

High-cost, high-capacity backbone for global brain communication

Martijn P. van den Heuvel^{a,1}, René S. Kahn^a, Joaquín Goñi^b, and Olaf Sporns^b

^aDepartment of Psychiatry, University Medical Center Utrecht, Rudolf Magnus Institute of Neuroscience, 3905 GA, Utrecht, The Netherlands; and ^bDepartment of Psychological and Brain Sciences, Indiana University, Bloomington, IN 47405

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Network studies of human brain structural connectivity have identified a specific set of brain regions that are both highly connected and highly central. Recent analyses have shown that these putative hub regions are mutually and densely interconnected, forming a “rich club” within the human brain. Here we show that the set of pathways linking rich club regions forms a central high-cost, high-capacity backbone for global brain communication. Diffusion tensor imaging (DTI) data of two sets of 40 healthy subjects were used to map structural brain networks. The contributions to network cost and communication capacity of global cortico-cortical connections were assessed through measures of their topology and spatial embedding. Rich club connections were found to be more costly than predicted by their density alone and accounted for 40% of the total communication cost. Furthermore, 69% of all minimally short paths between node pairs were found to travel through the rich club and a large proportion of these communication paths consisted of ordered sequences of edges (“path motifs”) that first fed into, then traversed, and finally exited the rich club, while passing through nodes of increasing and then decreasing degree. The prevalence of short paths that follow such ordered degree sequences suggests that neural communication might take advantage of strategies for dynamic routing of information between brain regions, with an important role for a highly central rich club. Taken together, our results show that rich club connections make an important contribution to interregional signal traffic, forming a central high-cost, high-capacity backbone for global brain communication.

connectome | graph | tractography

Integrative brain function depends on neuronal signaling within a complex network of connections linking brain regions (network nodes), the human connectome (1–3). A large proportion of cortico-cortical axonal connections link neurons locally through means of intracortical (gray matter) and short-range white matter axons (4, 5). In contrast, only a small fraction of axonal connections are involved in global communication between distant parts of the network. This long-distance cortico-cortical connectivity, accessible on the macroscopic scale to noninvasive diffusion imaging and tractography, is the primary focus of our study. Not all brain regions contribute equally to the global structure of the network. So-called “brain hubs” display an above-average level of connectivity and are more centrally embedded (6–11). In addition to being individually highly connected (“rich”), brain hubs exhibit a strong tendency to link to each other, forming a structural core (6) or “rich club” (7). A rich club is defined as a subset of nodes maintaining a large number of connections across the network (i.e., high degree) while at the same time forming mutual connections with a density significantly greater than expected on the basis of their degree alone (12, 13). The brain’s cortical rich club was recently shown to consist of a selective set of frontoparietal hubs, including portions of bilateral precuneus and superior frontal cortex, together with regions overlapping the anterior and posterior cingulate cortex and the insula (7). Individually, these brain hubs engage in a wide range of behavioral and cognitive tasks and have been

implicated in efficient integration of information between remote parts of the brain (14–16). Their aggregation into a connected rich club suggests the hypothesis that rich club regions do not act as separate entities but instead operate as a single coherent collective, a focal and centrally embedded network, with rich club connections forming a connectivity backbone linking diverse sets of regions across the brain.

In this report we investigate aspects of network cost and communication capacity for rich club connections based on in vivo diffusion magnetic resonance imaging (MRI) measurements, in relation to their topology and spatial embedding in the human brain network. Large-scale rich club connections are shown to be relatively high cost, with a tendency to link regions across long physical distances. At the same time, rich club connections participate in a large number of short communication paths, thus carrying a high proportion of the brain’s signal traffic. Closer examination of the structure of these paths across the brain reveals a sequential organization suggestive of some efficient strategies for dynamic routing of interregional signals, with a central role for rich club connections.

