BRAINtrinsic: A Virtual Reality-Compatible Tool for Exploring Intrinsic Topologies of the Human Brain Connectome

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Abstract. Thanks to advances in non-invasive technologies such as functional Magnetic Resonance Imaging (fMRI) and Diffusion Tensor Imaging (DTI), highly-detailed maps of brain structure and function can now be collected. In this context, brain connectomics have emerged as a fast growing field that aims at understanding these comprehensive maps of brain connectivity using sophisticated computational models. In this paper we present BRAINtrinsic, an innovative web-based 3D visual analytics tool that allows users to intuitively and iteratively interact with connectome data. Moreover, BRAINtrinsic implements a novel visualization platform that reconstructs connectomes' intrinsic geometry, i.e., the topological space as informed by brain connectivity, via dimensionality reduction. BRAINtrinsic is implemented with virtual reality in mind and is fully compatible with the Oculus Rift technology. Last, we demonstrate its effectiveness through a series of case studies involving both structural and resting-state MR imaging data.

Keywords: Connectomics · Connectome datasets · Intrinsic geometry · Neuroimaging

1 Introduction

Magnetic resonance (MR) imaging techniques such as *functional Magnetic Resonance Imaging* (fMRI) and *diffusion weighted imaging* (DWI) enable neuroimagers to collect and derive data about how different brain regions connect from both a structural and a functional point of view [15]. Analogous to the concept of *genome* for genetic data, a brain *connectome* is a whole-brain comprehensive map of neural connections [20]. As neural connections exhibit complex patterns of function and structure, the field of brain connectomics has emerged in order to understand these imaging big data. The brain connectome is typically mathematically represented using connectivity matrices that describe the interaction

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among different brain regions. To date, most connectome study designs use brain connectivity matrices to compute summary statistics on either a global or a nodal level [21].

In the current work, we introduce an innovative visualization technology with the ability to reconstruct and analyze the *intrinsic geometry* of brain data, that is, the topological space where brain connectivity natively resides (independent of anatomy). Understanding this intrinsic geometry could not only lead to a greater distinction of differences in clinical cohorts, but also help track longitudinal changes in individual brains in order to better deliver precision medicine. To the best of our knowledge, no such tool currently exists that effectively addresses these needs.

2 Intrinsic Geometry

The proposed *intrinsic geometry* represents the brain connectome after non-linear multidimensional data reduction techniques are applied. This means that the position of each node does not correspond to its anatomical location, as it does in the original brain geometry. Instead, its position is based on the strength of the interaction that each region has with the rest of the brain, whether structural or functional. To put into context why intrinsic geometry may be a better space to understand brain connectivity data, for decades cartographers have mapped quantitative data onto world maps to create unique, informative visualizations. For example, by resizing countries according the Gross Domestic Product (GDP), the viewer can easily appreciate that the United States has the largest GDP. Similarly, dimensionality reduction techniques remap the brain according to network properties. In the intrinsic geometry we are more interested in the shape the brain connectome assumes independent of the anatomical distances between nodes. Thus, the space in which the intrinsic geometry is plotted in is called a *topological space* [4].

Linear dimensionality reduction techniques such as multidimensional scaling (MDS) [2] and principal component analysis (PCA) [14] have been previously used in unrelated fields of medicine as a way to distinguish clinical cohorts through biomarkers, although it can be argued that they are not suitable for complex high-dimensional connectome data [13,22]. To the best of our knowledge, this study represents the first comprehensive application of non-linear dimensionality reduction techniques in the ever-expanding field of brain connectomics. This intrinsic geometry concept provides a connectomic visualization that is not obscured or constrained by the brains anatomy. Indeed, visualizing connectivity information within an anatomical representation of the brain can potentially limit one's ability to clearly understand the complexity of a human brain connectome; some meaningful patterns of structure or function may be much easier to appreciate in a topological space.

2.1 Data Acquisition and Intrinsic Geometry Reconstruction

Structural and diffusion-weighted imaging data were acquired from 46 healthy control subjects (HC, mean age: 59.7±14.6, 20 males). Resting-state functional MRI data were additionally acquired on a subset of healthy controls ($n = 10$). To obtain DTI-informed structural brain connectome, we used a pipeline reported previously [9]. Functional connectomes were generated using the resting state fMRI toolbox, CONN.[1] In brief, raw EPI images were realigned, co-registered, normalized, and smoothed before analyses. Confounding effects from motion artifact, white matter, and CSF were regressed out of the signal. Using the same 82 cortical/subcortical gray-matter labels as the structural brain networks [7], functional brain networks were derived using pairwise fMRI signal correlations.

