Cortical dysfunctions of the human visual system following mild Traumatic Brain Injury

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Abstract

Mild Traumatic Brain Injury (mTBI) affects millions of people worldwide and induces long-lasting deficits. The visual system has been well-characterized and is therefore the ideal test bed to study the cortical dysfunctions that occur after mTBI. The current understanding of visual perception in the mTBI population is constrained by measures of sensitivity and performance. Such metrics—whether acquired behaviorally or through non-invasive brain imaging—are limited in their mechanistic implications.

Psychophysical studies report many visual deficits following brain injury, and these are understood in terms of cortical integration dysfunction. However, we do not know whether that can be explained by cortical integration failure or internal noise increase, which would have different mechanistic consequences. I sought to disentangle their contribution to contour integration following mTBI using the equivalent noise technique. I found that mTBI increased internal noise without affecting efficiency. Because the task was designed to be sensitive to quadrant-specific group differences, I was able to find that mTBIs had hemifield biases that were absent from the controls. These findings demonstrate that in contour perception, cortical integration is maintained after mTBI at the cost of internal noise.

Patients continue to report difficulties executing tasks that do not require exceptional cognitive efforts for years, yet the measurement of these symptoms is eluding health care professionals. Instead, research has focused on pushing the demands of the tasks until TBIs' performance is affected. This is exacerbated by traditional functional imaging analysis that require conditions to be sufficiently different to induce a contrasting BOLD response—often operationalized as difficulty levels. These tasks have been instrumental to revealing discrepancies in cortical function after mTBI, but they are not ecologically

valid and hard to interpret. In contrast, I have used simple naturalistic movie stimuli to show that mTBI's cortical function differs from normal even when the task is not particularly demanding. Subtle differences with normal models of temporal patterns are localized in areas related to common patient complaints, and the imbalance between fronto-parietal and early areas could be explained by compensatory connectivity. I also found an increase in functional connectivity between early visual, ventral, dorsal and fronto-parietal areas, marking an increase in within subject synchrony in addition to the decrease in between subject synchrony.

Network analysis of neuroimaging data has recently offered a new perspective on altered functional connectivity after mTBI and suggests that functional connection density is not randomly adjusted post-injury. Using simple naturalistic stimuli, I was able to extract key network parameters to describe the mTBI's cortical visual system under normal processing demands. I found that connectivity degree was increased across the whole network graph, but so was global efficiency. The latter reflects cortical integration so both increases combined suggest utilization of additional compensatory pathways. Modularity was reduced in the mTBI group, suggesting a decline in specialized connections (segregation) and a muddling of functional boundaries. Clustering was increased, suggesting that the cortical network is more resilient to future injury. These findings are in line with highly demanding tasks and support the functional reorganization theory: even at low levels of difficulty, the injured brain relies on functional connections that are irrelevant in healthy controls.

In conclusion, the mildly injured brain compensates for increased internal noise by adjusting information integration and segregation unevenly across the visual system, to maintain behavioral performance even in low-demanding conditions.

Résumé

Les lésions cérébrales traumatiques légères (LCTl) affectent des millions de personnes dans le monde et causent des troubles cognitifs, perceptuels et de l'humeur. Le système visuel est idéal pour étudier les disfonctionnements corticaux visuels qui apparaissent à la suite d'une LCTl grâce à la riche littérature. Cependant, nos connaissances de la perception visuelle chez les LCTl sont limitées par les mesures de sensibilité et de performance. Ces mesures—qu'elles soient comportementales ou obtenues par imagerie médicale—nous informent quant à la capacité du système nerveux central mais sont limitées dans leurs implications mécanistiques.

La multitude de déficits visuels suites aux LTCl sont globalement compris dans le cadre de dysfonctionnement d'intégration corticale. Cela pourrait être expliqué par un échec d'intégration corticale ou par une augmentation du bruit interne, ce qui aurait des conséquences mécanistiques différentes. Afin de démêler leurs contributions à l'intégration de contours à la suite d'une LTCl j'ai employé la technique de bruit équivalent. J'ai appliqué un modèle mathématique établi et trouvé que la LTCl augmente le bruit interne sans affecter l'efficacité. J'ai pu trouver des biais dans le champ visuel chez les LTCl mais absents des contrôles. Ces résultats démontrent qu'au moins dans le cas de la perception de contours, l'intégration corticale est maintenue après une LTCl au prix du bruit interne.

Les patients ont de la difficulté à exécuter des tâches simples, pourtant, la quantification de ces symptômes est complexe. La recherche se concentre sur augmenter les demandes des taches en laboratoires pour affecter la performance. Cette tendance est exacerbée par les méthodes traditionnelles d'analyse de données d'imagerie médicale fonctionnelle parce qu'elles requièrent des conditions suffisamment différentes pour induire une

réponse BOLD contrastante. Ces taches poussées ont révélé les défauts de la fonction corticale après une LTCl mais elles ne sont pas valides écologiquement et leur interprétation est complexe. En contrepartie, j'ai utilisé des stimuli naturels dynamiques pour montrer que la fonction corticale visuelle diffère de la normale même lorsque la tâche n'est pas particulièrement exigeante. Les différences subtiles d'avec les modèles normaux de déroulement temporel sont localisées dans les régions liées aux plaintes communes des patients, et le déséquilibre entre les régions dorsales et primaires pourrait être expliqué par une connectivité compensatoire.

L'augmentation compensatoire de la connectivité fonctionnelle est l'un des résultats fréquents de la recherche sur les LTCl. L'analyse de réseaux dans les données d'imagerie médicale offre une nouvelle perspective sur la connectivité fonctionnelle qui serait altérée après une LTCl et suggère que l'ajustement de la densité des connections fonctionnelles suite au trauma n'est pas aléatoire. Pour extraire les paramètres de réseaux nécessaires à la description du système visuel cortical des LTCl sous des conditions normales de traitement de l'information, j'ai utilisé des stimuli naturels simples et j'ai trouvé que le degré de connectivité ainsi que l'efficacité globale étaient augmentés sur l'ensemble du réseau cortical visuel. L'efficacité globale reflétant l'intégration corticale, ces résultats suggèrent l'utilisation de voies compensatoires supplémentaires. La modularité était réduite chez les LTCl, suggérant un déclin des connexions spécialisées (ségrégation), ainsi qu'un brouillage des frontières fonctionnelles. Le partitionnement était augmenté, suggérant un réseau cortical plus résiliant aux traumas futurs.

En conclusion, le cerveau des LTCl compense l'augmentation du bruit interne en ajustant l'intégration, ainsi que la ségrégation de l'information de manière inégale dans

le système visuel, afin de maintenir des performances comportementales normales, et ce, même dans des conditions cognitives peu exigeantes.

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Contributions

Contribution to original knowledge

The following elements are original scholarship and distinct contributions to knowledge: application of the equivalent noise paradigm to the mTBI population, psychophysical modelling of internal noise and efficiency of mTBI patients, investigating early visual integration of good continuity in mTBI patients, finding increases in contour integration internal noise, using naturalistic movie viewing to find altered cortical processing following mTBI, creating normative timeseries of natural viewing to compare a clinical population to healthy controls, finding asynchrony of processing of naturalistic stimuli in the mTBI group, finding increase functional connectivity in response to naturalistic movie viewing in the mTBI group, graph analysis of mTBI participants cortical network activated by naturalistic movie viewing, finding increased connectivity degree, efficiency and clustering but decreased modularity in the mTBI cortical network in response to movie viewing.

Contribution of authors

I personally collected all the data in this thesis to the exception of the healthy control cohort neuroimaging data from chapter 3 and 4 that was acquired by my colleague Dr. Angela Zhang. I conceived and designed the analysis of Chapter 2 with the contribution of Dr. Alex Baldwin, Dr. Daniel Spiegel, and Dr. Reza Farivar, I performed the analysis and wrote the paper. I conceived and designed the analysis of Chapter 3 with the contribution of Dr. Reza Farivar, I performed the analysis and wrote the paper. I conceived and designed the analysis of Chapter 4 alone, my co-author Shael Brown contributed analysis tools and some graph theory discussion elements, he performed the analysis, and I wrote the paper with his contribution for the method section. I am

grateful to my supervisor Dr. Reza Farivar for his patience and guidance throughout my Ph.D.

List of Abbreviations

Anterior Cingulate Cortex: ACC

Department of Defense: DOD

Default Mode Network: DMN

Diffuse Axonal Injury: DAI

Functional Magnetic Resonance Imaging: fMRI

Glasgow Coma Scale: GCS

Magnetic Encephalography: MEG

Magnetic Resonance Imaging: MRI

Mild Traumatic Brain Injury: mTBI

Traumatic Brain Injury: TBI

Chapter 1 Introduction

Traumatic Brain Injury affects millions of people every year and is a leading cause of death and disability worldwide (W. D. Johnson & Griswold, 2017) but very little is understood about the cortical dysfunctions at the roots of the chronic deficits that many patients report for months or even years after an injury. Although some physiological mechanisms that follow a brain insult have been successfully investigated, the systemic consequences have yet to bring together various opposing views.

In this thesis, I will investigate three paradigms, whereby mild Traumatic Brain Injury (mTBI) is approached as (1) a disorder of cortical integration, (2) a disorder of brain activity, and (3) a disorder of connectivity.

Behavioral deficits following mTBI are widespread, but the seemingly diverse tasks that become difficult for patients have a distinct commonality: they all require integration over large cortical areas. Patients report difficulties related to vision such as reading or driving but behavioral deficits span over many other cognitive, emotional and perceptual functions, all requiring integration over larger portions of cortical matter. Thus, mTBI has been understood as a disorder of integration, potentially explained by diffuse injury that affects long range neuronal processes. Simple binary performance metrics are insufficient because they do not dissociate between a decrease in efficiency of processing and an increase in internal noise. The visual system is particularly affected by mTBI and has a rich history of empirically validated mechanistic models and refined stimuli that make it the ideal test bed to study the diffuse cortical impairments caused by mTBI. Thus, in my first paper (Chapter 2, (Ruiz, Baldwin, Spiegel, Hess, & Farivar, 2019)), I propose the equivalent noise approach to disambiguate the contribution of internal noise and integration to the diminished capacity of visual contour perception.

Because patients often report fatigue and strain, the research community has focused on challenging the cortical system to evaluate potential shifts in the limits of its processing power. Under overloading conditions, a pathological pattern has emerged where isolated cortical regions showed abnormally high levels of activity. This can be interpreted as a form of compensation—the injured brain needs to work harder to attain normal levels of performance when the task is particularly difficult. However, the overwhelming complaints of patients encompass simple daily tasks as well, and it is possible that the injured brain is always under load. Thus, in my second paper (Chapter 3, Ruiz et al, under submission) I propose to use naturalistic stimuli to allow for a comparison to a normal template of activity under normal processing demands instead.

In my last experimental paper (Chapter 4, Ruiz et. Al, under submission), I use graph theory to approach the long-standing debate regarding the way the cortical system springs back from traumatic brain injury. Indeed, comparing the sheer magnitude of brain activity is not enough to gather a comprehensive understanding of the mechanistic implications of compensation, reorganization, and recruitment of latent processes. Recent applications of network science on the functional topology of the injured brain have focused on tasks that are overbearing and have various scales of analysis, making it difficult to conciliate results across studies. To palliate these crucial gaps in the literature, I extracted functional connectivity correlation matrices of visual cortical areas to construct task-relevant graphs from participants experiencing naturalistic and dynamic visual stimulation.

1.1 TBI and cortical integration

1.1.1 How is cortical integration affected after a TBI?

Classification

A Traumatic Brain Injury (TBI) results from a mechanical insult to the brain from an external force such as a shock, a sheer, or a blast. It is considered mild when the verbal, motor and eye movement responses after the incident are not too severe: the patient is not too confused, disoriented nor unresponsive. When the patient does not lose consciousness for more than half an hour, does not present amnesia that spans over more than 24 hours, keeps their eyes open at least upon verbal stimuli, is able to answer a conversation, and directs their movement towards the pain, then the patient scores between 13 to 15 on the Glasgow Coma Scale (GCS) (Teasdale & Jennett, 1974) and is thus considered to have sustained a mild TBI (mTBI).

mTBI's definition is based on symptomatology since the Congress of Neurological Surgeons in 1966 where it was first defined on record. Unfortunately, the medical community is not unanimous regarding the defining criteria of mTBI. A few different guidelines are dictated by a series of medical organizations including the World Health Organization, the United States Department of Defense (DOD), and the Ontario Neurotrauma Foundation. They vary in terms of inclusion and exclusion criteria (Mayer, Quinn, & Master, 2017). For example, the DOD retains the best GCS score obtained in the first 24 hours (as opposed to the first one/the only one/30 minutes after the incident), while the American Academy of Neurology recommends a general assessment of the symptoms without using the GCS at all. Some organizations see structural damage to the skull or the brain such as a penetrating injury as an exclusion criterion while others do not. The list of criteria has broadened over time and now includes self report

of symptoms as well, showing an acknowledgement of the diversity of the pathology manifestation. The nosology itself remains unclear, with no determined differential diagnosis criteria between mTBI and concussion, although it is accepted that the term concussion refers to a less severe form of mTBI. It is thus not surprising that the research literature is akin to a complex bouquet of seemingly opposing results, with many debates ranging from neural mechanisms of recovery to neural correlates of reported symptoms. Note that the following introduction assembles mTBI and TBI literature when necessary (in cases where advancement in mTBI research is still lacking). The former being a milder version of the latter they can be understood as belonging to a continuum, even when (and especially when) evidence of certain symptoms is lacking from mTBI body of science.

Neuropathology

Three immediate and long-lasting neuropathological changes following a mTBI are all obvious obstacles to cortical integration: neuronal death, diffuse axonal injury, and abnormal cerebral blood flow.

Firstly, upon impact, entire regions of the cortex can be so damaged that neurons die—whether from necrosis (Rink et al., 1995; Ross, Graham, & Adams, 1993) or apoptosis. It is possible that apoptosis is an adaptive mechanism (Raghupathi, 2004), with more cells following in their footstep as inflammation takes place and induces neurodegeneration (Xiong, Mahmood, & Chopp, 2018). Tissue changes gradually escalate and various cells (central/peripheral, and neuronal/nonneuronal/originating from outside of the central nervous system) are made to interact and contribute to neuro-inflammation because of the injury-related disruption of the blood-brain barrier (Burda & Sofroniew, 2014).

Secondly and as a direct consequence, the long-range connections emanating from these dying cells are compromised. Connections between intact cells can succumb to compression and shearing, creating diffuse axonal injury (DAI) (Adams, Graham, & Murray, 1982; Meaney et al., 1995; Povlishock, Becker, Cheng, & Vaughan, 1983; D. H. Smith, Meaney, & Shull, 2003). Brain tissue is tolerant to some level of stretch and pressure and acts as a viscoelastic matter but rapid deformation (of the order of tens of milliseconds) causes axons to break, as the velocity of the shock renders white matter brittle (Metz, McElhaney, & Ommaya, 1970). The damage endured via DAI is consistent with persistent cognitive impairment (Scheid, Walther, Guthke, Preul, & von Cramon, 2006). The structural integrity of specific brain regions is correlated with a particular set of executive functions because axons are not equally damaged across the cortex (Kraus et al., 2007). The integration of information via brain networks is severely impeded by DAI, especially large-scale networks. For example, the structural integrity of the salience network—thought to regulate and coordinate other networks—was found by Bonnelle et al. (2012) to be predictive of the default mode network dysfunction and inefficient cognitive control. Primary axotomy injury caused by immediate disconnection occurs in severe cases of TBI, but in mild injuries, disconnections are mostly due to secondary axotomy. These disconnections endured over minutes to weeks are due to swelling, altered membrane permeability and neurofilament compaction (Büki & Povlishock, 2006; Pettus, Christman, Giebel, & Povlishock, 1994).

Thirdly, cerebral blood flow is perturbed by mTBI. It is unclear whether secondary injury is caused by abnormal blood flow or if blood flow is reduced due to reduced demands by injured neurons (Lok et al., 2015). Hypoperfusion was found in frontal, pre-frontal and temporal regions in mTBI (Bonne et al., 2003), and later confirmed in fronto-temporal regions (Y. Wang et al., 2015), while hyperperfusion was

detected in the bilateral inferior temporal gyrus which was correlated with cognitive impairments (Li, Lu, Shang, Chen, et al., 2020). Both imbalances can be deleterious for brain functioning, one menacing of leakage, and the other of oligemia or worse, ischemia, although the latter is rare (Vespa et al., 2005). In order to maintain perfusion, cerebral arteries adjust their resistance in response to pressure changes. That capacity—dynamic cerebral autoregulation—is an indicator of blood flow regulation. It was found to be diminished and associated with poorer cognitive performance in chronic stages of mTBI (Ding et al., 2020).

Neuroinflammation

TBI leads to adaptative and limiting cortical processes induced by inflammation. Within minutes, alarmins are released from damaged meninges (Jassam, Izzy, Whalen, McGavern, & El Khoury, 2017). Almost immediately after injury, resident microglial activation and peripheral neutrophil recruitment occur. Lymphocytes and monocyte-descendant macrophages infiltrate though the blood brain barrier diffusely in the case of mTBI, and in parallel, both pro- and anti-inflammatory cytokines promote and terminate the neuroinflammatory response. In the case of a lesion, inflammatory amplifiers like chemokine signaling activates and recruits immune cells on site (Simon et al., 2017).

