Immersive Virtual Reality Tool for Connectome Visualization and Analysis

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Abstract

Immersive Virtual Reality Tool for Connectome Visualization and Analysis

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The human brain is a complex organ made up of billions of neurons that are interconnected through a vast network of synapses. This network of connections enables the brain to perform a wide range of cognitive and motor functions. Studying and analyzing these brain networks is important for understanding how different regions of the brain communicate and work together to carry out specific tasks and how neurological disorders such as Alzheimer's disease, Parkinson's disease, or schizophrenia impact brain connectivity contributing to the development of these disorders.

Virtual reality technology has proven to be a versatile tool for learning, exploration, and analysis. It can expand the user's senses, provide a more detailed and immersive view of the subject matter, encourage active learning and exploration, and facilitate global analysis of complex data. In this dissertation, we present VRNConnect, a virtual reality system for interactively exploring brain connectivity data. VRNConnect enables users to analyze brain networks using either structural or functional connectivity matrices. By visualizing the 3D brain connectome network as a graph, users can interact with various regions using hand gestures or controllers to access network analysis metrics and information about Regions of Interest (ROIs). The system includes features such as colour coding of nodes and edges, thresholding, and shortest path calculation to enhance usability. Moreover, VRNConnect has the ability to be tailored to specific needs, allowing for the importation of connectivity data from various modalities. Our platform was designed with flexibility in mind, making it easy to incorporate additional features as needed.

In order to evaluate the usability and cognitive workload associated with using our system, we conducted a study with 16 participants. Our findings suggest that VRNConnect could serve as an effective academic and analytical tool.

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Chapter 1

Introduction

With the increasing availability of both functional Magnetic Resonance Imaging (fMRI) and Diffusion Tensor Imaging (DTI), it is increasingly becoming possible to study the structure and function of the brain. In particular, these imaging modalities give us the ability to map brain connectivity using various sophisticated modelling techniques (e.g. Structural Equation Modelling (SEM), Graph Theory Analysis (GTA), etc.) Conte et al. [34]. The study of brain connectivity and neuronal wiring diagrams falls under the field of “brain connectomics”, a growing field of neuroscience that aims to understand structural and functional brain connectivity and how neurons are connected and communicate.

In studying brain connectivity, we can advance our knowledge of both the function as well as dysfunction of the brain to deepen our understanding of various psychopathologies and neurological disorders. For example, by comparing the connectome of a healthy population with a population of patients with multiple sclerosis (MS), Dai and He [37] found that the default mode (i.e. the set of brain regions that are active when an individual is not engaged in a specific task), salience, and executive control networks were all altered in MS patients. Network disruption has also been found to correspond with disease severity when compared to clinical disability scores. Thus, connectome analysis can uncover MS-related brain network anomalies and follow illness progression. In the case of Parkinson’s disease (PD), De Schipper et al. [39] found that people with PD had broken connections in both the motor and frontoparietal networks. The study also showed that the severity of motor symptoms was linked to how much the network was broken.

As can be seen from these examples, connectomics or the study of the connections between neurons and neural networks in the brain can provide important insights into not only how the brain processes information and controls behaviour but also how it can malfunction in various neurological and psychiatric disorders.

1.1 Connectome Visualization

Connectome data can be represented as a graph where nodes represent different brain regions, and links (or lack thereof) represent the connections between those brain regions. Thus, graph theory definitions, statistics and algorithms are often applied to understand and analyze connectomic data. Further, a graph representation can be easily visualized in 3D, and in fact, most 3D connectivity analysis tools visualize the connectome as node-link diagrams, in which nodes are placed in relation to their corresponding anatomical locations, and links between nodes show how these anatomical locations are connected to each other. In general, node-link diagrams give a good overview of a graph, making it easy to see the relationships between directly and indirectly connected nodes. In work described in this thesis, we developed VRNConnect, a virtual reality system that can be used for exploring graph representations of brain connectome data (See Figure 1.1).

1.2 Virtual reality

Virtual reality (VR) is defined as a completely computer-generated environment that users experience with specialized equipment such as head-mounted displays (HMDs). VR is being increasingly used in the medical domain for medical education, surgical planning and training, patient education and rehabilitation. In neuroanatomy specifically, VR is proving to be a valuable tool as it provides a more immersive and interactive experience that can help researchers, clinicians and even patients to better understand the structure and functionality of the brain. VR in the specific domain of neuroanatomy and neurological disorders has been used for: (1) exploring brain mapping and thus allowing researchers to visualize the different regions of the brain and study their functions in a more interactive and engaging way [79, 122]; (2) neurosurgical planning where surgeons can practice surgical techniques prior to entering the operating room (OR) [92]; (3) rehabilitation in patients

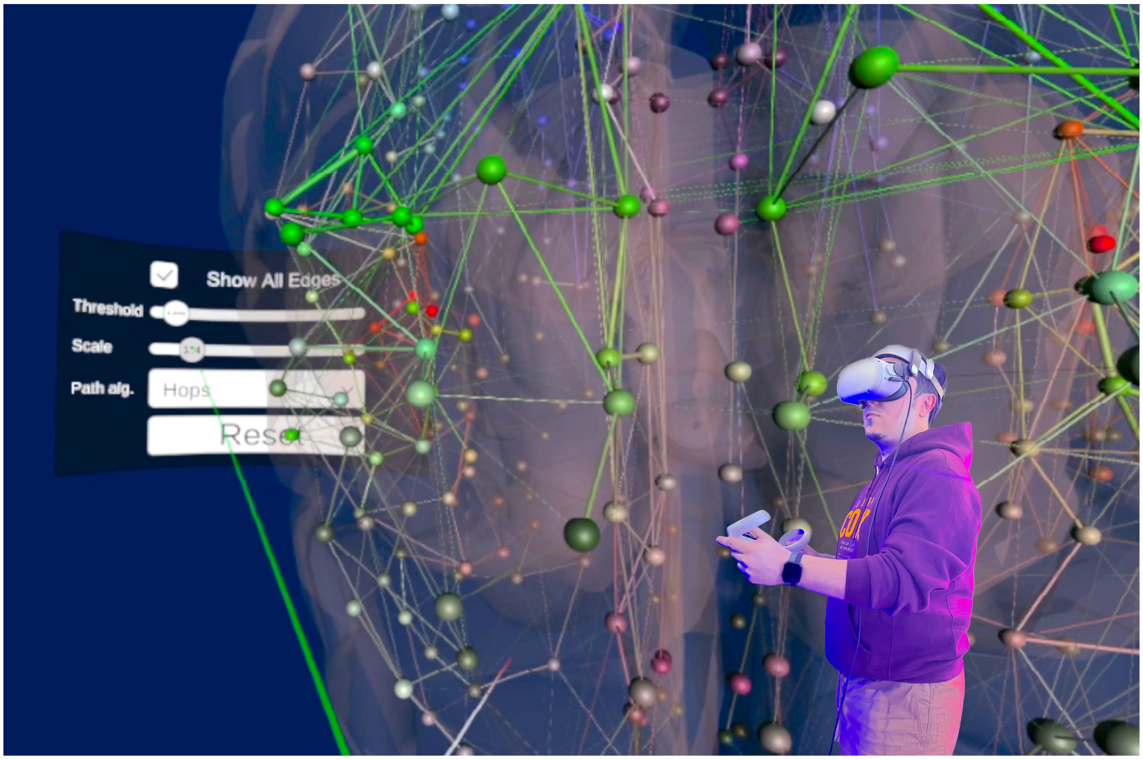


Figure 1.1: VRNConnect: An interactive virtual reality platform for connectomic data exploration.

who have suffered from brain injuries (e.g. stroke) or from neurological disorders (e.g. Parkinson's disease) by creating physiotherapy programs or virtual environments that simulate real-life activities[101]; (4) patient education to help patients better understand their neurological conditions by allowing them to explore brain structure and function with respect to their specific condition[76].

In this thesis, we focus on the development of a virtual reality platform for exploring brain connectivity data to enable researchers, students, and clinicians to map the different regions of the brain and study their functions in a more interactive, intuitive and engaging way.

1.3 Contributions

Brain connectivity data has been traditionally represented using connectivity matrices or graphs as described above. Connectivity matrices or graphs, however, do not necessarily allow easy and intuitive exploration of the brain connectome, whereas new immersive technologies can provide a more engaging and interactive way to explore and visualize brain connectivity data. Alper et al.

[4] have demonstrated that in some cases, visualizing 3D networks can enable more comprehensive analysis and understanding in comparison to 2D static representations, especially when considering complicated tasks.

In the field of “connectomics”, virtual reality can allow you to immerse yourself in a three-dimensional representation of the brain connectome, where you can freely navigate and interact with different brain regions and their connections. This immersive experience can facilitate a deeper understanding of the brain’s complex network and its underlying mechanisms, which can have important implications for neuroscience education, research and clinical applications.

In this thesis, we have developed a VR framework, VRNConnect, for exploring brain connectivity data. Specifically, our main contributions and features of the application can be described as follows:

- Development of a Virtual reality platform for visualization and analysis of brain connectivity data using Meta Quest 2 (see Section 3.3).
- Flexibility of input: although we used structural connectivity data for evaluating our system usability and features, users have the versatility of importing their own data, whether functional connectivity or structural (see Section 3.3.3).
- Intuitive interaction using controllers or hand gestures, allowing for better understanding and convenience of using either controllers or hand gestures (see Section 3.3.6).
- Development of python scripts that run in the background of our system, allowing for a connection to use Brain Connectivity Analysis tools during run-time (see Section 3.3.3).
- Dynamic display of graph network measurements such as node strength, degree, and clustering coefficient in the VR environment (see Section 3.3.6).
- Dynamic calculation and visualization of the shortest path between any selected 2 nodes (see Section 3.3.6).
- Evaluation of VRNConnect features and interactions using both hands and controllers in terms of usability and workload (see Section 3.4).

The goal of our VR visualization framework is to enable better exploration and visualization of brain connectomic data, allowing for (1) learning about structural and functional connectivity, (2) easier analysis of the distinction between healthy and unhealthy clinical differences in clinical cohorts, and (3) helping to track longitudinal changes in individual brains in order to deliver precision medicine better.

1.4 Organization of Thesis

The structure of the thesis is as follows. We begin with an overview of imaging techniques for brain mapping, visualization of connectivity data, and its clinical applications in Chapter 2. We also present an overview of virtual reality applications in health education, particularly neuroanatomy. In Chapter 3, we describe the implementation of VRNConnect, the developed interactive virtual reality platform for connectomic data exploration. Further, we describe a user study that was done to evaluate the usability and learnability of the system. Finally, in Chapter 4, we conclude the thesis by discussing potential topics of further research.

Chapter 2

Background

In this chapter, we begin by defining brain connectivity mapping and then discuss imaging techniques for data collection as well as different types of representations for visualizing connections. In Section 2.7, we discuss how virtual reality (VR) has been used in the field of neuroanatomy and ways that VR can be used for visualization and data analysis.

2.1 Connectomics

The brain is frequently regarded as the most complex network known to humans. A human brain is composed of roughly 100 billion (10^{11}) neurons linked by approximately 100 trillion (10^{14}) synapses that are structured over many spatial dimensions and interact across multiple temporal scales Sporns et al. [118]. The delicate processes that allow millions of neurons in our nervous system to communicate are in charge of our thoughts and emotions, as well as our overall cognition.

A connectome, which is sometimes referred to as the "wiring diagram" (see Figure 2.5) of the brain, is a map of these neuronal connections. The term connectome was coined by Sporns et al. [118] (and separately by Hagmann [59] in a Ph.D. dissertation). The connectome is crucial for understanding and connecting the brain's anatomical and functional mechanisms. Connectomics (the field of neuroscience that aims to understand the connectivity patterns of neural networks) can help determine how functional brain states originate from their structural foundations, providing insights into how brain function may evolve when neuronal structures are changed Sporns et al. [118].

Investigating connectivity data can help in getting a better understanding of mental health, cognition, and neurological function, as well as dysfunction. For example, dementia and schizophrenia are among the most serious worldwide health problems[139, 140] resulting in brain network changes [25, 9, 59]. Understanding brain network connectivity is a major goal of neuroscience, and many collaborative studies have emerged to map brain networks more thoroughly and in more depth [22, 72, 129].

Fornito et al. [50] mentions two converging factors pushing connectomics' scientific advancement. First, mathematical and conceptual advances in research on complex networks. Major theoretical improvements in the statistical physics of complex networks have occurred since the 1980s, as have more broad applications of network science to the analysis and modelling of large datasets. Researchers have found new ways to measure the topological complexity of large systems with many interacting parts. They have also found similarities in the organizational properties of many real-world networks, such as air transportation networks, microchip circuits, the internet, and brains. In Section 2.4.2, we discuss graphs/networks in more depth.

The second factor that has helped advance connectomics is the growth of monitoring tools for neural systems that have made it easier to measure and see the structure of the brain at many different levels of detail. Since the 1990s, human neuroimaging science has made a lot of progress, especially in the use of MRI to map the entire anatomical and functional networks of the brain at a macroscopic size (1-10 mm^3, order of $10^{-2}m$). This has led to a deeper understanding of both the healthy brain and the brains of patients with neurological and psychiatric illnesses [29]. In Section 2.2, we discuss MRI and fMRI imaging for brain connectivity data acquisition.

2.1.1 Brain Networks

Comprehensively looking at the parts of a complicated brain network isn't sufficient for determining how higher-level brain functions work [78]. It's important to think about the global parts of such complex systems. The complexity of the nervous system is held together by the large-scale architectural parts of the neural network that limit how neurons can talk to each other. Recent research suggests that, as a result of evolution, the structure of neuronal networks follows the basic rules of constraint minimization. This means that the brain's geometry is set up so that wiring costs are kept to a minimum, global energy use is kept to a minimum, and communication bandwidth is kept to a maximum[126, 77]. Human-made networks like electrical gadgets, power grids, and even more dynamic systems like the World Wide Web (WWW) all follow these basic design rules.

It was once thought that the topology of a network's connections was either completely **(1) regular**, like when the nodes are placed on a lattice and connected to their neighbours, or completely **(2) random**, like when the connection between any two nodes is determined by a probability that has nothing to do with their distance from each other. However, many technical, social, or biological networks don't fit these models. Instead, they adopt the characteristics of both regular and random networks. Watts and Strogatz [136] referred to these kinds of networks as "small world graphs" (defined in Section 2.4.2). Milgram [91] also showed that social networks, the US power grid, and the nervous system of C. elegans all have low average path lengths and high clustering coefficients.

Because C. elegans only has 302 neurons in its nervous system, biologists can use standard methods to figure out how its neural network is set up. Its structure has been studied in depth, and it has been shown that it is set up in 11 clusters called ganglia so that the total length of the wires is as short as possible. $1mm^3$ of the cortex of a mammal has 10^5 neurons, 10^8 synapses, and 4 km of axons, so it is not possible to use the same thorough and exhaustive methods[32]. But, as we will show in the next sections, diffusion MRI tractography can demonstrate that white matter (WM) axons connect over long distances. Even though it is a low-pass "picture" of the real, microscopic neural network, it tells us about the global architecture of neuronal projections in the human brain (without using invasive methods).

The study of brain connectivity has become increasingly important in neuroscience, as it provides insight into the organization and function of the brain at both the microscale and macroscale levels. At the microscale level, brain connectivity refers to the patterns of synaptic connections between neurons, while at the macroscale level, it refers to the connectivity between different brain regions.

Connectivity at the Microscale

Microscale brain connectivity has been extensively studied using techniques such as electron microscopy, which allow for the visualization of individual synapses and the reconstruction of neural circuits. Several parts of the way the brain's network is set up seem to have been chosen to lower the cost of wiring and/or the amount of energy it needs [98].

Connectivity at the Macroscale

At the macroscale level, brain connectivity has been studied using a variety of imaging techniques, including diffusion magnetic resonance imaging (dMRI) and functional magnetic resonance imaging (fMRI). We will explain further about these imaging techniques in Section 2.2. A study by Buckner and DiNicola [27] used resting-state fMRI to identify a set of large-scale brain networks, including the default mode network and the executive control network, that are involved in different aspects of cognitive processing.

2.1.2 Tract tracing and Tractography

Tract tracing is a valuable technique for studying the connectivity of the brain. It involves injecting a substance, such as a tracer or a virus, into a specific area of the brain and tracking its spread through neural pathways to other regions. Another approach is using mathematical models to simulate the diffusion of water molecules in the brain and to infer the connectivity of white matter tracts based on the patterns of diffusion, known as tractography.

