UNIVERSITY OF TURKU

Master's Degree Programme in Human Neuroscience

Association between structural brain connectivity and The Cambridge Neuropsychological Test Automated Battery (CANTAB) following mild traumatic brain injury

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Academic Year 2019/2020

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1 Introduction

During traumatic brain injury (TBI), movements of the head move back and forth the brain against the bony interior wall of the skull (Gaetz, 2004). During this movement, areas of varying density in the brain slide over each other at different speeds, and these movements can cause injuries. Bruising and swelling of the brain tissue may be caused by a violent impact, generating a contusion. However, in a low-speed movement, the arising damage may not be visible to the naked eye. A massive shearing force causes axons to tear and stretch from the cell body. This event takes the name of axonal shearing or diffuse axonal injury. Although hours or days have passed since the initial injury, brain damage may continue to occur over this period of time. When the axon is damaged, the result is the breakdown of communication among neurons in the brain. As the torn axons rapidly degenerate, the extracellular space fills with toxic levels of neurotransmitters, released by the axons themselves. Consequently, many of the surrounding neurons begin to die in the following 24 to 48 hours, making worse the initial effects of the injury (Raghupathi, 2004).

Mild cases of the diffuse axonal injury may lead to symptoms such as:

- Brief loss of consciousness
- Impaired long-term memory
- Reduced problem-solving ability
- Lover social inhibition
- Attention/Perception problems

Several cases of diffuse axonal injury may result in coma and persistent vegetative state. Computed tomography (CT) or magnetic resonance imaging (MRI) may reveal structural brain pathology. Mild traumatic brain injury (mTBI) typically is not visible on CT and MRI, in fact test results usually show a normal reading. Those imaging techniques may deficit in the sensitivity to detect brain dysfunction after a mild injury (Hartikainen et al., 2010). Patients with mTBI are usually characterized by the presence of cognitive disabilities. There is a specific interaction among brain regions and cognitive

abilities. A previous study has reported some evidence that the persistent symptoms after an mTBI are associated with executive function impairments (Hartikainen et al., 2010). Different cognitive methods and tests are usually adopted to check if there is any sign of deficits in the cognitive process (Fujimoto et al., 2004). Also, the analysis of brain connectivity through the properties of global networks, is an important step in the understanding of brain functions. Seven global network properties were investigated in this study. Each of these properties has a specific role in network connectivity:

- Small-worldness is the normalized characteristic path length divided by the normalized clustering coefficient. (Rubinov, Sporns, 2010);
- Betweenness-centrality is the shortest section of paths that contain a node (Rubinov, Sporns, 2010);
- Degree is the number of edges that connect one node with the others (Rubinov, Sporns, 2010);
- Normalized clustering coefficient is the measure of the degree to which nodes tend to cluster with neighbors (Rubinov, Sporns, 2010);
- Normalized global efficiency is the measure of how efficient the network exchanges information (Rubinov, Sporns, 2010);
- Normalized characteristic path length is the average of the shortest path length in the network (Rubinov, Sporns, 2010);
- Strength is the measure of connectivity strength across all the nodes (Rubinov, Sporns, 2010).

2 Review of the literature

TBI is a trauma induced by an external force that leads to the disruption of brain functions. TBI can be caused by different mechanisms, such as car accidents, falls, sports, and assaults.
The initial damage caused by an impact represents primary injury. During the impact, the brain moves back and forth inside the skull, causing bruising, bleeding of vascular structures, and tearing of nerve fibers. It is not always related to direct insult, but it can be also associated with structural changes from the mechanical force applied during the injury. After a blow to the head, a person may appear neurologically intact, but his or her condition may rapidly decline within minutes. When the brain starts to swell, it pushes against the skull leading to a reduction of oxygenated blood flow (Styrke et al., 2007).
Secondary injury is any injury that can develop after the initial injury. The causes of secondary brain injuries can be divided into intracranial and extracranial causes. Secondary injury comprises impairment of energy metabolism that is a consequence of multiple mechanisms which can be intracranial or extracranial. Intracranial causes include pathological pathways such as hypertension, hematomas, edema, or mitochondrial failure (Merenda, Bullock, 2006). While extracranial causes include hypoxia, hypotension, and acidosis (Kinoshita, 2016). Other mechanisms from both causes can be the increased energy need due to systemic trauma responses (Lu et al., 2009), seizures, or spreading depolarization. The condition is further convoluted by heterogeneous temporal evolution of brain injury and individual differences between the patients. Secondary brain injury worsens what is already happened with the primary injury, stimulating systemic inflammation, which leads to increased permeability of the blood–brain barrier. This contributes to the eventual white matter damage (Glushakova et al., 2014). This white matter damage can be a degeneration of itself associated with delayed microvascular damage and the prolonged inflammation response (Glushakova et al., 2014). Moreover, atrophy of white matter traits can result after TBI (Bramlett, Dietrich, 2002). TBIs are classified according to the severity of the injury into mild, moderate, and severe, assessed based on the state of consciousness (Styrke et al., 2007).

2.1 Types of traumatic brain injuries

These are different types of primary injuries.

- **Concussion** could cause a brief loss of consciousness but usually doesn't lead to permanents problems.
- **Contusions** are divided into coup injuries(the injured part is directly under the area of impact) and contrecoup (the injured part is the opposite side of the impact).
- **Diffuse axonal injury** occurs during the back and forth movement of the brain inside the skull, causing nerve cells to stretch and shear at the tissue level. In this way, the transmission of information is lost.
- **Traumatic subarachnoid hemorrhage (tSAH)** is the bleeding into the subarachnoid space, filled with cerebrospinal fluid(CSF), which acts as a protection for the brain. tSAH causes brain damage due to toxic degradation products of blood. which acts as a protection for the brain.
- **A hematoma** occurs as a consequence of blood vessels ruptures. It is a blood clot. Each hematoma differs from one another according to the location of the clot: epidural hematoma, subdural hematoma, intracerebral hematoma.

2.1.1 Definition of mild traumatic brain injury

According to the definition made by the mTBI Committee of the Head Injury Interdisciplinary Special Interest Group of the American Congress of Rehabilitation Medicine (Holm et al., 2005), a patient with an mTBI has had a physiological disruption of brain function, as manifested by at least one of the following (Holm et al., 2005):

- any period of loss of consciousness of no more than 30 minutes;
- any loss of memory for events immediately before or after the accident with post-traumatic amnesia (PTA) not greater than 24 hours;
- any alteration in mental state such as disorientation, at the time of the accident;
- an initial Glasgow Coma Scale (GCS) of 13–15 after 30 minutes.