Some level of post-traumatic inflammation is necessary and beneficial to clear out debris and regenerate areas. However, neuronal death and progressive neurodegeneration is also mediated by neuroinflammatory mechanisms that are detrimental to cortical recovery. It is important to note that pure anti-inflammatory approaches to acute TBI treatment can be harmful to patients' recovery because of this

duality. Simon et al. (2017) proposed a set of guidelines for future neuroinflammatory-centered therapy approaches that address this tricky balance.

Symptomatology

> *"Patients with mild traumatic brain injury (MTBI) challenge physicians' skills and test their patience. Their manifold symptomatology is often not supported by objective neurological findings."*
>
> *(Bonne et al., 2003)*

Initially, the scientific community supported the hope that a majority of patients recover fully from TBI without long-term neuropsychiatric sequelea (Karr, Areshenkoff, & Garcia-Barrera, 2014; McCrea et al., 2003). However, it is now unequivocal that a constellation of symptoms is debilitating and long-lasting for many TBI patients (Bieniek et al., 2015; Steven T. DeKosky, Ikonomovic, & Gandy, 2010; McKee et al., 2013; Whiteneck, Gerhart, & Cusick, 2004). Post concussion syndrome has been removed from the Fifth edition of the Diagnostic and Statistical Manual of Mental Disorders(Regier, Kuhl, & Kupfer, 2013) but was previously described within four brain dysfunction categories: cognitive, somatic, affective and circadian (King et al., 2012). The brain functions that are altered by mTBI all require cortical integration over short- and long-range connections.

Among the cognitive difficulties experienced by mTBI patients, working memory (Maki Kasahara et al., 2011) and episodic memory (Tsirka et al., 2011), attention (Malojcic, Mubrin, Coric, Susnic, & Spilich, 2008), and executive processing (Hartikainen et al., 2010; Little et al., 2010) are paramount. Respectively, Schlichting

and Preston (2015) (memory), Koelewijn, Bronkhorst, and Theeuwes (2010) (attention), Lipton et al. (2009) (executive functiona), and Caeyenberghs et al. (2014) (executive function) have shown that these processes require cortical integration.

Headache (Defrin, 2014), dizziness and balance (Fife & Kalra, 2015), and light and noise sensitivity (Assi, Moore, Ellemberg, & Hébert, 2018; Waddell & Gronwall, 1984) have been explored as somatic consequences of mTBI. These symptoms are related to functions also requiring integration over large areas of cortex.

Thirty to seventy percent of TBI patients live with sleep disturbances (Ouellet, Savard, & Morin, 2004) that can span from simple insomnia to chronic fatigue, and even narcolepsy and sleep apnea (Viola-Saltzman & Watson, 2012). Sleep regulation relies on integration over cortical columns too (Roy, Krueger, Rector, & Wan, 2008).

Between 30 to 60% of TBI patients are found to develop depression (Bowen, Chamberlain, Tennant, Neumann, & Conner, 1999; Hibbard, Uysal, Kepler, Bogdany, & Silver, 1998; Hurley & Taber, 2002; Jorge et al., 2004; Satz et al., 1998). In a large scale study about the incidence, outcome and treatment of mood disorders after TBI in Seattle, more than half of TBI patients met the criteria for major depressive disorder within the first year following injury, of which 60% were more likely to develop comorbid anxiety disorders (Bombardier et al., 2010). The pathophysiology of depression can be modelled as a failure of the cortico-subcortical integrative processes particularly involving the prefrontal cortex, the amygdala, striatum and hippocampus (Heller, 2016). Other more long term neuropsychiatric impairments linked with TBI include dementia and Alzheimer's disease (Corrigan, Arulsamy, Teng, & Collins-Praino, 2016). Based on self-report and family report, up to 30 % of TBI patients show

increased irritability (C. C. Yang, Hua, Lin, Tsai, & Huang, 2012), and anxiety (Ahmed et al., 2017).

Perceptual deficits following mTBI are widespread. In a visual assessment study, Costa et al. (2015) found that nearly all measurements of perceptual organization were worsened in the TBI group, whether local or global processing, or grouping of elements, both for accuracy and response time. Eye movement is also limited following mTBI (Cifu et al., 2015), as well as binocular disparity (Gunnar Schmidtmann et al., 2017) and visual acuity (Spiegel et al., 2016). Other senses are affected too, for example audition (Shah, Ayala, Capra, Fox, & Hoffer, 2014; Singh, Ahluwalia, Lal, & Chauhan, 1997).

In the previous section, we have explored the symptomatology of acute and chronic mTBI, as well as the physiological mechanisms underlying the cognitive, somatic, circadian and affective difficulties experienced following mTBI. They have been framed as dysfunctional integration. This thesis will focus on perceptual changes occurring after mTBI, specifically visual, for two main reasons. The human visual system is very well characterized, and patients consistently report visual disturbances. Thus, the visual system is a perfect test bed to address systemic changes following mTBI.

1.1.2 Visual integration in the healthy brain

The following section is an overview of healthy visual integration, with the goal of describing healthy processing of visual information before addressing the changes that occur following mTBI.

Cortical integration in the visual system

People report vision as their most important perceptual source of information regarding the world around them (Schifferstein, 2006). Vision is also the sensory

modality that people are most scared of loosing (Hutmacher, 2019), probably because we rely on it for most of our every-day life activities and to form impressions about our surroundings (Kandel et al., 2000). Vision is the most important and developed sense in humans and in other animals (Zimbardo & Ruch, 1975). As such, the visual cortex engages much more processing resources from the brain than any other sense (Stokes, Matthen, & Biggs, 2015). For these reasons, and because of ease and accessibility of investigation methods, the visual cortex is very well characterized (Yantis, 2013).

As early as the Renaissance, philosophers have started to piece together mechanisms of visual perception, beginning with Descartes and the understanding that images from both eyes are combined in a single image in the brain. Newton later postulated that color was an internal perceptual quality that did not belong to the light itself but to its sensation. Young then added that three receptors acted as combinators, and their relative activation signaled the color of an object. Very early on were we able to determine the importance of integration in vision.

To perceive a natural scene and distinguish between the various objects within it, we need to group features and characteristics meaningfully. Complex features are successively integrated to construct a comprehensive percept (Felleman & Van Essen, 1991)e. Without cortical integration in the visual cortex, basic cognitive object identification and accurate proprioception can be largely impaired (Riddoch & Humphreys, 1987).

The primary property of a detectable shape is the proximity of its defining elements (Koffka, 2013; Kubovy & Wagemans, 1995; Oyama, 1961; Wertheimer, 1938). Perceptual grouping was first described by the Gestalt movement who coined the importance of good continuity between elements defining a contour or a shape for its

accurate detection (Koffka, 2013). Good continuity includes alignment and limits in orientation changes between elements on a path (D. J. Field, Hayes, & Hess, 1993). The association field stipulates that multiple cells interact to detect contours, specifically ones with aligned edges, matching naturally occurring edge alignment.

Cortical integration is thus critical to combine receptive fields into complex percepts. The following section will briefly introduce contour integration as a example of visual integration occurring in early and mid level visual processing.

Contour integration mechanisms

Edges naturally occur in an aligned, co-circular or parallel fashion (Elder & Goldberg, 2002; Geisler, Perry, Super, & Gallogly, 2001; Sigman, Cecchi, Gilbert, & Magnasco, 2001), and at different spatial scales (Sigman et al., 2001). This gives rise to the study of contours, representing the co-aligned structured information (R. Hess, May, & Dumoulin, 2014). The spatial frequency filters implicated in the association field model correspond to low-level visual processing, namely the primary visual cortex (V1) as a first stage. One evidence for the implication of V1 in contour perception is the modulation of neural responses by neuronal interactions, independently of contrast levels (Allman, Miezin, & McGuinness, 1985). Neurons that are linked across orientation columns of V1 tend to have receptive fields that are oriented and aligned similarly (Kisvárday, Toth, Rausch, & Eysel, 1997; R Malach, Amir, Harel, & Grinvald, 1993; Weliky, Kandler, Fitzpatrick, & Katz, 1995), and neurophysiological data show increased responses to co-aligned stimuli in opposition to decreased responses to orthogonal orientations (Blakemore & Tobin, 1972; Knierim & Van Essen, 1992; Nelson & Frost, 1985; Sillito, Grieve, Jones, Cudeiro, & Davis, 1995).

However, in an fMRI study, the activity patterns in V1 were mostly explained by contrast variations, whereas the extra-striate cortex response variance could be explained best by contours, remaining independent of contrast modulations (Dumoulin, Dakin, & Hess, 2008). Some neurons of the early extra-striate cortex (V2) are angle selective, but their responses aren't specific enough to be angle detectors, instead, they would be useful to extract orientation changes in contours (Ito & Komatsu, 2004), or combinations of orientations within contours (Anzai, Peng, & Van Essen, 2007).

Further in the visual processing hierarchy structure, V4 has been shown to respond to more complex assemblages of contours, shape primitives, and certain curves (specifically convex curves) (Pasupathy & Connor, 1999).

Visual processing relies on successive steps of signal integration and transmission between computational units is inevitably imperfect. To understand the complications in signal processing following mTBI, we have to be mindful of the imperfections of healthy neural computations. The following section introduces the concept of noise and its role in limiting cortical integration in the healthy brain.

1.1.3 Noise can limit integration

Changes of neural membrane potential encode meaningful information, but some fluctuations seem to be random and irrelevant to the target signal at best and detrimental to its transmission at worst. Approaching the brain as a system, different fields have shaped the concept of "noise", with its most comprehensive definition, found in the Oxford English Dictionary, being "random or unpredictable fluctuations and disturbances that are not part of a signal [...] or which interfere with or obscure a signal or more generally any distortions or additions which interfere with the transfer of information" (Stevenson, 2010).

Neural noise

Neural coding's fundamental question is the extent of neuronal variability pertaining to meaningful signals as opposed to meaningless noise (W. Bialek, Rieke, de Ruyter van Steveninck, & Warland, 1991; A. Aldo Faisal, Selen, & Wolpert, 2008). The conceptualizations of neural noise have imposed varied restrictions on its definition depending on the scale of its operationalization, the technique, and the field of study. At a single neuron level, noise can be expressed by the Fano factor, measuring the variability of spiking from trial-to-trial (variance over mean) (Fano, 1947; Tolhurst, Movshon, & Dean, 1983) but ignoring temporal structure and higher-order statistics (A. Aldo Faisal et al., 2008). Both intracellular and synaptic signalling have biochemical noise limits (William Bialek & Setayeshgar, 2005). Extracellular noise can disrupt signal transmission. Noise affects the synaptic cleft where the postsynaptic response and the presynaptic stimulation are not perfectly consistent and show trial-to-trial variability as well, measurable with patch-clamps (Kleppe & Robinson, 2006).

In EEG recordings, the activity related to a certain process is mixed with signals from other processes as well as background oscillations. The analysis of single trials and that of the variability across trials thus requires the disentanglement of different source signals, for example using independent component analysis (ICA) (Makeig, Jung, Bell, Ghahremani, & Sejnowski, 1997; Milne, 2011), even if alpha rhythms can be treated as intra-individually stable (Gasser, Bächer, & Steinberg, 1985). Using functional Magnetic Resonance Imaging (fMRI), noise in the brain processes is also commonly understood as variability in activity, albeit at a more macro scale, using abnormally high responses given performance as a marker of unstable activity (Callicott et al., 2000).

Internal noise and the equivalent noise method

The equivalent noise method was first theorized by engineers for the study of amplifier responses, their limitations and their efficiency (Friis, 1944; Mumford & Schelbe, 1968; North, 1968). Like amplifiers, our brains, or at least the brain modules responsible for perceptual detection, processing, and decision, receive an input and return an output. No amplifier is perfectly capable of returning the exact input amplified, so the amplification transformation inescapably injects random fluctuations in the signal. This injection is conceptualized as internal noise, and is specific to an amplifier, a system, or an individual's brain. The incoming information received by the amplifier is also imperfect and noisy: input includes external noise. Qualifying internal noise by analyzing responses to a range of external stimuli to which noise was added is at the core of the equivalent noise method. If the amount of external noise added to the stimuli is lower than the internal—or intrinsic—noise of the amplifier system, the amount of signal needed to maintain constant output signal to noise ratio (SNR) across levels of external noise conditions is constant. Once external noise reaches values higher than intrinsic noise, increasing amounts of signal are needed to maintain constant SNR across levels of external noise (Dosher & Lu, 1998; Z. L. Lu & Dosher, 1999). Figure 1-1 illustrates the effect of contrast noise on grating detection—low amounts of contrast noise yield an almost constant visibility and as more external noise is added to the signal, the visibility plumets exponentially (thresholds rise) (Z.-L. Lu & Dosher, 2013).

External noise added to the stimuli has been thoroughly used to characterize perceptual processes and psychophysical performance in terms of internal noise (H. B. Barlow, 1956, 1957; Carter & Henning, 1971; Fletcher, 1940; Harmon & Julesz, 1973; Henning, Hertz, & Hinton, 1981; Parish & Sperling, 1991; Pavel, Sperling, Riedl, & Vanderbeek, 1987; Denis G. Pelli & Farell, 1999; Pollehn & Roehrig, 1970; Riedl & Sperling, 1988; Stromeyer & Klein, 1974; Swets, Green, & Tanner Jr, 1962).

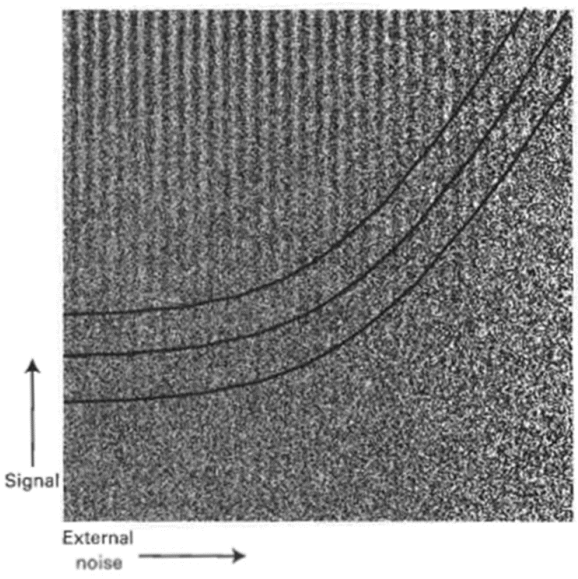

Figure 1-1: Added contrast external noise on a grating of increasing signal strength stimuli. The three lines represent distinct levels of equal visibility (adapted from Z.-L. Lu & Dosher, 2013).

Quantitative applications of the equivalent noise method in human perception

The first translation from engineering to psychology of the equivalent noise method looked at the effect of luminance noise on contrast thresholds in a disk detection task (Nagaraja, 1964). The results were interpreted in the light of fluctuations in the retina's absorption, attributing internal noise of the vision channel to quantum efficiencies. Barlow identified two potential main factors to characterize sensitivity—internal noise and efficiency (H. Barlow, 1977). Internal noise referred to independent random events liable to be confused with the effective absorption of a quantum of light (H. B. Barlow, 1956) constraining performance, and efficiency as an estimate of the proportion of the sample of dots that is effectively utilized in deciding about the pattern (H. Barlow, 1977).

Pelli reanalyzed Nagaraja's data in his thesis (Denis G Pelli, 1981), and used a linear amplifier as a model to yield two parameters from the observer: efficiency and equivalent input noise (D. Pelli & Blakemore, 1990; Denis G. Pelli & Farell, 1999). The latter, alternatively referred to as intrinsic noise, equivalent noise or internal noise, remains invariant with respect to certain properties of the stimulus and task.

The linear amplifier models the expected changes in threshold (c) as a function of external noise (σ_{ext}), to infer internal noise (σ_{int}) and efficiency (β) (adapted from Alex S Baldwin, Baker, & Hess, 2016).

$$c_{(\sigma_{ext})} = \frac{\sqrt{{\sigma_{int}}^2 + {\sigma_{ext}}^2}}{\beta}$$

For example, the Linear Amplifier Model (LAM) has been used to model visual sensitivity in infants from electrophysiological (EEG) data in a remarkable integration of methods across domains revealing internal noise as the limiting factor to visual sensitivity in both infants and adults (Skoczenski & Norcia, 1998). The authors derived thresholds of activity from the visually evoked potential (VEP) response, which were then plotted as a function of contrast and fitted to a LAM model. The "neural internal noise" parameter was obtained for each subject and correlated against behavioral measurements of contrast threshold. They were able to demonstrate that visual sensitivity in infants could adapt to changing conditions of stimulation dynamically and was limited by internal noise, in the same way that adults were.

We have established that cortical processes are limited by neural noise even in the healthy brain. The first paper of this thesis explores modelled internal noise after mTBI and shows that it suffers an increase whereas compensation ensures the conservation of performance and efficiency. Because modelled abnormal levels of

internal noise must have tangible neural correlates, I will next introduce neuroimaging measurements of abnormal cortical activity following mTBI and TBI.