These 82 anatomical regions were then further upsampled using an algorithm that continuously bisected each region across all subjects at an identical angle until the average region size reached a certain threshold. Previous studies using similar algorithms have shown that up-sampling regions into higher-resolution voxels maintains network connectivity [11]. The resulting parcellation converted 82 regions into 620 sub-regions for the structural data and 739 for the functional data. Brain networks formed by either the fiber tract counts or the functional correlations between up-sampled gray matter regions were generated using an in-house program in Matlab. These up-sampled regions were also re-registered to original subcortical/cortical regions in preparation for nonlinear dimensionality reduction. All networks were examined to ensure that all regions were directly connected to at least one other region preventing the formation of any isolated "islands". To compensate for inter-subject variations, we averaged individual subjects' networks together to obtain a group average network.

2.2 Intrinsic Geometry Reconstruction

Representing Functional and Structural Connectomes as High-dimensional Data. Before any dimensionality reduction can be applied, we need a representation of the connectome data in a high-dimensional space where a distance metric can be properly computed (such that a neighborhood could be defined). In the case of fMRI BOLD signal time series correlations, we propose to first transform inter-regional correlations (r) using the transformation: $s_{i,j} = log(\frac{1}{|r_{i,j}|})$. Here $r_{i,j}$ represents the correlation coefficient between i and j. Note this non-negative transformation yields $s = 0$ if two nodes are completely coupled (i.e., $r = 1$ or -1), and infinity when completely decoupled ($r = 0$). This transformation provides the building block for representing functional data in a high-dimensional space. To this end, we first note that for any brain region the n-dimensional vector $S_* = (s_{*,1}, s_{*,2}, s_{*,3} \ldots, s_{*,n})$ now encodes the pattern of coupling between this region and the entire brain (n denotes the total number of brain regions or nodes; $n = 739$ in our resting state imaging data). In the intrinsic geometry one would thus want to embed two nodes i and j next to each other if they exhibit very similar coupling patterns, i.e., the Euclidean distance $|S_i - S_j| = \sqrt{\sum_n (s_{i,n} - s_{j,n})^2}$

[1] http://www.nitrc.org/projects/conn

is small, where $S_i = (s_{i,1}, s_{i,2}, s_{i,3} \ldots, s_{i,n})$ and $S_j = (s_{j,1}, s_{j,2}, s_{j,3}, \ldots, s_{j,n})$. This intuitive example illustrates that we could simply represent functional connectome data in a $n = 739$ dimensional Euclidean space, with node k having the following coordinates, $S_k = (s_{k,1}, s_{k,2}, s_{k,3}, \ldots, s_{k,739})$. In the case of structural connectome (whose connectivity matrix codes the strength of white matter tracts) we propose, with similar rationale, to represent structural connectivity data in a $n = 620$ Euclidean space with node k placed at the following coordinates: $S_k = (GraphDist_{k,1}, GraphDist_{k,2}, \ldots, GraphDist_{k,620})$; here $GraphDist$ codes the shortest path length (i.e., graph distance) connecting two nodes; graph distances are usually computed by defining edge length as the inverse of the edge strength (i.e., fiber counts) followed by applying Dijkstra's algorithm [5]. Figure 1 visualizes these two different transformations for both the structural and functional connectivity matrices.

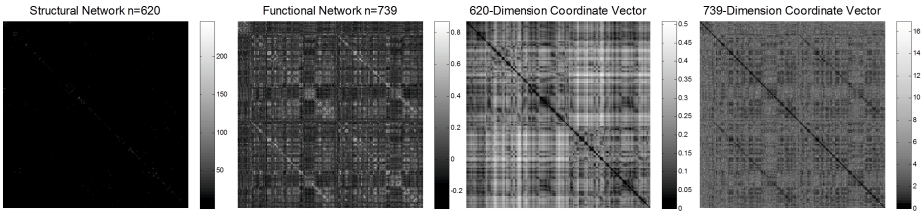

Fig. 1. The figure shows the adjacency matrices for both the structural and the functional group-averaged connectome. The (i,j) element represents the tractography-based fiber count or the BOLD fMRI signal correlation between brain regions i and j. The resulting n-dimensional row vectors describing the Euclidean coordinates of high-dimensional connectome data are shown on the right. See Section 2.2 for more details.

