RESEARCH ARTICLE

How to Direct the Edges of the Connectomes: Dynamics of the Consensus Connectomes and the Development of the Connections in the Human Brain

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Abstract

The human braingraph or the connectome is the object of an intensive research today. The advantage of the graph-approach to brain science is that the rich structures, algorithms and definitions of graph theory can be applied to the anatomical networks of the connections of the human brain. In these graphs, the vertices correspond to the small (1–1.5 cm^2) areas of the gray matter, and two vertices are connected by an edge, if a diffusion-MRI based workflow finds fibers of axons, running between those small gray matter areas in the white matter of the brain. One main question of the field today is discovering the directions of the connections between the small gray matter areas. In a previous work we have reported the construction of the Budapest Reference Connectome Server http://connectome.pitgroup.org from the data recorded in the Human Connectome Project of the NIH. The server generates the consensus braingraph of 96 subjects in Version 2, and of 418 subjects in Version 3, according to select-able parameters. After the Budapest Reference Connectome Server had been published, we recognized a surprising and unforeseen property of the server. The server can generate the braingraph of connections that are present in at least k graphs out of the 418, for any value of $k = 1, 2, . . ., 418$. When the value of k is changed from $k = 418$ through 1 by moving a slider at the webserver from right to left, certainly more and more edges appear in the consensus graph. The astonishing observation is that the appearance of the new edges is not random: it is similar to a growing shrub. We refer to this phenomenon as the Consensus Connectome Dynamics. We hypothesize that this movement of the slider in the webserver may copy the development of the connections in the human brain in the following sense: the connections that are present in all subjects are the oldest ones, and those that are present only in a decreasing fraction of the subjects are gradually the newer connections in the individual brain development. An animation on the phenomenon is available at https://youtu.be/yxlyudPaVUE. Based on this observation and the related hypothesis, we can assign directions to some of the edges of the connectome as follows: Let G_{k+1} denote the consensus connectome where each edge is present in at least $k + 1$ graphs, and let G_k denote the consensus connectome where each edge is present in at least k graphs. Suppose that vertex v is not

connected to any other vertices in G_{k+1}, and becomes connected to a vertex u in G_k, where u was connected to other vertices already in G_{k+1}. Then we direct this (v, u) edge from v to u.

Introduction

The Human Connectome Project [1] has produced high-quality MRI-imaging data of hundreds of healthy subjects. The enormous quantity of data is almost impossible to use in brain research without introducing some rich structure that helps us to get rid of the unimportant details and allow us to focus on the essential data in the set. We believe that the braingraph or the connectome is such a structure to apply.

The braingraphs or connectomes are discretizations of the diffusion MRI imaging data. Being a graph, it has a set of vertices and some pairs of these vertices are the edges of the graph. Each vertex corresponds to a small (1–1.5 cm^2) areas (called Regions of Interest, ROIs) of the gray matter, and two vertices are connected by an edge, if a diffusion-MRI based workflow finds fibers of axons, running between those ROIs in the white matter of the brain. In other words, the braingraph concentrates on the connections between areas of gray matter (this is an essential part of the data) and forgets about the exact spatial orbits of the axon-fibers, running between these gray matter areas in the white matter of the brain (these are the unimportant part of the data). The braingraphs may record the length or the width of these fibers as edge-weights but definitely does not contain any spatial description of their orbit in the white matter.

An important question is the determination of the direction of the graph—or connectome—edges in these braingraphs. By our knowledge, the present diffusion-MRI based workflows have no data showing the direction of the neuronal fiber tracts between the ROIs.

Hundreds of publications deal with the properties of the human connectome every year (e.g., [2–5], but very few analyze the common edges and the edge-distributions between distinct subjects and distinct brain areas [6, 7]. In [7] we have mapped the inter-individual variability of the braingraphs in different brain regions, and we have found that the measure of the variability significantly differs between the regions: there are more and less conservative areas of the brain.