Glasgow Outcome Scale Extended

The Glasgow Outcome Scale (GOS) is the most used functional outcome measure for traumatic brain injury (Wilson et al., 1998). The first version of the Glasgow Outcome Scale was proposed in 1975, defining a five-point scale of brain injury outcomes (Jennett, Bond, 1975):

1. death
2. persistent vegetative state
3. severe disability
4. moderate disability
5. good recovery

GOSE is an extended version containing eight categories instead of five(Wilson et al., 1998) and it is considered to be more sensitive to changes than GOS (Levin et al., 2001).

2.1.2 Symptoms

Patients with mTBI can have a functional disability, as a result of persistent emotional, cognitive, behavioral, and physical symptoms. These symptoms are categorized into the following (Holm et al., 2005):

1. physical symptoms of brain injury such as nausea, headache, sensory loss or fatigue that cannot be related to other causes;
2. cognitive deficits that include attention, perception, memory or executive functions with no other possible causes;
3. behavioral changes just as irritability or alteration in emotional state.

2.2 Cognitive impairments after mild traumatic brain injury

All mental processes essential in thinking, remembering, learning and problem solving, are summed in the single word of cognition. TBI is associated with cognitive deficits. Cognitive methods and tests are used to evaluate these cognitive processes including various aspects of information processing such as working memory, executive functions, attention, language, sensory

and motor functions. Cognitive problems are determined by a different number of variables (Rabinowitz, Levin, 2014) such as TBI severity and its complications (Losoi et al., 2015). These problems are also dependent on other pre-injury factors such as education, stress, neurological and psychological disorders, resilience, and gender (Carroll et al., 2014). Moderate and severe TBI is usually characterized by loss of consciousness for a short or long period of time (Rabinowitz, Levin, 2014). Instead, mTBI may occur with or without loss of consciousness but one-third of patients experience functional impairment within 3 months (McMahon et al., 2014). Memory, attention, executive functioning, and information processing are the most affected cognitive domains in mTBI, which tend to resolve within 3 to 6 months after injury (McMahon et al., 2014). Cognitive impairments interfere with everyday life. Especially, the deficits of the executive system are very common among patients with mTBI. The executive system region is the prefrontal region of the frontal lobe with neuronal connections to the brainstem, subcortical and cortical regions (McMahon et al., 2014). There are three main areas of executive function (McCalla, 2013):

- working memory
- cognitive flexibility
- inhibitory control

The **dorsolateral prefrontal cortex** is an important area that combines cognition and behavior in processing of information such as organization skills, problem solving, and planning ability. The executive function impairment is especially in this area (Lipton et al., 2009).
The **anterior cingulate cortex** is the connection to the emotional limbic system and the cognitive prefrontal cortex, implicated in empathy, impulse control, emotions, and decision-making (Lipton et al., 2009).
The **orbitofrontal cortex** is involved in impulse control, socially appropriate behavior, sensory stimuli, and the ability to evaluate emotional experiences (McCalla, 2013) (Figure2.1).

2.3 Cambridge Neuropsychological Test Automated Battery

The Cambridge Neuropsychological Test Automated Battery (CANTAB) was developed at the University of Cambridge. It is composed of 25 tests, which measure specific aspects of cognitive functions, which are correlated to

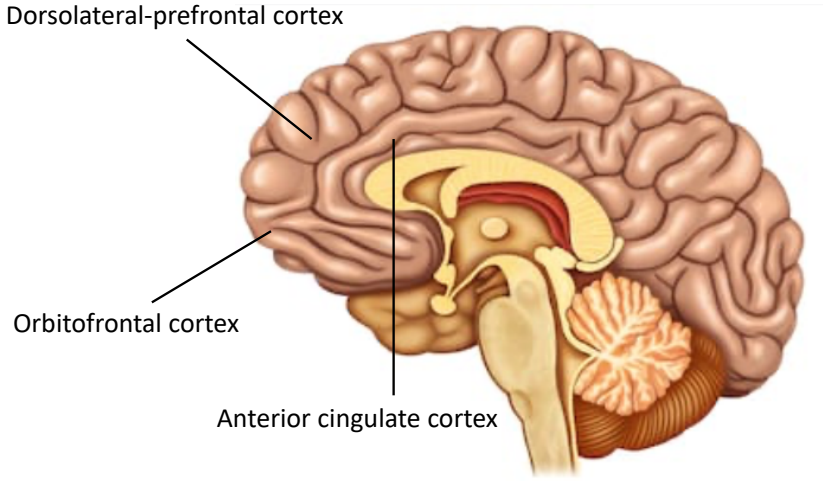


Figure 2.1: Cognitive regions of the brain cortex. The processing of information takes place in the dorsolateral prefrontal cortex; the emotional system is guided by the anterior cingulate cortex; social behavior arises from the orbitofrontal cortex.

neural networks. These tests are grouped according to four main cognitive domains: psychomotor speed, attention, memory, and executive function. Results in task performance are correlated with changes in brain structure. The CANTAB tests can be often used to assess neuropsychological performance on a high range of metabolic, neurodevelopmental (Luciana, Nelson, 2000), psychiatric (Levaux et al., 2007), neurodegenerative diseases (Foltynie et al., 2004) and TBI (Maillard-Wermelinger et al., 2009), showing its sensitivity in the detection of impairments in neuropsychological domains (Wild, Musser, 2014). Attention and reaction time tests are the most analyzed functions to detect disabilities in TBI (Whyte et al., 2006) (Niogi et al., 2008).

Rapid Visual Information Processing

Rapid Visual Information Processing is a measure of sustained attention. Numbers from 2 to 9 appears in the center of a white box on the screen. These numbers appear in a random order, at a rate of 100 numbers per minute. Participants have to detect a sequence of numbers and press the button in the center of the screen when they see that sequence as quickly as possible. The test lasts for 7 minutes and the outcome "RVPA" measures the speed of response, quality of response based on false alarms, and sensitivity.

Simple Reaction Time

Simple Reaction Time is a measure of motor speed, alertness and, mental response. Participants have to select the button as soon as they see a square that appears at intervals on the screen. The test lasts for 6 minutes and the outcome "SRT" measures the response speed, error of response, and correct responses.
Frontal lobe dysfunction is considered susceptible to injury after TBI (Hartikainen et al., 2010).