Constructing 3-Dimensional Embedding. To promote uniformity throughout the analyses, we used the dimensionality reduction toolbox introduced by van der Maaten for all reductions [17]. The number of dimensions was reduced from 620 and 739 to 3, for the structural and functional connectome respectively. We used the compute_mapping routine, with the "Isomap" and the "k-nearest neighbor" options. The number of nearest neighbors (i.e., k) during local neighborhood construction was increased iteratively such that all points were included in the embedding. For structural connectome, k was determined to be 17, and for functional 27.

3 Design Features of BRAINtrinsic

A range of interesting approaches to visualizing the human brain connectome are available. Some recent connectome visualization tools include a 3D node-link representation to provide meaningful spatial information relative to the real anatomical position [10,16,24]. However, in these tools, the overall visual clutter

tends to increase in large networks with dense interconnections between nodes. In this context, interaction helps limit the potential visual clutter that may occur when visualizing the human brain connectome. A possible solution is to let the user easily choose the level of details of the exploration within a Virtual Reality (VR) environment.

Since the advent of this technology, VR systems have been used for visualizing scientific datasets [19]. Additionally, recent VR tools have provided new ways to interact with and explore complex datasets effectively. For example, Ware et al. evaluates the effectiveness of 3D graph visualization when using high resolution stereoscopic displays [23]. Recently, Forbes et al. presents a stereoscopic system to visualize temporal data of the brain activity responding to external stimuli [8], providing new insights when dealing with the temporal dimension in a 3D environment. Broadly speaking, multi-purpose immersive VR environments, such as the CAVE2 [6], enable a more engaging and effective exploration of complex datasets.

Although, the effectiveness of utilizing 3D for representing data has been debated [18], recent work by Alper et al. [1] has shown that in some situations visualizing 3D networks can outperform 2D static visualization, especially when considering complex tasks. To the best of our knowledge, *BRAINtrinsic* presents the first dynamic and interactive VR-compatible visualization platform for connectome representation and exploration.

3.1 Design and Functionality

BRAINtrinsic uses an interactive 3D node-link diagram to visualize connectome data. The individual nodes represented different brain regions and are visualized using circular glyphs, while edges representing a functional or a structural connection between these regions are displayed using lines.

A main concern with the use of node-link diagrams is the potential for visual clutter when displaying a highly interconnected graph. Instead of showing all the connections simultaneously, by default BRAINtrinsic only shows nodes while hiding all links unless explicitly required. Through interaction, users are able to display or hide connections according to their preferences and current needs. We also allow the user to view the connections only within a particular sub-graph. This edges-on-demand technique allows exploration tasks to be performed by showing only the connections starting from a specific region that is currently being interrogated. The user can pin the connections in the scene by simply clicking on the node itself. We use varying degrees of transparency to visually encode the strength of edge weights; stronger connections are represented using opaque lines while weaker edges are more transparent. Transparency is scaled relative to only the currently displayed edges.

Colors are used to highlight the neuroanatomical membership of each node in the brain. Here, each glyph belongs to one of the 87 neuroanatomical gray matter regions as defined by Freesurfer [7]. However, the data structure is flexible enough to accept any membership or affiliation definition. Additionally, we implemented a range of user interactions to support visual analysis including the following:

- Dynamically display the nodal strength for any node being interrogated [3];
- Dynamically create the shortest-path tree rooted in the node selected by the user;
- Visualize the shortest path between any two nodes;
- Select or deselect any regions in any topological space (anatomy versus intrinsic) during visualization;

We again used Dijkstra's algorithm [5] to create the shortest path tree. The user can filter the shortest path tree according to two different measures: graph distance and number of intermediate nodes or "hops". In the first case the user can filter the tree according to the relative distance with respect to its farthest node. Given a threshold t, all the nodes that satisfy the following inequality are drawn: $d(r,i) \leq maxDistance(r) \cdot t$, where r is the root node, i is the node considered, $maxDistance(r)$ is the distance between the root node and the farthest node, and t is the threshold chosen by the user. If $t = 0$ then only the root node is displayed, while if $t = 1$ the entire shortest path tree is drawn. In the latter case, the user is able to filter out nodes that are not reachable within a certain number of nodes from the root.