Results

Rich Club Organization. Diffusion tensor imaging (DTI) data of 40 healthy subjects were used to map the large-scale connectivity structure of the brain network, parcellating the cortical sheet into 1,170 distinct evenly sized parcels and determining a group-averaged level of connectivity as the number of reconstructed streamlines between all parcels. A second set of 40 healthy subjects was used to replicate the findings of the principal dataset. Confirming an earlier report (7), the human connectome, mapped here in an independently acquired dataset, was again found to exhibit rich club organization, indicated by a significant tendency for highly connected hub nodes to show an above-random level of interconnectivity, with up to 40% more connectivity than expected by chance ($P < 0.05$, Bonferroni corrected, Fig. 1A). Confirming previous findings, the rich club comprised a set of spatially widely distributed brain regions (7, 17), including portions of the precuneus, anterior and posterior cingulate cortex, superior frontal cortex, superior parietal cortex and the insula, all in both hemispheres (Fig. 1B). All results reported here refer to the rich club with a degree $k > 10$ (Fig. 1A, other levels give

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Data deposition: The group connectivity matrices of streamline densities and lengths reported in this paper are publicly available at the Web site of the Dutch Connectome Laboratory, Rudolf Magnus Institute of Neuroscience, The Netherlands, http://www.myconnectome.nl/data_depository.html.

¹To whom correspondence should be addressed. E-mail: m.p.vandenheuvel@umcutrecht.nl.

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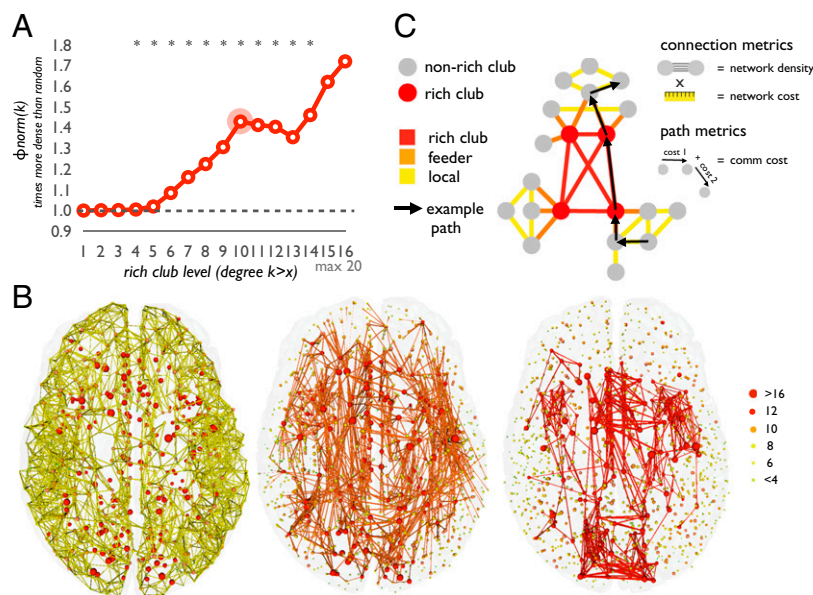


Fig. 1. (A) Rich club curve relative to random model, showing a rich club organization of the human connectome ($*P < 0.05$, Bonferroni corrected). The selected rich club level of $k > 10$ is indicated by a red circle. (B) Network representation of local (Left), feeder (Center), and rich club connections (Right). (C) Schematic illustration of local, feeder, and rich club connections.

similar results), comprising a total of 16% of the nodes and 12% of the (binary) edges of the network.

Physical Length. Nodes of the group network were divided into rich club and nonrich club nodes, and edges were divided into three topological categories (Fig. 1C): (i) “rich club connections (R)” linking rich club nodes, (ii) “feeder connections (F)” linking rich club nodes to nonrich club nodes, and (iii) “local connections (L)” linking nonrich club nodes to each other. Statistical analysis revealed differences in connection lengths between topological classes. Rich club connections were found to be significantly longer than feeder and local connections [$P = 0.0002$ and $P = 0.0002$ for local and feeder connections, respectively, 10,000 permutations; mean (SD) rich club connections, 37 (38) mm; feeder connections, 26 (23) mm; local connections, 19 (9) mm]. When dividing connections into short (<30 mm, 81% of all connections), medium (30–90 mm, 17%) and long-distance connections (>90 mm, 2%), large proportions of long-distance connections were found to be rich club (48%) and feeder (38%) connections, indicating their strong involvement in long-distance connectivity (Fig. 2A). Examining the weights of the connections in the three distance classes revealed that network density (i.e., streamline count) of long-distance rich club connections was significantly higher than that of long-distance nonrich club connections, underscoring the high-cost aspect of long-distance rich club connections ($P = 0.0002$ and $P = 0.0012$ compared with local and feeder connections, respectively; 10,000 permutations).