2.4 Neuroimaging

2.4.1 Magnetic resonance imaging

Magnetic resonance imaging (MRI) is considered to be a powerful research and diagnostic tool in many areas of medicine because it can supply great soft-tissue delineation for different regions of interest (Jacobs et al., 2007). The production of an MR image requires the combination of a computer that is the command and control center and specific equipment (the magnet, radiofrequency coils, and gradients) that generates and receives the MR signal. A magnetic field is able to align hydrogen nuclei(protons) that are contained in water molecules. The human body is made up of 60 % water (Lewis, 2017). During an MRI experiment, water protons are excited using a strong magnetic field (Mori, Barker, 1999). As the MRI scanner applies the magnetic field, the proton spins are aligned. At the same time, a radio frequency (RF) current is produced that creates a changeable magnetic field. The energy that comes out from the magnetic field, is absorbed by the protons, which flip their spins. Consequently to the shutdown of the field, the nuclei come back to their resting state as a result of various relaxation processes (Lewis, 2017). Tissue can be described by two relaxation times T1 and T2. T1 is the longitudinal relaxation time, which is a measure of how quickly a proton returns to its ground state (Curry et al., 1990). T2 is the transverse relaxation time, which is the measure of the proton dephasing time (Allisy-Roberts, Williams, 2007). At this moment, an RF signal is emitted and thanks to Fourier transformation, the signal is decomposed into its frequency components (Huettel et al., 2004). According to the intensity levels of each signal location, there will be different shades of gray in the image. The variation of the RF pulse sequence creates distinct images. An RF is characterized by the repetition time (TR) which is the amount of time between pulse sequences and the time to echo that is the time between the release of the pulse and its acquisition. The contrasts between body tissues

are seen between T1 and T2-weighted images. In fact, it is easy to make this differentiation in the image by looking at the CSF. The T1-weighted image has dark CSF, while the T2-weighted image has bright CSF (Preston, 2006). Numerous types of MRI techniques use the difference in MRI properties of water in the tissues in order to get specific regions of interest (Mori, Barker, 1999). One of the most common types is diffusion-weighted imaging.

2.4.2 Diffusion-weighted imaging

Diffusion-weighted imaging (DWI) (Basser et al., 1994b) was used to acquire data for this thesis because it is shown to be more sensitive in detecting microstructural abnormalities after mTBI (Gui et al., 2008) (Wilde et al., 2008). This diffusion technique is based on the water diffusion process, called random Brownian motion of water molecules, inside a voxel of tissue (Mori, Barker, 1999) (Hagmann et al., 2006). The diffusion constant of these molecules can be measured relating signal intensity information to the diffusion process (Mori, 2007). Gradient coils (electromagnetic coils) are applied to modify the strength of the magnetic field, increasing or decreasing along a specific direction, which could be parallel to the main field (z) or perpendicular to the main field and also to each other (x,y). The signal intensity is sensitive to diffusion by applying a pair of gradients to a T2-weighted spin-echo sequence. As shown in Figure2.2, the gradients are applied in the same direction, before and after the 180° refocusing phase(Mukherjee et al., 2008). The diffusion-weighting factor (Figueiredo de et al., 2011) (Stejskal, Tanner, 1965), named b-value (given in units of s/mm2), reflects different properties, which are the gyromagnetic ratio (γ), diffusion weighting gradients strength (G), the length of gradient pulse (δ) and the duration (Δ):

$$b = \gamma^2 G^2 \delta^2 (\Delta - \delta/3)$$

By increasing G, δ, and Δ, the amount of signal loss can be controlled (Malayeri et al., 2011).

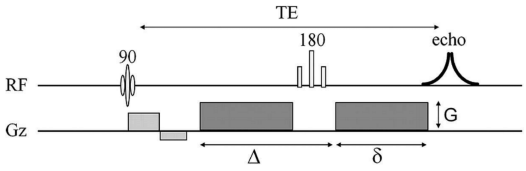


Figure 2.2: Spin-echo sequence. Factor b depends on G (diffusion weighting gradients strength), δ (the length of gradient pulse), and Δ (the duration). RF is for the radiofrequency pulses; Gz is for gradient pulses. These gradients are applied along the same direction, before and after the 180° refocusing phase(Mukherjee et al., 2008).

Water molecules move due to the osmotic gradient. When they displace in the tissue, they produce an attenuated signal during scanning. In the existence of a microenvironment with abnormal cell membrane or with fewer cells, water molecules are free to move (Basser et al., 1994b)(Malayeri et al., 2011). Diffusion-weighted imaging is especially used in stroke diagnostics (Wittsack et al., 2002). During a stroke, as water molecules move intracellularly, it creates local swelling, which produces a bright signal on the image. This bright image appearance is a consequence of the high signal intensity in the area where the lesion is located (Hagmann et al., 2006). This means that the diffusion of water molecules is directly proportional to the amount of cells in the tissue (Basser et al., 1994a). Diffusion Tensor Imaging (DTI) is developed from DWI and it is used to delineate white matter tracts in the brain (Basser et al., 2000) (Vedantam et al., 2014).

2.4.3 Tractography

The diffusion process can be isotropic if water molecules diffuse along all directions in the same amount or it can be anisotropic (for living tissue) if water molecules follow preferential axes (modeled with an ellipsoid in 3-D). This ellipsoid is defined by six parameters, three lengths (λ) also called eigenvalues and three vectors (v) also called eigenvectors (Mukherjee et al., 2008) (Basser, Pierpaoli, 2011). DTI is a DWI technique useful to measure the magnitude and the direction of water diffusion. It is possible to calculate DTI indices from the diffusivities through the three axes. Fractional anisotropy (FA) and apparent diffusion coefficient (ADC) are two of the most important indices (Basser et al., 1994a). FA represents the degree of anisotropy

and ADC is equivalent to mean diffusivity (MD), which is the measure of overall diffusivity in the tissue (Alves, 2018) (Vedantam et al., 2014). DTI data allows 3-D visualization of the fiber tracts (Hagmann et al., 2006). The structural network also called connectivity matrix, can be reconstructed from structural connectivity by estimating the number of fibers among the cortical regions (Tsai, 2018). Tractography is a computer-aided 3-D tract reconstruction technique suitable to understand tract trajectories and their connections through which information is transferred between brain regions. (Mori, 2007). Tractography can vary according to the diffusion modality used to take data and it depends also on the tracking algorithm used (Hagmann et al., 2006). Fiber bundles direction is deduced by measuring diffusion along different directions. Tractography uses colors of red (left-right), green (anterior-posterior) and blue (inferior-superior) to differentiate the preferred direction of diffusion (Sotiropoulos et al., 2013). A line starts to propagate from the center of the seed pixel based on its own orientation. Then, the line exits the seed pixel and changes direction based on the second pixel, creating a smooth curve. For each small step, a new fiber orientation is calculated (Mori, 2007). The streamline is obtained by connecting up a set of pixels that follow a specific direction. Sometimes it is problematic to fully reflect the vector information because each point can have more than one connection. Probabilistic tractography estimates the possible fiber orientations but also it estimates how each orientation is set along a fiber. All these paths form a set which is the measure of the connection probability (Sotiropoulos et al., 2013). Both Bonilha, L. et al. and S Khalsa, et al. affirm that probabilistic technique is more valid for the connectivity calculation between cortical regions than deterministic approach (Bonilha et al., 2015)(Khalsa et al., 2014)(Bastiani et al., 2012). In this thesis, networks were reconstructed based on probabilistic streamlines tractography and constrained spherical deconvolution method, performed on DWI data and gray matter parcellation (Fischl et al., 2004) was performed on T1-weighted MRI data (Figure2.3).