Following the computation of the shortest-path tree, the user then can proceed to select a second "destination" node and visualize the shortest route connecting this node to the root. In this case, we display all the nodes in the network to provide the overall perspective of the route course.

3.2 System Details

BRAINtrinsic was developed in *Javascript* using the *threejs* library (http://threejs.org) an open source wrapper for the hardware accelerated graphics functionality provided by *WebGL* (http://webgl.com). BRAINtrinsic was designed to be fully compatible within a virtual reality environment, and has been specifically calibrated for use with the Oculus Rift VR headset (http://oculus.com). Through stereographic rendering, we emulate the way human eyes perceive the real world, creating a natural navigation for the user. The code developed is open source and publicly available at the authors' code repository [2].

4 Results

4.1 Visualizing the Intrinsic Geometry and Simulated Rich-club Removal

Figure 2 visualizes the intrinsic geometry of the structural and the functional group-averaged connectome, as well as illustrates the rich-club property of the human connectome (second row). The basic concept behind the rich club property is the tendency for nodes with high nodal strengths to form tightly interconnected groups [12]. Mathematically speaking, given a graph N and the parameter

[2] https://github.com/CreativeCodingLab/BRAINtrinsic

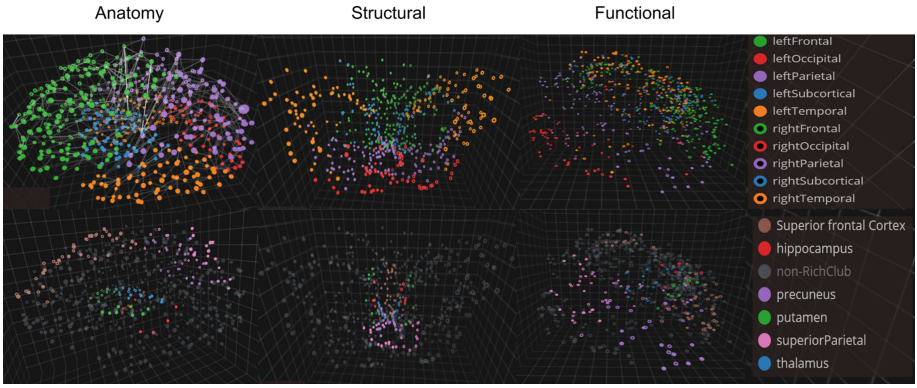

Fig. 2. This figure visualizes the intrinsic geometry of the tractography-derived structural and the resting-state fMRI connectome (middle and right panel, respectively), as well as the locations of rich-club regions in these spaces (second row). For comparison, their corresponding locations in the original neuroanatomical space are also shown (left panel).

k which defines a nodal strength cut off, the rich club property is defined as

$$\phi(k) = \frac{2E_{>k}}{N_{>k}(N_{>k} - 1)} \tag{1}$$

where $E_{>k}$ is the number of edges in N between the nodes of nodal strength greater than k and $N_{>k}$ is the number of nodes in N with nodal strength greater than k. Visually and intuitively, it is clear that rich-club nodes form the center of the structural connectome's intrinsic geometry (lower middle panel). To further appreciate the power of BRAINtrinsic, we demonstrate gross changes in the shape of the structural connectome's intrinsic geometry when rich-club nodes are removed.

Figure 3 (top left) again visualizes the bowl-like shape of the complete structural connectome, while the connectome without rich club nodes (top right) shows a ring-like structure with a "hole" in the middle. Visually, rich-club nodes thus keep the entire network intact by forming the center. When they are removed, remaining brain regions are now topologically dispersed and less coupled. Similar simulations were further conducted by removing an equal number of nodes with respect to the following criteria: a) nodal strength (high to low), b) clustering (low to high), c) nodal path length (low to high), and d) random removal. While random removal(top middle) as expected only induces subtle changes to the intrinsic geometry, interestingly removing nodes based on clustering (lower left) also minimally changes the overall shape, supporting the fundamental differences in what local properties such as clustering capture relative to global properties. The immersive VR environment provided by BRAINtrinsic helps user better appreciate the differences mentioned above. BRAINtrinsic