Tract tracing has been used to map the structural connectivity of the brain and to identify neural pathways that are involved in specific functions such as motor control, sensory processing, and memory [58]. Tracer injection techniques are invasive but have provided valuable insights into the brain's connectivity.

In recent years, tractography has become a popular technique for mapping brain connectivity in humans and animals. Diffusion tensor imaging (DTI) is commonly used to acquire the data required for tractography. DTI measures the diffusion of water molecules in the brain, which is influenced by the orientation of white matter fibres. By analyzing the patterns of water diffusion, tractography can infer the location and trajectory of white matter tracts [68].

The tracts identified through tract tracing, represent the white matter pathways that connect different regions of the brain. These pathways are crucial for the transmission of information between brain regions and for the integration of sensory, motor, and cognitive processes. The structural connectivity of the brain is thought to underlie its functional connectivity, and understanding the structural connections between brain regions is critical for understanding brain function.

In general, tract tracing using injection and tractography are valuable techniques for studying the structural connectivity of the brain. These techniques have provided valuable insights into the neural pathways that underlie specific functions and have facilitated the development of connectome maps. These maps represent a comprehensive understanding of the structural connections between different regions of the brain and provide a foundation for understanding the brain's complex functional networks. In Section2.2.1, we explain more about diffusion tensor imaging as we used DTI imaging to construct connectivity data (in Chapter 3) and since it is a non-invasive method of acquiring tractography. We further discuss fibre tracking in Section 2.3.2.

2.2 Imaging

The data used to construct a connectome can be obtained from various neuroimaging techniques, including MRI (magnetic resonance imaging), DTI (diffusion tensor imaging), PET (positron emission tomography), electroencephalography (EEG), etc. These imaging techniques can provide different types of data, including functional connectivity data, structural connectivity data, and anatomical data. In the following sections, we give an overview of various MRI imaging techniques used to capture connectivity data.

2.2.1 MRI

MRI brain scans use a strong, stable, static magnetic field to align the nuclei in the part of the brain being studied. Then, a magnetic field with a gradient is used to find the exact location of each nucleus. Lastly, a radiofrequency (RF) pulse is used to boost the magnetism of the nuclei. Depending on where the nuclei are (e.g. type of tissue), the effect will be different. When the RF field is taken away, the nuclei go back to how they were before. The energy given off is measured with a coil to determine where the nuclei are. In so doing, MRI gives a static picture of the structure of brain matter. The process of acquiring MRI is shown in Figure 2.1.

MRI is a useful tool for assessing brain activity and structural integrity. MRI can be used in both clinical and preclinical settings, e.g. to find out how the brain has changed after a stroke. The combined effect of in vivo functional MRI and DTI methods, in particular, gives researchers a unique way to look at how the remodelling of neural networks affects function. Thus, MRI plays a pivotal role in (a) determining how the brain changes over time, due to illness or during recovery, (b) predicting brain development or changes, and (c) developing therapies that may help the brain heal. In this chapter, we focus on MRI as it is the most commonly used imaging modality to study connectivity data [29, 128].

Functional magnetic resonance imaging (fMRI)

Functional magnetic resonance imaging (fMRI) measures brain activity by noticing changes in blood flow. This method is based on the principle that the activity of neurons and the flow of blood to the brain are tightly connected. In other words, when neurons become more active, they require more oxygen and glucose, which results in an increase of blood flow to that region of the brain which can be detected by fMRI Huettel et al. [63].

In the 1990s, Seiji Ogawa discovered the phenomena of blood oxygen level-dependent (BOLD) contrast in MRI, which was foundational to the development of fMRI. Ogawa and his team found that the magnetic resonance signal from oxygenated and deoxygenated blood was different; thus, it was possible to detect changes in blood flow and oxygenation levels in the brain associated with neural activity. Since the early 1990s, fMRI has been one of the most popular methods for mapping the brain as it doesn't require injections, surgery, drugs, or exposure to ionizing radiation. The high spatial resolution of fMRI is another benefit. This can help find the parts of the brain that are involved in certain cognitive processes. However, fMRI does not have the same temporal resolution as EEG or MEG, which can measure changes in brain activity in milliseconds. Despite this, fMRI is frequently used in cognitive neuroscience and neuroimaging research.

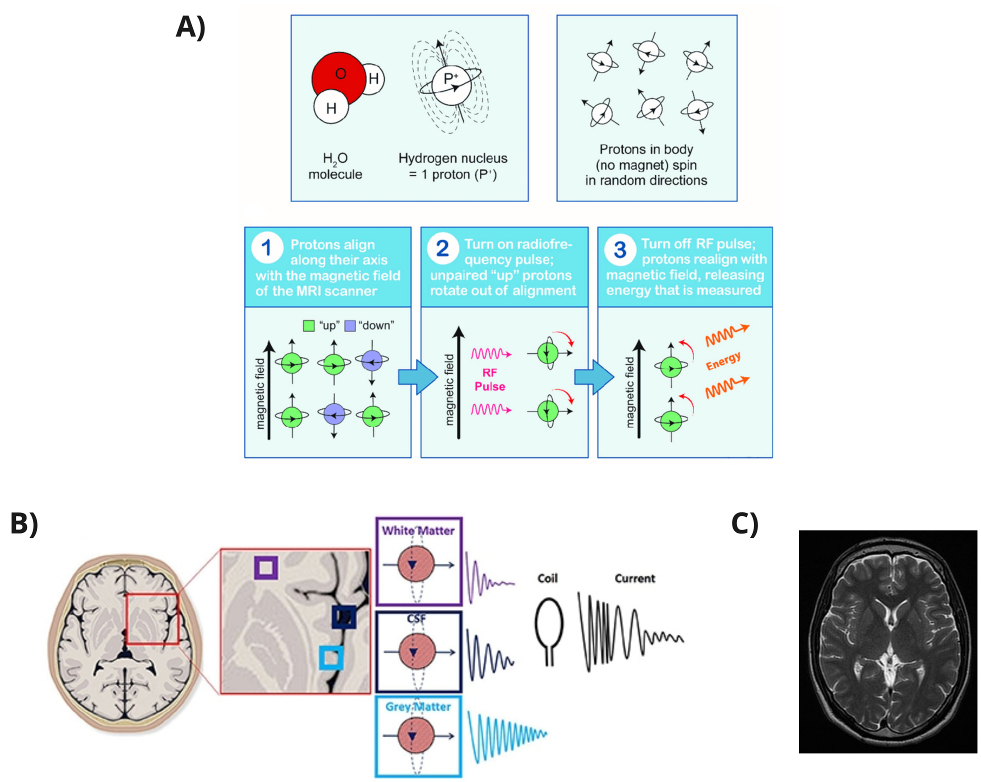


Figure 2.1: The process of acquiring an MR image is depicted. A) the microscopic phenomena behind the MRI [48], which results in B) different energy emissions from various materials in the brain, accumulated in the coil of the MRI device [26]. C) The resulting image after conversion of the accumulated signals of energies emitted from different matters in the Brain.

Resting state fMRI (rs-fMRI) and task-based fMRI (tb-fMRI): fMRI can be used to measure the resting state or the negative-task state, which is taken when a subject is at rest and not performing any task. In contrast, task-based fMRI measures brain activity while the subject is performing a specific task. Task-based fMRI is thus used to identify brain regions that are involved when performing a specific task and to investigate the functional connectivity of those brain regions with other brain regions.

fMRI is used in research and, to a lesser extent, in medical practice. It can be used with other brain physiology tests, like electroencephalography (EEG) and near-infrared spectroscopy (NIRS), to get a more detailed understanding of brain connectivity. Researchers are looking into new ways to improve both spatial and temporal resolution, and most of these don't use the BOLD signal. Despite extensive research and use, the use of fMRI in commercial applications is still limited and requires further validation. One issue with fMRI is its dependability and reproducibility. Variability exists in fMRI data both within and between individuals, making it difficult to draw firm conclusions. This was highlighted in a recent review by Poldrack et al. [102], which called for greater standardization and reproducibility in fMRI research, implying that more research is needed to validate fMRI for use in commercial applications.

Diffusion MRI

In contrast to fMRI which measures changes in blood oxygen levels in the brain, diffusion MRI measures the directionality and extent of water diffusion in the tissues of the brain. This information can be used to look at the microstructure of grey and white matter tissue [13, 94]. Diffusion Tensor Imaging (DTI), a specific type of diffusion MRI, uses an analytical technique to estimate the direction and magnitude of water diffusion specifically in the brain's white matter tracts, i.e. the axons/nerve fibres that connect different regions of the brain and allowing these regions to communicate. Since water molecules diffuse more easily along the length of axons rather than across them (see Figure 2.3), it is possible to use DTI to use the information about the directionality and extent of water diffusion in order to create a 3D map of the brain's white matter pathways.

Water diffusion is represented mathematically by an effective diffusion tensor with nine matrix components (shown in Figure 2.2). The organized structure of axons, the cell membrane, and the myelin sheath all have a big effect on how water moves through the brain, and there is a direct link between water movement and the direction and integrity of axons. When DTI is done in a compact tract with parallel running axonal trajectories, like the corticospinal tract, the Diffusion Tensor (DT) is mostly non-uniform, and its primary eigenvector matches the direction of the fibre tract. Figure 2.3 shows the theory behind DTI by illustrating the diffusion in water molecules as an oval shape. Figure 2.4 shows the bigger image with the tensor orientations when doing a diffusion MRI.

DTI can provide information about the structural integrity and connectivity of white matter pathways and can be used to study brain development, connectivity, and changes that occur as a result of disease or injury, such as multiple sclerosis, dyslexia, Alzheimer's disease, schizophrenia, brain tumours, periventricular leukomalacia, and spinal cord injuries [25, 9, 59].

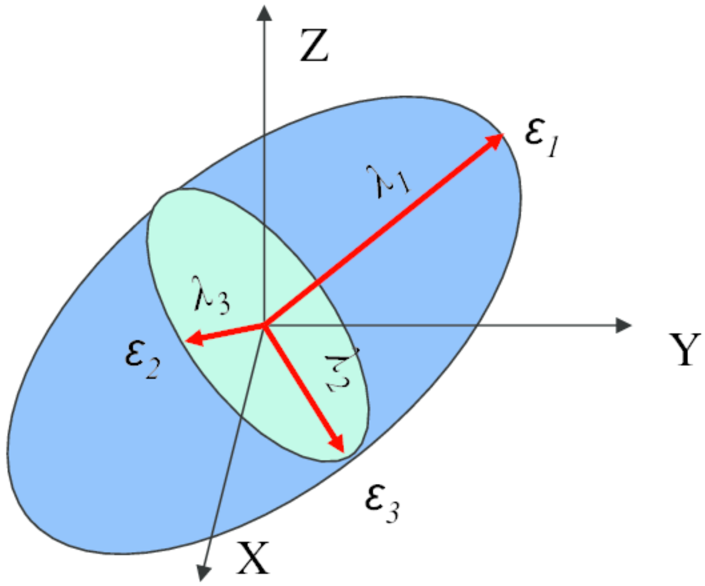


Figure 2.2: The diagram shows the components of a diffusion tensor matrix. The diffusion direction is represented by ϵ_1, ϵ_2, ϵ_3. The dominant direction of diffusion, and thus the orientation of the underlying fibre bundle, is represented by the principal eigenvector (ϵ_1). The eigenvalues - λ_1, λ_2, λ_3 - specify the amount of diffusion in the direction of the eigenvectors.[106].

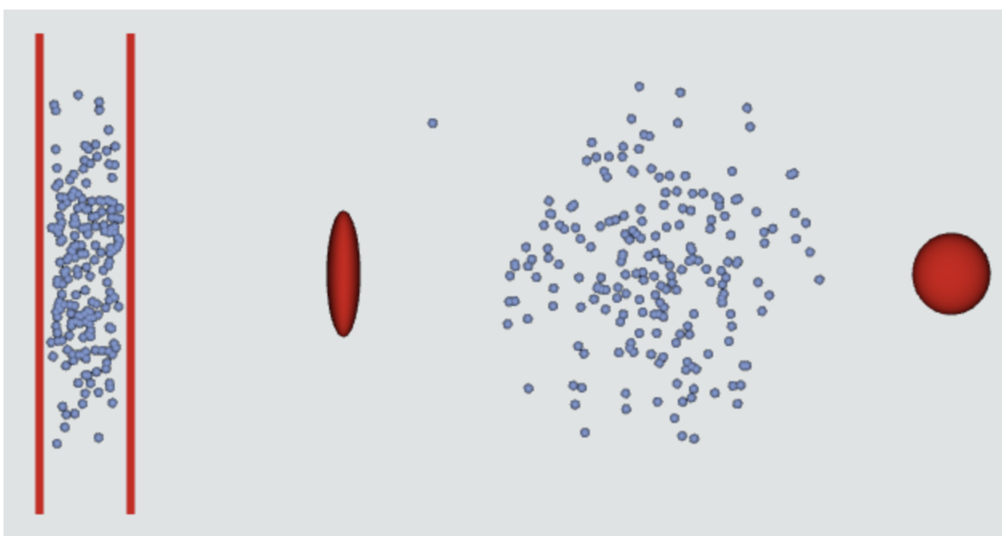


Figure 2.3: This figure illustrates how the water molecules tend to take the shape of the tissue, taken from `https://rodben.github.io/DTI_Visualization_Project/`.

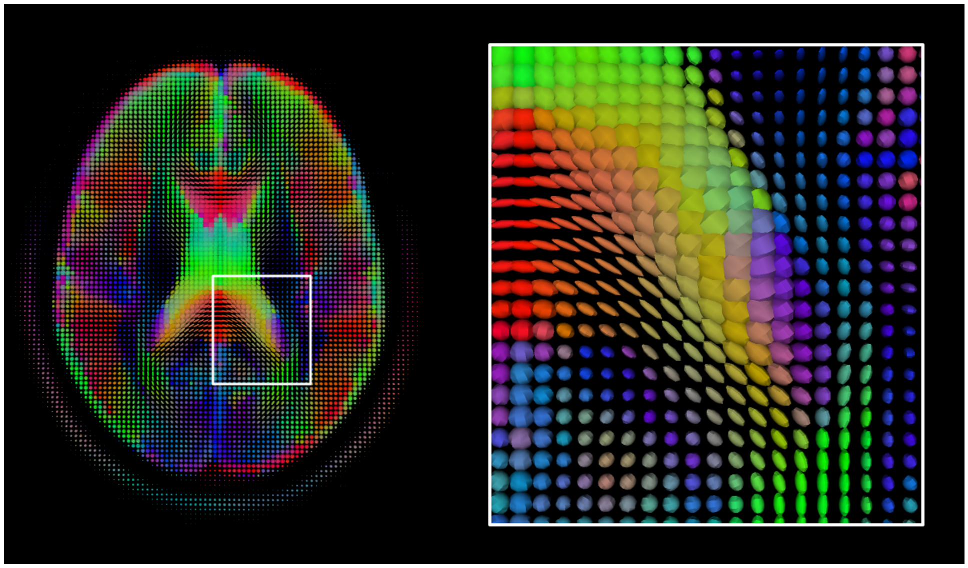


Figure 2.4: A sample visualization of Diffusion Tensor Imaging. Taken from https://rodben.github.io/DTI_Visualization_Project/.

2.3 Processing of MRI Connectivity Data

2.3.1 Acquisition and Preprocessing

As described above, diffusion tensor imaging (DTI) and functional magnetic resonance imaging (fMRI) are two commonly used imaging techniques to study the structural and functional connectivity of the human brain. Whereas DTI measures the diffusion of water molecules in brain tissue, allowing for the reconstruction of white matter tracts, fMRI measures changes in blood oxygenation levels that are associated with neural activity. To acquire DTI data, a series of diffusion-weighted images are acquired in different directions, and a diffusion tensor model is then fit to the data to estimate the orientation and strength of the diffusion in each voxel [14]. For fMRI, a series of blood oxygenation level-dependent (BOLD) images are acquired while the participant either is at rest or performs a task [87].

After data acquisition and prior to connectivity analysis, preprocessing of these images is required to address various sources of noise and artifacts. For DTI data, preprocessing typically involves correcting for eddy currents, motion, and gradient nonlinearity distortions [70]. For fMRI data, preprocessing typically involves correcting for head motion, slice-timing, and physiological noise, as well as spatially smoothing the data and registering it to a common brain space [103].