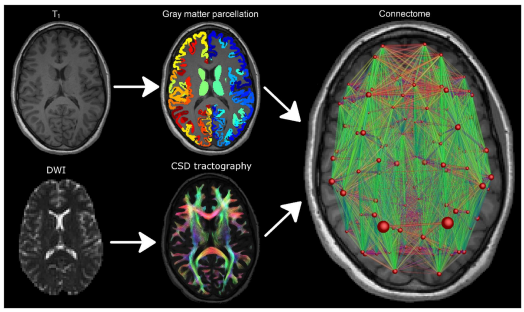


Figure 2.3: Networks reconstruction. Fiber orientation is given by different colors, which help the whole brain visualization for each tract. In the big brain picture to the right of the image, the red dots represent the nodes that are connected by green lines which are the links of this connection. This architecture represents the network connectivity design (Roine et al., 2019)

2.4.4 Structural brain networks

The brain is a complex network. Mapping its elements and connections is essential in order to understand its function (Sporns, 2011). Anatomical connectivity studies provide information about brain characteristics, which are related to cognitive processes and cortical dynamics, but they also furnish the mechanisms that arise if the structural basis of the brain is disrupted (Yan et al., 2011). The entire network properties can be investigated by the application of the model of graph theory-based network analysis (Tsai, 2018) (Rubinov, Sporns, 2010). This model of a real system gives a map of how elements are linked to each other (Sporns, 2011). This network connectivity is also known as "small-world" (Yan et al., 2011). This complex system is designed by nodes (vertices) and links (edges) between pairs of nodes. Nodes usually denote brain regions and links denote both anatomical and functional connections (Vecchio et al., 2017). Graph theory is a mathematical representation of vertices that are linked through edges (Vecchio et al., 2017). The networks are constructed by calculating the network metrics based on weighted structural network (Gong et al., 2009). One network measure may mark one or more aspects of global and local brain connectivity (Rubinov, Sporns, 2010). Edges can be of four types and they are essential to describe brain networks. These edges can be directed or indirect from the origin to the destination but also, they can be binary or associated with a weight. A connection matrix is the simplest representation of a graph in which nodes are displayed as matrix rows and columns, while edges are displayed as binary or weighted matrix portals (Gong et al., 2009). Neighbor nodes are the ones linked by edges and their degree derived from the adjacent matrix (connec-

tion matrix). Depending on the type of edges, the degree corresponds to the number of edges connected to a node, or to the number of incoming/outgoing edges. Degree distribution is formed by all nodes degree and it is very informative about the network architecture. In this way, it is possible to know whether or not the node degree varies widely. The connection between nodes can be direct, which means that there is a single edge or this connection can be through sequences of intermediate nodes and edges, which take the name of path. When a path links a node to itself, the path takes the name of cycle. Nodes can be connected with a traversing sequence of edges from other nodes. The length of the shortest path reflects the distance between two nodes. In fact, shortest paths have more effect on the internode communication (Sporns, 2010). Small-world networks combine high clustering with short path length (Watts, Strogatz, 1998). The networks are composed of local and global properties. Global properties include the ones across the entire network, while local properties include the ones related to a specific considered node (Liu et al., 2017). He and Hevans describe how the detection and characterization of modules of the brain can facilitate the identification of those groups with associated components that may be useful for specific behavioral functions. Figure 2.4 shows the graph-theoretical approach in which modules connections are dense inside themselves (He, Evans, 2010). The research demonstrated how changes in brain networks characterize cognitive impairments, after a TBI (Caeyenberghs et al., 2014)(Fagerholm et al., 2015)(Van Der Horn et al., 2017).

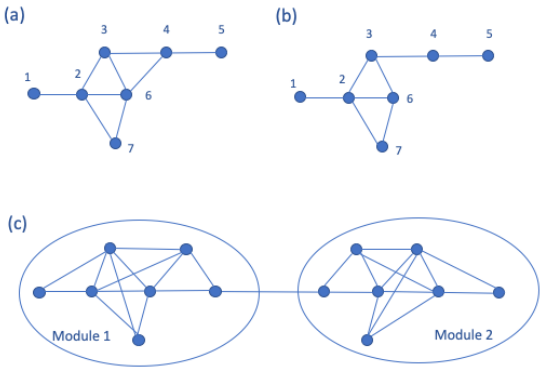


Figure 2.4: Graph theoretical modeling. (a) and (b) represent clustering coefficient of nodes. Nodes are the dots connected by lines which are the edges. (c) Interestingly, each module has denser connections inside themselves than between them (He, Evans, 2010).

3 Aim of the Study

After an mTBI, many patients do not immediately notice psychological problems or impairments in their cognitive abilities. Their conventional brain images are usually normal and do not give an explanation for their symptoms. Their cognitive problems often appear as diminished working ability (Binder, 1997). This study investigates the associations of global brain networks properties with two CANTAB domains (Rapid Visual Processing Attention and Simple Reaction Time) on average eight months after an mTBI. With combining network properties and CANTAB results, we aimed to detect interaction among brain regions and cognitive abilities, which may be related to mTBI. Structural brain connectivity networks may be important in the process of mTBI diagnosis.

The work is based on the following hypothesis:

- We hypothesized that structural connectivity disruption following mTBI represented by global network connectivity measures is associated with neuropsychological findings.

4 Materials and methods

4.1 Subjects

Eighty-five patients with mTBI were used in this study. One subject was excluded from the study because its CANTAB results were very different from other patients and possibly erroneous, so finally, only eighty-four subjects were considered. As gender and age may affect the white matter properties (Bartzokis et al., 2004)(Hsu et al., 2008), these data will be included (Table4.1). All the mTBI subjects included in the study were diagnosed clinically having an mTBI using the GCS in a range from 13 to 15. These patients underwent a head MRI scanning at about eight months after the injury. The CANTAB tests were performed on the same day as the time of the MR scan. Patients were only divided into two groups of recovery according to the GOSE outcome: patients with complete recovery having GOSE = 8 and patients with incomplete recovery with GOSE <8.