Network Density and Network Cost. Rich club tractography streamlines were found to include 15% of the total network density, defined as the number of streamlines detected by tractography across the whole brain, but accounted for 24% of the total network cost, defined as the number of streamlines multiplied by their physical length. This percentage results in a cost/density ratio of 1.6 for rich club connections, relative to 1.1 and 0.8 for feeder and local connections, respectively (Fig. 2*B*).

To visualize the spatial arrangement of rich club, feeder, and local connections, Fig. 2C depicts a graphical representation of the group connectome with brain regions (1,170 nodes) arranged on a circle. The ordering of nodes along the circle's perimeter was

determined by an optimization algorithm based on simulated annealing (*SI Materials and Methods*). This algorithm attempts to rearrange the nodes of the network such that most of the connections are placed along the circle's perimeter. Taking the elements of the input matrix as the inverse of network cost (i.e., density times physical distance), this procedure resulted in placing nodes linked by low-cost connections in close proximity on the ring (e.g., nodes linked by short connections representing cortico-cortical U-fibers) and nodes linked by high-cost connections farther

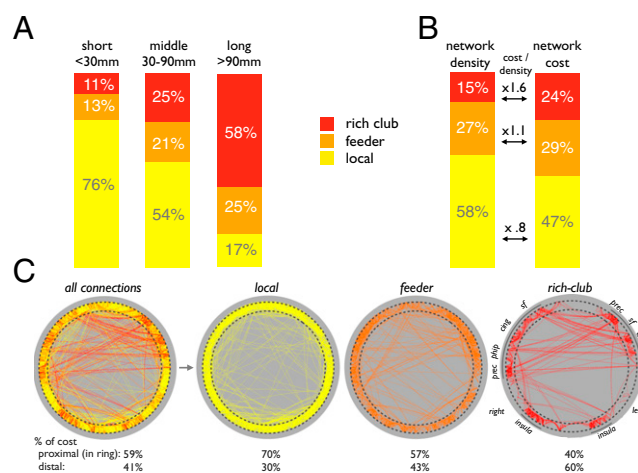
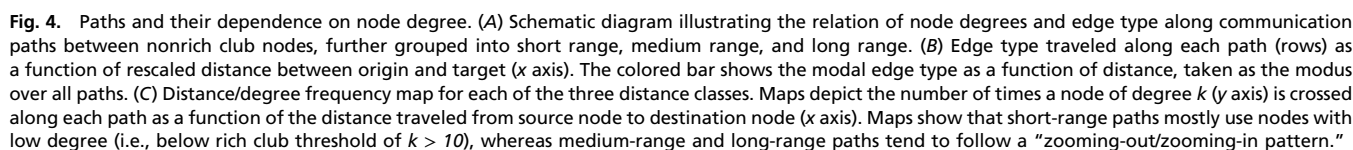


Fig. 2. (A) Proportions of short- (<30 mm), medium- (30–90 mm), and long-range (>90 mm) connections belonging to different topological classes. (B) Contributions to network density and network cost of local, feeder, and rich club connections. (C) Nodes are depicted on a ring, organized according to minimization of the inverse of network cost, placing nodes of low connectivity cost in close proximity on the ring (*SI Materials and Methods*). “% of cost” expresses the proportion of total network cost taken on by connections in close proximity on the ring (proximal) and by connections placed on different parts of the ring (distal connections). cing, posterior and anterior cingulate cortex; insula, insular cortex; phip, parahippocampal; prec, precuneus; sf, superior frontal cortex.