2.3.2 Fiber Tracking and Connectivity Matrix Construction

Once the DTI data has been preprocessed, fibre tracking algorithms can be used to reconstruct the white matter tracts in the brain [93]. Fibre tracking involves seeding a region of interest and following the estimated direction of the diffusion in each voxel to generate a trajectory through the white matter. The resulting tracts can then be used to construct a connectivity matrix, where the rows and columns correspond to different brain regions, and the values represent the strength of the connections between them [60].

For fMRI data, functional connectivity analysis can be used to identify regions of the brain that are coactivated during rest or a task [20]. This is typically done by computing the temporal correlation between the BOLD time series of different brain regions and then thresholding the resulting correlation matrix to identify the strongest connections.

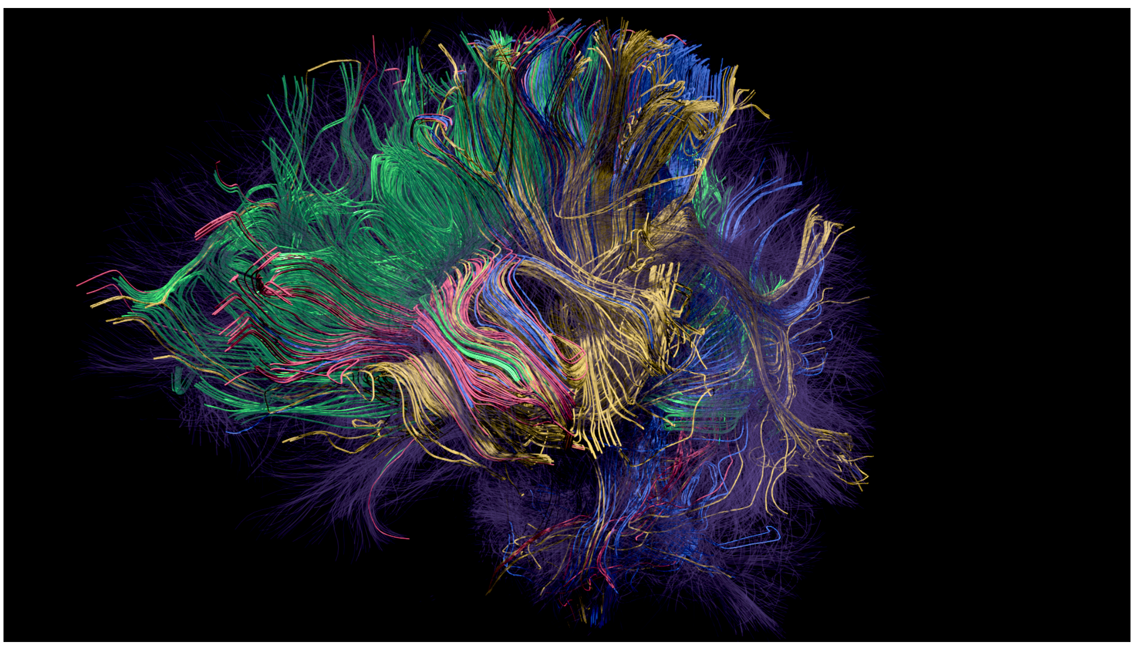


Figure 2.5: A “brain wiring” diagram visualized from tractography data (white matter tracts of the brain).

2.3.3 Network Analysis

Once the connectivity matrix has been constructed, graph theory can be used to analyze the network properties of the brain [29, 109]. Graph theory provides a framework for characterizing the topology of complex systems, such as the brain, in terms of measures such as degree, clustering coefficient, and betweenness centrality. These measures can be used to identify hubs or highly connected regions in the brain, as well as to investigate the relationship between the brain's network properties and various cognitive or clinical measures.

2.4 Data Representation

Graph theory has been very important in recent efforts to understand how complex systems are put together and how they work. Since nervous systems are complex, it makes sense to think that graph theory could be useful in neuroscience. Neural connection matrices can easily be used to make graph-based models of brain networks. In the graph, each row or column in the matrix that represents a different part of the brain is shown as a node, and the values in each matrix element are shown as edges. A network can be shown as both a matrix and a graph, and many problems in graph theory can be formulated and solved using matrix theory.

2.4.1 Matrices

A two-dimensional matrix is often used to show how every pair of nodes in a network are linked to each other. Each row and column in this matrix represents a different node, and the information about the link between regions i and j is stored in the matrix element at the intersection of the i^{th} row and j^{th} column. This representation, entitled "connectivity matrix" [118] is an important part of network analysis and is the basis for almost all of the analytical methods in connectomics; you can see an example of a connectivity matrix in Figure 2.6. Since both matrix and graph representations are the same, we can use either to study how brain networks are connected.

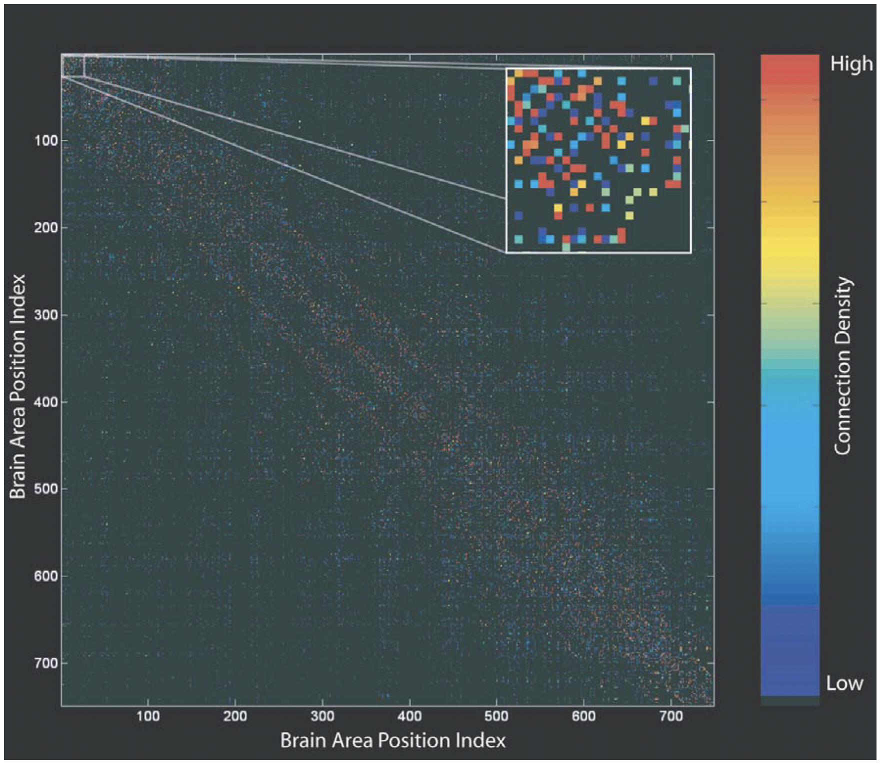


Figure 2.6: This figure illustrates a sample connectivity matrix for 750 brain regions of interest. [50]

2.4.2 Networks and Graphs

The Swiss mathematician Leonhard Euler is considered the first person to use a graph to explain a real-world system (1707-1783). In 1735, Euler lived in Königsberg Prussia (now Kaliningrad, Russia). The city was built around seven bridges that crossed the Pregel River and connected the two main riverbanks and two islands in the middle of the river. At the time, a big question was whether or not you could walk all the way around town by crossing each bridge only once. Euler solved this problem by showing the seven bridges as connected edges and the four land masses separated by the river as nodes (Figure 2.7). He was able to show that for such a walk to be possible, no more than two nodes (the places where the walk starts and ends) should be connected to the rest of the network by an odd number of edges. In reality, each of the four nodes in the Königsberg network had an odd number of edges. This made it impossible to make a path around the city that only crossed each bridge once. Euler proved once and for all that the city's bridges and islands were set up in a way that made the “Königsberg walk” impossible from a topological point of view. Euler’s analysis

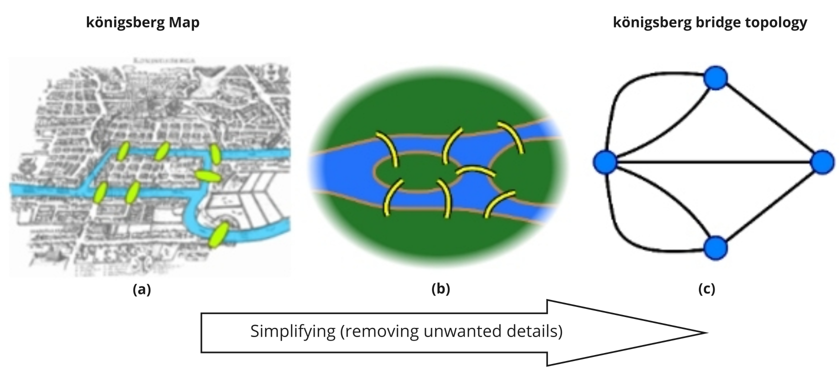


Figure 2.7: This illustration shows how Euler solved the problem known as “Königsberg walk” by simplifying the complex map of Königsberg (a) and the bridges connection into a topological graph (c)

is important not because of the small details of Königsberg’s geography in the eighteenth century but because it ignored so many of those details and instead focused on what became known as the “topology” of the problem (Figure 2.7 (c)). The topology of a graph describes how the connections between the parts of a system are set up. In fact, Euler’s graph is mostly about the bridges that connect islands and riverbanks. It has nothing to do with the length of the bridges or the distances between them, or any other physical feature of Königsberg. In theory, the results of this and any other topological analysis will stay the same even if there is a continuous change in space across the whole system. If we consider taking a physical map of Königsberg and making it bigger or smaller, spinning it, reflecting it, or making it longer, none of these or any other continuous changes to space will change the number of bridges that connect a certain island to the rest of town.

In complex network science and, more specifically, brain network science, there are three basic ideas of graph topology:

(1) Small-worldness is a complex network property that describes the balance of local and global connectivity. Small-world networks have high clustering, which means that nodes tend to be connected to their neighbours, and short path lengths, which means that nodes are connected to distant nodes via only a few intermediate connections. The brain connectome is thought to be small-world-like, optimized for efficient information processing [136].

(2) Degree distribution of a network is a measure of the distribution of connections between nodes. A node's degree in the brain connectome is determined by the number of connections it has with other nodes. The degree distribution can be used to identify brain regions with a high degree of connection to other regions, known as hub regions [118].

(3) Modularity is the presence of distinct modules or communities within a network. Modularity in the brain connectome refers to the network's arrangement into separate functional or anatomical modules that are highly coupled inside the module but less connected to regions outside the module. Modularity is regarded to be a crucial component of the brain connectome that enables the effective processing of information within diverse functional networks [118]. The discovery of modules in the brain connectome can reveal insights into the brain's functional organization and how different brain regions collaborate to complete specific tasks.

There is also growing interest in splitting a network into a small core or rich club of highly connected high-degree hubs and a larger perimeter of low-degree nodes that don't connect to each other as often [33]. Important work has also been done to find a network's topological patterns, which are the basic building blocks of connection characteristics between small groups of three or four nodes that happen more often than would be expected by chance.

2.4.3 Graph-theoretic analysis of the brain

Nodes and edges are the most basic parts of a network, and they must be described exactly for a graph theoretical model of network structure to make sense [30]. Unfortunately, there is no one method that can measure all of the important spatial and temporal dimensions of brain networks. This means that if you want to look at connectomics at different scales, you have to use distinctive methods of measurement. Because the network is shown abstractly as a set of nodes and edges, graph theory gives us a common way to talk about its topology, no matter how big or small it is or how it is measured.

The first graph-theoretic analysis of human brain *functional* networks used functional connection matrices made from data from functional MRI and M/EEG [119, 42, 110, 2]. Correlation or coherence between time series collected at different brain sites (nodes) was looked at for every possible pair of nodes, and pair-wise correlations were set at random thresholds to make binary edges that make up a graph of the large-scale functional network. It was found that the functional connectivity networks in the human brain are organized in the same way as the anatomical networks of the macaque, cat, and C. elegans (i.e. roundworm), as well as a wide range of other naturally complex systems.

The first graph-theoretic studies of the human brain's *anatomical* networks were based on tractography analysis of diffusion MRI data and structural covariance analysis of traditional MRI data [60, 61, 3]. Regardless of the imaging modality used to create the connectivity matrix, anatomical networks of the human brain have been found to have the same complex topological features. Functional MRI networks, for example, are small-world, have hubs and a modular, hierarchical structure, and seem to be driven by the need to cut down on wiring costs (estimated by the Euclidean distance of edges [131]). In fact, trade-offs between space constraints (such as reducing the cost of wires) and topology are an important and unchangeable part of human brain networks [15, 49, 17].

2.5 Visualization

Connectome visualization techniques have been rapidly evolving in recent years. Researchers have developed a variety of different visualization methods to display the intricate connections between brain regions in the connectome. In this section, we will some of the most common types of visualizations for brain connectome data, including their strengths and limitations.

Connectograms (Figure 2.8-B) are one of the most common methods for visualizing the brain connectome. They are circular plots that show the patterns of connectivity between different brain regions. Each brain region is represented as a node in a connectogram, and the connections between regions are represented as edges. The strength or directionality of the connections can be represented by the thickness or colour of the edges. Connectograms can be used to identify hub regions with strong connections to many other regions as well as to visualize the overall network structure of the brain [130]. However, for large or complex datasets, connectograms can be difficult to interpret.

Matrix plots (Figure 2.8-E) depict connectivity patterns between brain regions in the form of a matrix. Each row and column represent a different part of the brain, and the cells in the matrix represent the strength or directionality of the connections between them. Matrix plots can be used to identify specific connectivity patterns, such as communities or modules of brain regions that are strongly connected to one another. Similar to connectograms, though for large or complex datasets, matrix plots can be difficult to interpret [118].

Brain surface visualizations (Figure 2.8-A) or cortical surface maps show the cortical surface of the brain as a two-dimensional map. Each brain region is represented by a coloured patch, with different colours representing different connectivity measures, such as connection strength or directionality. Surface visualizations are useful for identifying specific regions involved in a specific functional network or task. They do not, however, provide information about brain connectivity patterns in subcortical regions [45].

Three-dimensional (3D) visualizations (Figure 2.8-C) such as fibre tractography, which is a 3D visualization of the brain connectome, allows you to see the anatomical connections between different brain regions in 3D space. Fibre tractography reconstructs the trajectories of white matter fibres in the brain using diffusion-weighted magnetic resonance imaging (dMRI). These 3D visualizations can help identify specific white matter tracts that connect different brain regions as well as understand the overall organization of the brain's white matter architecture. However, for complex datasets, fibre tractography can be difficult to interpret, and the accuracy of the tractography is dependent on many factors, including the quality of the dMRI data and the tractography algorithm used [93].

Network graphs (Figure 2.8-D) are another type of visualization for connectome data that show brain regions as nodes and connections between regions as edges. Network graphs can be used to investigate the brain network's small-world properties, which are characterized by high clustering and short path lengths between nodes. Network graphs can also be used to identify highly interconnected communities or modules of brain regions [29].