4.2 Data acquisition

All MRI images were acquired with a Siemens Magnetom Trio 3T scanner (Siemens Healthcare, Erlangen). For DWI data, spin-echo echo-planar imaging was used with a repetition time of 11.7 s, an echo time of 106 ms, a field of view of $192 \times 192mm$, a voxel size of $2 \times 2 \times 2mm$, and applying a b-value of $1000s/mm^2$ in 64 directions. Finally, magnetization-prepared rapid acquisition with gradient echo was used to collect T1-weighted images (Brant-Zawadzki et al., 1992), using an echo time of 2.98 ms, a flip angle of 9 degrees, and a voxel size of $1 \times 1 \times 1mm$.

4.3 Image processing

Data preprocessing was done with FSL that is the Functional Magnetic Resonance Imaging of the Brain Software Library (Jenkinson et al., 2012). The raw data were denoised and after that, they were corrected for bias field, eddy current distortions, and subject motion. Distortion reduction for echo planar imaging was done with a nonlinear registration to T1-weighted data (Gallichan et al., 2010). Constrained spherical deconvolution (CSD)

Table 4.1: Demographic Data Table

	Overall	Complete recovery	Incomplete recovery	p-value
Variable	n = 84,	n = 31	n = 52	n = 84
Age (years) Mean (SD)	46.6 (20.0)	43.1(21.2)	48.3(19.1)	0.256[a]
Gender (male/female)	58/26	24/7	33/19	0.189[b]
Male [N(%)]	69(%)	42.1(%)	57.9(%)	
Female [N(%)]	31(%)	26.9(%)	73.1(%)	
Glasgow Outcome Scale Extended 8 [N(%)]	31(%)	-	-	-
Missing	1			

[a] Univariate t-test
[b] Chi-square test

method (Tournier et al., 2004) was used to calculate fiber orientation distributions and probabilistic streamline tractography was performed in MRtrix3 (Tournier et al., 2007) (Tournier et al., 2012). Parcellation of the cerebral cortex was executed using FreeSurfer (Fischl, 2012) with the Desikan-Killiany atlas (Desikan et al., 2006). Finally, 84 gray matter areas resulted in the structural brain connectivity network.

4.4 Graph theoretical analysis

Graph theoretical analysis was used to investigate structural brain connectivity networks by using Brain Connectivity Toolbox (Rubinov, Sporns, 2010) and customized Matlab scripts. The Brain Connectivity Toolbox[1] is widely used by many brain-imaging researchers. Seven global network properties (Small-worldness; Betweenness centrality; Degree; Normalized clustering coefficient; Normalized global efficiency; Normalized characteristic path length; Strength) and three local network properties (Betweenness centrality; Local efficiency; Strength) were investigated by comparing them to 100 randomized networks with an equal degree, weight and strength distribution (Rubinov,

[1] `https://sites.google.com/site/bctnet/Home`

Sporns, 2010).

4.5 Cambridge Neuropsychological Test Automated Battery

Neuropsychological performance was assessed using the computerized neuropsychological test automated battery CANTAB. According to the fact that for this study global properties are analyzed, two out of the twenty-one tests performed seemed to be better suited to the side of global cognitive functioning. Relevant domains for this thesis involve attention and executive functions, including the two tests: "Rapid Visual Information Processing" and "Simple Reaction Time"[2]. These two tests evaluate those cognitive functions most related to the global aspect of the brain.

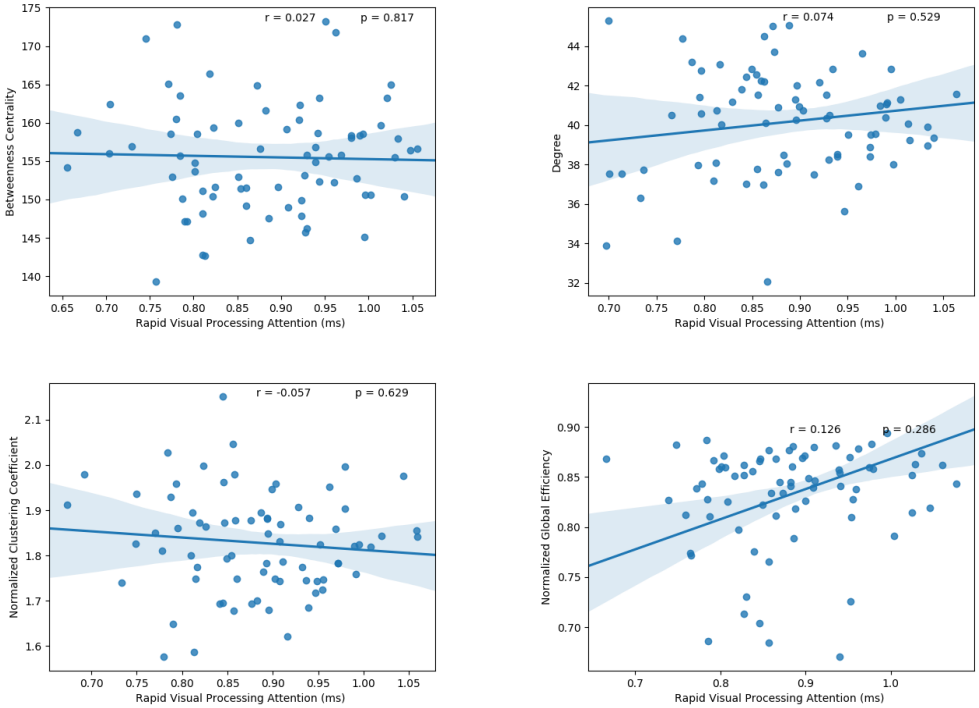
[2]CANTAB

4.6 Statistical analysis

SPSS (IBM SPSS statistic, version 26.0) was used for analysis. Normality test (Shapiro-Wilk Test) was performed for each variable to check if the sample distribution was normal. Data was considered consistent with normality if p-value >0.05. Since four of the global metrics follow a normal distribution, while three deviate from it, two correlation approaches were used. Global network properties were correlated with the outcome GOSE. For normal variables (Betweenness centrality, Degree, Normalized clustering coefficient, and Strength), a parametric partial correlation was performed, instead, a non-parametric Spearman partial correlation was performed for non-normal data (nefficiency, nlambda, and SW). RVPA and SRT were correlated with all the seven global properties using a Spearman partial correlation. In order to correct the results for multiple comparisons, Bonferroni's correction method was used and the p-value <0.007 was considered significant (Nichols, Hayasaka, 2003). A multivariate t-test for RVPA and SRT was performed to asses if there were any significant differences among complete and incomplete recovery patients. Age and gender were considered as covariates for all statistical analyses.