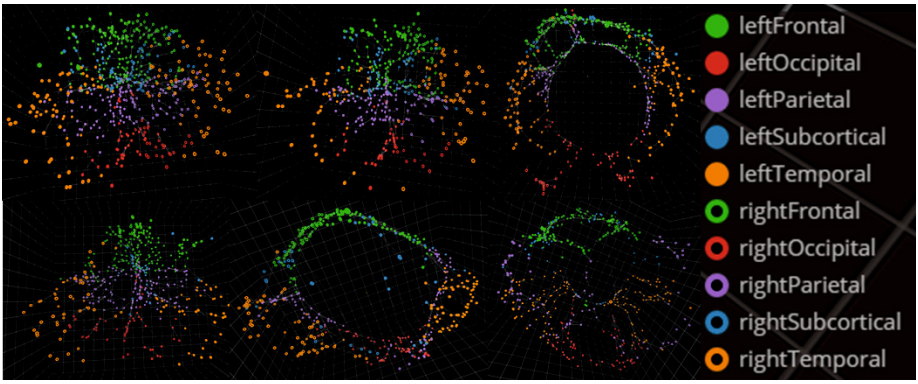

Fig. 3. This figure compares the intrinsic geometry of the structural connectome when different node removal strategies are applied. Top Row (from left): the first image depicts the connectome in its entirety, the second visualizes the intrinsic geometry when a 20% random-removal procedure is applied, and the last when rich-club nodes are removed (20% of all nodes). Bottom Row (from left) depicts the intrinsic geometry after removing nodes ranked within the bottom 20% with the respect to the clustering coefficient, bottom 20% with respect to the nodal path length and top 20% with respect to the nodal strength.

is particularly effective when experts aim at understanding and comparing the overall shape of the entire connectome.

4.2 Resting State Functional Connectome

The right panel of Figure 2 visualizes the intrinsic geometry of resting-state fMRI connectome, which exhibits a very different pattern compared to its structural counterpart. Due to the strong inter-hemispheric fMRI connectivity between homologous regions, here one does not see the left-right symmetry as in the

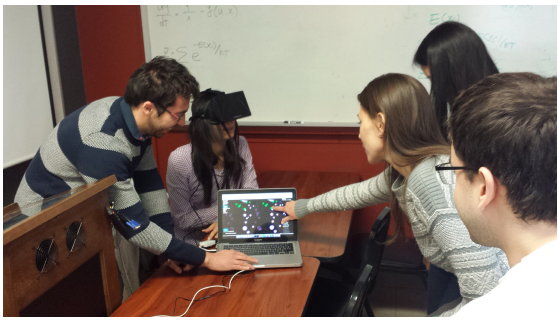

Fig. 4. Exploring connectome data using BRAINtrinsic within the Oculus Rift environment.

structural case; instead homologous regions now coalesce into a single cluster. More interestingly, while rich-club regions are located at the center of structural connectome's intrinsic geometry, this is no longer the case for functional connectome. BRAINtrinsic allows for such an appreciation to easily occur when exploring functional datasets. The choice of using different glyphs and colors to encode different regions-of-interests coupled with effective VR rendering provides a clear understanding of the underlying neuroanatomy even in this topological space.

5 Discussion and Conclusion

This paper introduced *BRAINtrinsic*, a novel VR-compatible visualization application that enables users to interactively explore the human brain connectome and its intrinsic topology. Since in the intrinsic space, spatial vicinity equates to stronger connectivity, the user is able to explore freely and easily the terrain of brain connectivity, either functional or structural. Indeed, the real advantage of exploring in the intrinsic space (especially when coupled with virtual-reality technology), is the ability to understand the connectivity relationship among a number of brain regions as neuroimagers unfold complex high-dimensional connectivity data into easily understandable and relatable configurations in 3D (Figure 4). By representing structural or functional connectomes using high-dimensional data followed by dimensionality reduction, this visualization software creates a "road map" of the human brain. While the actual connectivity matrix can be parsed much like knowing the distance to any stop of a road trip it is hard to comprehend these strict numerical quantities without a map to help guide relative locations. BRAINtrinsic facilitates this appreciation and further provides methods for interacting with individual nodes to discover highly integrated circuits in both functional and structural connectomes.

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