1.2 Dysfunctional patterns of brain activity following TBI

The following section reviews current brain imaging approaches and findings in the TBI literature and proposes a novel design that is sensitive to subtle cortical activity changes.

1.2.1 Heterogenous chronic brain dysfunction

Brain tissue that survived acquired brain injury relies on a series of coordinated biomolecular events for repair that require increased metabolism (Chodobski, Zink, & Szmydynger-Chodobska, 2011). Some genetic alterations contribute to TBI's pathophysiology (Dash, Moore, & Dixon, 1995; S. T. DeKosky et al., 1994; Dutcher, Underwood, Walker, Diaz, & Michael, 1999; Hayes, Yang, Raghupathi, & McIntosh, 1995; Katano, Masago, Harada, Iwata, & Yamada, 1998; Phillips & Belardo, 1992; K. Yang et al., 1994) and they inevitably weigh on energy consumption, even beyond the acute phase (Lynch & Marinov, 2015; Wagner, 2005).

In the barrel cortex of the rat, TBI caused hyperexcitation in the upper cortical layers, potentially because of changes in inhibitory processes (Carron, Alwis, & Rajan, 2016).

This hyperexcitability is long-lasting, even after a single episode of experimental closed head trauma. In humans, both structural and functional alterations in inhibitory and excitatory processes were found by Santhakumar, Ratzliff, Jeng, Toth, and Soltesz (2001) which are likely putative in the development of hyperexcitable foci in posttraumatic limbic circuits.

Despite the severity and frequency of complaints reported by patients with post concussive syndrome (PCS), structural imaging data are most often normal and do not corroborate subjective reports (Miller & Cohen, 2001). Thus, functional imaging is necessary to investigate how mTBI affects cortical activity, especially in relation to neuropsychological data.

It is widely reported that mTBI tends to induce an increase in brain activity, which I intermittently refer to as "hyperactivity" in this review of the literature. For example, the activity of the anterior cingulate cortex was increased in the TBI group compared to the healthy control group while the participants performed an attention demanding task (Bonnelle et al., 2011). After repetitive injury, boxers showed a marked decrease in frontal cortex metabolism (Provenzano et al., 2010), which could be explained by the fact that persistent hyperactivity keeps neurons under metabolic stress that can lead to neurodegeneration (de Haan, Mott, van Straaten, Scheltens, & Stam, 2012; Saxena & Caroni, 2011).

Thus, the analysis of the cortical activity of the injured brain has shown that alterations are not unidirectional and that some areas seem to increase in their activity while others decrease. Various tasks and conditions yield different results and the portrait of cortical activity after TBI is heterogenous. Many interpretations relate to the concept of compensation, whereby some areas compensate for others by hyperactivating. The following section describes the debate around the terminology of recovery and compensation.

1.2.2 Recovery and compensation from brain damage

To clarify the terminology, we hereby report considerations from (Reinkensmeyer et al., 2016) in parallel with those of (Levin, Kleim, & Wolf, 2008). The

term “recovery” has been used interchangeably to describe a return to normal, an adaptation to a pathological condition, or a state of functional balance attained via compensatory mechanisms. It is necessary to distinguish between the recovery of behavior and that of neural substrate normality. Behavioral recovery can happen through anatomical restitution, repair, restoration (also coined as “true recovery”) of the structural integrity of the injured brain, but it can also occur through functional compensation where remote or local neural elements that were not involved in normal processing are recruited to attain behavioral performance (Reinkensmeyer et al., 2016). The key point is that both recovery and compensation can refer to either anatomical structures or functional processes or both, and they should not be referred to without their contextual attributes. Restitution can be behavioral and rely on compensatory functional mechanisms. In contrast, recovery can refer to full return to normal (both behavioral and neural) and compensation or adaptation can be considered an entirely separate concept, by principle (Levin et al., 2008). Training can induce recovery of behavior via learned compensatory mechanisms whether they are behavioral or neurological, but Reinkensmeyer et al. (2016) warn that when compensation relies on the finding of new neural pathways, global functioning can be limited by local minimum of efficient performance. However, they explain that restoring of dysfunctional pathways is akin more to restitution.

It is then not surprising that although symptoms (behavioral recovery) and routine structural imaging (neural substrate recovery) were found to be back to normal 14 days after injury in model mice, fMRI (functional compensatory processes) was still reflecting of biological and molecular changes (To & Nasrallah, 2021). The mismatch between structural and functional damage at onset and after recovery went beyond that of symptom subsidence.

Thus, long lasting cortical changes can be compensatory although behavioral performance is recovered. We sought out to evaluate compensatory cortical activity in the context of non-demanding tasks using fMRI. The following section introduces naturalistic stimuli as a solution between resting state and demanding tasks.

1.2.3 Stimulus designs scope functional imaging findings

"Naturalistic stimuli can be advantageous because while artificial and highly controlled stimuli are designed for group comparisons, their results may not be ecologically valid."

(Zhang & Farivar, 2020)

Abstract and artificial stimuli that are stripped down to their most fundamental, idealized and controllable parameters have been instrumental (Einhauser & Konig, 2010) in the past century of neuroscience to approach the incredible complexity of the human brain. However, as the Gestalt movement has extensively demonstrated (Koffka, 2013; Sigman et al., 2001; Wertheimer, 1938), natural stimuli are not simply a superimposition nor an addition of isolated pure stimuli like high contrast bars. Complex cells are more sensitive to the phase regularities of natural images (Felsen, Touryan, Han, & Dan, 2005). Moreover, feature segregation is maintained during complex stimuli processing and specialization is concomitant with integration. Activity in these feature specific modules is still representative of the perceptual intensity related to the corresponding stimuli parameters (Bartels & Zeki, 2004).

A popular exercise in recent years has been to attempt to decode perceptual context from brain activity. Simple stimuli have yielded satisfactory decoding accuracies, but so have natural images (Kay, Naselaris, Prenger, & Gallant, 2008).

Decoding of detailed information about the object and the action categories in natural movies from fMRI data of brain activity was achieved as well (Huth et al., 2016).

Resting state and task-related functional connectivity are not in agreement, however, intrinsic brain topology and connectivity are predictive of brain dynamics during natural vision (Betti, Corbetta, de Pasquale, Wens, & Della Penna, 2018). Watching movies requires an integrated brain response that orchestrates natural cortical activation and connectivity (Demirtas et al., 2019). Movies are processed differently from static images but temporal information is important to understand the typicality of visual processing, even in the early visual cortex, creating maps of separable tuning properties (Baker & Issa, 2005) shared between individuals.

The most important characteristic of cortical brain response to natural stimuli is the synchronization of activity across individuals, showing widespread shared patterns of information processing that correlate with emotionality and visual field localization (Hasson, Nir, Levy, Fuhrmann, & Malach, 2004).

The similarity of individualized brain response to natural stimuli is such that functional alignment is far exceeding anatomical alignment's between subject classification (Haxby et al., 2011). The typicality and reliability of the brain response to natural stimuli, in addition to the ease of acquisition, make it and ideal test bed to explore clinical populations and their idiosyncrasies (Gao et al., 2020).

For example, although responses within subject were reliable in healthy controls and in participants with autism spectrum disorder (ASD), brain activity in response to movie-viewing was atypical and highly variable in participants on the spectrum (Hasson et al., 2009).

Depression severity correlates with decreased and out-of-sync activity of the ventromedial prefrontal cortex during natural movie viewing in a cohort of melancholy-burdened depressed participants suggesting a re-allocation of resources (Guo, Nguyen, Hyett, Parker, & Breakspear, 2015). Children with more severe depressive symptoms showed atypical patterns of cortical activity when watching Despical Me, a result that was exacerbated during low-emotional scenes of the movie (Gruskin, Rosenberg, & Holmes, 2020). Higher depression descriptive item-level similarity between individuals also yieled higher similarities in brain activity. Depressive symptoms could thus shape the way the brain responds to complex information dynamically.

In the case of TBI, the human brain that is otherwise unencumbered by disease or neural atypicality, should follow highly typical patterns of activity when faced with natural stimuli if functional processing is maintained—read not reorganized nor compensating nor relying on latent processes—as typicality goes beyond temporal patterns and down to meso-scale spatial functional organization (Zhang & Farivar, 2020).

As true as it is that block-design holds important advantages over event-related experiments such as ease of implementation and statistical power in relation to the scanning time (Calautti & Baron, 2003), some limitations are inherent to the method and threaten proper interpretation of the results. BOLD signal is likely to include brain activity associated with additional cognitive processes that are not directly tied the stimuli (Fassbender et al., 2004), nor to the particularities of a stimuli versus the next one. This functional overlap could prove devastating in the understanding of clinical populations if they employ distinct cognitive strategies. Natural stimuli offer marked methodological advantages over block-design.

In the previous section, we have described the puzzling heterogeneity of cortical activity magnitude following mTBI and evoked neural compensation as a possible mechanism of behavioral recovery. The second paper in this thesis shows that natural movie viewing can be utilized to show important differences in cortical activity between healthy controls and mTBI participants.

1.3 TBI and dysfunctional connectivity

In the following section, we will introduce functional connectivity and how an mTBI can disrupt cortical dynamics beyond the acute phase. Brain activity changes delimited in cortical regions are not isolated from the rest of the cortex and induce systemic changes that are important and potentially eye opening to our understanding of mTBI.

1.3.1 History of connectivity in neuroscience

"Behavioural impairments that arise from damage to the CNS may often be the result of how the insult affects distributed neural dynamics, rather than of its impact on the lesioned site alone"

(A. Fornito, Zalesky, & Breakspear, 2015)

Connectionism

To form a coherent percept, the human brain relies on combination of sensory information (Robertson, 2003). Thus, for sensory integration to take place, neural pathways need to converge (Zamora-López, Zhou, & Kurths, 2010).

Galen was the first (in 130 AD) to propose that disease could spread from one brain region to another, albeit his formulation was archaic and supposed that animal spirits flowed between areas via neuronal connections (Galen & Siegel, 1976).

Much later, Von Monakow coined the term "diaschisis" to describe the spread throughout the brain of the damage from a focal shock. Distal regions are thereby affected by a remote lesion through neuronal connections (Finger, Koehler, & Jagella, 2004). Presently, a diaschisis includes alterations of functional connectivity as well (Carrera & Tononi, 2014) and refers to a temporary dysfunction of a non afflicted region due to a distal lesion (A. Fornito et al., 2015).

Associationism

Wernicke is considered the father of the disconnection theory of brain disorders (Gasser et al., 1985). In his associative theory of brain function, he depicts a hierarchical system where high order processes arise from the integration of multiple modular systems that are spatially distributed. Disorders like aphasia and schizophrenia are thus interpreted through that lens and considered to be possible consequences of a disruption of connectivity (Wernicke, 1885). His pupil and colleague, Dejerine, continued his work further by stipulating that these high order processes are localized too. Wernicke believes this to be a step backwards in the direction of phrenology and not a worthwhile model of higher function cortical areas (Bub, Arguin, & Lecours, 1993). In his work on alexia, he proposes the existence of a "visual verbal center" that subserves higher order reading and writing (Dejerine, 1892).

Disconnectionism

Building on this work follows the theory of disconnectionism that stipulates that high order dysfunctions result purely from white matter lesions in the primary specialized areas, while associative areas act as relays (Geschwind, 1974). Geschwind had an evolutionary perspective in his behavioral neurology manifesto. Apart from TBI, autism (Frith, 2001), schizophrenia (E. T. Bullmore, Frangou, & Murray, 1997) and dyslexia (Démonet, Taylor, & Chaix, 2004) have been considered disconnection disorders. Geshwind's model has evolved to a more comprehensive framework of neuropathology in which high order dysfunctions result from a combination of damage to connectional pathways and loss of a specialized area's function (Marco Catani & ffytche, 2005), so that a topological dysfunction of a cortical area can be one of deficit, hyperactivity or both. Today, Geshwinds' model would be worded as distributed and specialized brain networks, clustered into modules that are connected in parallel.

It is crucial to understand that more recent perspectives consider a disorder of connection to englobe disconnections as well as hyperconnection, or a combination of both (Marco Catani & ffytche, 2005). In this hodotopic framework, the frontal disconnection from other brain regions in the autism spectrum is coherent with hyperconnectivity found within the frontal areas (Courchesne & Pierce, 2005).

Occipito-temporal connections have been confirmed in humans, and visual network disorders would inevitably affect long range connections from occipital to temporomedial regions (M. Catani, Jones, Donato, & Ffytche, 2003). The functional and spatial split between a lateral system integrating visual perceptual qualities with indirect connections with the early visual areas, and a more medial system incorporating emotions and memory to the visual experience with direct connections to the occipital

cortex has holistic consequences on the connection dysfunction. DAI would impair visual processing of holistic tasks but less in specific artificial and distilled tasks. To shine a light on visual cortical dysfunctions following mTBI, we need to present the injured system with a task that requires integration over multiple brain areas.

Mechanisms of disconnection disorders

Both increases in activity and increases in functional connectivity in brain disorders have been attributed to compensation (A. Fornito et al., 2015) and many brain disorders disproportionately affect tightly connected hub regions (Crossley et al., 2014) (Buckner et al., 2009). It is also possible that compromised activity and connectivity patterns could result from permanent functional reorganization (M. Kasahara et al., 2010).

One mechanism by which neural wiring can become dysregulated during development is through dedifferentiation. Areas that are not normally intended to be specialized for a task are diffusely recruited after a disruption of the excitation/inhibition balance (A. Fornito et al., 2015). The break down of specialization and segregation can lead to disconnection disorders where neuromodulation and signal-to-noise ratio are abnormal (Georg Winterer & Weinberger, 2004).

In an interpretation powered by the association theory, Wernicke's assistant Lissauer (1890) studied in Breslau the case of a patient with severe traumatic brain injury who lost visual perception after a prolonged period of unconsciousness. The patient suffered from agnosia following brain injury. Though the patient was able to locate objects, he was not able to recognize them accurately. Lissauer delineates two types of blindness: apperceptive, caused by a cortical lesion within the visual system itself, and associative, resulting from a transcortical lesion of the associative fiber

connections. In the latter, he stipulates that sensory images are "disconnected" from other brain areas and cannot elicit recognition.

There is some evidence showing that structural damage can correlate with functional deficits, in TBI for example (Caeyenberghs et al., 2011). However, anatomical connections do not absolutely have to be severed (van Meer et al., 2010) for behavior to be affected by a disconnection disorder. Even with apparently intact structural connections, functional connectivity can be correlated with behavior, arguing for a functional deafferantiation (A. Fornito et al., 2015).

Moreover, disease can propagate through synapses and white matter tracts like in the case of the morphing of focal epileptogenic activity into a generalized seizure (Coan et al., 2014), or the spread of neurodegeneration (Goedert, Spillantini, Del Tredici, & Braak, 2013), or dysfunctional network dynamics caused by a local ischemia (Rehme & Grefkes, 2013).

Thus, dysfunctional connectivity is a major concern after an insult to the brain, as cortical processing relies on orchestrated dynamics between functional regions. The following section is an overview of the effects of mTBI on functional connectivity.

1.3.2 Functional connectivity after Traumatic Brain Injury

> *"Symptom resolution, in conjunction with abnormal biomarker levels, may reflect a degree of redundancy within neural networks in which gross behavioral performance can be compensated for, even in the presence of a subtly damaged node or network connection."*
>
> *(Mayer, Mannell, Ling, Gasparovic, & Yeo, 2011)*

Changes in connectivity are central to behavioral deficits following TBI. Functional connectivity between the default mode network and the precuneus is predictive of behavioral impairments in attention even in the absence of focal brain damage (Bonnelle et al., 2011) but compromised anatomical structure within the default mode network correlates with attentional performance.

During a simple choice-reaction task, the same cortical regions were activated in both the TBI and the control group (David J. Sharp et al., 2011) but a positive relationship between functional connectivity (increased metabolism) and performance was found. Their performance was slow and variable but generally accurate. The group had a disparate distribution of structural disconnection but patients who had worse damage to their white matter tended to also have lower functional connectivity at rest.

An fMRI study of working memory following TBI by Maki Kasahara et al. (2011) showed an imbalance in cortical activity with hypoactivation of the left inferior parietal gyrus and a hyperactivation of the inferior frontal gyrus in the clinical population compared to the healthy control group. The activity of the first was correlated with task accuracy in controls and the latter with that of patients who performed significantly worse. Functional connectivity between the two regions was compromised in patients, reflecting a desynchronization of the collaborative activation of these two regions. So, when two areas are necessary for a task, DAI affects functional networks—the more compensatory activity is required by one of the two, the more performance is affected.

In their connectome-scale assessment of structural and functional connectivity in mild traumatic brain injury at the acute stage, Iraji, Chen, Wiseman, Zhang, et al. (2016) used DTI and resting state fMRI. They revealed that 41 out of 358 networks were anatomically affected by the injury. Intra-network connectivity was decreased within the

emotion network and between the emotion and cognition networks, while connectivity between action and emotion networks, and action and cognition, as well as within the perception networks were increased.