5 Results

The study sample consisted of 84 subjects (age 47 ± 20 years) and they were assessed for the outcome at about eight months post-injury (Table4.1). A total of 77.4% were male with complete recovery and 22.6% were female with complete recovery. In total, 31% of subjects had a GOSE = 8. No significant correlation was found between global network properties and either RVPA and SRT tests.
Dividing patients into recovery groups (complete/incomplete), SRT and RVPA were also tested for correlation. This test was performed to see if any correlations could be observed between the global metrics and the tests, dividing patients based on their outcome. Also, in this case, the results were no significant. On that account, contrary to hypotheses, no associations between global properties and cognitive tests were observed. The results of the correlation analyses were shown in figures 5.1 and 5.2.



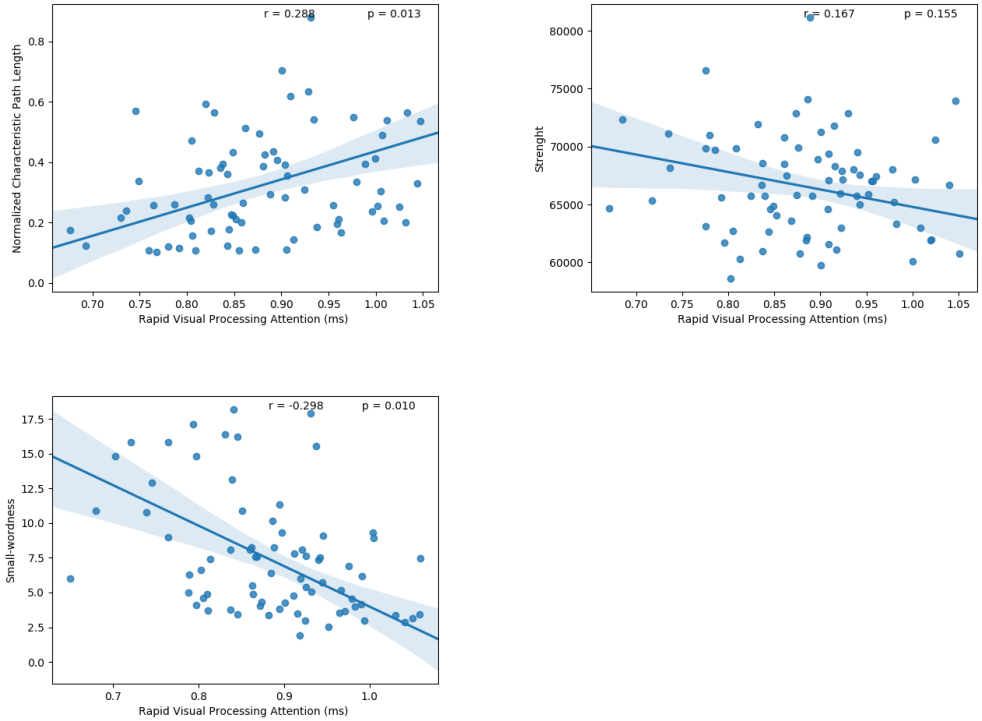
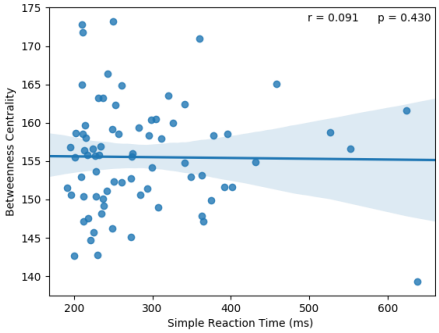
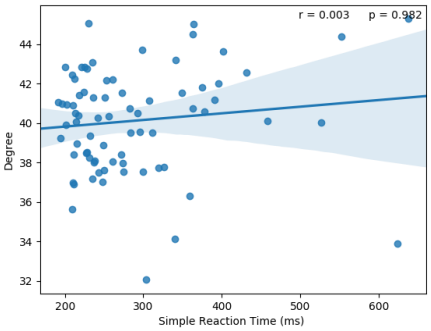
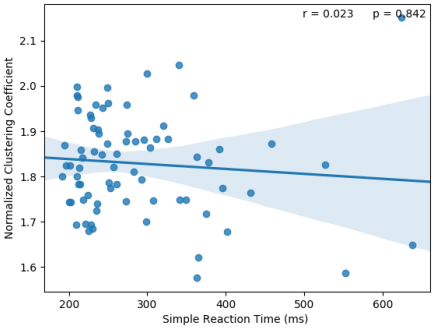
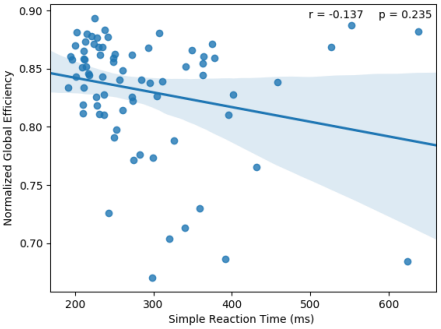


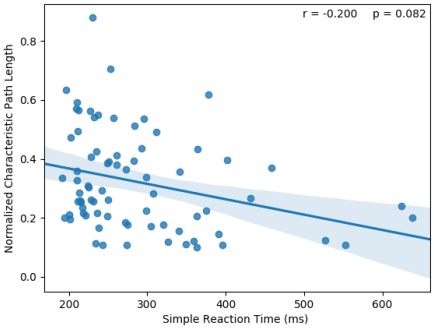
Figure 5.1: Correlation of global networks and rapid visual processing attention. The regression line shows the direction of the correlation between variables. The subjects are spread all over the plot, resulting in a non-correlated interaction.

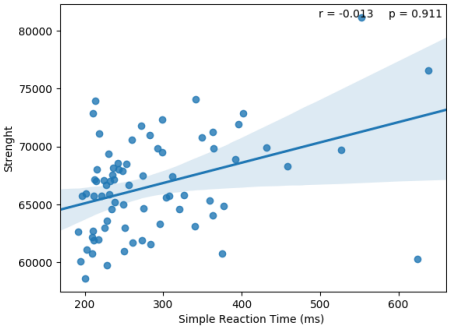

r = 0.091 p = 0.430
Betweenness Centrality
Simple Reaction Time (ms)


r = 0.003 p = 0.982
Degree
Simple Reaction Time (ms)


r = 0.023 p = 0.842
Normalized Clustering Coefficient
Simple Reaction Time (ms)


r = -0.137 p = 0.235
Normalized Global Efficiency
Simple Reaction Time (ms)


r = -0.200 p = 0.082
Normalized Characteristic Path Length
Simple Reaction Time (ms)


r = -0.013 p = 0.911
Strenght
Simple Reaction Time (ms)

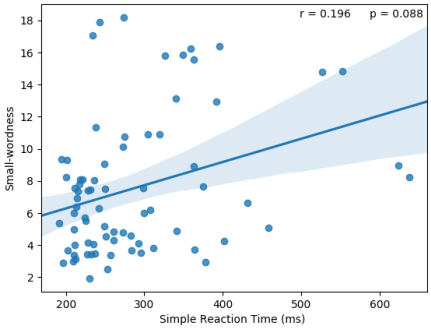


Figure 5.2: Correlation of global networks and simple reaction time. All the subjects are concentrated in the first part of the plot with a lower reaction time. The plots do not show any correlation.

