areas are very likely to occur, given the high probability for many short cycles in the system (Sporns et al., 2000b). The actual nature of recurrent activations, however, is still poorly understood. For example, different cortical projections frequently possess specialized morphology, and show characteristic patterns of laminar origins and terminations, arising and terminating in specific intracortical micro-environments. The functional role of corticocortical connections, and their clustered arrangement, therefore may become clearer once the integration of long-range projections with specific laminar circuits is better understood.

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