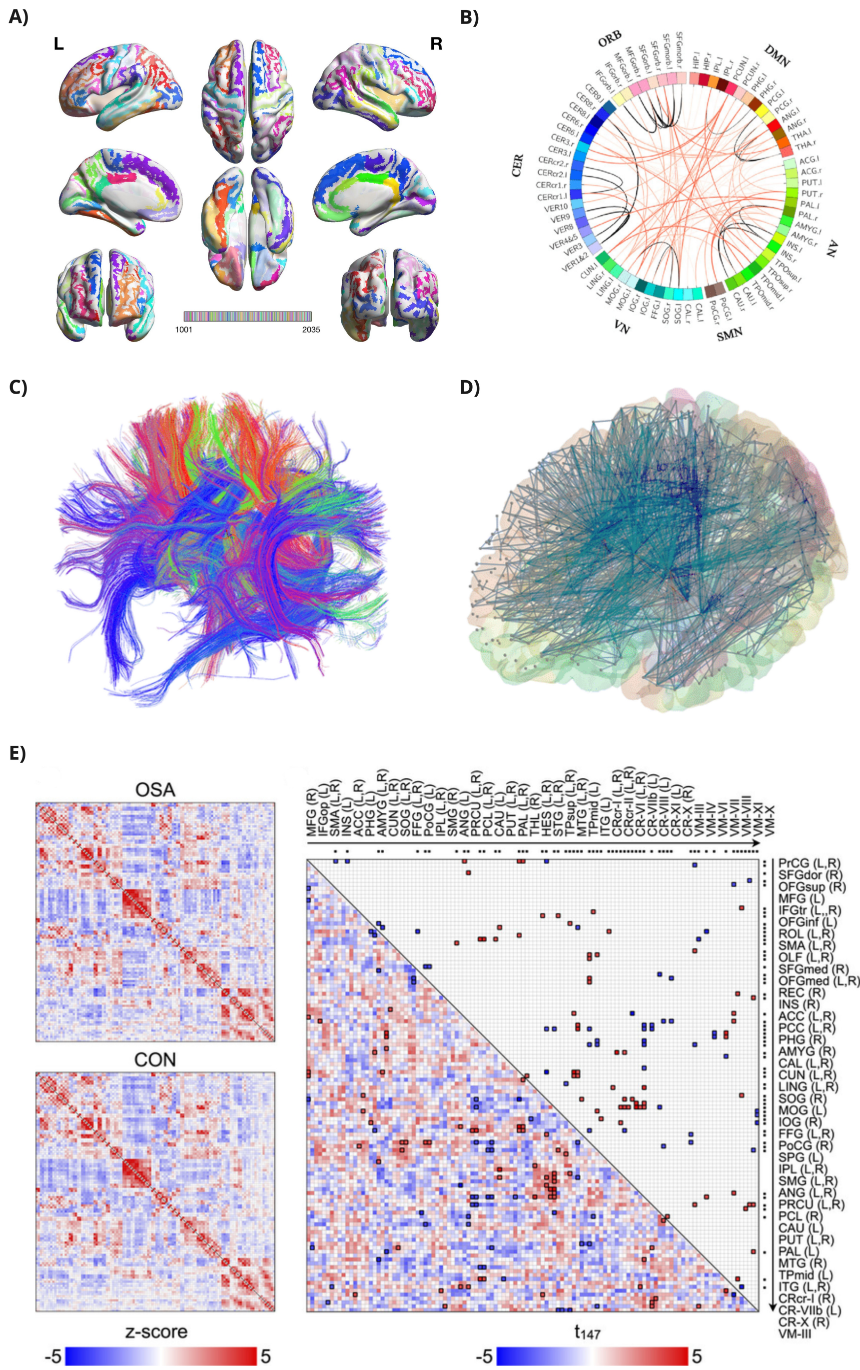


Figure 2.8: Examples of popular connectome visualization techniques: A) Brain Surface visualization [141], B) Connectogram [86], C) Three-dimensional fibre tractography [6], D) Network graph [6], E) Matrix plots [100].

2.6 Clinical Applications

Pathological changes or lesions that start in one part of the nervous system often spread through axonal fibres to affect other parts – similar to how a stone dropped into a pond causes ripples. Galen, a Greek physician and philosopher (129-216 AD), was one of the first people to notice this Finger et al. [44]. More than 1000 years later, the Greek term "diaschisis", meaning "shocked everywhere," began being used to describe brain areas that stopped working despite no damage to those areas but rather through links to areas that were damaged.

Clinicopathological correlation supporters in the 19th and 20th centuries also recognized the importance of neural connections in illness. This led to the definition of a new class of neurological disorders called "disconnexion" disorders [55]. Connectomics and graph theory offer a good way to map, track, and predict disease spread patterns in brain disease [50, 120]. From this point of view, changes in the brain caused by illness can be described at the level of network connectivity or topology. Clinical use of connectomics is now proving Galen and others' early ideas by showing that the network architecture of the brain controls how diseases spread in the brain. Neurodegeneration, for example, happens in networks that are both functionally and structurally connected [105, 113], pathology builds up in highly connected brain hubs [28, 36], and the cognitive effects of a brain injury or disease are closely linked to the way the affected area is connected [135]. Computational models of the dynamics of large-scale brain networks have shown that the functional effects of "lesions" depend on how the "lesioned" nodes are connected [8, 31, 62]. Further, the success of invasive and noninvasive brain stimulation treatments for a wide range of diseases is very dependent on how well the stimulation site is connected [51, 107]. These findings indicate that knowing the topology of a network can help in predicting the severity of an injury and the likelihood a patient will get better or recover [50]. Additionally, connectomics can assist in discovering personalized treatments that are most likely to be effective.

2.7 Virtual Reality Applications

Virtual reality (VR) is being increasingly used in the medical domain for medical education, surgical planning and training, patient education and rehabilitation. In the following section, we describe related work in the field of virtual reality in neuroanatomy and surgery.

2.7.1 VR in Medical Education

VR in education offers numerous potential advantages, such as broadening sensory perception, presenting a heightened version of reality, enhancing student engagement, accommodating individual learning styles, promoting exploratory learning over deductive reasoning, facilitating active participation, encouraging interaction, enabling comprehensive analysis, and providing insight into the interconnectivity of various concepts [80, 114, 95, 71]. In a recent review by Samadbeik et al. [111], which explored the potential of technology in medical education, found that the use of virtual reality demonstrated enhanced learning outcomes in 74% of the trials reported and resulted in improved accuracy in medical practice in 87% of the studies. Collectively, the findings indicate that virtual reality has the potential to significantly enhance the capabilities of various healthcare professionals.

The results were not as significant in another meta-analysis that assessed the effectiveness of virtual reality (VR) as a training tool for healthcare professionals, measuring outcomes such as knowledge, cognitive skills, attitudes, and satisfaction Kyaw et al. [82]. The analysis revealed that, in comparison to conventional learning methods, VR resulted in only minor improvements in healthcare professionals' knowledge scores and cognitive skills. The researchers also noted that the overall certainty of the evidence was moderate to low and recommended future studies to investigate the efficacy of immersive and interactive VR.

In neuroanatomy education, Kockro et al. [79] developed the Dextrobeam VR environment, which uses stereoscopic projection for exploring spatial models of neuroanatomy. To test Dextrobeam, the authors administered an audio lecture to a group of students, coupled with either a PowerPoint presentation or a 3D animated tour on the same topic. Immediately after the lecture, the students were tested on their comprehension of the subject matter and asked for feedback on the teaching method employed. Results indicated that students who used Dextrobeam performed statistically as well as those in the 2D group. Moreover, students expressed a preference for 3D instruction in four areas: spatial knowledge, potential utility in future anatomy classes, effectiveness, and enjoyment. The authors concluded that 3D stereoscopic lectures are an effective teaching tool for conveying knowledge about the brain's anatomy. However, they recommend further research to optimize the usefulness of large-group VR systems in neuroanatomy classes.

In similar work, Stepan et al. [122] conducted a study to determine how effective, satisfying and motivating immersive VR simulations are for teaching neuroanatomy. Neuroanatomical structures were studied using either online textbooks or in a virtual reality environment. Students were then tested on the anatomy, and other measures related to learning and motivation were captured. Although there was a minimal disparity between the two groups' anatomy knowledge on pre-intervention, post-intervention, and retention assessments, participants in the VR group reported greater interest, enjoyment, and perceived usefulness in their learning experience. Furthermore, students who used VR exhibited significantly higher motivation levels than their counterparts.

2.7.2 VR in Surgical Simulation

VR has been used in the medical field to simulate operations, for example, in training in video-laparoscopic surgery, preoperative planning, and intraoperative assistance. The objective of using VR is to enhance and refine practical skills that are difficult to acquire in real-world scenarios (e.g. reducing the need for cadavers) [65, 137, 75]. A recent review on the usefulness of VR for surgical training suggests that VR can improve knowledge and skills compared to both traditional education and/or other forms of digital education [83]. Virtual environments have been shown to provide cost-effective, safe, and successful surgical training environments.

In a VR surgical simulation, virtual digital anatomical models are advantageous as they provide a three-dimensional view of organs, allow observation of their internal structures, enable the identification of relationships between organs and their topographies, and permit the creation of personalized visualizations of the human body. Furthermore, there are no restrictions on the duration of using VR in surgical simulations [145].

2.7.3 Serious Games and VR

In recent years, "serious games" have been developed with instructional and educational goals in mind. However, there are few studies that have been done to explore the potential and limits of VR games, especially when it comes to recent VR devices that offer new ways to play [96].

One exception is Billinghurst and Duenser [19], which found that immersive VR can help people learn through repetition or more complex ways of thinking. Whether one is playing a game for fun or to learn, being able to interact with others in an immersive environment can facilitate learning. Furthermore, creating games that provide users with a sense of ”flow” can enhance motivation and promote more effective learning. The authors concluded that immersion, presence, and spatial information presentation can all contribute to improving training outcomes.

In a study by Oberdörfer and Latoschik [99], a virtual training environment was designed like a game to enable learners to apply their knowledge and receive immediate feedback in an interactive manner. The results showed that the participants in the experimental group, who received the interactive 3D training, demonstrated significant improvements as opposed to the ones who didn't go through the same interactive gamified training. Moreover, As a response to the increased demand for remote and distant learning during the Covid-19 pandemic, Souza et al. [117] developed a virtual reality game aimed at improving neuroanatomy teaching and learning. Their findings suggest that the game has the potential to be effective for individual and group learning, as well as for distance education. Moreover, the participants reported enjoying the game, and the authors observed a significant improvement in knowledge test performance and retention rates in the virtual condition.

Overall, the research indicates that immersive experiences are an effective tool for medical training, education, and simulation, and users find VR as effective as or even more effective than traditional learning and training methods. However, the impact of immersive experiences varies depending on the type of activity, the virtual world style, and the VR system setup. Building on the positive findings described in the related research above, we developed an immersive VR connectome visualization application called VRNConnect to facilitate the teaching, learning and analysis of neuroanatomy, specifically of brain connectivity data. We describe VRNConnect in the next chapter.

Chapter 3

VRNConnect: A virtual reality immersive environment for exploring brain connectivity data

An abstract version of this chapter was submitted to OHBM 2023, and a full paper has been submitted to the Journal of Medical Information Research:

- Jalayer S., Xiao Y., Kersten-Oertel M. *VRNConnect: An interactive virtual reality platform for connectomic data exploration* was accepted to Organization of Human Brain Mapping (OHBM) 2023.
- Jalayer S., Xiao Y., Kersten-Oertel M. *VRNConnect: A virtual reality immersive environment for exploring brain connectivity data.* Submitted to Journal of Medical Information Research (JMIR).

3.1 Introduction

Virtual Reality (VR) technology has rapidly advanced in recent years, offering new and innovative ways to visualize and interact with data in a purely digital environment. In the clinical domain, VR is increasingly being used to explore anatomical and imaging data. In the case of brain connectivity data, i.e. the mapping of the connections within the brain, studies have shown that visualizing the data in 3D can outperform 2D static representations, particularly when dealing with complex tasks [4]. This has led to an increased interest in using VR as a tool to study the human brain, particularly in the area of connectomics.

Connectome data, which can be obtained through various imaging techniques, including functional MRI (fMRI), diffusion tensor imaging (DTI), and magnetoencephalography (MEG), among others, is vital to understanding the underlying mechanisms of brain function and behaviour. The study of brain connectivity data is not only essential to understanding how the brain works but also happens in the case of neurological and psychiatric disorders and how we can treat these disorders.

The goal of visualizing brain connectivity data are various, including enabling a better understanding of brain structure and function, facilitating the identification of patterns and relationships and guiding treatment decisions. The purpose of this research was to develop a VR connectome, ”VRNConnect” application that can be used to visualize and interact with neuroimaging data in a virtual environment to facilitate these types of tasks. The primary objective of VRNConnect was to provide an immersive and intuitive way to explore the connectome. The VRNConnect application, which will be made available to the public, is expected to be of great value for educational and analytical purposes in the field of neuroimaging.

In this chapter, we provide a comprehensive overview of the methodology used for developing this application, including the design and implementation of the VR environment, the methods used to integrate the neuroimaging data, the interactions and features of the application as well as the results of a preliminary user study conducted to evaluate the application's usability.

3.2 Related Work

There are many tools that can be used to study connectome data in either 2D or 3D [90]. Most 3D tools visualize the connectome as node-link diagrams, in which nodes are placed in relation to their corresponding anatomical locations, and links between nodes show how these anatomical locations are connected to each other. Some examples of 2D and 3D tools are the Connectome Visualization Utility [85], the BrainNet Viewer [141], and the Connectome Viewer Toolkit [54]. In general, node-link diagrams give a good overview of the whole graph, making it easy to see the relationships between nodes that are directly and indirectly connected.

Software Tool	Type of Connectivity Data		Types of visualization			VR	Defining features
	Functional	Structural	Surface	Volume	Graph		
DSI Studio [1]	x	✓	✓	✓	✓	x	Diffusion Spectrum Imaging (DSI) analysis Brain connectivity analysis in MRI data Tractography visualization and analysis
Brainnetome - DiffusionKit [2]	x	✓	✓	✓	✓	x	Large-scale analysis of brain functional and structural connectomes Advanced visualization and analysis tools Integration with other imaging and neuroimaging data
Connectome Explorer [3]	x	✓	x	✓	✓	x	Visualization and analysis of brain connectivity data Interactive exploration of brain connections Support for a variety of connectivity data formats
VidView [4]	✓	x	✓	x	✓	x	Video-based analysis of brain connectivity data Interactive exploration of brain connections Supports a variety of imaging modalities
BrainBundler [5]	✓	x	✓	x	✓	x	Analysis and visualization of brain connectivity data Detection of connections between brain regions Support for multiple imaging modalities
Fubraconnec [6]	✓	x	✓	x	✓	x	Study of brain connectivity based on diffusion MRI data Advanced visualization and analysis tools Support for a variety of connectivity data formats
REST [7]	✓	x	x	x	✓	x	Analysis of resting-state functional MRI data Identification of patterns of brain connectivity Advanced visualization and analysis tools
CONN [8]	✓	x	✓	✓	✓	x	Functional and structural connectivity analysis in fMRI data Advanced visualization and analysis tools Support for multiple imaging modalities
BRAINtrinsic [9]	✓	x	x	x	✓	VR Compatible	Study of brain connectivity and network organization using intrinsic functional connectivity MRI (fcMRI) data Advanced visualization and analysis tools Integration with other neuroimaging data and tools
BrainTrawler [10]	✓	x	x	✓	✓	x	Exploration and analysis of brain connectivity data, with a focus on the human brain and functional MRI (fMRI) data Advanced visualization and analysis tools Integration with other neuroimaging data and tools
Connectome Viewer [11]	✓	✓	✓	✓	✓	x	3D visualization and exploration of connectome data Interactive exploration of brain connections Support for a variety of connectivity data formats
Connectome Workbench [12]	✓	✓	✓	✓	✓	x	Open-source platform for analyzing brain connectivity data Advanced visualization and analysis tools Support for multiple imaging modalities
BrainNet Viewer [13]	✓	✓	✓	✓	✓	x	Visualization and exploration of brain connectivity data Interactive exploration of brain connections Support for multiple imaging modalities
Brain Connectivity Toolbox [14]	✓	✓	x	x	✓	x	MATLAB-based toolbox for analyzing and visualizing brain connectivity data Advanced visualization and analysis tools Integration with other neuroimaging data and tools
Visual Connectome [15]	✓	✓	✓	x	✓	x	Visualization and analysis of brain connectivity data Interactive exploration of brain connections Support for multiple imaging modalities
MNET [16]	✓	✓	x	x	✓	x	Exploration and analysis of brain connectivity data with a focus on multiscale analysis Advanced visualization and analysis tools Integration with other neuroimaging data and tools
BrainX3 [17]	✓	✓	x	✓	✓	VR Compatible	Analysis and visualization of brain connectivity data with a focus on spatiotemporal analysis Advanced visualization and analysis tools Integration with other neuroimaging data and tools
AlloBrain [18]	✓	✓	x	✓	x	VR Compatible	Analysis and visualization of brain connectivity data, with a focus on the human brain Advanced visualization and analysis tools Integration with other neuroimaging data and tools
NeuroCave [19]	✓	✓	x	x	✓	VR Compatible	Virtual reality platform for exploring and visualizing brain connectivity data Interactive exploration of brain connections Support for a variety of imaging modalities
TempoCave [20]	✓	✓	x	x	✓	VR Compatible	Virtual reality platform for exploring and visualizing the temporal dynamics of brain connectivity data Interactive exploration of brain connections Support for a variety of imaging modalities
VRNConnect	✓	✓	x	x	✓	**True Immersive VR**	Virtual reality platform for exploring and visualizing brain connectivity data Interactive visualization of functional and structural connectivity data. Advance graph network metrics and analysis

Table 3.1: Features of various brain connectivity, analysis and visualization tools with VRNConnect.