RVPA and SRT were compared between the recovery groups to see if there is any difference in RVPA or SRT between groups with complete/incomplete recovery. As shown in figure 5.3, no significant difference between the complete recovery group (blue) and the incomplete recovery group (orange) was evident. There is no variability between the mean of all of the groups. No significant differences were found in mean scores between the two groups (RVPA with p = 0.877; SRT with p = 0.721).

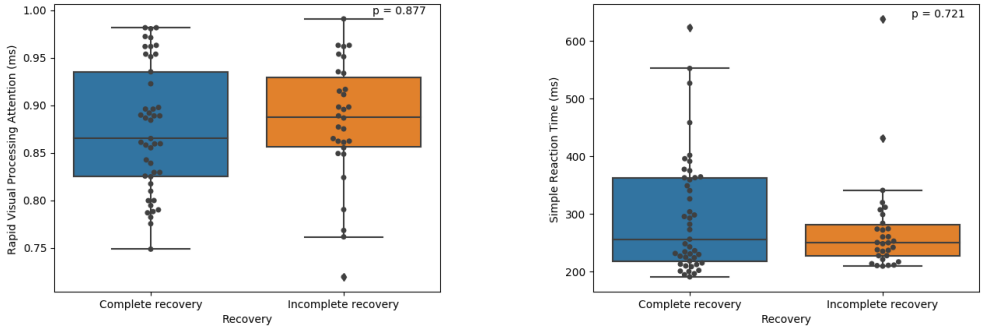


Figure 5.3: Boxplots of Cambridge Neuropsychological Test Automated Battery tests in patients with complete or incomplete recovery

In the same way, as can be seen from figure 5.4, there are not any differences in global network properties between patients with complete and incomplete recovery. Subjects are equally distributed in both cases of recovery.

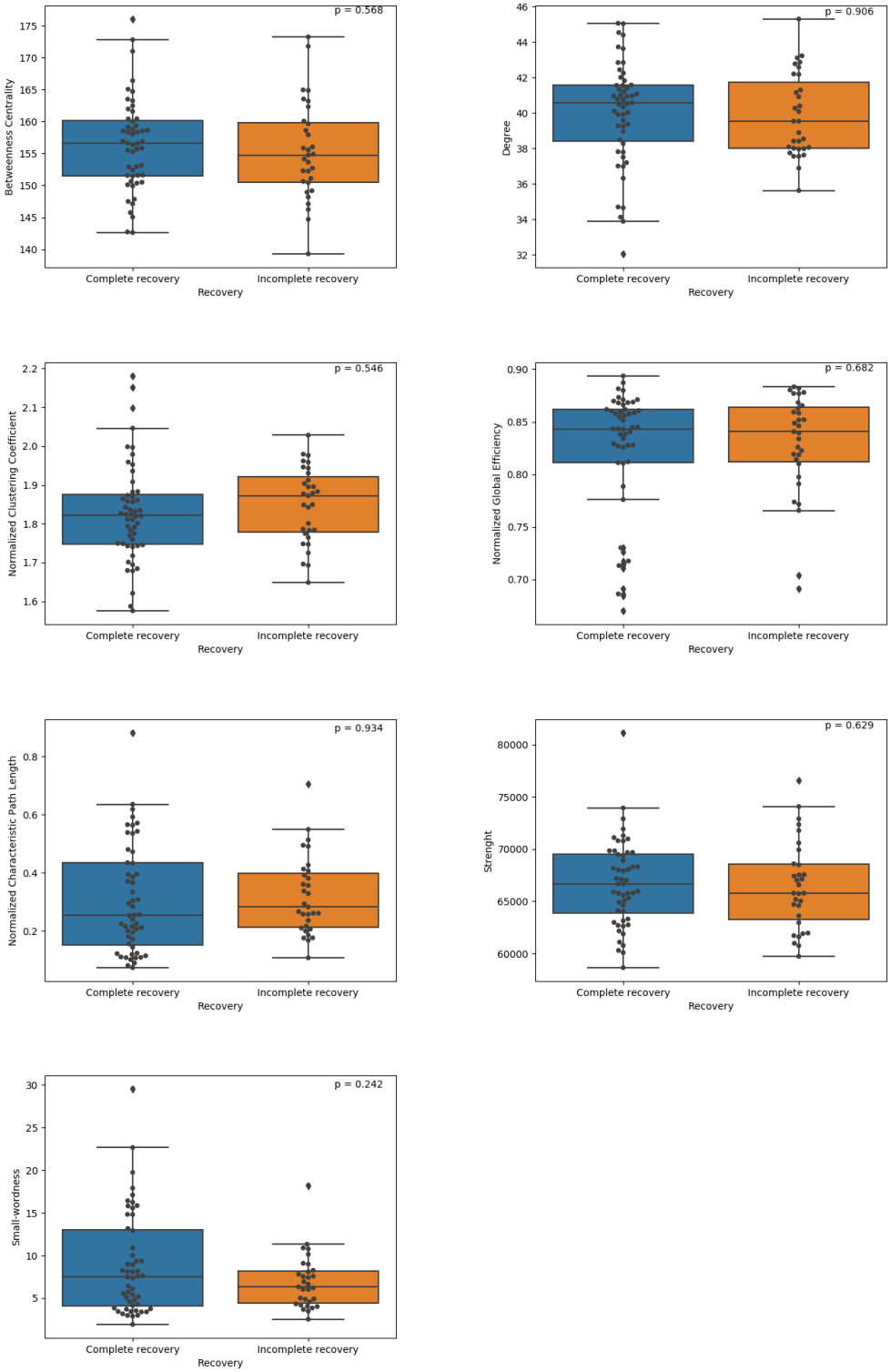


Figure 5.4: Boxplots of global networks properties in patients with complete or incomplete recovery

The possible relationship between global network properties and the patient outcome GOSE was examined.