Results

In the construction of the Budapest Reference Connectome Server http://connectome.pitgroup.org [6] not those edges were mapped that differ [7], but, on the contrary, those that are the same in at least k subject's braingraphs, for $k = 1, 2, \ldots, 418$. These parametrized consensus-graphs describe the common connectomes of healthy humans, parametrized with k.

For $k = 418$ we get only those edges that are present in all the 418 braingraphs. For $k = 1$ we get those edges that are present in at least one braingraph from these 418. Therefore, if we change the value of k, one-by-one, from $k = 418$ through $k = 1$, we will have more and more edges in the graph (Fig 1).

We have observed that the order of the appearance of the new edges when we were decreasing the value of k from 418 through 1, is not random at all. More precisely, it resembles a growing shrub: the newly appearing edges are usually connected to the already existing edges. This phenomenon is observable in the animation at https://youtu.be/yxlyudPaVUE. The same observation was done in Version 2 (with 96 braingraphs) and Version 3 (with 418, 476 and 477 braingraphs, depending on the fiber-numbers selected) of the server.

We call this phenomenon "Consensus Connectome Dynamics", and abbreviate it by CCD.
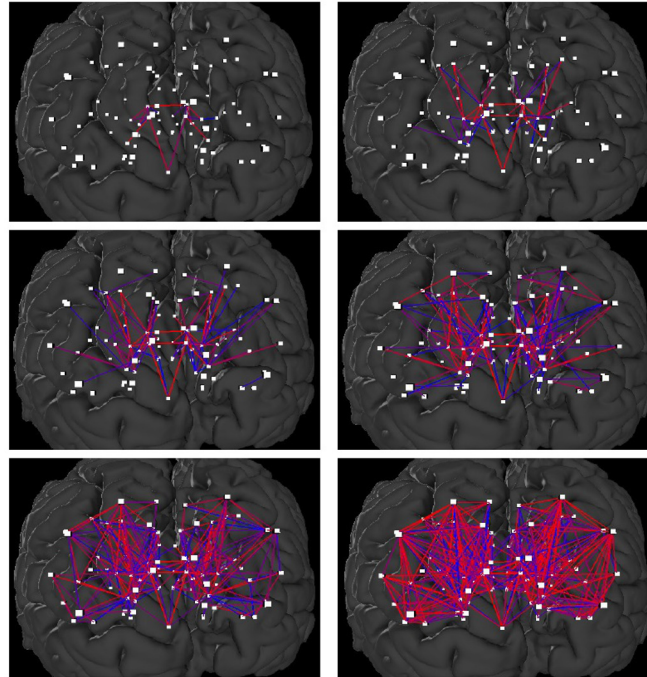
Fig 1. Snapshots on the shrub-like structure of the Budapest Reference Connectome Server v2.0. The edges of the smallest graph can be identified easily with using the webserver. For example, the edges that are present in all braingraphs include edges between Right-Caudate and Right-Pallidium, Left-Thalamus-Proper and Brain-Stem, Right-Thalamus Proper and Right-Putamen.

Discussion

Comparison with the random model

The observation is verified by Fig 2, made for the Version 3.0 of the server, with 418 brain-graphs. For steps $\ell = 0$ through $\ell = 417$, for $k = 418 - \ell$, we have visualized the sum of the
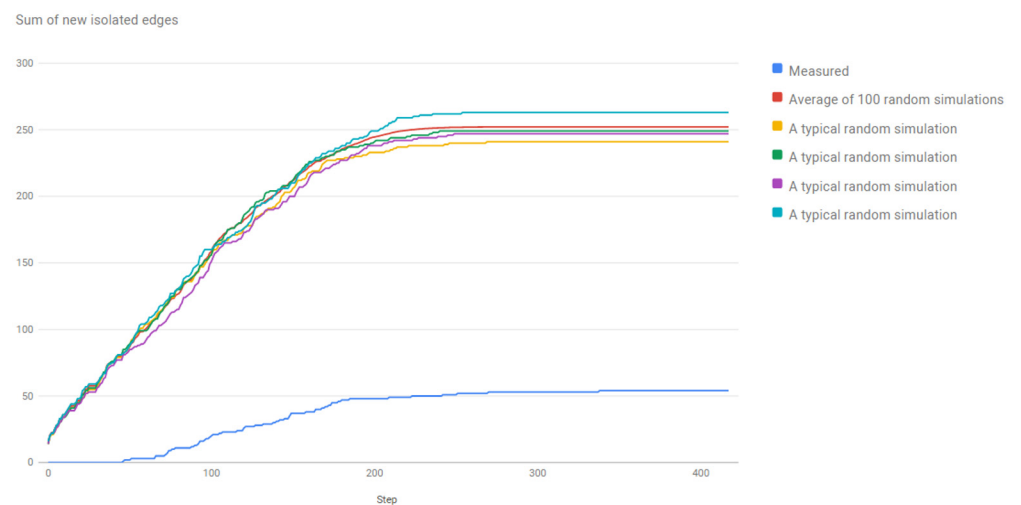