Table 3.1 gives an overview of commonly used tools for visualizing brain connectivity datasets. In the table, we focus on software that uses graph visualizations of a connectome and/or that supports VR headsets, as these are the most related tools to our developed software. Virtual reality tools which allow for visualization of connectivity data include AlloBrain [125], BrainX3 [10, 16],

[1] [41]
[2] [24]
[3] [18]
[4] [132]
[5] [23]
[6] [52]
[7] [116]
[8] [97]
[9] [34]
[10] [53]
[11] [54]
[12] [64]
[13] [141]
[14] [81]
[15] [133]
[16] [144]
[17] [10]
[18] [125]
[19] [73]
[20] [142]

BRAINtrinsic [35] and NeuroCave [73]. The majority of current connectome visualization tools are desktop applications (even those that allow for VR), whereas VRNConnect, is developed specifically for a virtual reality (VR) environment, which has been shown to allow users to move things around, identify and classify objects and images, and understand complex scenes, more efficiently, e.g. [21, 47, 89]. Furthermore, in the specific case of 3D representations of graphs, VR visualizations have been shown to be better at relaying information than their non-immersive counterparts when combined with the highlighting of nodes Alper et al. [5].

Despite the fact that some of the visualization toolkits mentioned above have features such as visualizing 3D graphs, highlighting nodes, etc., to the best of our knowledge, none of them make use of the full immersion of a virtual reality environment. Rather, they are simply VR-compatible and allow the user to view a 3D projection of a 2D scene (Desktop/Web mode) with a VR headset. (i.e. when you watch a 3D movie with 3D glasses, you don't feel like being in the middle of everything that's happening, you can't move around or watch the scene from another angle, and you are just seeing objects in 3D with volume and depth, which is not full immersion). VRNConnect, in contrast, was designed exclusively for VR, and all interactions and visualization techniques are optimized for a fully immersive environment. Although this approach may be more resource intensive when viewing larger datasets with more nodes and connections, it enabled us to design a more intuitive way to explore brain connectivity data, whether for education or analytical analysis. VRNConnect also has many of the VR features of the visualization tools presented in Table 3.1; similar to CONN [138], DSI Studio [143], Brainnetome [69], etc., as we integrate functionality from existing toolboxes, by connecting our application to the Brain Connectivity Toolbox for Python [108] which provides a comprehensive collection of graph analytic methods for investigations of functional and structural brain connectivity.

3.3 Methods

3.3.1 Overview of the system

An overview of the developed application, starting from data input to visualization of the final results for the user in VR, is shown in Figure 3.1. As can be seen in the diagram, input into VR-Connect requires connectivity data in matrix form and a parcellation of the brain (in a *CSV* (comma separated value) file). C# scripts and the Unity 3D game engine (v2021.3) are used to create the brain connectivity network graph using the structural connectivity matrix. For graph analysis and network measurements, the Brain Connectivity Toolbox [108] Python extension is used. The *Oculus integration SDK v38* was used for interactions with the Oculus headset [104].

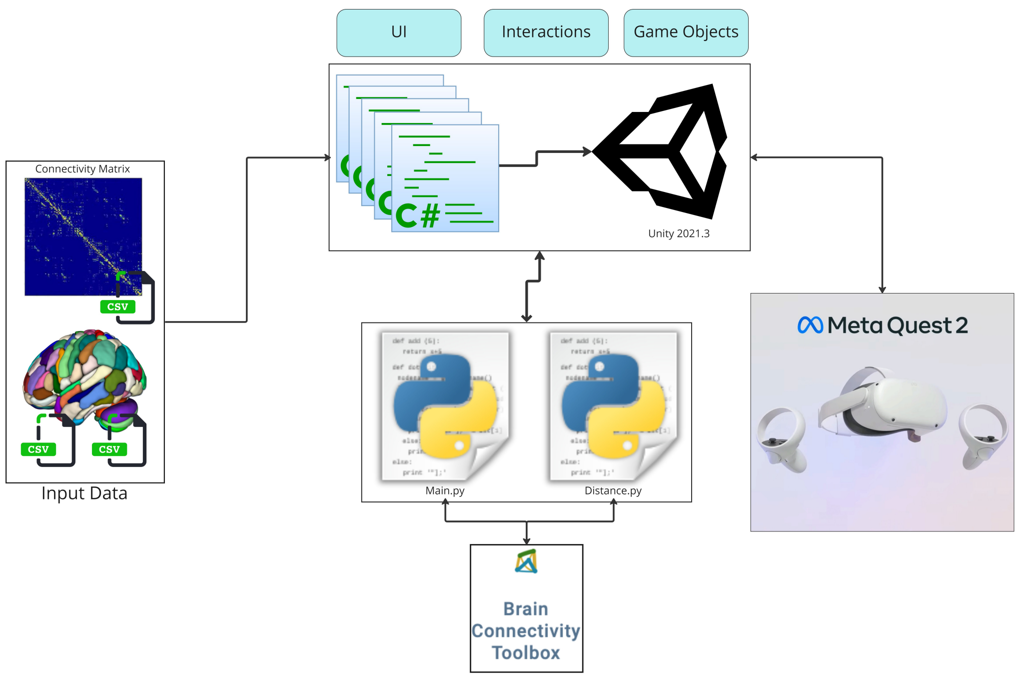


Figure 3.1: VRNConnect architecture

3.3.2 Example Data Preperation

Though not part of our system, we give a high-level description of how we created the connectivity data for input into VRNConnect for our study. We followed the B.A.T.M.A.N tutorial Tahedl

[124], which is a comprehensive guide for tractography analysis and visualization that uses MRtrix3 Tournier et al. [127], FSL Smith et al. [115]) as well as other optional packages. A number of processing steps were followed to create the structural connectivity matrix and parcellation from the sample input data (*MR*, *DWI* and *T1-high-resolution* images). The four main steps of the tutorial (see Figure 3.2) are as follows:

(1) **Preprocessing:** Denoising, unringing, motion and distortion correction, etc.

(2) **Fiber orientation distribution (fODs):** Estimating the orientation of the fibres (voxel by voxel) taking into account the position and the tissue for streamline creation.

(3) **Whole brain tractogram:** Creating the tractography data and normalizing all estimated results.

(4) **Connectome construction:** Generating the connectivity matrix or the connectome by mapping the tractography data on top of a brain atlas and finding the connections going in/out of a region in the atlas parcellation.

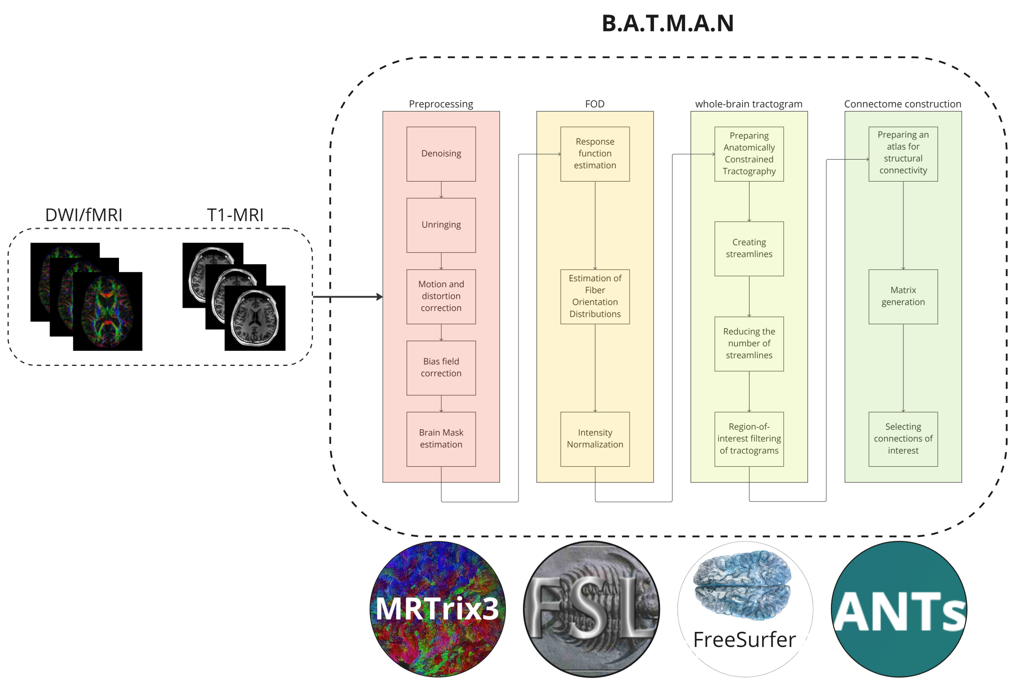


Figure 3.2: The B.A.T.M.A.N tutorial follows a number of steps, as shown in the figure.

The result of the B.A.T.M.A.N tutorial using the provided sample data is a 2D *379x379* structural matrix with *180* parcellation areas on each cortical hemisphere based on the HCPMMP atlas (v 1.0), plus *19 subcortical regions* as depicted in Figure 3.3.

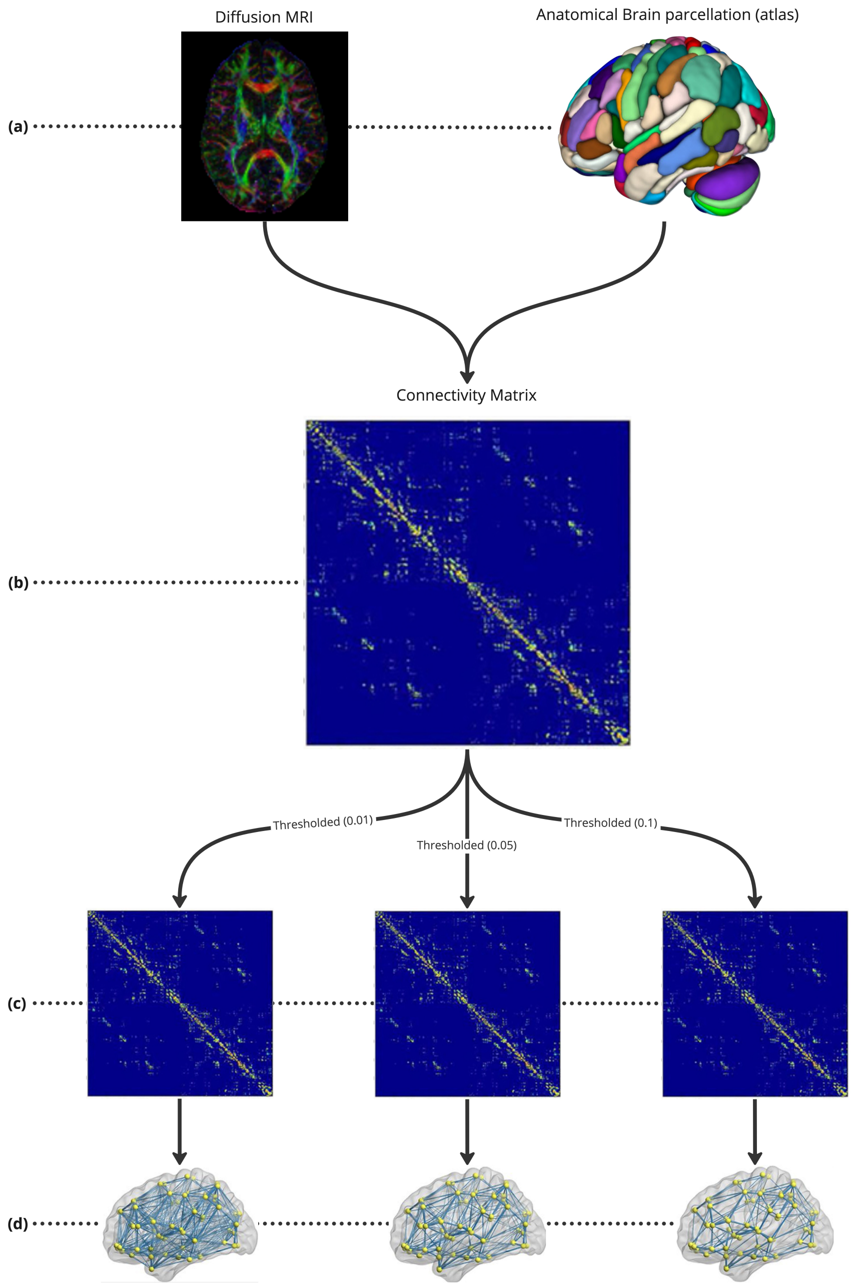


Figure 3.3: High-level overview of brain connectome data preparation, (a) our input data from dMRI, alongside with a brain parcellation, results in (b) the connectivity matrix (output from B.A.T.M.A.N), (c) the different thresholding introduced on the data in order to produce (d) connectome graphs with variable edge densities.

3.3.3 VRNConnect Implementation

As mentioned above, we chose Unity 2021.3 game engine for application development. To support the best integration of functionalities and have the latest features of the Meta Oculus Quest 2 headset, the Oculus Integration SDK (v38) [104] was used. C# was used for the scripts to communicate with the Unity engine, and Python v3 was used as a bridge between the C# scripts of Unity and Brain Connectivity Toolbox python library (bctpy) [109] which was used in order to provide graph analysis and network measurements for our connectome graph. The Human Connectome Project Multi-modal Parcellation version 1 (HCP-MMP1) [57] atlas (containing information about the regions of the atlas and colour-coded information) was added as assets for development.

As can be seen in Figure 3.1, the connectivity data is loaded on the fly at run-time, using a C# script in Unity to read the corresponding CSV files and to start instantiating the objects (nodes/edges), calculating the centre of mass, assigning the atlas region information and colours to each node, in a nutshell, generating the connectome graph. This is an important feature of our application as it gives users the ability to load their own data to explore, interact with, and run analyses on. The following input is required for users to load their own data:

- CSV file containing the 2D connectivity matrix - whether structural or functional.
- CSV file containing the regions of the atlas and information regarding each region (note: this needs to be the same atlas parcellation that is used to create a connectivity matrix in order for the mapping of nodes/regions to be done properly).
- CSV file containing colour-coding of regions in the brain atlas (optional: if not provided, all nodes will have the same grey colour).

3.3.4 Visualization

To visualize the connectome data, we use a 3D graph (nodes and edges) where the colour coding of the nodes is obtained from the HCP-MMP1 atlas parcellation as depicted in Figure 3.4. Edges connecting nodes are visualized as a gradient of the two colours of the nodes they interconnect, and weight is visualized by adjusting the thickness of the edge. To calculate the thickness, since we could not use the raw strength values from the connectivity matrix because the upper bound was not limited, and the lower bound of many was almost close to zero, we mapped all the weights between lower (least visible diameter for a rendered obj) and upper diameter (same as the node's diameter). In addition, a brain mesh created from a segmentation of the MR images is also visualized for greater anatomical context. The mesh was generated using 3D Slicer [43] and added to the resource folder of our Unity project. In order to help better align the brain mesh with our connectome graph, we calculate the centre of mass for the graph during run-time, and this will be the zero origin for the brain mesh.