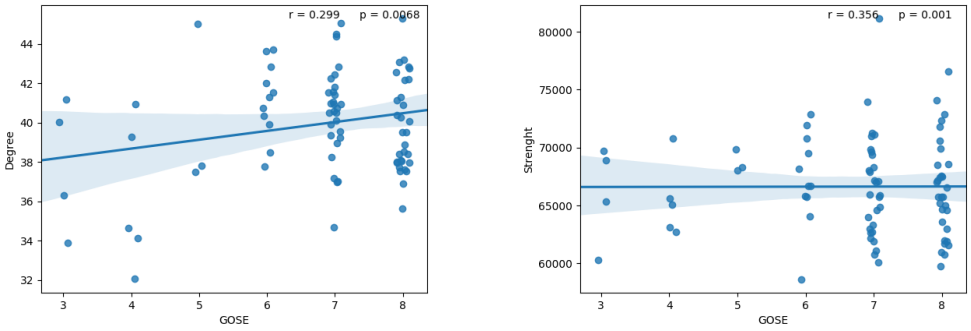


Figure 5.5: Degree and Strenght correlations with Outcome (GOSE)

The results of the correlation analysis are shown in figure 5.5.
From parametric partial correlation, Degree and Strength were positively correlated with the outcome (p= 0.0068, r= 0.229 ; p= 0.001, r= 0.356).
Regarding strength scatter plot, it seemed that the correlation line is horizontal, which usually means that there is no correlation. But having a correlation coefficient of 0.356, it is a weak correlation.

6 Discussion

The purpose of this study was to investigate the association of global brain network properties with two different CANTAB domains on average eight months at their chronic stage, after mTBI. After mTBI, patients deal with cognitive problems which often appear as diminished working ability.
The usage of a neuropsychological test is a common element in the TBI evaluation (Girard et al., 1996), such as in the detection of cognitive impairment after a TBI in athletes (Echemendia et al., 2001). In fact, a decrease in attention, memory, and other functional performances was found by neuropsychological test, which provides the quantification of brain function in injured athletes (Tysvaer, Løchen, 1991)(Chen et al., 2004)(Echemendia et al., 2001). Furthermore, neuropsychological tests are criticized, because they are not considered perfectly suitable for the prediction of cognitive disability (Sherer et al., 2002). This is because the neuropsychological assessment does not test the ability needed in the real world functioning (Sbordone, Long, 1996) (Hart, Hayden, 1986). We hypothesized that by combining global network properties and two CANTAB domains, it could be possible to identify some interactions among brain regions and cognitive abilities, which characterize mTBI.
Contrary to expectations, this study did not find any association between global network properties and neurophysiological tests. These findings are in contrast to other previous studies, where global network properties were significantly correlated with executive function performance (Caeyenberghs et al., 2014) (Sharp et al., 2014).
Some studies report that neuropsychological tests may be invalid after a TBI (Moore, Donders, 2004) (Donders, Boonstra, 2007). Sometimes, some factors such as patients with pre-injury history of psychiatric problems may contribute to invalid tests (Mooney et al., 2005) In this study, executive functions could be probably the most affected cognitive function if we considered a p-value<0.05. However, having adjusted for FWE-correction ($p<0.007$), there are no significant values that explain it through global properties and CANTAB tests.
Van der Horn, et al. conducted a study on brain networks in mTBI in 2017. They were looking for an interaction between functional networks, complaints, depression, and anxiety. All network measures showed the same values for both healthy controls and mTBI patients, suggesting that there is a week influence of mTBI on network functions (Horn van der et al., 2017).

From our analysis, there are also no differences in the mean of global network properties between patients with complete and incomplete recovery.
Even though no clear associations with neuropsychological tests were found, we could say that two global network properties Degree and Strength are significantly correlated with patients outcomes. Degree is one of the most important properties in a brain network as it is the number of edges that connect one node with the others. This means that higher is the degree, higher will be the number of connection in the network. Strength is the measure of connectivity strength across all the nodes (Liu et al., 2017). Both of them are important properties of a network because they are related to the connection between nodes, which could characterize the connectivity.
The correlation line of the plots 5.5 showed a not perfectly horizontal line, which is a moderate correlation. These plots suggest that as the two global properties values increase, so does the patient recovery, approaching complete recovery. It can be concluded that, when patients have a trauma, the global network properties decrease. From our results, this correlation could demonstrate that structural brain networks are affected by the trauma. In fact, they are directly proportional to each other. As the properties increase, the patient's condition is better and near to complete recovery. This finding is supported by some evidence of research, which demonstrates a decrease in structural connectivity in the white matter networks in TBI patients, suggesting how structural connectivity changes after TBI (Caeyenberghs et al., 2012). Several studies adopted the structural connectivity analysis to examine abnormal structural connectivity features in TBI or to reveal if there is any relationship between network connectivity measures and neuropsychological outcomes (Yuan et al., 2017) (Kasahara et al., 2010). A prior study discovered that in subjects with persistent symptoms after mTBI, changes in structural connectivity are linked to these symptoms (Yuan et al., 2015). Detection of network abnormalities can be helpful to predict cognitive impairments after TBI (Sharp et al., 2014), such as the observation of reduced connectivity within the motor network (Kasahara et al., 2010). Furthermore, it usually takes over 1 year after trauma to have improvements in cognitive performance especially in executive function and working memory (Dall'Acqua et al., 2017).

Limitations of the study

The main limitation of this study was that we do not have baseline CANTAB results on the patients and we are therefore unable to completely state that the CANTAB results are affected by TBI. Based on previous studies, the CANTAB tests were considered effective in finding differences in functional

level between healthy individuals and individuals with mild cognitive impairment (Saunders, Summers, 2010) (Égerházi et al., 2007). Although it is capable of measuring general cognition, Smith et al. (Smith et al., 2013) affirmed that the CANTAB tests might not be capable of measuring specific cognitive functions. This finding was also validated by another research, which confirmed that CANTAB tests were not able to discern one specific cognitive function from another (Lenehan et al., 2016).
Limitations of the current study could also be caused by the small sample size and by DWI acquisition.

7 Conclusion

By investigating the possible relationship between global network properties and neuropsychological tests, this thesis has shown different results from the starting statement. The initial hypothesis that the global network properties were related to neuropsychological findings has not been confirmed. Interestingly, all global network properties do not show any important correlation with the RVPA and SRT tests. In addition, other results arised from the analysis. When the patient reaches the complete recovery, the global network properties have high values. In conclusion, it could be hypothesized that any decrease in global network properties is related to a decrease in recovery after mTBI. The results of this study need to be validated in an external cohort.

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