Fig 2. The comparison of the random simulation and the real buildup of the edges in the Budapest Reference Connectome server v3.0.

numbers of those new edges (that were present in k connectomes, but were not present in $k + 1$ connectomes), which connect two vertices, which were not adjacent to any edges before (i.e., they were isolated vertices). We have compared

- a random model, where exactly that many new edges were added randomly in uniform distribution, as in the graph generated by the Budapest Reference Connectome Server,

- and the graph of edges drawn by the Budapest Reference Connectome Server.

In the random model, in each step, the same number of edges were added to the graph randomly (independently, in uniform distribution), as the number of new edges in that step in the Budapest Reference Connectome Server. Clearly, in the random model, dramatically more new edges appear that are not connected to the old ones.

Component tree visualization

Another visualization of this surprising phenomenon is the component-tree of the evolving graph, made for Version 2 of the Budapest Reference Connectome Server with 96 braingraphs. As k decreases from 96 to 1, zero or more new edges are added to the existing graph in each step. In the step corresponding to k, those edges appear that are present in exactly k graphs. This may result in the forming of new connected components, and/or the merging of some older components of the graph. The phenomenon can be visualized on a graph-theoretical hierarchical tree, called component tree.

In this subsection we describe the construction of the component tree. In order to clarify when we are talking about the component tree and when about the growing braingraph, we call the vertices of the component tree "nodes" and the vertices of the braingraph "vertices".

In this component tree, nodes correspond to the components of the building graph: a single-vertex component (i.e., isolated vertex) is denoted by a node with the anatomical name (we call it an anatomically named node), and if more than one vertex form a component, then the multi-vertex component is denoted by a node with a positive integer number (we call it a numbered node). See Fig 3. Multi-vertex components are connected recursively to the components they are formed from. Therefore, numbered nodes are either connected to other numbered nodes or anatomically named nodes; anatomically named nodes are never connected to each other. The node corresponding to the newly appearing multi-vertex component is labelled by the next available positive integer. Consequently, if two numbered nodes are connected by an edge in the component tree, then the node with the smaller label was formed before (i.e., with larger k) the node with the larger label; if they are connected, then the components corresponding to them were not born in the same k-decreasing step. Let us consider a node labeled by number s. The children of this node are its anatomically named neighbors and its numbered neighbors with smaller label than s. If u is a child of v, then v is a parent of u. A parent node is always a numbered node.

We can also assign colors to the nodes according to the following scheme: If a new component of at least two vertices is formed in a k-decreasing step from isolated vertices, such that none of the vertices of the component is connected to older components, then the new component gets a new color (i.e., the numbered node and the anatomically labelled nodes all get the same new color). If isolated vertices get connected to an existing component X, then the new component and the isolated vertices inherit the color of component X. In general, the parent node gets the color of its child node corresponding to the largest merged component.