Adolescents living with sport-related concussion disturbances were imaged with fMRI at rest to correlate functional connectivity alterations with potential white matter damage data obtained with DTI (Muller & Virji-Babul, 2018). They found a lack of dynamic flexibility during the shift between three distinct brain states within resting-state in the TBI group that was correlated with hyperconnectivity in the left middle frontal gyrus. This could be due to functional reorganization in the attentional network.

In a cohort of acute mild TBI participants, functional connectivity within the motor-striatal network was diminished concomitant with psychomotor cognitive deficits (Shumskaya, Andriessen, Norris, & Vos, 2012). They also found that functional connectivity in the right frontoparietal network was increased in the mTBI group which they interpreted in the light of excessive cognitive fatigue, headache, and increased photosensitivity hyperacusis.

Coordination and integration between brain regions is undoubtedly altered by TBI, so Stevens et al. (2012) sought out to characterize the diffuse consequences of mild TBI on the cortical network in a resting state fMRI study. Using independent component analysis on the connectivity of the whole brain, they looked at twelve distinct networks and found that the TBI group had abnormal functional connectivity in all of them, including the visual, the executive and the cognitive networks. Deficits in functional connectivity were accompanied by increases in other subnetworks which was interpreted as compensatory mechanisms.

Functional connectivity can bring crucial additional information to understand whether TBI's induced patterns of activity is due to a structural reorganization, a functional compensation, or a revelation of latent processes. For example, the increase in brain activation of the left middle frontal gyrus was negatively correlated with the severity of hyperactivity and impulsivity symptoms in healthy controls but not in the TBI participants in a study investigating visual attention processing using near infrared spectroscopy (Wu et al., 2018). Functional connectivity analysis of these data on the other hand, showed a positive relationship between the right calcarine gyri to inferior occipital cortex functional connectivity (which was increased in the TBI participants) and the severity of hyperactivity and impulsivity symptoms in patients, but not in the controls. Here, higher functional connectivity was accompanied with an increase in negative symptoms, equivalent to a decrease in social performance, reinforcing the idea that TBI forces the system to rely on latent processes.

In a longitudinal whole brain functional connectivity analysis, out of 358 landmarks preserving structural and functional correspondence, 258 functional pairs of nodes showed heightened functional connectivity in the TBI group, mostly in areas related to executive and cognitive functional domains. The posterior cingulate cortex and the association areas showed hyperconnectivity, and so did connections between the occipital and the frontal lobes of the brain. Hyperconnectivity was interpreted again as compensatory adaptation to pathophysiological alterations (Iraji, Chen, Wiseman, Welch, et al., 2016).

In mild TBI, despite normal anatomical scans and neuropsychological measures, patients reported cognitive, emotional and somatic complaints, patients also demonstrated increased functional connectivity between the default mode network and the lateral prefrontal cortex but decreased functional connectivity within the default

mode network (Mayer et al., 2011). These measures were predictive of cognitive complaints. The resting-state fMRI obtained functional connectivity did not remain abnormal 4 months after the injury, however. Patterns of functional connectivity seem to normalize along with recovery.

In a similar exploration of resting state functional connectivity of the whole-brain network, following sport-related concussion in the acute and sub-acute (day 8, 15 and 45) phases. The psychological distress and neuropsychological measurements were abnormal but decreased by day 8. They found a global increase in connectivity in the concussed individuals 8 days after the injury but not at the 48hour mark or any of the subsequent scanning sessions. This was especially true in the subset of patients dealing with post-concussive symptoms which drove the group-difference results as it was not present in the asymptomatic participants. These findings reveal that functional connectivity abnormalities evolve over time as recovery takes place, but that they are a sign of latent processes as they appear to be correlated with behavioral disturbances (negative relationship between increased energy demands and performance).

Although functional connections seem to be strengthened in the TBI group in contrast with the healthy controls (Caeyenberghs, Leemans, Leunissen, Michiels, & Swinnen, 2013), increased connectivity cannot simply reflect diffuse compensation because when modelling the cortex as computational network, two important factors appear as crucial criteria. First, node wiring must follow metabolic cost minimization, and second, the topological features of the network have to be optimized. Compromised networks are more likely to rely on cognitive reserve, stretching systems to their limits and their resources thin to the point of running out which would bring about defective performance at lower levels of difficulty (Caeyenberghs et al., 2012).

In this section, we have demonstrated the importance of functional connectivity in depicting an accurate and informative portrait of cortical activity changes following mTBI. Much like activity magnitude changes in response to demanding tasks, functional connectivity changes are interpreted in the light of compensation. Compensatory collaboration between regions can elicit higher levels of functional connectivity while asynchrony can arise when healthy collaboration between regions is compromised by injury. The evidence for functional connectivity changes is as heterogenous as that of activity change, so systemic descriptors of network organization are helpful to get a global understanding of dynamic changes following TBI.

1.3.3 Complex network analysis: graph theory analysis of brain disorders

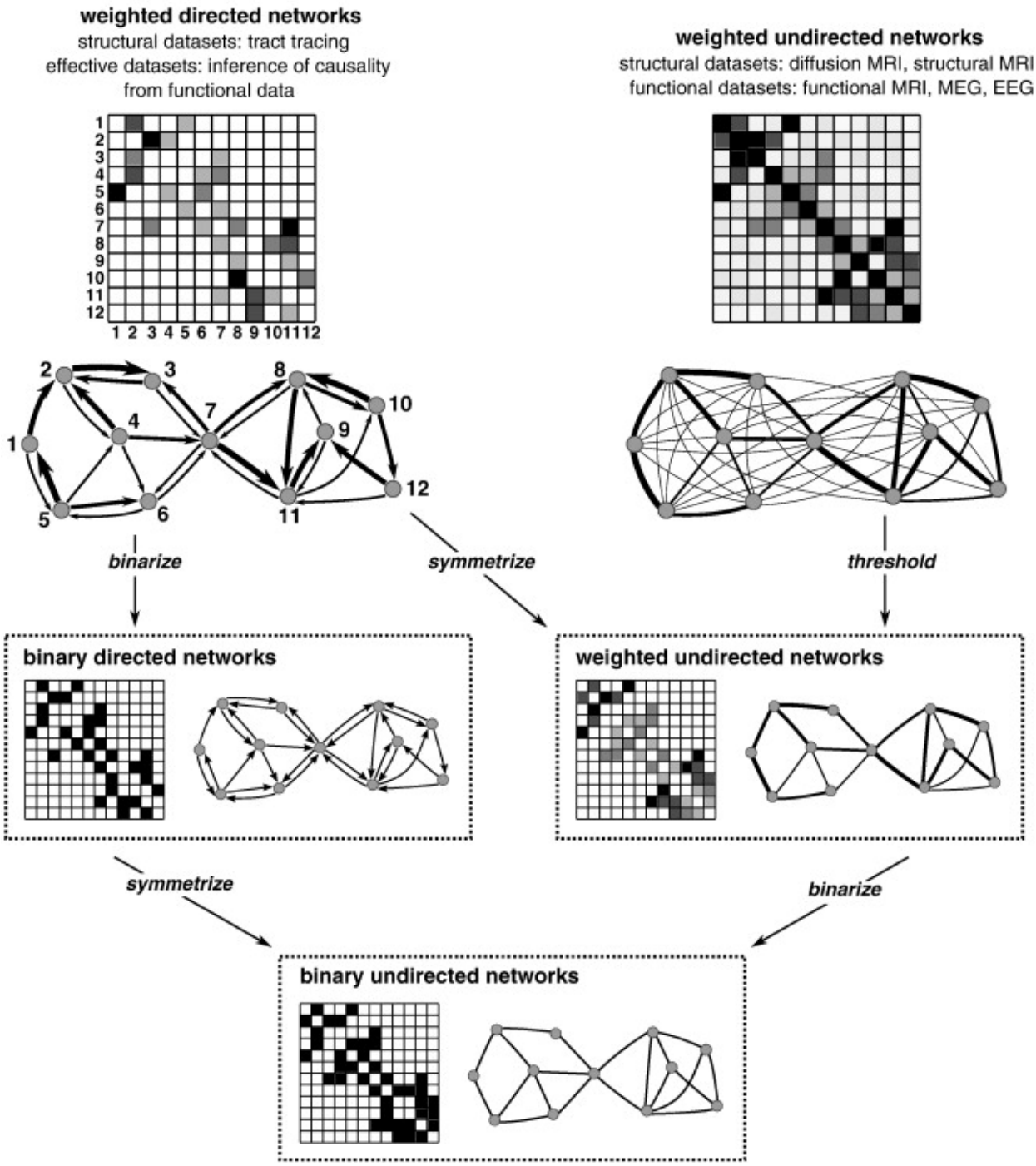

Figure 1-2 Taken from Rubinov et al (2009) Construction of brain networks from large scale anatomical and functional connectivity datasets. Structural networks are commonly extracted from histological (tract tracing) or neuroimaging (diffusion MRI) data. Functional networks are commonly extracted from neuroimaging (fMRI) or neurophysiological (EEG, MEG) data. For computational convenience, networks are commonly representing nodes and matrix entries representing links. TO simplify analysis, networks are often reduced to a sparse binary undirected form through thresholding, binarizing, and symmetrizing.

To understand in more detail how information is relayed, integrated and processed, graph theory analysis describes the cortical network in terms of topological and hodological relationships.

> *"Structural brain networks can be described as graphs that are composed of nodes (vertices) denoting neural elements (neurons or brain regions) that are linked by edges representing physical connections (synapses or axonal projections)"*
>
> *(Ed Bullmore & Sporns, 2009)*

Nodes are defined as processing units, neural elements—either neurons in the case of electrophysiology or cortical regions of interest of various scales in the case of brain imaging. The surface projected data is parcellated and functional connectivity matrices are calculated as correlation matrices (Pearson for example). Two nodes are then considered to be connected by an edge if their correlation p value exceeds a critical p calculated after FDR correction (see figure 1-2).

The number of nodes connected to a single node on average is the connectivity degree of that node. The lowest number of node relays necessary to reach a node S from another node T is the shortest path length (Zamora-López et al., 2010). Once averaged and inversed, this information is understood as efficiency and reflects the system's capacity to integrate information: how well does a signal travel from one area to another. Very small shortest paths mean information transfer is easy and does not require much intermediate processing, when taken in isolation from other critical network descriptors. Modularity is the number of connections that are situated within a

functional module of a certain network compared to a random network of similar size and reflects the tightness and segregation of computational processing.

Centrality is the measure of how much influence one node has on other nodes (A. Fornito et al., 2015), the number of shortest paths that pass through a given node in respect to the total number of shortest paths that link these two same nodes (Zamora-López et al., 2010). Central hubs are referred to as rich clubs and have strong integrative connectivity that links functional modules together (A. Fornito et al., 2015). These connector hubs show high connectivity with nodes from distributed areas.

Primary sensory cortices tend to have low centrality (van den Heuvel & Sporns, 2011) so damage there causes more constraint effects on the system's network. When topologically central areas that connect subnetworks are affected by disease or injury, the damage to the whole system is more diffuse. Most of the central hubs belong to associative cortices whose function is broadly integrative which explains why damage to these hubs creates widespread functional disturbances.

In contrast, groups of nodes that are not hubs and that show strong inter-module connectivity are called provincial modules. They show high connectivity with other nodes from the same module. They have an active role in functional specialization and show high level of segregation.

"damage to provincial hubs should yield specific clinical deficits, whereas damage to connector hubs will result in more complex and pervasive dysfunction"

(A. Fornito et al., 2015)

It has been shown that the cortical network of the macaque monkey follows three main characteristics (Zamora-López et al., 2010). First, nodes are organized in clusters that are topographically distinct. Second, the cortical network of the macaque monkey is highly connected (high density of connections). Third, finally, the degree distribution is broad, and the network contains highly connected tight areas called hubs Sensory integration is an intrinsic role of cortical hubs (Zamora-López et al., 2010). The authors go on to define necessary criteria for a node to be a participant in cortical integration, and thus, verify their definition of integration in the sense of sensory integration of information into a comprehensive percept.

"[integration is] The capacity of one of more nodes to receive information of different character and combine it to produce new useful information"

(Zamora-López et al., 2010)

To play an active role in sensory integration, a node must first have access to information contained in the system. Second, two or more nodes can collaborate in their integrative role only if they are effectively connected with one another. Third, if a node is putative to the integrative function taking place within a system, its removal must affect the integrative capabilities of the whole system.

In networks and graphs obtained through functional connectivity between nodes calculated as time series correlation, for example obtained from fMRI data, the degree is influenced by the size of the network (Power, Schlaggar, Lessov-Schlaggar, & Petersen, 2013; Warren et al., 2014).

In their manuscript, Power et al. (2013) differentiate between "target" hubs which show integrative functionalities and are highly participative in many modules,

and “control” hubs that display high degree centrality. Damage to the former creates diffuse behavioral problems but damage to the latter affects more specialized functions.

The probability that two nodes connected to the same third node are also connected with each other—the clustering coefficient—is low in hub regions. This equates to a certain level of functional overlap, a certain topological degeneracy, that allows for compensation (A. Fornito et al., 2015). Moreover, rich club nodes often act as bridges connecting two nodes that are otherwise not connected, forming an apex node. Its removal cuts communications between these two nodes. From this ensues that nodes that are deep in a module display high clustering and high potential for compensation, forming tightly interconnected cliques of nodes (Power et al., 2013).

Damage to a topologically central associative hub would cause more frequent and pervasive dedifferentiation and diaschisis, and many of the connections going through and coming from hubs are long range which could explain their susceptibility to traumatic brain injury and its clinical profile of diffuse cognitive impairments (A. Fornito et al., 2015).

This section has briefly introduced how graph analysis of neural networks can inform us of their dynamic organization. The following section reports findings from studies using graph theory to describe the injured brain network.

1.3.4 Topological organization findings on traumatic brain injury

Quantitative descriptors of network organisation provide valuable insight to our understanding of computational systems (Muldoon, Bridgeford, & Bassett, 2016) such as the human cortex (Rubinov & Sporns, 2010). Functional integration and segregation are biologically meaningful features directly interpretable from complex network measures brought about by network graph analysis within the graph theory framework.

Although they are extracted from functional connectivity matrices obtained via neuroimaging, they obviously also reflect the structural integrity of the anatomical connections. Diffuse axonal injury (combined with neuronal death and blood flow abnormalities) is thought to be putative to the disconnection hypothesis in traumatic brain injury research. This is supported by graph analysis studies based on functional connectivity and structural abnormalities have been related to behavioral deficits after TBI (David J. Sharp, Scott, & Leech, 2014).

However, in a study combining event-related (task switching) fMRI and fiber tractography, Caeyenberghs et al. (2013) could not find strong overlap between hubs and graph metrics in either the TBI group nor the control group. Functional topology was not accounted for by structural limitations and there was no correlation between structural graph metrics obtained via DTI and those from functional connectivity. The authors concluded that impaired nodes fail to utilize existing (and possibly intact) anatomical connections effectively, which would explain the findings of increased functional connectivity in the absence of reduced structural connectivity. This could possibly be caused by a functional reorganization that induces a decoupling of structural and functional connectivity. Note here that the term “reorganization” does not refer to a permanent rewiring but more a functional adaptation whereby the remaining anatomical connections are reoptimized in their usage rather than in their structural positions.

In another study supporting the idea of a functional reorganization, Caeyenberghs et al. (2012) found higher local efficiency in a TBI group. Stronger short-range connections between neighboring nodes suggest adaptative mechanisms and a better organization and tolerance to future attacks to the system, literally bracing for

further traumatic instances. The injured brain tends to form highly clustered cortical regions that preserve efficient local communications as a compensatory mechanism.

Recovery following neurorehabilitation restored network parameters—namely network strength, path length, efficiency, clustering and energetic cost—to normal levels (Castellanos et al., 2011). This supports the compensation theory, as it underlines the positive relationship between metabolic demands and behavioral performance. During the recovery process however, in another study, network strength decreased but the number of functional connections did not (Nakamura, Hillary, & Biswal, 2009).

The outcome of an attention and executive focused neurorehabilitation training following TBI was predicted by the modularity of the cortical network—the extent at which the distributed network is integrated and segregated (Arnemann, Chen, Novakovic-Agopian, Gratton, Nomura, & Esposito, 2015). This shows that a more modular brain network that sustains an injury is more likely to recover its cognitive functions strategically and be more adaptative to training.

Recovery and rehabilitation studies highlight the importance of hodological measures of functional changes following TBI. Thanks to graph theory we can quantify topological features from neuro-imaging data and uncover important network abnormalities (Caeyenberghs, Verhelst, Clemente, & Wilson, 2017). In their review, the authors assembled studies using graph network analysis to study connectivity abnormalities in the TBI population. They found evidence that integration is generally compromised by TBI and that hyperconnectivity is accompanied by a decrease in network efficiency. These findings rely on datasets from very specific regions of interest, without whole graph high resolution analysis, and using highly demanding tasks.

Finally, this last section of introduction has recognized the contribution of graph metrics to our understanding of brain functional connectivity and dysfunctional connectivity in the case of TBI. Directly meaningful network descriptors have been used to show important discrepancies in the injured brain cortical dynamics. The fourth chapter in this thesis will add to the body of TBI graph network analysis literature by broadening the scope of the functional brain: how does the TBI network behave when facing normal day-to-day natural vision stimuli? Can such non-demanding tasks reveal functional changes even in the mild TBI population?