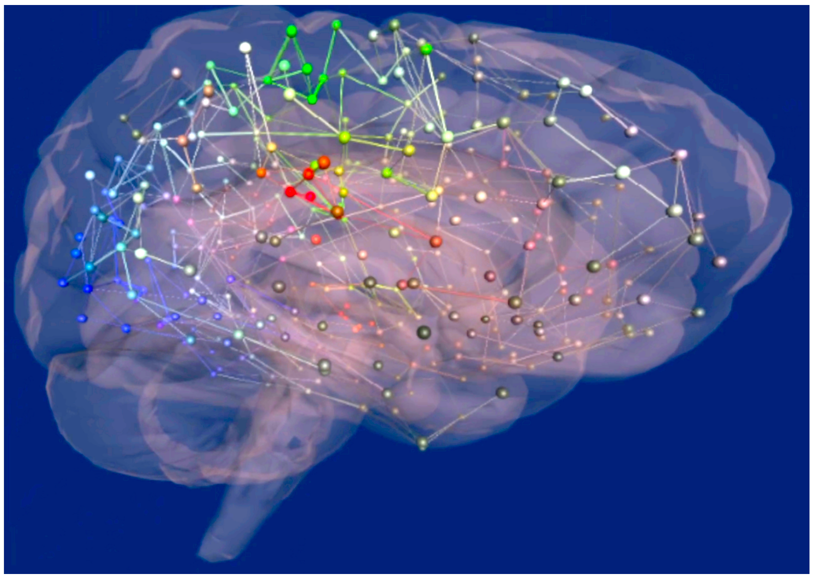


Figure 3.4: The brain structural connectivity is shown as a graph in VR. **Node colours are based on brain atlas parcellation*

3.3.5 User Interface Canvas

An interface panel was added inside the VR environment to allow the user to change some of the visualization settings at run-time. Users can manipulate the threshold, enable/disable edges, change the scale of the brain, select the algorithm to use for the shortest path and reset everything to the default settings. The interface is shown as a screenshot in Figure 3.5. As can be seen in the figure, the user can threshold the number of edges visualized 3.3 (by default, this is set to 5%). Lowering the number of depicted edges allows for smoother run-time and a more appealing visualization to the eye. It should be noted that thresholding is often used when visualizing connectivity data, where weak connections do not have to be visualized and are considered as noise. Thus, the most important connections are kept, which helps lower the number of objects rendered, allowing for a smoother and faster experience. All functionalities that you can manipulate from the interface panel are explained below:

- **Show All Edges:** With this toggle, you can enable/disable the edge visualization; in some cases having all the edges enabled seemed too distracting to the users, so we added this option for convenience.
- **Threshold:** This slider, as explained above, allows you to change the thresholding done on the data on the fly (i.e. the value 5% means that we only keep the edges that have weights larger than 5% of the maximum weight).
- **Scale:** With this slider, you can change the scale multiplier of the connectome and the brain mesh overlay from zero to 10X magnification.
- **Path algorithm:** The dropdown, which refers to the shortest path calculation method, has two options (1) Hops: Dijkstra's algorithm, and (2) Distance: Floyd-Warshall's algorithm.
- **Reset:** This button, as the name suggests, resets all the changes done in terms of visualization, selection, rotation, etc.

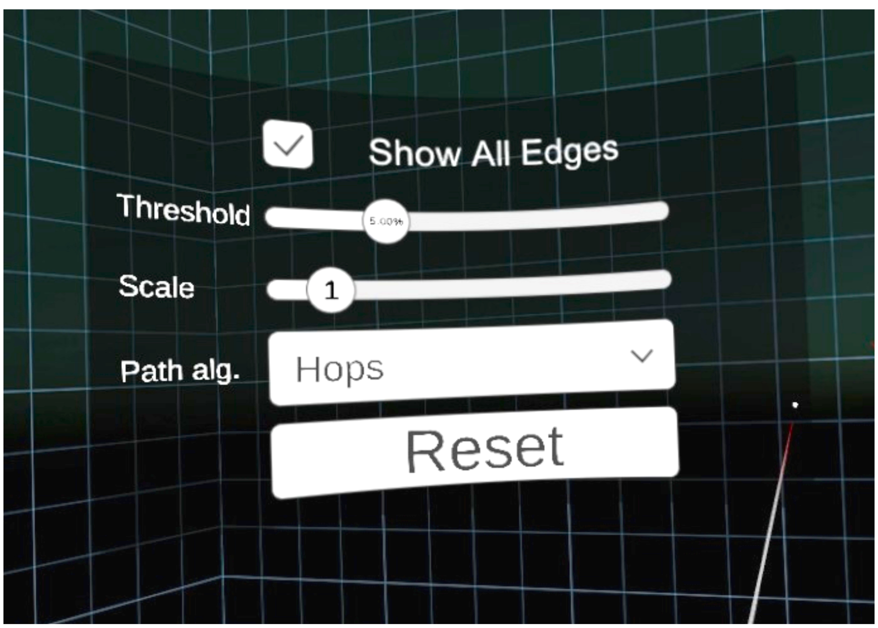


Figure 3.5: The interface panel to change visualization settings at run-time.

3.3.6 User Interaction

In order to increase the ease of use and give some versatility to the user, we implemented both controller-based and hand gesture-based interactions in our application. Both of these features were integrated using the Oculus integration SDK (v38) [104]. Although some of the features, such as hand gesture detection, are still in the early stages of development, we were able to implement the pinch gesture for selecting a node alongside the controller trigger button, which can be used for the same purpose. The controller mesh object was visualized in the virtual environment in order for the user to see the actual controls and buttons when in VR since they cannot see the outside world.

Moreover, the user can move around and rotate the brain connectivity object with the controller's Axis2D thumbstick buttons (a typical implementation in every VR application). In the current version of the application, the user cannot rotate the object using hand gestures; however, the user can walk around or even into the brain as if they were walking in the real world. As for the other interactions with the controller, the users can rotate the brain with the a/b or x/y buttons on the right/left controllers so that they can change the angle of their viewpoint as they like. A sample of Oculus controllers and key bindings is shown in Figure 3.6.

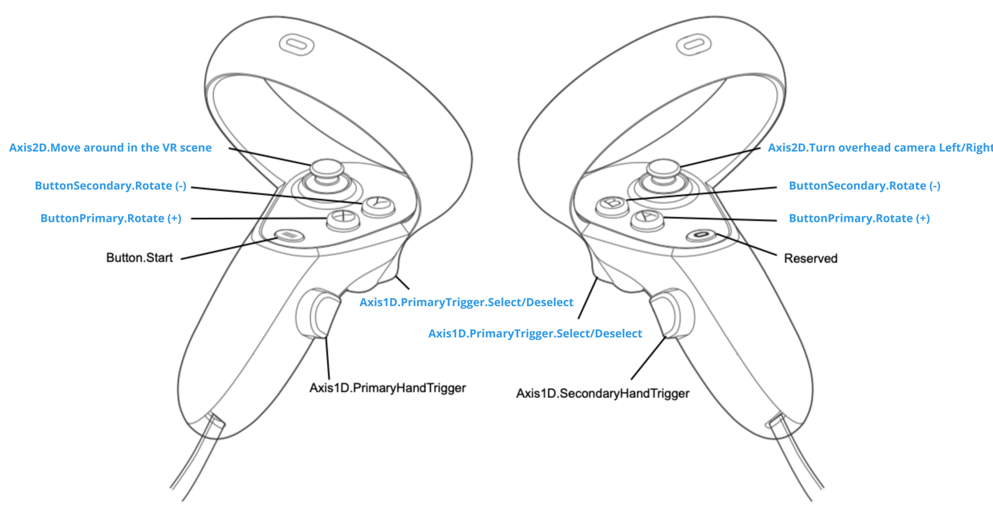


Figure 3.6: Meta Quest 2 controllers with labelled buttons and their functionality in VRNConnect *Image taken from `https://developer.oculus.com/documentation/unity/unity-ovrinput/`*

Whenever a user points to a node with the laser (the line coming out of either the hand or controllers), the node is highlighted, and also the user is presented with the node's information, i.e. the region name and the corresponding name acquired from the parcellation. If the user selects a given node (by pressing the button on the controller or pinching), an extended version of the node's data is shown on a panel attached to the user's left hand (Figure 3.7). The node information shown to the user is given in Table 3.2.

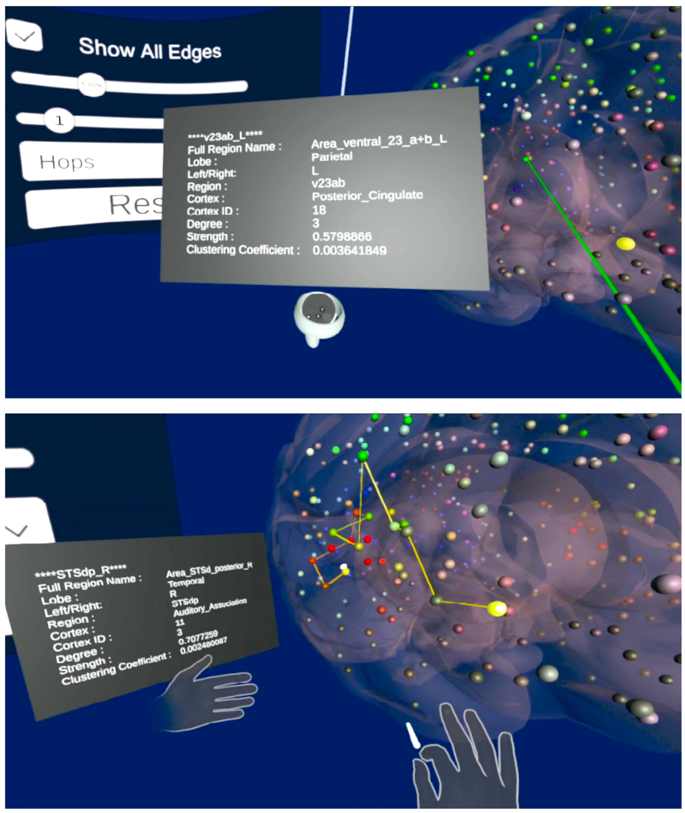


Figure 3.7: Panel showing node's region information available to the user both using hands/controller

Another feature of VRNConnect is to show the shortest path between the two selected nodes to the user. We calculate this with the help of a python script we developed in order to handle the intermediate data creation, processing of the algorithm and publishing of the results back to Unity. The shortest path can be calculated using two different algorithms, which can also be changed from the interface inside the VR. One is distant-based using *Floyd-Warshall's* [46] algorithm to consider the weight of the edges. The other algorithm only considers the least number of hops [40].

Information Title	Short description
Full Region Name	The regions name corresponding to the atlas parcellation
Lobe	The Lobe it belongs to
Left/Right	Shows whether the region belongs to the left/right lobe
Region	The regions tag corresponding to the atlas parcellation
Cortex	Depicts which part of the cortex it belongs to
Cortex ID	The ID of the corresponding cortex
Degree	Is the number of connections going in/out of a node
Strength	Is the sum of the strength of all edges going in/out of a node
Clustering Coefficient	It gives a rough idea of how well connected the area around the node is.

Table 3.2: The table shows the information viewable by the VRNConnect user when selecting a node

Screenshots of the various described features are depicted in Figure 3.8.

3.4 User Study

To evaluate the usability of VRNConnect, we conducted a user study. The participants used the Oculus Quest 2 with the Oculus link cable connected to a PC to run VRNConnect. Prior to the study, participants had to pass a developed tutorial in order to become familiar with the application and its interactions and also to calibrate their eyesight with the HMD (head-mounted display) to prevent motion sickness and dizziness.

3.4.1 Task Description

For the user study, in order to prevent distraction and since some users might not be comfortable with the VR immersive environment, a few adjustments were made from the description above. First, the sky-box (the background in the VR environment) was changed to solid dark blue instead of black with grid lines (e.g. as in the screenshots in Figure 3.8). Furthermore, all the node/edge colouring was removed except the nodes that the participants had to interact with to enable comparison across participants and tasks.

Participants performed two different tasks: (1) Selecting a node and reading a specific detail, and (2) Selecting two nodes and determining the distance/number of connections between the two nodes. For each task, 3 different sets of nodes were chosen prior to the study, and each of the tasks

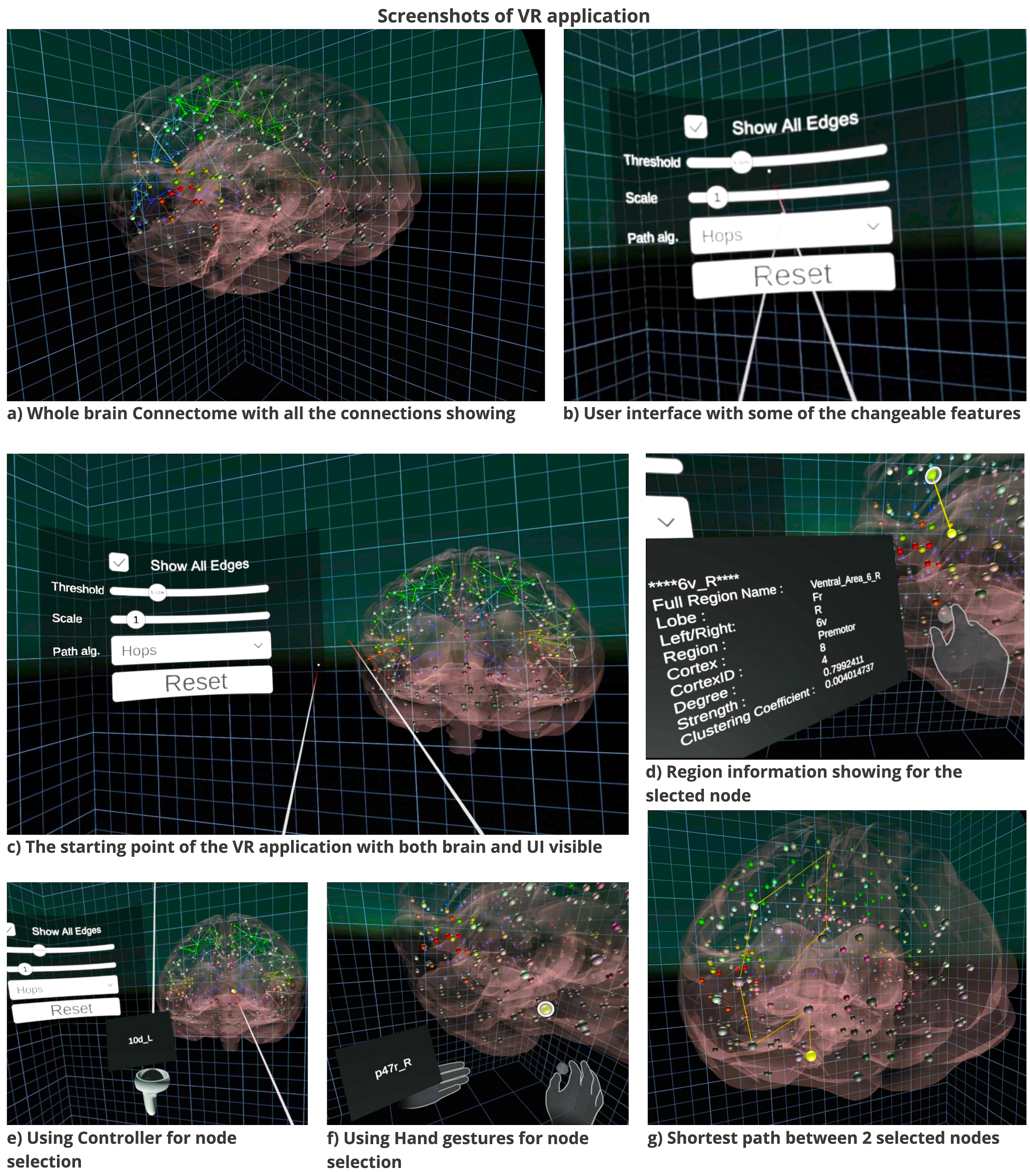


Figure 3.8: Screenshots taken from VRNConnect.

was done under one of two interaction methods: hand-based/gestures or controller. Thus in total, each participant performed 12 trials, 3 node selections (Figure 3.10 (a)), and 3 shortest paths (Figure 3.10(b)) was done under 2 interaction methods (hands and controller). The ordering of interaction technique, to start with, was randomized across subjects.