For example, on Fig 3, in the upper left corner, the lh_rostralmiddlefrontal_1 and the lh_medialorbitofrontal_4 nodes form component 56 (here component 56 is actually the
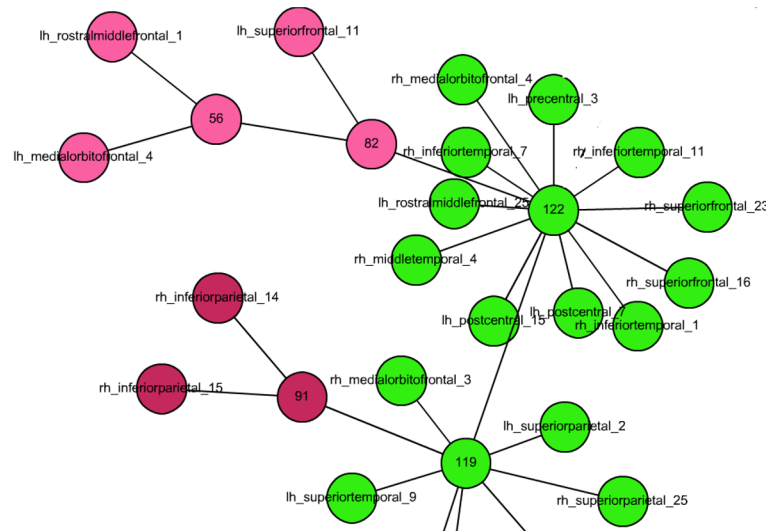
Fig 3. A very small detail from the large component-tree, available at http://pitgroup.org/static/graphmlviewer/index.html?src=connectome_dynamics_component_tree.graphml.

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component in the building graph corresponding to the node 56), then lh_superiorfrontal_11 is connected to node 56, forming component-node 82; node 82 inherits the color of the 2-node component 56. Then component 82 is merged with component 122, and since the largest child of node 122 is 119, and it is green, node 122 will also become green.

The component-tree of the graph is visualized on a very large, labeled interactive figure at the site http://pitgroup.org/static/graphmlviewer/index.html?src=connectome_dynamics_component_tree.graphml. One can easily observe that the largest component is colored by green, and this is the component that "attracts" all nodes (colored by green) and non-single vertex components (non-green colored).

The development of brain connections and the Consensus Connectome Dynamics

We hypothesize that those edges that are contained in many of the graphs were developed in an earlier stage of the brain development than those that are present in fewer subjects. As a possible explanation, we think that those neurons that connect to the developing braingraph at https://youtu.be/yxlyudPaVUE will not receive apoptosis signals (or the withdrawal of the neuronal growth factor) [8–10] and will survive, while other neurons, which are not connected to the vertices of the older graph, will be eliminated. Other authors have found that if the axon does not connect to the dendrites of the target cell, then it retracts and searches for the proper cell to connect to [11]. Postsynaptic activity (that is, the activity of neurons to which the axon connects to) could be also a factor showing that the axon has reached its target [11]. These postsynaptic activity could be more natural in the already "networked" neurons than in those without any connections to other neurons; that is, in the neurons with live axonal connections to other neurons. Therefore, we hypothesize that the direction of the axonal growth is from the non-connected neurons to the already connected ones in the growing graph.

In other words, we assume that the connections that are present in almost all braingraphs (c.f., upper left panel of Fig 1) were developed first. Next, new connections were developed, but those neurons whose connections were disconnected from these oldest neurons were

eliminated [8–10] or their axons retracted and re-directed [11]. Next, new neuronal connections were developed, but only those axonal connections remain active that were connected to the building network, since in those neurons there are postsynaptic activity. Since the deviation between the new edges among the subjects was increased step-by-step, the newer the connections, the fewer the subjects have those edges.

This assumption explains our findings, and it is related to the "competition hypothesis" of the brain development [10].

How to direct the edges of the human connectome?

For any neuron, there exists a well-defined direction of the signal propagation from the soma through its axon. Diffusion MRI-based methods can be used to identify the spatial location of the fiber tracts, consisted of axons, but their directions, by our present knowledge, cannot be discovered from the MRI data.