1.4 References

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Chapter 2 Increased noise in cortico-cortical integration after mild TBI measured with the equivalent noise technique

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2.1 Preamble

Visual deficits following mTBI have been reported by patients and investigated using psychophysics. They affect visual processes relying on cortical integration, but they could emanate from cortical noise independently from integration failure. In this chapter, I propose to investigate the contribution of both mechanisms to contour integration deficits in mTBI participants based on the translation of a physics paradigm—the equivalent noise method. This chapter aims to disentangle the influence of integration efficiency and internal noise on early visual cortex deficits of mTBI participants.

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2.2 Abstract

The bulk of deficits accompanying mild traumatic brain injury (mTBI) is understood in terms of cortical integration—mnemonic, attentional, and cognitive disturbances are believed to involve integrative action across brain regions. Independent of integrative disturbances, mTBI may increase cortical noise, and this has not been previously considered. High-level integrative deficits are exceedingly difficult to measure and model, motivating us to utilize a tightly controlled task within an established quantitative model to separately estimate internal noise and integration efficiency. First, we utilized a contour integration task modelled as a cortical-integration process involving multiple adjacent cortical columns in early visual areas. Second, we estimated internal noise and integration efficiency using the linear amplifier model (LAM). Fifty-seven mTBI patients and 24 normal controls performed a 4AFC task where they had to identify a valid contour amongst three invalid contours. Thresholds for

contour amplitude were measured adaptively across three levels of added external orientation noise. Using the LAM, we found that mTBI increased internal noise without affecting integration efficiency. mTBI also caused hemifield bias differences, and efficiency was related to a change of visual habits. Using a controlled task reflecting cortical integration within the equivalent noise framework empowered us to detect increased computational noise that may be at the heart of mTBI deficits. Our approach is highly sensitive and translatable to diagnostic and rehabilitative efforts for the mTBI population, while also implicating a novel hypothesis of mTBI effects on basic visual processing—namely that cortical integration is maintained at the cost of increased internal noise.

2.3 Significance statement

Traumatic brain injury symptoms are largely understood in terms of neuronal and axonal loss, reflected in deficits that are largely understood in terms of cortical integration. An untested idea is that integration is maintained and compensated, but that injury causes increased computational noise. We tested this hypothesis using a psychophysical task with a strong neurophysiological basis that requires cortical integration and utilized an established approach to separately estimate internal noise and integration efficiency. Our results demonstrate that injury increases noise in cortical circuits without affecting integration efficiency. This sensitive and informed approach has important implications for diagnosis and rehabilitation of the two million U.S. patients affected annually by traumatic brain injury.

2.4 Introduction

Traumatic brain injury (TBI) affects over 2,000,000 people in North America every year, with a sizeable portion of patients continuing to report deficits of attentional, mnemonic, or sensory nature many months after injury (Corrigan and Hammond; Lye and Shores, 2000; Millis et al., 2001; Malojcic et al., 2008; Masel and DeWitt, 2010). The cognitive deficits of mild TBI (mTBI) can be present across different types or modes of injury, suggesting them to be general in nature (Rosenfeld et al., 2013). These deficits are often interpreted as a decreased capability of the cortical system to integrate information after injury.

Loss of tissue could have two distinct effects on the performance of a system—it could impair the integrative capacity of the system by reducing the efficiency with which information is processed, or it could increase the internal noise of the system. Here we aim to assess whether cortical changes caused by mTBI increase noise or decrease integration, or both.

Of the domains potentially affected by mTBI, the cortical visual system is the most characterized and best understood—the human visual system has high homology to multiple animal models, and over 50 years of neurophysiology and psychophysics make it the most characterized cortical system (Kandel, 2013; Yantis, 2013). Visual complaints are common after mTBI (Adams, 2009), and we and others have successfully used visual psychophysics to quantify cortical visual deficits caused by mTBI (Kurylo et al., 2006; Chang et al., 2007; Spiegel et al., 2015; Spiegel et al., 2016; Schmidtmann et al., 2017). The availability of highly sensitive psychophysical methods with physiologically-motivated computational models behind them make vision an excellent platform for characterizing and understanding cortical changes that follow mTBI.

High-level deficits such as memory and attentional losses can be broadly described as impairments of cortical integration over large cortical scales (Naghavi and Nyberg, 2005; Schlichting and Preston, 2015; Zhang et al., 2017). A highly controllable model of cortical integration is contour integration—the perception of a shape through pooling of local edge segments that together describe a shape (Field et al., 1993; Hess et al., 2003). Contour integration is a crucial step in the processing of visual shape representation and is understood to require well-characterized integrative mechanisms at the lowest levels of the cortical visual hierarchy (Gilad et al., 2013). Recently, a new contour integration approach has been developed that has the capability to allow measurements of both efficiency and internal noise (Baldwin et al., 2017) something not attainable from the original approach of Field et al (1993).

We therefore measured cortical integrative capacity and noise using the tightly controlled visual contour integration task (Baldwin et al., 2017). Importantly, we can quantify both the capability of the cortical integration process that occurs for contours, as well as the amount of "noise" that is limiting the system's performance. To enhance our sensitivity to changes in integrative capacity and/or internal noise, we made our measurements independently for the four visual quadrants, which simultaneously enabled us to probe previously-reported visual field biases in mTBI (Pavlovskaya et al., 2007; Spiegel et al., 2015).

2.5 Methods

2.5.1 Participants

All participants gave their informed consent prior to taking part in the experiment. All procedures were in accordance with the Code of Ethics of the World

Medical Association (Declaration of Helsinki) and were approved by the Research Ethics Board of the McGill University Health Center.

All participants were screened for anomalous vision loss or vision disorders (glaucoma, retinal detachment, macular degeneration, etc.). They had normal or corrected to normal visual acuity (wore their usual refractive correction). The average age of the participants was 39.7 years old (SD = 14.4 years, n=56) in the mTBI group and 35.5 years old (SD = 13.8 years, n=24) in the control group.

2.5.1.1 TBI group

Participants (Table 1) were recruited through the McGill University Health Center out-patient TBI clinic. The diagnostic criteria for mild TBI were: Glasgow Coma Scale score between 13 and 15, less than 30 minutes of loss of consciousness, and less than 24 hours of amnesia regarding events immediately before or after the accident. Patients with mild TBI who gave their authorization to be contacted went through a phone screening interview. The exclusion criteria were (1) family history of epilepsy or seizure, or the administration of prescription medication with increased risk of seizure, (2) severe tremors or involuntary movements, (3) general anesthesia in the past 6 months, (4) mTBI occurred less than 1 month ago or more than 2 years ago, (5) presence of a brain lesion, (6) a history of multiple brain injury. During validation of patient's clinical history, we found that five of them had had previous head traumas, with their last one being a mild TBI (GSC 13-15). We removed these five subjects from our analysis, but their data were not discarded and instead, we analyzed them separately. We did not exclude participants on the basis of having received an intervention or not. Following our previous publication, participants filled a

questionnaire adapted from Assessment with Mild Traumatic Brain Injury for the Defense Centers of Excellence for Psychological Health and Traumatic Brain Injury (Spiegel et al., 2016) investigating blurred vision, migraines, behavioral change to palliate visual discomfort etc. The final sample size of tested mTBI participants was 55, (13 males and 42 females), with an additional 5 polytrauma participants (two males, three females).

2.5.1.2 Control group

Healthy participants were recruited through public announcements in the Montreal General Hospital and on social media. Demographics of the mTBI sample population were evaluated and the control group was sampled accordingly. Exclusion criteria included conditions 1-4 outlined above, and no history of any acquired brain injury. The control group was comprised of 23 individuals (12 males and 11 females). Despite the unequal proportions of males and females in both groups, sex had no effect on any of the LAM parameters, neither when taken as an average nor when assessed individually per quadrant ($p > 0.05$) and was therefore ruled out as a potential extraneous variable.

2.5.2 Supplementary evaluation

The Trail Making Test B (Giovagnoli et al., 1996), the Bells Test (Gauthier, Dehaut, & Joanette, 1989) and the clock-drawing test (Ishiai, Sugishita, Ichikawa, Gono, & Watabiki, 1993) were administered to mTBI participants to assess visual attention and spatial neglect. All participants responded normally on these tests. Monocular and binocular visual acuity was measured with a Snellen chart at four meters (Logarithmic Visual Acuity Chart; Precision Vision, Lasalle, IL, USA) and their ocular dominance was assessed using the Miles test. Maddox rod, cover/uncover and alternating-cover tests

were performed to detect presence of strabismus. Participants were excluded from the study if a strabismus was found.

2.5.3 Display

Stimuli were produced using Psychtoolbox (Brainard & Vision, 1997) through MATLAB® (2014b, The Math Works Inc., Natick, Massachusetts) and presented on a gamma-calibrated LG Flatron 915FT Plus monitor using a 10-bit graphics card (Nvidia Quadro 2000). Calibration was done using a photometer, and the mean luminance was 62 cd/m². Subjects were placed consistently at a 77 cm viewing distance from the monitor, with a spatial resolution of 96 pixels per degree of visual angle.

2.5.4 Stimuli and Procedure

Subjects fixated on a marker at the centre of the screen. On each trial, four contours appeared simultaneously. Each contour was centred in one quadrant of the visual field, at an eccentricity of 2.8° from fixation. Each contour was comprised of seven log-Gabor wavelets (Meese, 2010) resting on an invisible curved path. The wavelets had a peak spatial frequency of 6 c/deg with a bandwidth of 1.6 octaves. They were presented in cosine phase (white bar with dark flanks) and had an orientation bandwidth of ±25°. The full-width at half-magnitude of the wavelet envelopes measured 1.17 cycles along the stripes, and 0.91 cycles across them. For the target the orientation of each wavelet was aligned with the path of the contour. In the three distractors, the orientations of the wavelets were consistent with a contour curving in the opposite direction. Discriminating the target from the distractors required the subject to combine the orientation and position information of the wavelets (Figure 2A).

The contour paths that specified the wavelet locations had the same amplitude for the target and for the three distractors. For large curvature amplitudes the task is easier, as the target appears to be a smoother contour than the distractors. Stimuli were presented for 400 ms, and subjects selected the smoother contour (with "good continuation") (Wertheimer, 1938) in a four-alternate forced choice (4AFC) task (Figure 2 B). This task was chosen to ensure data could be collected efficiently from inexperienced subjects (Jäkel & Wichmann, 2006). The amplitude of the curvature was modulated through a performance-dependent staircase (2-down 1-up), converging at an amplitude where the subject selected the target 70% of the time. The staircase was terminated after 40 trials or following 12 reversals. Thresholds for identifying the smooth contour were obtained using psychometric function fitting (see below). Thresholds were obtained both for stimuli without any added external noise, and for stimuli where the orientations of the individual wavelets were randomly jittered. Measuring performance at different levels of external noise allows the equivalent internal noise and processing efficiency of the contour integration system to be characterised. This method has been previously validated, with human performance measurements quantified compared to that from the ideal observer (A. S. Baldwin, Fu, Farivar, & Hess, 2017).

We measured discrimination thresholds at three levels of orientation noise: 0°, 8°, and 16°. The orientation of each wavelet was resampled from a Normal distribution centred on its original value (aligned with the contour for the target stimuli, and consistent with a contour of opposite curvature for the distractors). The standard deviation of the Normal distribution controlled the level of external orientation noise. We divided data collection into separate blocks for each noise level (10-15min each). The order of these blocks was randomised across participants. We have created an

interactive illustration of the procedure and corresponding psychometric performance hosted at http://www.farivarlab.com/stimuli-software.

2.5.5 Experimental design and statistical analysis

2.5.5.1 Experimental design

We utilized a 2x2x2 factorial design, with a between-subjects factor (mTBI vs controls) and two within-subject factors of vertical visual field (upper vs. lower) and horizontal visual fields (left vs. right). To make inferences of differences in internal noise and efficiency across the subjects and quadrants, we analysed these parameters as estimated by the Linear Amplifier Model (see below) using non-parametric tests (Noguchi, Gel, Brunner, & Konietschke, 2012). To make inferences about quadrant biases, we used the rank assignment of each quadrant for internal noise and efficiency and carried out the same non-parametric tests on these rank values.

2.5.5.2 Statistical analysis

mTBI subjects tend to be heterogenous and their performance often does not follow a normal distribution—something we have previously observed (Gunnar Schmidtmann et al., 2017; Spiegel et al., 2016). Our data here also were not normally distributed, and we therefore carried out all our analyses using non-parametric inferential tests, which are more conservative and do not depend on normality of the data distribution and here report the Wald-type statistic (WTS) estimated using the nparLD (Noguchi et al., 2012) package in the R Statistical Package (R Core Team, 2013), which is a non-parametric analog of the repeated-measures factorial ANOVA.

2.5.5.3 Data preprocessing and psychometric fitting

Psychometric function fitting was performed using the Palamedes toolbox (Prins and Kingdom, 2009). The number of trials at each curvature amplitude, and the number of correct responses for each amplitude were fitted with a Gumbel psychometric function. The guessing rate parameter was fixed at 25% (guessing rate for a 4AFC task). The lapse rate was allowed to vary from 0% to 5%, while the threshold and the slope were allowed to vary across noise levels and quadrants.

The equivalent noise method, borrowed from engineering (North, 1942; Friis, 1944; Mumford and Scheibe, 1968; Pelli, 1981), uses external noise added to the input of a system to measure the equivalent internal noise level within the system. When the external noise is much smaller than the equivalent internal noise then its effects will be negligible. As the external noise is increased it will reach a point where its effects exceed those of the equivalent internal noise. Beyond this point the external noise will dominate performance, making the system's equivalent internal noise no longer the limiting factor. Psychophysically, noise masking experiments typically find that thresholds are unaffected by low levels of external noise. Beyond some critical value however, the thresholds increase in proportion to the standard deviation of the masking noise. The simplest model for analyzing data from equivalent noise studies is the Linear Amplifier Model (LAM), which has two parameters

$$A_{\text{threshold}} = \frac{\sqrt{\sigma^2_{\text{external}} + \sigma^2_{\text{internal}}}}{\beta}$$

This predicts a threshold A_threshold for each external noise level σ_external. The fitted σ_internal parameter indicates the point at which the system transitions from being dominated by internal noise to being dominated by external noise. This is taken as

the external noise level that is equivalent to the internal noise level. The second fitted parameter β indicates the processing efficiency of the system (Baldwin et al., 2016). Elevated internal noise will affect thresholds when the external noise is low or absent but will not change behaviour once external noise is greater than internal noise. Reduced efficiency however will increase thresholds at all external noise levels. In the context of our contour task, internal noise indicates the inherent internal limitations affecting the representation of each wavelet, while the efficiency is the capability of the system to combine all of that noisy information to detect good continuity. Thus, the LAM model effectively captures the two key dimensions of performance that we aimed to measure.

The LAM was then fitted to the discrimination thresholds to determine internal noise and efficiency (Figure 2). Outlier participants were removed if one of their LAM parameters was further than 1.5 interquartile below Q1 or above Q3 for each group (Tukey, 1970; Hoaglin et al., 1983), leaving 21 controls (two2 outliers) and 502 mTBI subjects (five4 outliers).

Following data collection, we noted that the highest amplitude of curvature produced contours that were difficult to discriminate for several participants in both groups. This was true even at low noise levels. We designed an unbiased means of eliminating these points and validating that our procedure did not bias the results. The data points collected at these amplitudes were unreliable (they resulted in non-monotonic psychometric functions). We removed these data points if doing so significantly improved the fit of the Gumbel function to the data, as determined by a Chi-square goodness-of-fit test. Eleven control subjects and 20 mTBI subjects had points removed. Within-subject comparison of before and after the outlier removal showed no significant difference across groups for all quadrants and all noise levels which means that the

group differences found after fitting the LAM were not biased by our outlier removal procedure (WTS 0.89 p > 0.3). The unbiased preprocessing step significantly decreased variability across the pool of all participants across both groups for quadrants 1, 2 and 3 (WTS 8.5 p = 0.0035, WTS 4.4 p = 0.035, WTS 9.57 p = 0.002) and for noise level 2 (WTS 6.67 p = 0.01).

2.6 Results

2.6.1 Higher internal noise following TBI

Internal noise was significantly higher in the mTBI group than in the control group (Figure 3 A, B) ($WTS = 8.64$, $p = 0.003$). We noted a significant interaction in the visual field biases between group and horizontal hemifields ($WTS = 7.97$, $p = 0.005$). Control subjects had lower internal noise than mTBI subjects (in both horizontal hemifields) with even lower internal noise in the right hemifield than in the left.

Analyzing the data within groups, we found that control subjects presented a significant horizontal bias ($WTS = 4.86$ $p = 0.03$) with lower internal noise in the right hemifield as opposed to mTBIs who did not have any hemifield bias in internal noise (horizontal $WTS = 2.78$ $p = 0.09$, vertical $WTS = 3.43$ $p = 0.06$) (Figure 3 C).