The rich club was found to constitute a high-cost, high-capacity feature of brain connectivity. Rich club tractography streamlines composed a relatively small proportion (15%) of the total network density, but consumed a disproportionately large share (24%) of the total network cost (Fig. 2B). Concordantly, rich club connections were found to span larger physical distances than feeder connections and local edges (Fig. 2A and C), interconnecting the spatially distributed members of the rich club. Sixty-nine percent of all communication paths were found to pass through the rich club, and rich club connections together with connections feeding pathways into the rich club accounted for 77% of the total communication cost between all brain regions (Fig. 3A). The central role of rich club connections in global brain communication is further underscored by their high prevalence in communication paths (Fig. 3B), in particular those paths that span medium and long distances (Fig. 4). All metrics related to network density and network cost are greatly reduced in random networks that preserve node degrees but degrade

Our findings support the idea that neural architecture is organized to achieve a high level of global information integration along short communication paths (14, 15), while at the same time conserving material resources such as metabolic energy and wiring volume (22–25). Previous analyses of connectivity in nonhuman primates suggested that long-distance projections, although violating strict minimization of wiring volume, act as long-distance shortcuts, ensuring high levels of global information integration while lowering the number of processing steps during communication (26). These shortcuts may confer important advantages, as a lower number of communication steps shortens transmission

delays, facilitates synchronous information processing, and reduces noise during communication, which apparently offsets their higher network cost. Classic “small-world” models (27) incorporate random shortcuts to achieve high efficiency while maintaining high local clustering and thus conserving cost. Elaborating on this, our findings now suggest that the brain is organized as a “rich-world” network with high-degree nodes that support a coherent and interconnected system of long-distance projections whose cost is offset by attracting a high volume of interregional signal traffic.

In our analysis, network cost and communication cost of connections and paths were defined as the number of streamlines multiplied by their physical length, thus representing an aspect of cost related to the network’s spatial embedding (26, 28, 29). This definition of cost assumes that cost is proportional to axonal volume (24, 26), here estimated as the product of streamline density and length. Although neurobiological interpretations of streamline density remain uncertain (30), several studies combining diffusion MRI and histology have demonstrated good overlap between pathways identified by tractography and tract tracing (31–33), as well as an association between streamline density and tract volume (34, 35). More specific estimates of axonal volume may become possible with more sophisticated measurements of axonal microstructure, including variations in the diameter of myelinated axons (36). Future enhancements of high-resolution diffusion imaging may thus allow further refinement of cost-based analyses of brain connectivity.

Methodological limitations inherent to computational streamline tractography likely lead to an underestimation of the density of long-range connections, because longer tractography streamlines are more difficult to complete (37). This underestimation can result in missing connections, for example interhemispheric pathways interconnecting homotopic regions, which are generally underrepresented in diffusion imaging, including in our study (Figs. 1*B* and 2*C*). With respect to our analysis, this underestimation of long-distance tracts likely leads to an underestimation of the contribution of rich club connections to network cost and, given their physical length, an underestimation of their cost/density ratio and overall contribution to global brain communication. Indeed, recomputing streamline density favoring longer streamlines (by linearly adjusting the density of a fiber streamline according to its length) further increased the contribution of rich club connections to overall communication cost (communication cost/density ratio: rich club, 2.58; feeder, 1.12; local, 0.13). Eliminating streamline density altogether, we also examined a binary representation of the brain network by using only information on the presence or absence of pathways. The analysis again resulted in a disproportionately high contribution of rich club and feeder connections to global communication cost (communication cost/density ratio: rich club, 2.44; feeder, 1.44; local, 0.53). Considering that intracortical and very short-range connectivities were not measured with DTI, future studies examining the local connectivity profile of rich club regions may be of particular interest, by clarifying their contribution to overall network and communication cost.

The global structure of brain communication showed a prevalence for shortest communication paths to follow an ordered sequence of nodes that fed into, then traversed, and finally exited the rich club (following an “L-F-R-F-L” path motif; Fig. 3*C*), while passing through nodes of increasing and then decreasing degree (Fig. 4*C*). Our observation of a “zooming-out/zooming-in” structure of shortest paths suggests a role for the high-degree rich club to facilitate neural communication, as it allows distant brain regions to take advantage of degree-based “greedy routing” strategies. In technological and transportation networks greedy routing refers to a strategy for efficient navigation where steps along a path are selected on the basis of local information only, without knowledge of the global structure of the network (38, 39). The brain likely represents another example of a system