If the order of development of the edges in the connectome is known then we can easily assign a direction to those edges that connects a vertex to another one, such that the first vertex was not connected to any other vertices before, but the second vertex was already connected to the network, when we consider the transition of the edges that were present in at least $k + 1$ graphs through the edges that were present in at least k graphs.

More exactly, the observation described above implies a straightforward method for directing some (but not all) the edges of the connectome. Consider the undirected edge u, v, and our goal is to assign a direction to this edge. Let G_{k+1} denote the consensus connectome where each edge is present in at least $k + 1$ graphs, and let G_k denote the consensus connectome where each edge is present in at least k graphs. Both G_{k+1} and G_k have the same set of vertices, all the edges of G_{k+1} are also the edges of G_k, but G_k typically has more edges than G_{k+1}. Suppose that vertex v was not connected to any other vertices in G_{k+1}, and becomes connected to a vertex u in G_k, where u was connected to other vertices in G_{k+1}. Then we direct this (v, u) edge from v to u, and denote it as an ordered pair (v, u) (Fig 4). Obviously, if our hypothesis is correct, then the undirected edge u, v remained in the consensus connectome since vertex v did not get an apoptosis signal, since u was already been connected to the growing network.

We remark that those new edges that connect two, previously isolated points ("isolated edges"), or those that connect two vertices, where both of them were connected to the network before, cannot be directed this way.
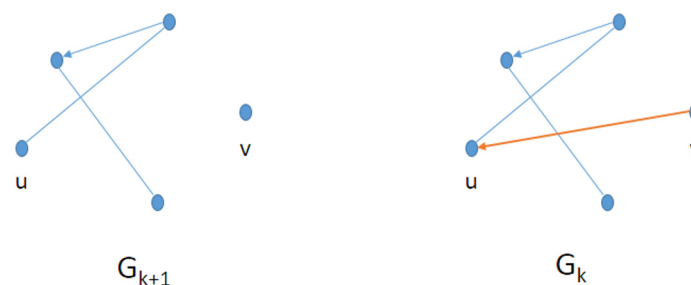

Fig 4. Let G_{k+1} denote the consensus connectome where each edge is present in at least $k + 1$ graphs, and let G_k denote the consensus connectome where each edge is present in at least k graphs. Both G_{k+1} and G_k have the same set of vertices, all the edges of G_{k+1} are also the edges of G_k, but G_k typically has more edges than G_{k+1}. The (v, u) edge is directed from v to u, if v is not connected to any other vertices in G_{k+1}, and becomes connected to a vertex u in G_k, where u was connected to other vertices in G_{k+1}. Then we direct this (v, u) edge from v to u.

Methods

The description of the program and the methods applied in the construction of the Budapest Reference Connectome Server http://connectome.pitgroup.org is given in [6].

The animation at https://youtu.be/yxlyudPaVUE were prepared by our own Python program from the tables generated by the Budapest Reference Connectome Server [6] with the following settings: Version 2 (i.e., 96 subjects), Population: All (i.e., both male and female subjects), Minimum edge confidence running from 100% through 26%, Minimum edge weight is 0, Weight calculation model: Median. It contains the common edges found in k subject's braingraphs, from $k = 96$ through $k = 25$. The number of vertices is 1015.

Conclusions

We have observed that the buildup of the consensus graphs in the Budapest Reference Connectome Server is far from random when the k parameter is changed from $k = 418$ through 1. This observation suggests an underlying structure in the consensus braingraphs: the edges, which are present in more subjects are most probably older in the individual brain development than the edges, which are present fewer individuals. This assumption is in line with the "competition hypothesis" of the brain development [10]. We believe that this observation is applicable to discover the finer structure of the development of the connections in the human brain.

Based on this hypothesis we were able to assign directions to some of the otherwise undirected edges of the connectome, built through a diffusion MRI based workflow.

Acknowledgments

Author Contributions

Conceived and designed the experiments: CK VG. Performed the experiments: CK BS BV. Analyzed the data: CK BS VG. Contributed reagents/materials/analysis tools: BV BS CK. Wrote the paper: VG. Discovered the phenomenon of the consensus connectome dynamics: CK.

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