2.6.2 Abnormal efficiency distribution across the visual field after TBI

Although there was no group difference in efficiency overall ($WTS = 0.85$ $p = 0.36$), efficiency remained constant across hemifields in the control group (all p's > 0.1) whereas mTBI subjects presented significant horizontal and vertical biases (horizontal $WTS = 12.52$ $p = 0.0004$, vertical $WTS = 11.78$ $p = 0.0006$) with higher efficiency in the lower right quadrant (Figure 4 D).

2.6.3 Consistent visual field ranking after TBI

To assess potential visual field imbalances caused by mTBI, for each subject we rank-ordered the quadrants in terms of internal noise and efficiency (separately) and analyzed these rank scores using the same non-parametric method described above. The mTBI group exhibited visual field biases as measured by rank of both efficiency and internal noise (efficiency $WTS = 20$ $p = 0.0002$, internal noise $WTS = 9.5$ $p = 0.23$); this was not observed in the control group (efficiency $WTS = 0.3$ $p = 0.96$, internal noise $WTS = 2.15$ $p = 0.54$).

mTBI subjects presented significant horizontal and vertical biases ($WTS = 9.9$ $p = 0.0016$; $WTS = 9.1$ $p = 0.002$, respectively) in efficiency, and a significant vertical bias ($WTS = 5.74$ $p = 0.017$) in internal noise. Control participants presented none of these biases.

2.6.4 Efficiency and internal noise correlated in both groups

To understand the dynamic relationship between efficiency and internal noise, we tested for correlations between these parameters for each individual quadrant in each group and found a significantly positive correlation between internal noise and efficiency in all quadrants for both groups (Spearman, $rho > .4$, $p < .001$). However, when looking at the parameters averaged across quadrants this positive correlation was only maintained in the mTBI group (Spearman, $rho = .36$, $p = .01$). All participants tended to have higher efficiency in the quadrants where they also exhibited higher internal noise, but only participants from the mTBI group compensated for higher internal noise with higher efficiency when all quadrants were taken into account.

2.6.5 Internal noise, efficiency and visual dysfunctions report

To investigate the relationship between the internal noise and efficiency parameters as measured by our task and the symptoms experienced by the patients, we tested whether their answers to the Visual symptoms questionnaires were correlated to their internal noise and efficiency. Interestingly, changes in visual habits were inversely correlated to the efficiency on the good-continuity discrimination task (Spearman, rho = - 041, p = 0.04), meaning that the more patients made changes to their visual habits (screen time, reading, driving…) the less efficiency they exhibited at discriminating between valid and invalid contours. Although the strength of the correlation was small, this would suggest that patients who adapted their behavior to their visual impairments also showed less efficiency in using the available orientation information to render a perceptual decision.

2.6.6 Time since injury

Studies looking at post-concussive symptoms typically span their data collection between the time of injury and the following year, finding a decrease when comparing time points (Bryant & Harvey, 1999; Emanuelson, Andersson Holmkvist, Björklund, & Stålhammar, 2003; Sigurdardottir, Andelic, Roe, Jerstad, & Schanke, 2009). Surprisingly, when we tested whether internal noise or efficiency on the good-continuity discrimination task were correlated with the time elapsed since injury, we did not find any significant relationship (Spearman, rho <-0.1, p > .4). We did not find any relationship between the time since injury and any of the neuropsychology tests either.

2.6.7 Multiple concussions participants

For the five multiple concussion participants that were tested on the contour discrimination task, internal noise was marginally higher than in the controls ($WTS = 3.76$ $p = 0.053$), and not different from the single mTBI group ($WTS = 0.27$ $p > 0.6$). When analysing all three groups at once, we found a significant main effect of Group on internal noise ($WTS = 9.9$ $p < 0.007$), as well as a significant interaction between the factors Group and Quadrants ($WTS = 37.8$ $p < 0.000001$). The multiple TBI group had higher internal noise (pseudo-median = 6.69°, conf.int = 5.29°-8.56°) than the single TBI group (pseudo-median = 6.1°, conf.int = 5.65°-6.58°), and the control group had even lower internal noise (pseudo-median = 4.51°, conf.int = 3.99°-5.06°).

Efficiency of the multiple TBI patients did not vary compared to either group separately (controls/multiple TBIs $WTS = 1.12$ $p > 0.2$, TBIs/multiple TBIs $WTS = 0.45$ $p > 0.4$). When the data from the three groups were combined into a single analysis, neither Group nor Quadrants had a significant relative effect on efficiency ($WTS = 1.5$ $p = 0.48$; $WTS = 2.2$ $p = 0.53$, respectively), but there was an effect of the interaction of Group and Quadrants on efficiency ($WTS = 20.8$ $p = 0.002$).

2.7 Discussion

Cortical integration is understood to be at the heart of many cognitive symptoms related to attention and memory following mTBI—a large network of cortical regions is engaged to carry out these fundamental cognitive processes (Fagerholm, Hellyer, Scott, Leech, & Sharp, 2015; Naghavi & Nyberg, 2005; Schlichting & Preston, 2015). Directly measuring impairments of cortical integration is a serious challenge, because of the absence of informed quantitative models that fully capture the two crucial limiting factors, namely cortical integration and internal noise. By utilizing contour integration—

a fundamental step in visual shape recognition that is well-characterized in terms of cortical integration (A. Gilad, Meirovithz, Leshem, Arieli, & Slovin, 2012; Ariel Gilad, Meirovithz, & Slovin, 2013)—within the framework of the equivalent noise technique, we were able to overcome the limitations posed by cognitive measures while assessing changes in visual processing following mTBI.

We have discovered that mTBI may not actually result in less efficient cortical integration *per se*, but rather in increased internal noise. This is a first quantitative characterization of the post-TBI changes using a model-driven behavioural task (Z. L. Lu & Dosher, 1998, 1999, 2008; Denis G. Pelli & Farell, 1999; Skoczenski & Norcia, 1998). Our results also corroborated the previous finding of visual field biases being affected by mTBI—we found that cortical integration efficiency was different between the vertical and horizontal hemifields. Finally, we found that poorer cortical integration efficiency was correlated with greater change in visual habits of mTBI patients.

We observed a significant increase in internal noise despite the recognised variability in the mTBI population (Ware et al., 2017; Yue et al., 2017), suggesting that internal noise is a valuable and valid construct in describing the visual processing changes that occur in this disorder. Occipital injury was not a common mode of insult, yet the bulk of the group exhibited elevated internal noise on a visual task. Adding to the emerging scientific evidence for cortical visual impairments following mTBI (Chang, Ciuffreda, & Kapoor, 2007; Pavlovskaya, Groswasser, Keren, Mordvinov, & Hochstein, 2007; Gunnar Schmidtmann et al., 2017; Spiegel, Lague-Beauvais, Sharma, & Farivar, 2015; Spiegel et al., 2016), our experiment relied on a non-invasive psychophysical method to probe cortical errors and inefficiencies in the low- to mid-level visual areas of the human brain (A. Gilad et al., 2012; Ariel Gilad et al., 2013; Pasupathy & Connor, 1999).

2.7.1 Cortical integration during contour perception

Contour integration is a basic building block of visual perception, and yet, it requires complex and balanced interactions (D. Field & Hayes, 2004; D. J. Field et al., 1993; R. F. Hess, Hayes, & Field, 2003; Kisvárday et al., 1997). This integrative process can be effectively probed using simplified stimuli consisting of colinear Gabor elements along a path defining a shape—in our case, a simple arc. Such colinear sets tend to pop-out against a background of randomly-oriented Gabors, as captured by the Gestalt rule of Good Continuation (Elder & Goldberg, 2002; Koffka, 2013; Wertheimer, 1938). Thus Good Continuation is the fundamental feature of a contour perception, and the task used here (A. S. Baldwin et al., 2017) directly measures this key aspect of visual perception.

The perception of a contour is not instantaneous (R. F. Hess et al., 2003; Lamme, Super, & Spekreijse, 1998; Zipser, Lamme, & Schiller, 1996) suggesting multiple levels of computation, and recent evidence suggests at least two major steps are involved—a first step where the individual elements are detected by V1 neurons and a second step where secondary connections (lateral in V1 and/or feedback from extrastriate areas) "fill-in" the gaps between the Gabor elements (Ariel Gilad et al., 2013). In other words, the individual Gabor elements of a synthetic contour each have distinct cortical representations in the retinotopic map of V1 (D. Field & Hayes, 2004). These individual cortical representations then interact and integrate into a new form—the full contour—thus describing a simple and elegant example of cortical integration that can be tightly controlled via stimulus manipulations.

Although there are diverging views regarding the cortical mechanisms involved in contour perception, namely if linking between stimulus elements is explicit or not (D. J.

Field et al., 1993; Hansen, May, & Hess, 2014; May & Hess, 2008), some form of integration remains unavoidable, whether it follows a step-by-step summation or an algorithmic overlap of orientation and template filters across hierarchical processing levels. We propose that contour integration can serve as an effective model of cortical integration, because the individual elements of a contour have distinct cortical representations and because the integration of the contour requires pooling and interactions across a set of such cortical nodes. The magnitude of these interactions can be controlled by stimulus parameters such as collinearity, gap, and path curvature (Blakemore & Tobin, 1972; Knierim & Van Essen, 1992; Sillito et al., 1995; von der Heydt & Peterhans, 1989), unlike cortical interactions engaged in complex cognitive tasks. Given the tight control that is granted by stimulus manipulations on this well-characterized integrative cortical process, contour integration is an effective and efficient method of probing complex interactions in the injured brain.

2.7.2 Cortical visual deficits after TBI

We had previously speculated that long-range fibers—i.e. those that integrate information across visual fields and cross at the corpus callosum—are most vulnerable to injury in mTBI (Spiegel et al., 2015). We and others (Lachapelle, Ouimet, Bach, Ptito, & McKerral, 2004; Gunnar Schmidtmann et al., 2017; Spiegel et al., 2015; Spiegel et al., 2016) have documented several changes to cortically-mediated visual processes after mTBI. Traumatic brain injury results in decreased contrast sensitivity across spatial frequencies, especially for second-order modulated patterns (Spiegel et al., 2016). Binocular disparity perception is also affected by mTBI (Gunnar Schmidtmann et al., 2017), in addition to inter-ocular signal propagation (Spiegel et al., 2015). That contour perception is also affected by mTBI suggests multiple components of the ventral visual pathway, needed for shape and object analysis, may be affected by mTBI. In contrast,

motion perception—putatively subserved by the dorsal visual pathway—is not affected in mTBI patients (Costa et al., 2015). The emerging pattern from these results is that the ventral visual pathway may be more vulnerable to injury, and more studies are needed to assess this possibility.

2.7.3 Visual field biases after TBI

We speculate that the vertical bias (greater efficiency in the lower visual field) may be related to the importance of this hemifield for shape perception---Schmidtmann et al. (2015) have reported that while on orientation discrimination tasks performance is balanced between the upper and lower hemifields, there is a distinct advantage in normal individuals in discrimination of complex shapes in the lower visual field. We build on this finding to suggest that perhaps following mTBI, patients increase efficiency selectively in the lower visual field because of its importance to shape recognition, as a compensatory effort.

The left-right bias is admittedly more difficult to explain, but a clue may lie in the bias already present in the normal controls—internal noise is significantly lower in the right hemifield. We did find that this bias is eliminated by mTBI. We speculate that this bias may be part of normal visual processing, and its disruption by mTBI may be compensated by a biased increase in efficiency corresponding to our observations.

2.7.4 Internal noise and neural noise

The concept of noise utilized here—internal noise, captured as a Gaussian random variable within the Lam model—can be understood as a generalization of multiple sources of neural noise including spike-timing variability, synaptic noise, membrane potential variability, etc (A. Aldo Faisal et al., 2008). Complex circuits of neurons would likely exhibit complex noise properties that are not linearly related to the

noise within individual units (A Aldo Faisal, White, & Laughlin, 2005; Laughlin & Sejnowski, 2003; Prinz, Bucher, & Marder, 2004).

The concept of internal noise, as measured by the equivalent noise technique (Z. L. Lu & Dosher, 1999, 2008) has been effective at capturing a variety of phenomenon that were previously understood as limited by processing capacity or sensitivity, including contrast sensitivity (Skoczenski & Norcia, 1998), attention (Z. L. Lu & Dosher, 1998), and cortical blindness (Cavanaugh et al., 2015). Previous studies had described the observed changes as a modulation of performance capacity or sensitivity but estimates of internal noise within an equivalent noise framework revealed performance was noise-limited not capacity-limited, highlighting the value of a generalized measure of internal noise in characterization performance changes.

A key component of the LAM is the distinction between internal noise and efficiency—the latter denoting the capacity of the system to utilize all the available information. In the present contour task, efficiency has a simple interpretation: it is an estimate of the capacity of the integrative cortical process to pool orientation signals across the retinotopic map to give rise to a coherent representation of the contour. In this respect, mTBI patients did not differ from controls, suggesting that cortical integration is not affected by putative injury.

2.7.5 Neurophysiological basis of TBI

TBI results in an array of changes to the brain physiology, including axonal injury (Hammoud & Wasserman, 2002; V. E. Johnson, Stewart, & Smith, 2013; Povlishock et al., 1983; Rubovitch et al., 2011; David J Sharp & Ham, 2011), neuronal death (Raghupathi, 2004; Rink et al., 1995; Ross et al., 1993), neurotransmitter rebalance (Erin D. Bigler, 2016; Hunt, Scheff, & Smith, 2011; Walter et al., 2004), glial activation

(Ramlackhansingh et al., 2011), vascular changes (Bonne et al., 2003; Y. Wang et al., 2015), and cortical spreading depression (Church & Andrew, 2005; Giza & Hovda, 2001; Lauritzen et al., 2011), amongst other factors. Any of these factors would be expected to affect performance on a complex task such as ours. Thus, it is exceedingly difficult to relate the neurophysiological changes that accompany TBI to any aspect of performance on our task.

Crucially, however, participants performance for *integrating* information during contour perception is not what was affected by mTBI—mTBI seemed to only inject noise in this integration mechanism. Compensatory mechanisms activated after TBI maintained a similar degree of cortical integration, thus keeping neural circuits and networks intact, but at the cost of added noise. This is in contradistinction to the notion that tissue loss after TBI causes capacity loss—we speculate that post-TBI compensation seeks to minimize loss of connectivity and circuitry, and the observed deficits are not due to loss of network interactions, but due to increased noise in those interactions.

We did not select participants following the location where the head was hit, nor did we aim to specifically recruit patients who suffered from torsion, direct hit, or indirect jolt, meaning that our cohort included a wide range of mild TBI type. Because none of our participants had any brain lesion (to the visual system or otherwise), heightened internal noise is a general consequence of mTBI stemming from a diffuse cortical imbalance that cannot possibly be restricted to the visual system. We speculate that other sensory modules would be similarly affected by mTBI, and that the LAM could be adapted to capture an general perception internal noise profile.

One cortical location previously thought to be instrumental in the modulation of visual processing noise, namely the Frontal Eye Field (Noudoost & Moore, 2011), and

modulation of FEF activity with non-invasive methods such as transcranial magnetic stimulation or direct current stimulation (Grosbras & Paus, 2003), may serve to modulate internal noise and, coincidentally, modulate attentional control effects as well.

2.7.6 Limitations

Abnormal integrative noise levels are a hallmark of other other clinical populations as well. In the Autism Spectrum Disorder for example, noise has been measured via psychophysical methods (Vilidaite, Yu, & Baker, 2017) as in the present study, and operationalized as intra-individual variability in evoked EEG (Milne, 2011) and fMRI responses (Haigh, Heeger, Dinstein, Minshew, & Behrmann, 2015). Crucially, studies that tie physiological and cognitive measurements together allow for stronger claims and more encompassing interpretations, as in the case of schizophrenia (G. Winterer et al., 2004). As such, functional imaging data should build on our findings to uncover the neural correlates of visual representation internal noise. We found no effect of gender on any of our measurements, but our sample did exhibit a gender bias, and it will be important to include gender as a factor in future mTBI studies because TBI may have gender-specific effects (Farace & Alves, 2000).

Increased integration noise was not previously considered as an encompassing feature of mTBI. We therefore stress the value of this encouraging first step towards understanding the functional mechanisms behind visual dysfunctions that follow mild Traumatic Brain Injury.

2.7.7 Conclusion

In conclusion, we have demonstrated that cortical integration following mTBI is limited by abnormally high levels of internal noise as measured by our contour

integration task, and that efficiency levels are not altered except in terms of visual field biases, possibly as a compensatory mechanism.