where individual elements, be they regions or neurons, can access only local information about connectivity and hence cannot select shortest communication paths on the basis of global knowledge about the brain’s topology. Each minimally short communication path represents a unique and optimally efficient sequence of nodes and edges that is vastly outnumbered by longer alternative routes between source and target. Hence discovering optimally short paths in the absence of global knowledge is a demanding task and constitutes a key problem for navigation and routing in many complex networks. Selecting paths through means of local information, such as through means of greedy routing (38) and/or through means of a mixture of degree-based and similarity-based routing (39), has been shown to be a fruitful strategy for navigation in these systems. Our findings show that a large proportion of the most efficient communication paths, particularly those crossing long distances in the brain, appear to be routed toward and through the rich club along ordered sequences of nodes and edges. In this context, we propose the hypothesis that the brain’s connectivity structure, and in particular its central rich club, is organized to facilitate or promote a variant of degree-based routing of neuronal information. Future studies examining in more detail which strategies drive communication in the brain are of fundamental interest to understand how neurons and brain regions can exchange signals efficiently, in the absence of global knowledge of the brain’s structural connectivity.

Taken together, examining the topology and spatial embedding of the rich club, our findings suggest that rich club connections constitute a feature of human brain connectivity that results from a trade-off between conserving material resources and boosting dynamic performance. Because rich club connections link spatially distributed and remote hub nodes, their overall network cost is high, but this high cost is offset by their disproportionately large contribution to efficient communication. Rich club connections compose a densely interconnected backbone whose central position in the network suggests that it attracts, transforms, and disseminates a large proportion of signal traffic among remote brain regions. Disruption of this “rich club backbone system” may have significant impact on the brain’s functional integrity.

Materials and Methods

A detailed description of the included subject data and the diffusion data preprocessing steps is provided in *SI Materials and Methods*.

Rich Club Detection. The so-called rich club phenomenon in networks is said to be present when the high-degree nodes of a network tend to be more densely connected among themselves than expected by chance (12). The rich club was identified by comparing the density of connections among nodes with a minimum degree k to the density found in randomized networks preserving degree sequence. Formally, the rich club coefficient $\phi^w(k)$ is given by (13)

$$\phi^w(k) = \frac{W_{>k}}{\sum_{l=1}^{E_{>k}} w_l^{\text{ranked}}} \quad [1]$$

with $E_{>k}$ denoting the subset of edges between the nodes with a degree $>k$, $W_{>k}$ denoting the total sum weights of this subset, and w_l^{ranked} denoting the ranked collection of weights in the network, with weights W representing the number of streamlines (network density) of the edges (7). $\phi(k)$ was normalized relative to the rich club coefficient ϕ_{random}^w of a set of comparable random networks ($n = 10,000$) of equal size and degree sequence, giving a normalized rich club coefficient ϕ_{norm} (12) (*SI Materials and Methods*).

Connection Metrics. Network density was defined as the number of tractography streamlines and thus captured an aspect of network topology. Network cost was defined as the number of streamlines multiplied by their physical length, thus representing an aspect of cost related to the network’s spatial embedding (26, 28, 29).

Path Metrics. Communication cost was based on the path length (topological distance) between any node i and any node j in the network. First, all unique shortest paths between all $n = 1,170$ nodes in the network were traced. Second, the total communication cost of the shortest path between nodes i and j was computed as the sum of the product of the physical lengths and density (i.e., number of streamlines) of the edges that were used while traveling from node i to j in the network. Subsequently, for each path, the proportion of the total communication cost spent on rich club, feeder, and local connections was computed. Once aggregated across all paths, the communication cost expresses the total amount of signal traffic carried along each edge of the network, taking into account its density, its length, and the number of short paths it supports.

Path Motifs. All shortest communication paths were classified according to the type (R, F, and L) and sequence of connections passed. We refer to each class as a path motif due to its conceptual resemblance to motifs in graph theory (40). A path motif reflects a specific sequence of edge types that a path crosses when traveling between the source and the target node. For

example, the motif R-F-L represents paths that sequentially pass edges of type R, type F, and finally type L, including paths consisting of three edges (RFL), paths consisting of four edges (RRFL or RFLFL), paths consisting of five edges (RRRFL, RRFLFL, etc.), and so on (see Fig. S2 for examples of path motifs). Note that some sequences of edges are impossible due to the definition of edge types (e.g., RL or RFFL). Path motifs with a frequency exceeding 1% were compared with a population of 1,000 random networks. This population of random networks yielded a null distribution of the number of times a path motif occurs in a network with a random topology. Using this null distribution, each path motif was assigned a P value, expressing the percentage of random values that were found to be more extreme.

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