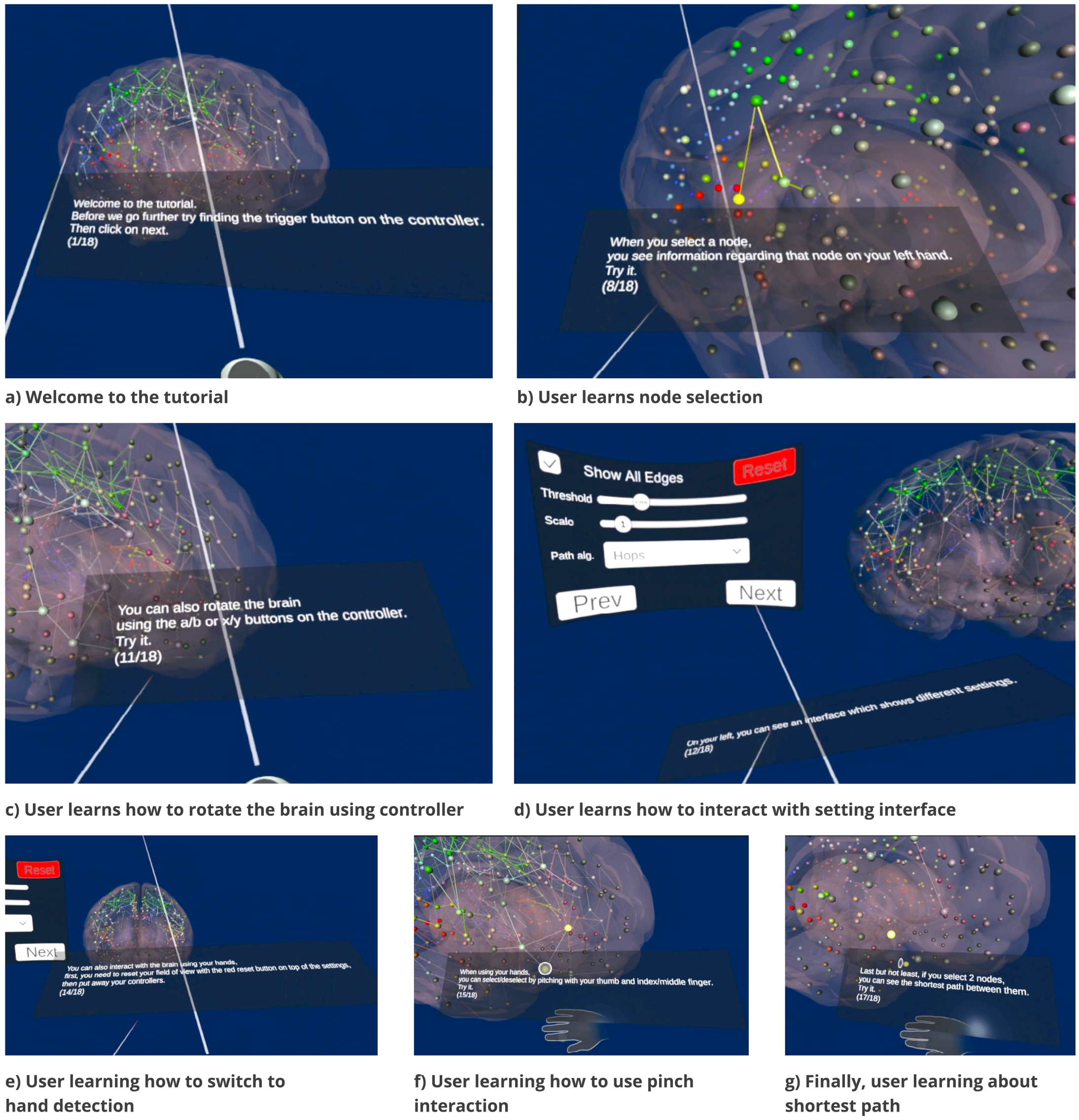
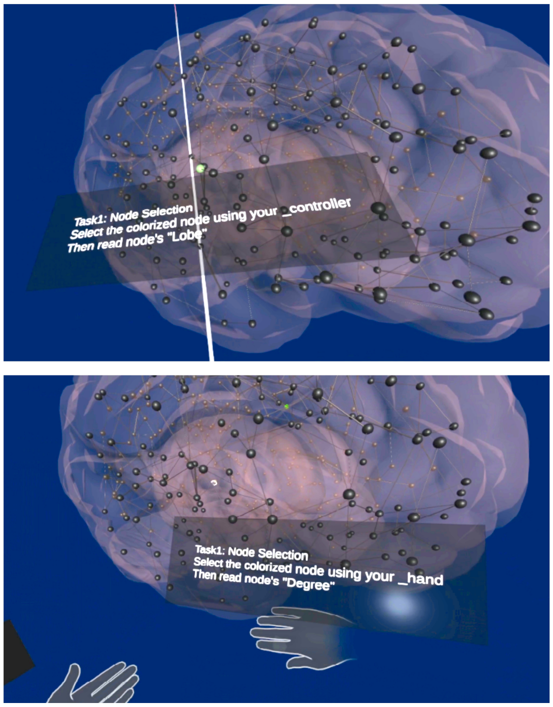


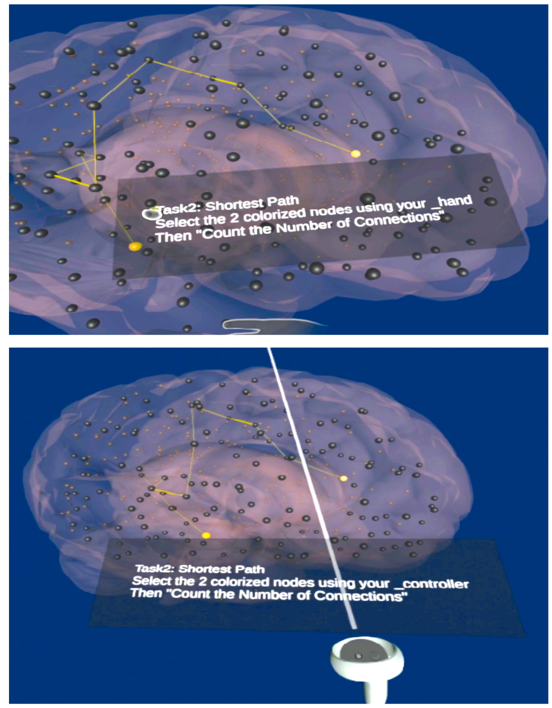
Figure 3.9: Screenshots taken from the tutorial section of the application. The user goes through 18 different steps to learn about the different functionalities of the application.

3.4.2 Procedure

Each participant completed a pre-test questionnaire before the study to acquire basic information about their level of knowledge of the included technology and anatomy. Following that, they were provided information about the system and the data they were viewing, and each participant was required to go through a developed tutorial in order to get more comfortable using the application. During the tutorial, participants went through 18 steps to become acquainted with Oculus



(a) Task 1: Node Selection



(b) Task 2: Shortest Path

Figure 3.10: VRNConnect user study tasks

Quest 2, controller interactions, pinch gestures, and the overall flow of the application. Screenshots of the tutorial are shown in Figure 3.9. When the participants were comfortable, they performed the 12 trials as described above. Task completion time and the number of clicks/pinches were recorded for each trial. Following the completion of all trials, participants completed a post-test questionnaire that included the System Usability Scale (SUS) and NASA Task Load Index (TLX) items for both hand gestures and controller interactions, as well as some other qualitative and open-ended questions.

3.5 Results

A total of 16 participants (8 female and 8 male), with an average age of 28 years (SD = 5.8), participated in the study. 62.5% had little to no experience with VR, and only 12.5% were very experienced with VR. One person had previously experienced motion sickness in VR. More than half of the users had little to no knowledge about brain connectivity or connectivity analysis (62.5%)

and about the role of the connectome in brain function and diseases (75%). Lastly, 68.8% of our participants were interested in learning about brain connectivity data.

3.5.1 Time and Error

The average completion time for the two tasks (i.e. node selection and shortest path) and each interaction method is shown in Figure 3.11. Since each task required a different number of clicks to complete (2-clicks for Task 1:node selection and 3-clicks for Task 2:shortest path), rather than using the number of clicks/pinches, errors (i.e. extra clicks) made by the users are shown (Figure 3.12). A summary of the data is also shown in Table 3.3 (Time) and Table 3.4 (Errors). As can be seen from the table, tasks with the controller took almost half the time as doing the same task with gestures. In terms of the errors, participants committed significantly more errors with gestures than with controllers.

Paired samples t-tests were performed to compare the time and error with gestures and controllers. We found a significant difference in time between gesture-based interaction and controller based for both node selection and shortest path ($p < 0.01$). Regarding the time between task 1 and task 2 using hand gestures, we did not see any significant difference ($p < 0.92$). For errors, we found a significant difference in doing tasks with controllers and hands ($p < 0.05$). Lastly, for the difference in error across tasks using the same interaction method, we found no significant difference ($p > 0.01$).

Time (s)	Task 1: Node Selection		Task 2: Shortest Path	
	Controller	Gestures	Controller	Gestures
Min	16.8	21.4	17.8	20.1
Max	40.2	115	43.7	87.8
Median	22.7	44.5	29	54.5
Average	24.6	51.2	29.6	50.4
STDev	7.5	26.6	7.5	19.4

Table 3.3: Average task completion time from the recorded data during task 1 and task 2 done with controllers and hand gestures.

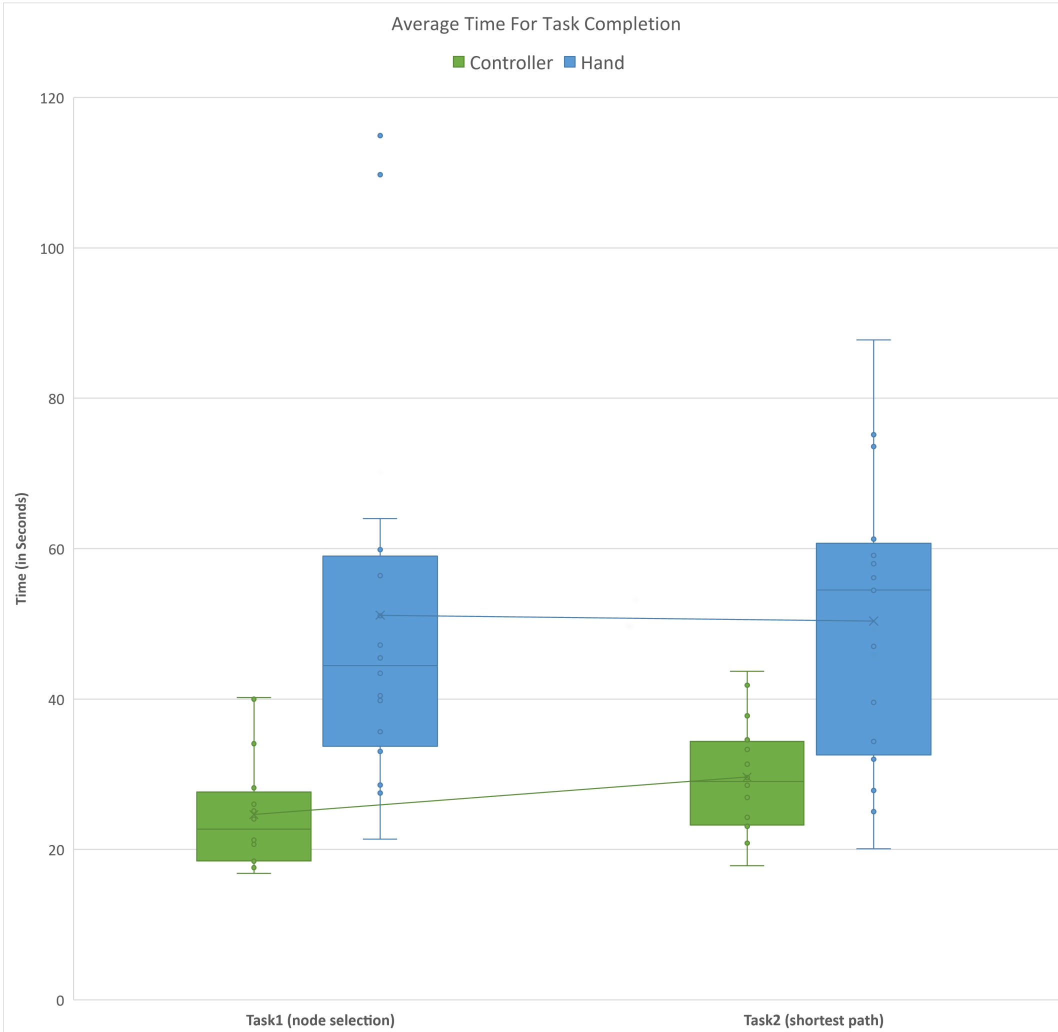


Figure 3.11: The chart shows the distribution of average task completion time for tasks 1 & 2, both with controller and gestures **Task 1: Node selection, Task 2: Shortest Path*

Error (clicks)	Task 1: Node Selection		Task 2: Shortest Path	
	Controller	Gestures	Controller	Gestures
Min	0	0	0	0
Max	1	16	2	8
Median	0	1	0	1
Average	0.2	2.8	0.4	2
STDev	0.4	4.3	0.6	2.3

Table 3.4: This table shows the averages of task completion errors from the recorded data during task 1 and task 2 done with controllers and hand gestures.

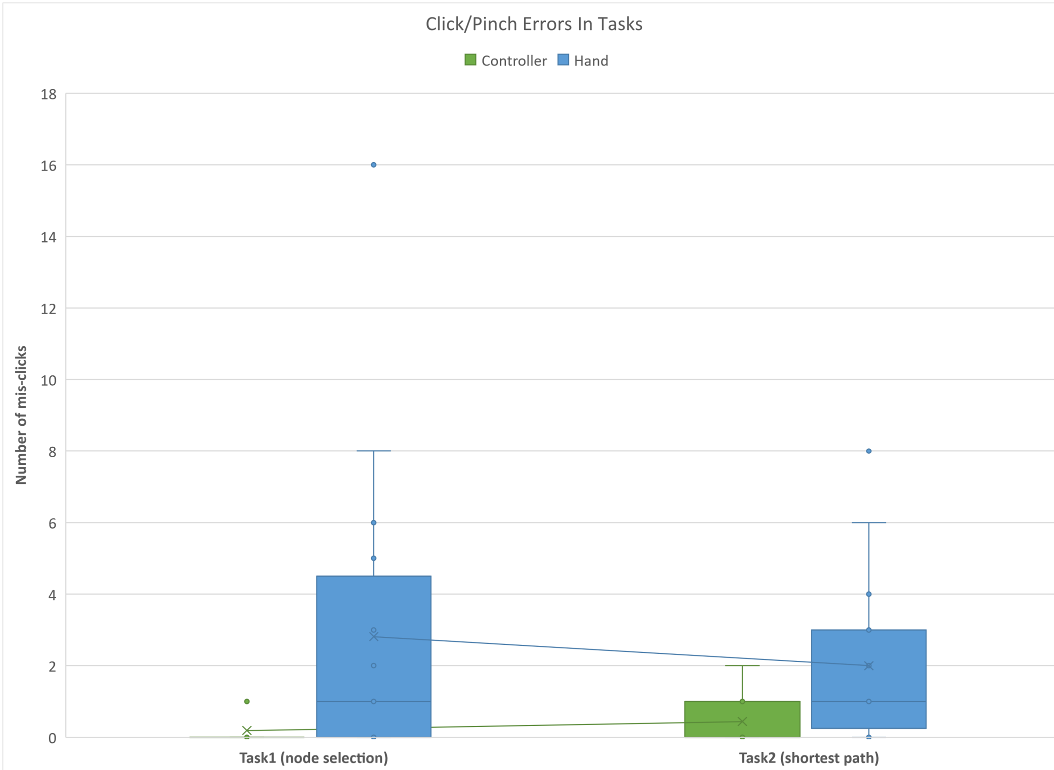


Figure 3.12: The chart shows the distribution of errors in selection for tasks 1 & 2, both with controller and gestures **Task 1: Node selection, Task 2: Shortest Path*

3.5.2 Usability (SUS)

The system was evaluated using the System Usability Scale (SUS), a standardized questionnaire used to assess system/interface/product usability. The SUS is a 10-item questionnaire, each with five response options ranging from "strongly disagree" to "strongly agree." The questions have been designed to assess the user's subjective perceptions of the usability and user-friendliness of a system, including factors such as ease of use, efficiency, learnability, and overall satisfaction. An SUS score will range from 0 to 100, with higher scores indicating better usability. The calculated SUS score for VRNConnect was 86.25, which is considered excellent; according to SUS evaluation scoring a system with a score greater than 71.1 is considered acceptable, and a score above 84.1 is considered excellent in terms of ease of use [112, 11]. The SUS results are presented in Table 3.5.

System Usability Scale	Average
I think that I would like to use this system frequently.	4.25
I found this system unnecessarily complex.	2.84375
I thought this system was easy to use.	4.125
I think that I would need assistance to be able to use this system.	1.8125
I found the various functions in this system were well integrated.	4.625
I thought there was too much inconsistency in this system.	1.25
I would imagine that most people would learn to use this system very quickly.	4.1875
I found this system very cumbersome/awkward to use.	1.1875
I felt very confident using this system.	4.375
I needed to learn a lot of things before I could get going with this system.	1.375
SUS Score Calculations	
Mean	86.25
Std Dev	8.164965809
Min	70
Max	97.5

Table 3.5: The 10 questions of the System Usability Scale (SUS) with the average score from 1 (strongly disagree) to 5 (strongly agree), and the resulting overall SUS score calculation.