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2.9 Figures

Table 1. Participants

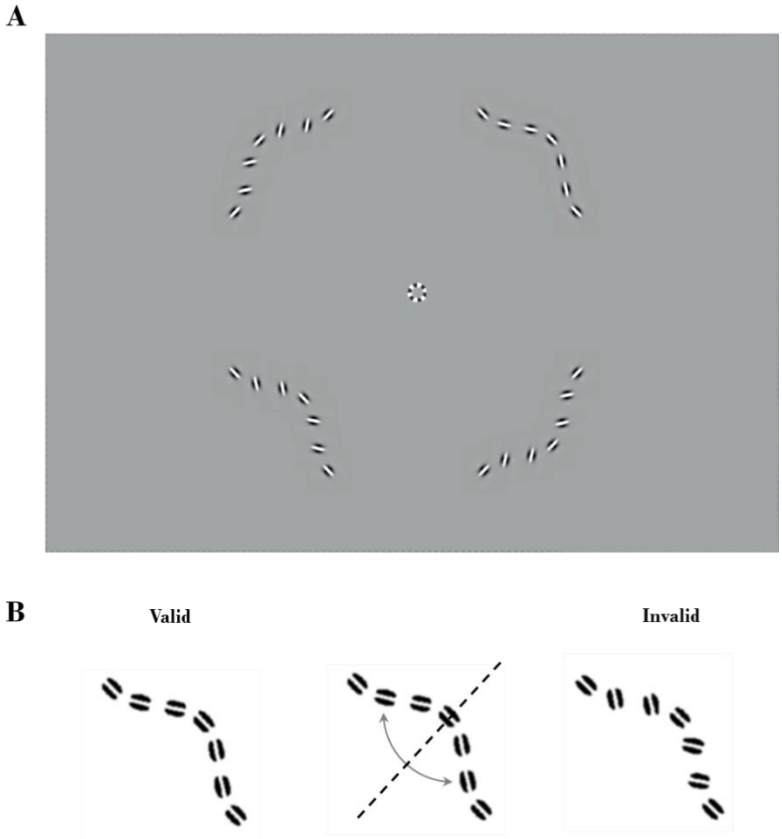
Subject	Age	Gender	TMT time	TMT errors	Bells Time	Bells missed	Education Level	Handedness	Diagnosis	Loss of Consciousness
t1	59	M	29.699	0	66.38	5	11th Grade	Right	Mild complex	Yes
t2	56	F	35.07	0	126.163	0	11th Grade	Right	Mild simple	No
t3	57	M	111.16	0	116.11	6	Bachelor's Degree	Right	Mild	Yes
t4	33	M	23.107	0	89.576	10	Bachelor's Degree	Right	Mild simple	Yes
t5	57	F	20.779	0	150.143	2	Master's Degree	Right	Mild	Yes
t6	58	M	29.117	1	67.399	0	Master's Degree	Right	Mild simple	No
t7	54	F	25.989	0	115.183	1	Bachelor's Degree	Right	Mild	Yes
t8	40	M	16.01	0	65.93	0	Bachelor's Degree	Right	Mild	No
t9	64	M	24.6	0	80.29	5	11th Grade	Left	Mild	No
t10	38	F	38.2	0	115.1	2	11th Grade	Right	Mild	No
t11	38	F	33.646	0	82.928	6	11th Grade	Right	Mild simple	Yes
t12	31	F	20.842	1	61.49	9	Doctoral Degree	Right	Mild complex	Yes
t13	23	F	26.58	0	131.79	0	Bachelor's Degree	Right	Mild simple	No
t14	32	F	21.84	0	94.18	1	11th Grade	Right	Mild simple	Yes
t15	55	F	39.204	0	80.945	7	Bachelor's Degree	Right	Mild simple	Yes
t16	55	F	37.65	0	117.786	2	Bachelor's Degree	Right	Mild simple	No
t17	53	F	22.019	0	77.569	4	Bachelor's Degree	Right	Mild trivial	No
t18	32	F	26.398	0	107.426	5	Doctoral Degree	Right	Mild simple	No
t19	41	F	15.442	0	74.9	1	Bachelor's Degree	Right	Mild	Yes
t20	18	F	25.933	0	76.599	3	11th Grade	Right	Mild simple	Yes
t21	50	F	23.369	0	68.446	6	Professional DEC	Right	Mild simple	Yes
t22	20	F	27.62	0	50.909	13	General DEC	Right	Mild simple	Yes
t23	22	F	14.8	0	60.5	14	Bachelor's Degree	Left	Mild simple	No
t24	46	F	48.862	0	103.052	2	Bachelor's Degree	Right	Mild simple	No
t25	19	F	19.98	0	46.6	6	11th Grade	Right	Mild complex	Yes
t26	41	F	36.64	1	127.91	5	Professional DEC	Left	Mild	No
t27	69	F	31.57	0	122.43	1	Professional DEC	Left	Mild simple	No
t28	61	M	58.65	0	101.05	3	Bachelor's Degree	Left	Mild	Yes
t29	34	F	32.72	0	93.83	4	10th Grade	Right	Mild simple	Yes
t30	56	F	26.94	0	70.08	6	Master's Degree	Right	Mild simple	No
t31	29	F	27.62	0	38.09	10	Bachelor's Degree	Right	Mild simple	Yes
t32	33	F	20.23	0	71.09	5	Master's Degree	Right	Mild simple	No
t33	57	F	27.33	0	75.3	7	Bachelor's Degree	Left	Mild simple	Yes
t34	32	F	25.72	0	88.5	1	Professional DEC	Right	Mild simple	Yes
t35	63	F	22.14	0	89.19	1	11th Grade	Right	Mild complex	No
t36	18	F	23.11	1	101.84	1	11th Grade	Right	Mild simple	No
t37	40	M	26.53	1	88.21	1	Master's Degree	Right	Mild simple	Yes
t38	23	F	22.2	0	32.18	5	Bachelor's Degree	Right	Mild simple	Yes
t39	44	F	19.93	1	62.08	11	Bachelor's Degree	Right	Mild simple	No
t40	24	F	33	1	78.48	0	Bachelor's Degree	Left	Mild simple	Yes
t41	31	F	23.28	0	119.65	2	Bachelor's Degree	Right	Mild	Yes
t42	28	M	32.35	1	65.43	7	General DEC	Right	Mild complex	Yes
t43	24	M	28.28	0	87.75	3	Bachelor's Degree	Right	Mild simple	Yes
t44	28	F	20.55	0	46.37	7	General DEC	Right	Self reported	Yes
t45	44	M	22.35	0	88.36	1	Bachelor's Degree	Right	Mild simple	No
t46	19	F	13.28	0	78.84	2	General DEC	Right	Self reported	No
t47	37	F	22.53	0	62.68	2	11th Grade	Right	Mild	Yes
t48	27	F	31.26	0	122.4	1	Bachelor's Degree	Right	Mild simple	Yes
t49	24	M	35.49	1	183.07	0	General DEC	Right	Mild simple	Yes
t50	45	F	30.21	0	153.87	0	General DEC	Right	Mild simple	No
t51	53	M	35.63	1	138.45	0	Master's Degree	Right	Mild simple	Yes
t52	39	F	24.58	0	61.93	2	Bachelor's Degree	Right	Mild simple	No
t53	50	F	22.25	0	67.93	3	Bachelor's Degree	Right	Mild simple	No
t54	20	M	16.8	1	77.47	3	General DEC	Right	Mild simple	Yes
t55	40	F	43.1	0	171.8	1	Bachelor's Degree	Right	Self reported	n/a
poly1	24	M	24.5	0	122.57	1	Bachelor's Degree	Right	Multiple	n/a
poly2	18	F	14.3	0	40.74	4	Master's Degree	Right	Multiple	n/a
poly3	26	F	37.92	0	124.68	2	n/a	Right	Multiple	n/a
poly4	49	F	36.34	0	98.31	10	Bachelor's Degree	Right	Multiple	n/a
poly5	23	F	33.44	0	110.39	1	Bachelor's Degree	Right	Multiple	n/a
c1	42	F	n/a	n/a	68.345	1	Doctoral Degree	Right	None	n/a
c2	40	F	n/a	n/a	76.398	4	EGEP General DE	Right	None	n/a
c3	53	F	n/a	n/a	73.679	7	Master's Degree	Left	None	n/a
c4	70	M	n/a	n/a	108.24	2	Bachelor's Degree	Right	None	n/a
c5	19	M	n/a	n/a	68.66	1	n/a	n/a	None	n/a
c6	54	M	n/a	n/a	92.8	1	Master's Degree	Right	None	n/a
c7	49	F	n/a	n/a	80.239	1	GEP Professional D	Right	None	n/a
c8	18	F	34.87	0	65.58	7	11th Grade	Right	None	n/a
c9	25	M	18.25	0	48.4	7	Bachelor's Degree	Right	None	n/a
c10	21	F	34.91	0	81.69	6	Bachelor's Degree	Right	None	n/a
c11	53	F	36.48	1			Bachelor's Degree	Right	None	n/a
c12	42	M	12.92	0	57.43	1	Bachelor's Degree	Right	None	n/a
c13	27	M	21.12	0	65.05	2	Bachelor's Degree	Right	None	n/a
c14	50	F	21.15	0	42.39	6	n/a	n/a	None	n/a
c15	20	F	28.32	0	56.76	1	EGEP General DE	Left	None	n/a
c16	26	M	21.54	0	46.37	5	Master's Degree	Right	None	n/a
c17	35	F	23.55	0	77.94	1	Doctoral Degree	Right	None	n/a
c18	46	M	12.63	0	66.11	3	Bachelor's Degree	Right	None	n/a
c19	25	M	16.85	0	72.67	3	11th Grade	Right	None	n/a
c20	22	F	19.1	1	68.7	0	Bachelor's Degree	Right	None	n/a
c21	28	M	23.53	0	62.98	4	Doctoral Degree	Right	None	n/a
c22	27	M	15.16	1	48.19	3	Master's Degree	Right	None	n/a
c23	33	M	32.72	0	126.14	0	Doctoral Degree	Right	None	n/a

Table 2. Result Summary.

Single mTBI	Polytrauma
Higher internal noise than controls	Higher internal noise than controls and single mTBIs
Abnormal efficiency distribution across visual field	No effect found on efficiency

Figure 1

Figure 1 **Visual stimuli**. Contrast has been enhanced for illustration purposes. (A) An example trial of the Good continuation discrimination task, the upper right quadrant contains the valid contour (0° noise). (B) Construction of the invalid contour by inverting elements across the valid contour diagonal. Because of the systematic nature of this process, it is not to be confused with the addition of orientation noise. (C) Cartoon showing valid and invalid contours varying in amplitude under noise levels 1, 2 and 3 (respectively 0°, 8° and 16° of SD of orientation noise). Note the increasing difficulty of discriminating between the valid (on the right) and invalid (on the left) contours as amplitude decreases.



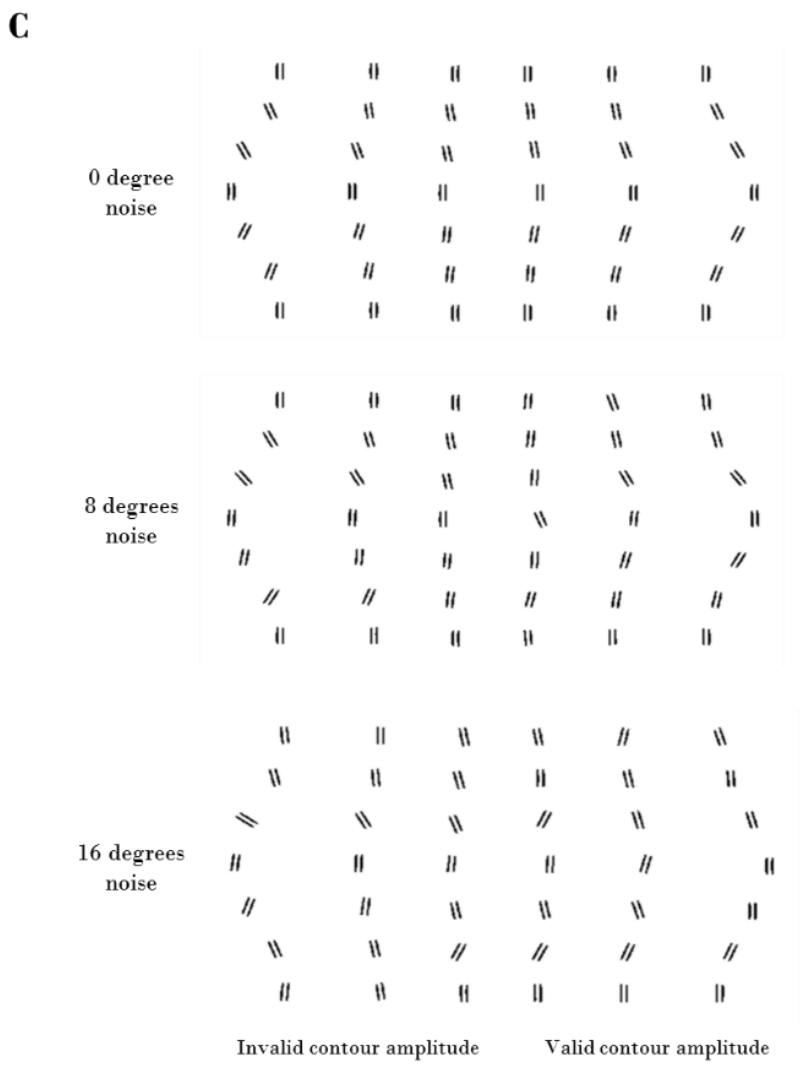


Figure 2

Figure 2 **Linear Amplifier model (LAM) graphical description with mock-data**. (A) The LAM function describes the dynamics of performance thresholds along levels of added external noise—thresholds (t), as a function of external noise (σ_{ext}), internal noise (σ_{int}) and efficiency (β). At low levels of external noise, performance is not dependant on external noise and remains constant and limited by internal noise. After the equivalent noise point, additional external noise shifts thresholds upwards, and becomes the major limiting factor of performance. (B) A higher internal noise curve (in grey) with unchanged efficiency shows a shift in the equivalent noise point towards higher noise. The thresholds are shifted up, as the tail of the function asymptotes towards the same slope. (C) A higher efficiency curve (in grey) with unchanged internal noise shows a global shift towards lower thresholds and maintains the same equivalent noise point.

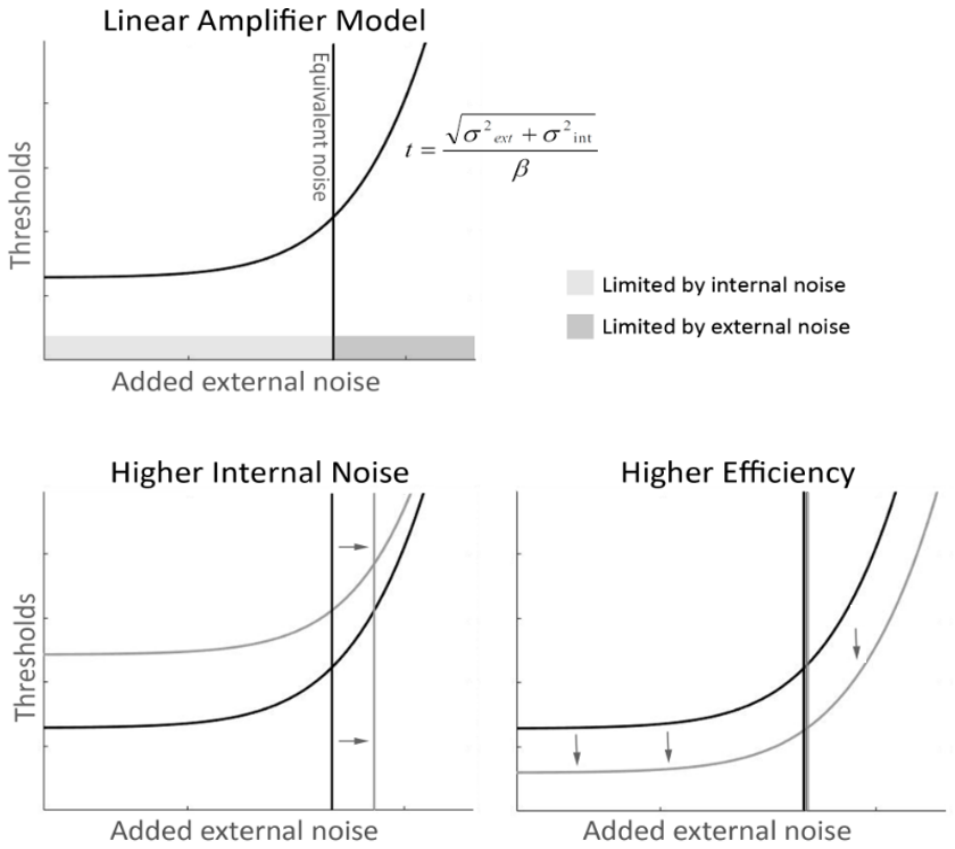
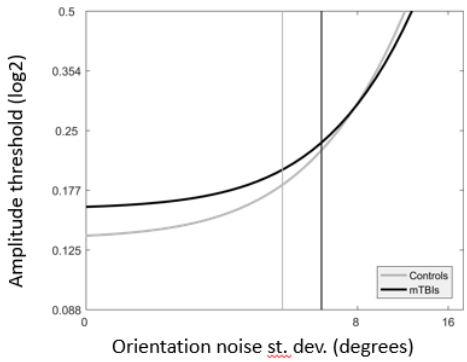


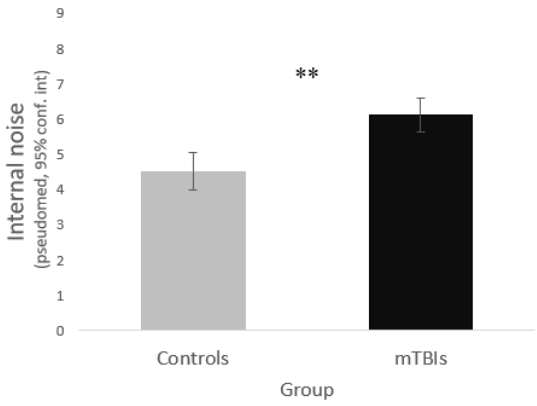
Figure 3

Figure 3 **Main results**. (A) LAM functions for the mTBI subjects (in black) and the control subjects (in grey). (B) The mTBI group shows significantly higher internal noise than the control group. (C) The left and right hemifields varried significantly in internal noise in the control group but not in the mTBI group. (D) mTBI subjects had significant biases in efficiency across both the vertical and horiontal hemifields.