3.5.3 Workload (NASA TLX)

To assess the workload of each interaction method on users, the NASA Task load index (TLX) was used. This evaluation technique computes a subjective cognitive workload based on six factors: mental demand, physical demand, temporal demand, performance, effort, and frustration. We scaled each individual question from 1 to 10, and users answered two sets of the same questions, one for hand gestures and one for controllers. The overall cognitive load of utilizing the system with hands was calculated to be 45, and the controllers' cognitive load was calculated to be 36.67, both deemed to be somewhat high (30-49) according to Stanton et al. [121]. Figure 3.13 illustrates a detailed side-by-side comparison of subjective cognitive workload when using a controller and hand gestures. As can be seen from the graph, although the controller had a lower cognitive workload associated with it overall, for both the controller and hand gestures, subjects felt they had to work hard to perform the tasks well.

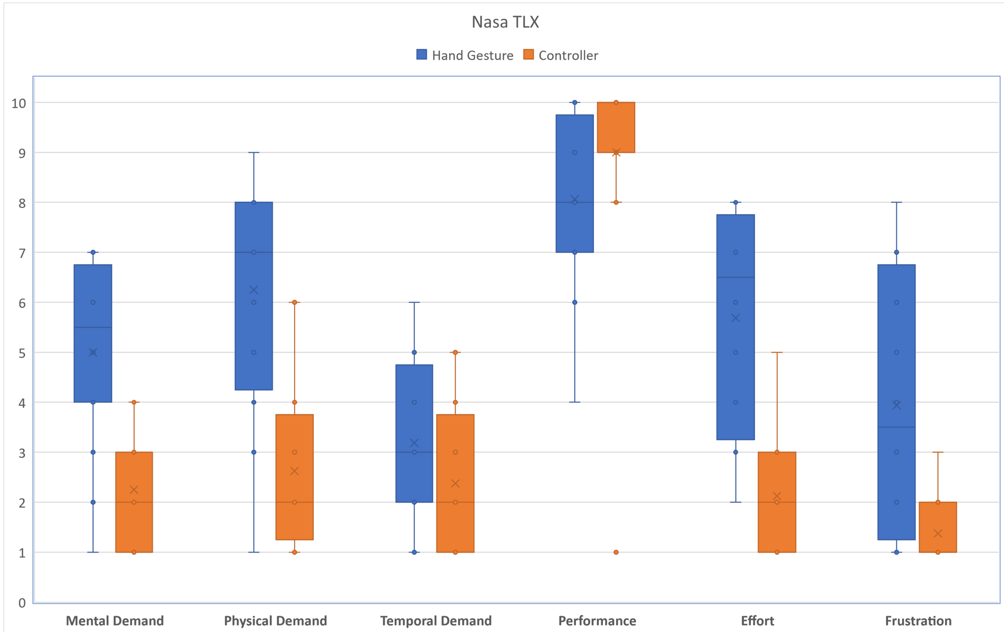


Figure 3.13: NASA TLX result for for Hand Gestures (blue) and Controllers (orange) interaction techniques.

3.5.4 User Experience

Lastly, participants were asked questions regarding the usability, intuitiveness, enjoyability and learnability of VRNConnect, all scaled from 1 (low) to 5 (high). The results of which are shown in Figure 3.14. Based on these results, we found that almost all users preferred controllers as opposed to hand gestures, and only 1 participant was neutral towards hands/controllers. We also asked open-ended questions to know more about the user's experience, the improvements needed, and further comments regarding our app. Below are selected comments from the questionnaire:

- *"Selecting with a controller is easier; also, it provides more functions like moving that makes selecting the nodes easier. Moreover, we can move in a limited territory, so selecting some nodes by hand would be more difficult without the controller."*
- *"Controllers were easier to use because of the line they draw to the target, but hands were more fun."*
- *"I liked hand gestures when being able to walk into the brain and actually pinch the objects, but it was harder for far nodes to use hand gestures and also more tiring for the arms "gorilla arm"."*
- *"being able to immerse in the full VR experience inside a brain gives you a different perspective of how things are tied together"*

- *“the scalability is really useful to considering all the parts of lobes.”*
- *“Rendering was nice, and everything was informative. Very cool!”*
- *“pinching was a bit difficult to achieve with hands”*
- *“The system is easy to use and user-friendly. Using hands to select far nodes was challenging.”*

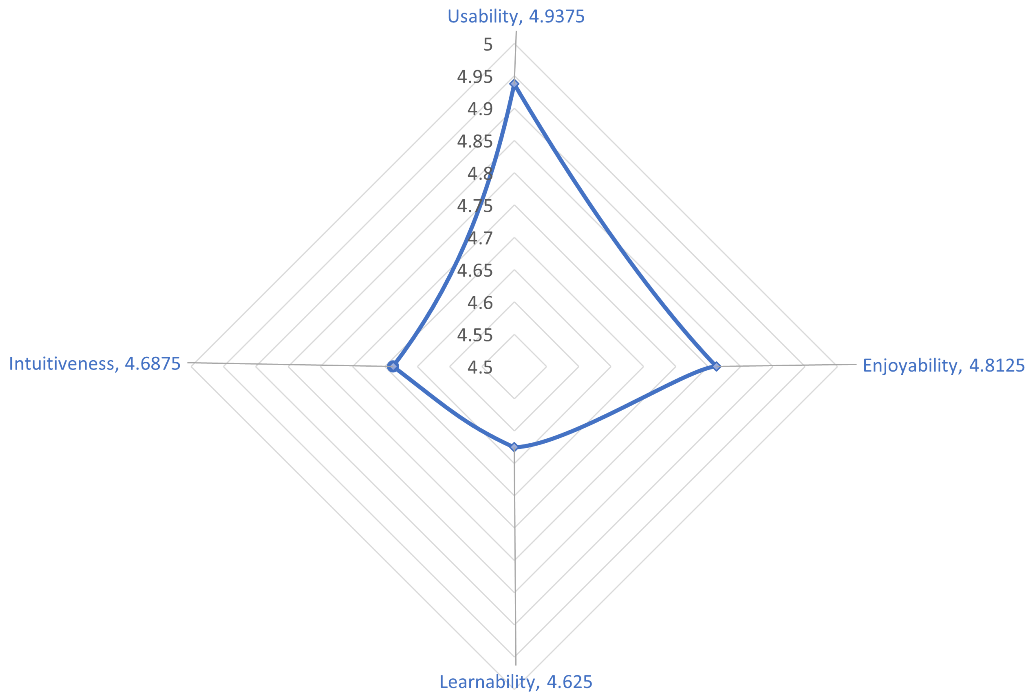


Figure 3.14: The average results of the qualitative questions regarding Usability, Intuitiveness, Enjoyability and learnability (scaled from 1-5). As can be seen, users felt VRNConnect is very usable, intuitive, enjoyable and easy to learn.

3.6 Discussion

With all the qualitative (Intuitiveness, Usability, Enjoyability, Learnability) results being higher than 4.5/5, our study’s findings confirm that VRNConnect can be an asset for exploring, analyzing, and learning about brain connectivity. In terms of the interaction methods, almost all participants performed significantly better, doing tasks with the controller as opposed to hands in both task completion time and task errors. The survey results showed that the majority of participants were critical of using gesture-based interaction, suggesting significant improvements need to be made in this area. Interestingly, we found that the upper quartile of people who had lots of errors in hand gestures were the ones who started their tasks with their hands. Furthermore, almost all the people who struggled with hand gestures during node selection (task 1) showed improvement in doing the shortest path task with hands, and on the other hand, people who did not struggle during node selection (task 1) with hands showed significant errors in the shortest path task. This suggests the possibility of a significant learning curve for gesture-based interaction. Despite a fairly detailed tutorial and training, further system usage with hands may improve gesture-based interaction. Some users also suggested that they came up with schemes to improve hand selection over the course of the study, e.g. they learned to walk up very close to the node to select it more accurately and easily.

3.6.1 Limitations

One of the main obstacles during the development of VRNConnect was the lack of a standard framework to support all VR headsets, so we had to choose between the functionalities of various headsets alongside the features of the SDKs they provide. For example, going with XR interaction toolkit [1] for Unity still did not support hand gestures, and the Oculus integration SDK (v38) that we used had some of the functionalities only in an experimental scheme; thus, not stable enough. Going further, the PC and the VR headset had problems in the rendering of too many nodes and edges; it became resource intensive, resulting in a laggy experience on certain hardware. We introduced thresholding which has its own challenges [84, 123] to our connectivity data as mentioned in Section 3.3 on top of an instantiating technique in Unity to improve rendering many objects, but still, it would be difficult to render atlases with more regions or connectivity matrices with thousands of connections. Jaeger et al. [67] also outlines some of these challenges regarding modelling and thresholding, rendering, etc. and other challenges of visual brain analysis in immersive environments.

3.6.2 Future work

In terms of interaction, multi-sensory interactions, such as haptic interfaces, data sonification, or gesture detection, have the potential to improve the analytical experience significantly; for this reason, hand gestures were introduced. Based on the results of our studies, in future work, we will focus on improving and adding more gestures in order to align with the level of freedom that users have with the controller functions. Adding a visual laser to the hands similar to the controller is a simple way that participants suggested could improve targeting. Optimization of rendering of objects, shadows and lighting will further allow for smoother experiences when adding more nodes/edges in the environment. More efficient rendering would also allow us to visualize a colour-coded mesh of each anatomical region.

In the future, we also plan to add more types of connectivity data visualization and analysis to VRNConnect. In some circumstances, adjacency matrices outperform node-link diagrams in managing big connectome datasets [7, 88]. However, some visual analysis tasks, such as detecting graph changes in group studies, are difficult to do using matrix representations [56, 74]. Other visualizations used in 2D, such as the connectogram, which is a popular two-dimensional method for showing important brain connectivity patterns [66], are currently lacking good 3D equivalents that could be explored in an immersive environment. A future goal will be to develop and implement a more intuitive and immersive 3D representation of 2D connectivity visualization (e.g. connectogram) that allow for intuitive and efficient visual analysis of brain connectivity data.

3.7 Conclusion

In this work, we introduce VRNConnect, an immersive environment for exploring brain connectivity data. VRNConnect was developed not only to allow users to learn about connectivity data (e.g. through the tutorial and by intuitively interacting with the data) but also in order to allow users to import their own data for analysis. Due to the architectural choices that were made, we allow a fully 3D immersive experience and the possibility to easily extend VRNConnect with new visualizations and analysis. Furthermore, to allow the tool to be used by the community, we are making it open source.

Chapter 4

Conclusion

In this dissertation, we developed VRNConnect, a virtual reality platform to interactively explore brain connectivity data. Our first prototype provides users with a number of measures to allow them to conduct brain network studies and analysis in an immersive virtual environment. With the current application, the user is immersed in an environment where they can see a larger-than-life transparent brain mesh as well as the connectome network graph generated from a supplied structural connectivity matrix file. The node and edge can be coloured in correspondence to the region colours in a user-provided brain atlas parcellation. In addition, the user can rotate the brain around the horizontal axis and move about and modify the scale of the brain using the buttons on the Oculus controllers, allowing for a better view over dense areas.

The graph threshold is also changeable by the user in the run-time UI. The user can see network analysis metrics (provided by the Brain connectivity toolbox ”bctpy” library) and information about the corresponding node using one of two methods of interaction, controller or hand gestures. In addition, the viewer can see the shortest path between two selected nodes, which might be valuable for research into brain networks. The developed system is an example of how the latest virtual reality technology can be used to show and interact with anatomical data. The system was also built to be easily extendable to use toolboxes other than ”bctpy” to perform more complex analyses on brain networks.

Our system has shown impressive results from the user study in both usability scale (SUS) and cognitive load (NASA TLX), having the potential to be used as an academic and analytical tool, with a customizable design for importing connectivity data from different modalities and flexible and intuitive interaction methods. In addition, the system could be used as an academic or diagnostic tool.

In comparison with existing VR-based network visualization software that rely on the 2D projection of 3D data, VRNConnect offers a truly immersive visualization and the capacity for quantitative analysis. We will continue to build additional interactive analysis functions for the system in the future.

4.1 Future Work

First and foremost, as mentioned in Section 3.6.2 and based on the feedback from the user study, there is room for improvements in the system performance and interactions, especially for hand gesture detection, as well as adding more visualization methods for added versatility and comprehensiveness (since our first milestone for this tool was to be used in an educational setting).

We will explore adding more visualizations, such as having the ability to show more graph network analysis metrics, for example, hub nodes or rich clubs, and also finding a convenient way of showing a figure similar to the popular 2D connectogram (See Figure 4.1). In addition, we are looking into a way to show disconnect when we remove a node which can prove helpful to see what regions will be affected and how the connection is disrupted in cases such as brain tumours, strokes, multiple sclerosis (MS), Alzheimer's, etc. [37, 39, 146, 12].

We have seen impressive results in terms of usability and task load. However, a longer and more in-depth user study needs to be performed to assess the system further. In addition, we also need to evaluate the possibility of using our VR application in a clinical setting for diagnostic purposes.

Furthermore, we have shown the performance and usability of VRNConnect by working with structural connectivity matrices, but further evaluation of functional connectivity networks (FCNs) is still needed. Because of the unique qualities and limits of this use case, cutting-edge methodologies cannot simply be translated into FCN visualization. Since FCNs are modelled as entire weighted networks, even thresholded networks can be quite dense. Although network visualization

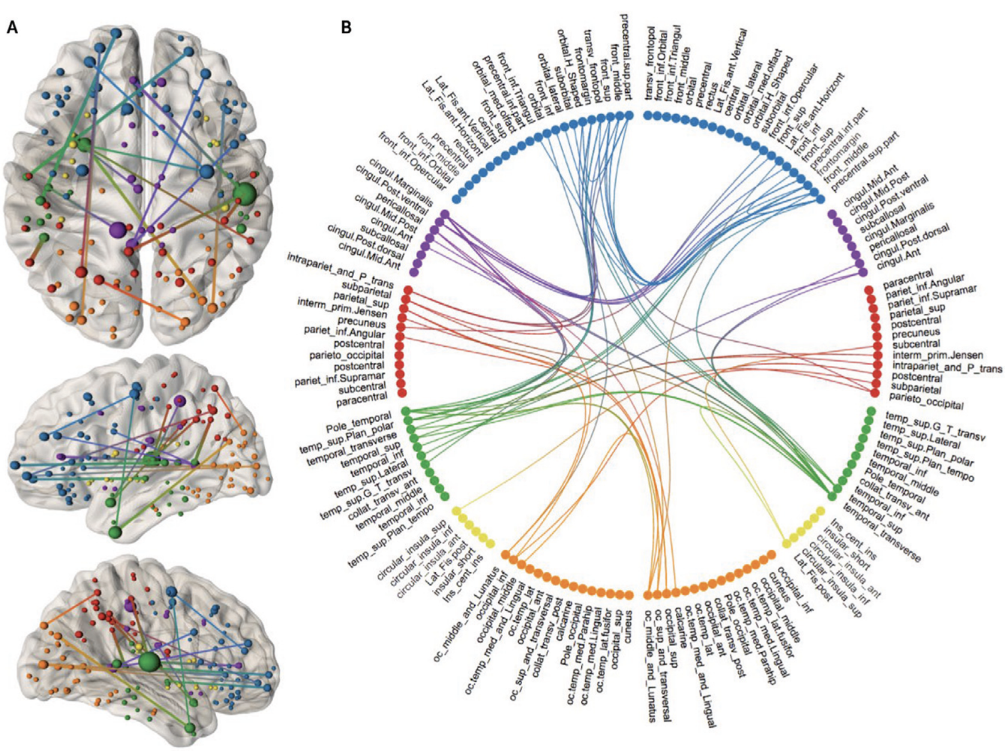


Figure 4.1: The figure illustrates the Connectogram visualization of the brain connectivity (B) alongside the graph representation of the same brain connectivity from 3 different angles (A) [134]

can be used to evaluate different FCNs, there are several potential difficulties due to high data complexity, human perception, and uncertainty created by, for example, parcellation or thresholding[38]. We will explore potential solutions in the future.

Last but not least, we are also looking into the possibilities for more in-depth clinical analysis, such as adding visualization of the streamlines and having the ability to show two different datasets for side-by-side comparison, which could either be shown as two different views or on single view overlaying the datasets on top of one another and using transparency. In general, further evaluation needs to be done for all the mentioned improvements in order to reach the best possible outcome.

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