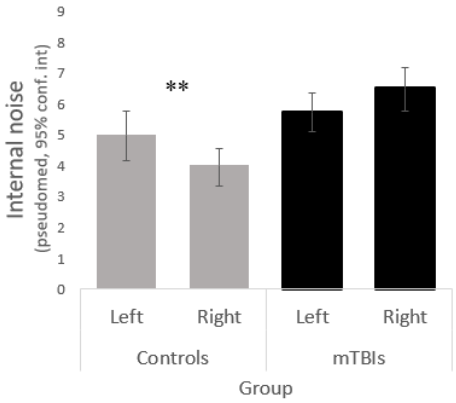
A


Amplitude threshold (log2)
0.5
0.354
0.25
0.177
0.125
0.088
0
8
16
Orientation noise st. dev. (degrees)
Controls
mTBIs

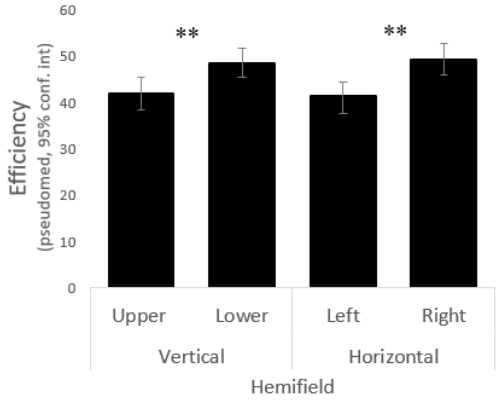
B


Internal noise
(pseudomed, 95% conf. int)
**
Controls
mTBIs
Group

C


Internal noise
(pseudomed, 95% conf. int)
**
Left
Right
Left
Right
Controls
mTBIs
Group

D


Efficiency
(pseudomed, 95% conf. int)
**
**
Upper
Lower
Left
Right
Vertical
Horizontal
Hemifield

Chapter 3 Naturalistic movie viewing reveals decreased inter-subject synchrony and increased within-subject functional connectivity after mild TBI

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Keywords: fMRI, intersubject similarity, MVPA, naturalistic stimulation, visual perception

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3.1 Preamble

We have established that increased levels of internal noise limit cortical integration in early visual areas following mTBI. This novel finding was obtained using psychophysical modelling of behavioral performance which isolated the processing of good continuity from other key visual features that form natural stimuli. Although investigating visual functions separately is necessary and useful to our understanding of perceptual mechanisms (Hubel & Wiesel, 1968), each visual process does not happen in a functional vacuum. Visual features are processed in parallel to form a coherent percept of our environment, and cortical activity is affected by injury (Kohl, Wylie, Genova, Hillary, & Deluca, 2009). Naturalistic movie viewing recruits the visual system as a whole and has been used to flag abnormal distribution of cortical activity in autism spectrum disorder (ASD) (Hasson et al., 2009). The following chapter aims at probing natural vision following mTBI by presenting naturalistic movies to participants while they are being scanned.

The following manuscript is in preparation for submission to NeuroImage.

3.2 Abstract

Although symptomatic mild Traumatic Brain Injury (mTBI) patients report daily visual complaints months after their injury, these have been difficult hard to corroborate in laboratory settings. Performance at low levels of task difficulty is hardly different from normal, but high-demand tasks also may put pressures that are not ecologically valid and therefore reveal effects that are not related to the mTBI symptoms. Moderate-demand tasks are thus more ecologically valid and generalizable to mTBI's natural cortical processing, so we sought out to determine whether naturalistic viewing would

reveal differences in visual processing between mTBIs and normal controls. We used classic fMRI analysis and novel independent modelling of normal temporal pattern of cortical activity. We imaged 17 mTBI and 54 healthy participants while they watched natural underwater scenes devoid of narrative or semantic structure. We found that the mTBIs fit poorly to our normative timeseries models. They showed lower activity in early areas but a tendency to increased activity in fronto-parietal areas compared to controls. This was corroborated with higher functional connectivity between fronto-parietal areas and early, ventral and dorsal areas. Taken together, our results suggest a compensation for dysfunctional cortical regions. The increased connectivity affected visual areas related to typical mTBI symptoms (attention, integration of visual features, motion and scene perception). In conclusion, moderate-demand tasks such as movie viewing are enough to reveal subtle cortical changes following mTBI, potentially contributing a valid biomarker of TBI.

3.3 Introduction

Functional recovery following mild Traumatic Brain Injury (mTBI) relies on residual neural substrates but does not follow a linear progression (To & Nasrallah, 2021) and is often incomplete even after months or years (Shenton et al., 2012). Patients consistently report difficulties executing daily tasks that do not require excessive cognitive efforts—they experience difficulties reading (Tabet et al., 2020), driving (Preece, Horswill, & Geffen, 2010), planning (Bottari, Gosselin, Chen, & Ptito, 2017) and doing other low-demand activities that rely on high-level functions such as focus (Eisenberg, Meehan, & Mannix, 2014), attention (Malojcic et al., 2008), and memory (Smits et al., 2009).

Symptomatology of mTBI is most apparent during high-demand tasks. Surprisingly, while patients are aware of functional abnormalities in their cognition, their behavioral

performance at low levels of laboratory task difficulty is often close to normal. In a dual-task study looking at the effects of environmental demands on locomotion performance after mild to severe TBI, Vallée et al. (2006) measured cognitive performance (on a modified Stroop task) and locomotion (walking speed, stride length and obstacle clearance margin). They found that the most complex dual-task impaired the TBI group's locomotion performance and concluded that challenging conditions were more difficult and revealed locomotor and attentional deficits.

Although experimental tasks are intentionally tailored to test the complaints of TBIs, current behavioral metrics constrain their ecological validity. Tanguay, Davidson, Guerrero Nuñez, and Ferland (2014) argue that the fact that psychophysical measures are generalizable to real-world behavior—the assumption of such designs—is questionable. They found that computerized measurements of cooking skills using the Breakfast task (Craik & Bialystok, 2006) did not correlate with real-world meal preparation. Others have repeatedly warned that laboratory measures of executive functions do not necessarily correlate with everyday life comportment (Barker, Andrade, & Romanowski, 2004; Chevignard et al., 2000; Fortin, Godbout, & Braun, 2003; Manchester, Priestley, & Jackson, 2004). Given that high-demand laboratory tasks have poor predictive value for real-life performance, we would do well to develop low-demand tasks that are more ecologically valid for studying mTBI.

A simple, engaging, low-demand task is the natural viewing of a dynamic scene. Functional magnetic resonance imaging has been effective in showing that temporal and spatial patterns are similar between healthy subjects when watching natural scenes (Hasson et al., 2004) and these studies have been replicated numerous times (see Vanderwal, Eilbott, and Castellanos (2019) for a review). Data from such studies can be analyzed simply in terms of intersubject correlation, or with multivariate methods that

explore shared components (i.e., principal or independent components analysis). However, such approaches are hard to relate to classic fMRI studies or to interpret within hypothetical pathophysiology. Alternatively, conventional fMRI analysis with General Linear Models (GLM) allow one to compare conditions and groups in a hypothesis-driven way but require well-defined event times and durations to create a predicted hemodynamic timeseries for each voxel, making them difficult to implement in movie-fMRI studies.

We combined classic fMRI analysis with unbiased models of normative hemodynamic timeseries models within a naturalistic movie-viewing paradigm. We hypothesized that low-demand, naturalistic tasks will reveal subtle differences between symptomatic mild TBI and normal controls. We measured fMRI while normal and concussed participants viewed natural scenes devoid of narrative or semantic structure. We then created estimates of normal patterns of activity and functional connectivity matrices. We found that mTBI cortical activity deviates from normal patterns and that early visual areas have lower magnitudes of activity, possibly compensated by fronto-parietal areas in concussed patients. Functional connectivity was increased between fronto-parietal areas and other visual areas which hold key-roles in complex visual feature integration.

3.4 Methods

3.4.1 Participants

All participants gave their informed consent prior to taking part in the experiment. All procedures were in accordance with the Code of Ethics of the World Medical Association

(Declaration of Helsinki) and were approved by the Research Ethics Board of the McGill University Health Center.

All participants were screened for anomalous vision loss or vision disorders (glaucoma, retinal detachment, macular degeneration, etc.). They had normal or corrected to normal visual acuity (wore their usual refractive correction as needed). The average age of the participants was 36 years old (SD = 10 years, n=17) in the TBI group and 26 years old (SD = 6 years, n=54) in the control group.

TBI participants

Participants were recruited through the McGill University Health Center out-patient TBI clinic. The diagnostic criteria for mild TBI were: Glasgow Coma Scale score between 13 and 15, less than 30 minutes of loss of consciousness, and less than 24 hours of amnesia regarding events immediately before or after the accident. Patients with mild TBI who gave their authorization to be contacted went through a phone screening interview. The exclusion criteria were (1) family history of epilepsy or seizure, or the administration of prescription medication with increased risk of seizure, (2) severe tremors or involuntary movements, (3) general anesthesia in the past 6 months, (4) mTBI occurred less than 1 month ago or more than 2 years ago, (5) a history of multiple brain injury. Following our previous publication, participants filled a questionnaire adapted from Assessment with Mild Traumatic Brain Injury for the Defense Centers of Excellence for Psychological Health and Traumatic Brain Injury (Spiegel et al., 2016) investigating blurred vision, migraines, behavioral change to palliate visual discomfort etc. All participants experienced visual symptoms. None of our self-reported and neuropsychological measures (clock drawing test, trail making test,

bells test) correlated with any of our neuroimaging results. The final sample size of tested mTBI participants was 17 (9 females and 8 males).

Control participants

Healthy participants were recruited through public announcements in the Montreal General Hospital and on social media. Exclusion criteria included conditions 1-4 outlined above, and no history of any acquired brain injury. The group was comprised of 54 control participants (28 females and 26 males).

3.4.2 Stimuli and procedure

Stimuli were presented using MATLAB® (2014b, The Math Works Inc., Natick, Massachusetts) and synchronised with acquisition start time by Sterescopic Player (http://www.3dtv.at) and ActiveX connection using a 10-bit graphics card (Nvidia Quadro 2000) on a gamma-calibrated 3-D LCD BOLD screen reflected by a mirror above the participants' head. They were placed at a 170 cm viewing distance from the monitor, spanning 9.4 by 17 degrees of visual angle at a pixel resolution of 1920 by 1080. Participants were scanned while watching two five-minute-long movie clips twice, once in 2D, and once in 3D (using polarized glasses), cut from the movie "Under the Sea 3-D: IMAX" (Hall, 2009). We verified that the participants did perceive the movies in 3D after each scan. Scenes included marine fauna and flora, constituting naturalistic stimuli with no human made objects or other elements that could have biased representations depending on culture, gender or age. Participants were instructed to fixate on the center of the screen (white fixation cross present for the entirety of the stimuli), and a blank screen with fixation cross was presented before each clip for four seconds.

Data acquisition

Data was acquired on a 3T Siemens TIM Trio scanner (TR=2000ms, Resolution $3mm^3$, TE=30ms, flip angle=76, matrix size=64x64, Field of View=192x192mm, number of slices=37) at the Montreal Neurological Institute (McGill University Health Center). Anatomical data (T1-weighted multi-echo magnetization prepared – rapid gradient echo sequence—MEMPRAGE— 1mm isotropic resolution) was acquired first, followed by functional imaging.

3.4.3 Analysis

Data preprocessing

fMRI data was preprocessed with Analysis of Functional NeuroImages (AFNI) (Cox, 1996). To minimize spatial blurring, we applied all spatial transformations in a single step following slice-time correction. Motion and distortion corrections and anatomical registration were concatenated into one transform and applied once. We also applied detrending and denoising (to remove structured noise along white matter boundaries from the time series) algorithms from ANATICOR (Jo, Saad, Simmons, Milbury, & Cox, 2010). Cortical surfaces were first extracted with Freesurfer (http://surfer.nmr.mgh.harvard.edu/), and corrected segmentation errors after visual inspection. Statistical analysis was performed on surface-projected data because they preserve individual subjects' topology and allow for better registration across subjects, which strengthens statistical power compared to voxel-based analysis (Saad & Reynolds, 2012). Each node from one subject's mesh (36,000 nodes per hemisphere) directly corresponds to the same node from other subjects, which allows for direct inter-subject comparisons.

Normal template

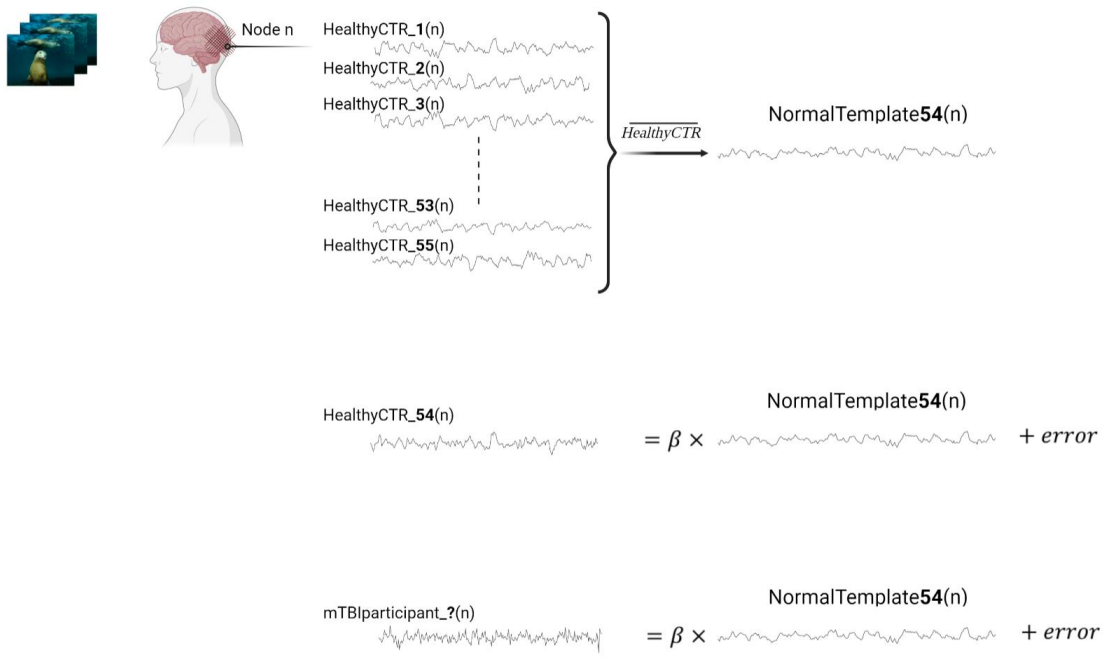

Figure 3-1 Construction and attribution of the normal template. After a leave-one-out average of healthy control timeseries, a given normal template is used to fit the timeseries of the left-out healthy control and of a random mTBI participant. The procedure is repeated at each node of the surface mesh.

We devised a method to assess how the injured brain's activity related to the normal brain by creating templates of normal cortical activity using a leave-one-out procedure. Each participant in the healthy control group was attributed a "normal template"—a node-specific average timeseries of every *other* control subjects. For example, normal template 54 was the average timeseries per node across all the healthy control subjects *except* subject 54 (see Figure 3-1). This allowed us to create unbiased timeseries models of the hemodynamic response so we could carry out a GLM analysis within a naturalistic stimulation situation.

Data from all subjects (from both groups) were fitted to a normal template—for normal controls, we used a leave-self-out template, while for mTBI subjects, we randomly

assigned one of the control templates. All models were thus independent of the data that was fitted to them.

This procedure yielded two parameters for each subject-to-template linear fit: a scaling factor (Beta) and the residual error which was converted into Root Mean Square Error (RMSE). The scaling factors were then compared between groups via a two tailed t-test (controls-mTBIs), and the RMSE with a non-parametric Mann-Whitney U test, since RMSE values do not follow a Gaussian distribution, and converted to z-scores for interpretation. These results were computed at every node of the 36,000-node mesh excluding some frontal areas that were not covered by the acquisition window. Both were subsequently corrected for multiple comparison using false discovery rate with q = 0.05 (Benjamini & Hochberg, 1995b). This procedure was repeated for each hemisphere and each stimulus condition (2D and 3D).

Functional connectivity

As a secondary analysis, we wanted to know whether mTBI affected the dynamic aspect of visual cortical activity, so we sought to perform a visual area-wise functional connectivity analysis.

Timeseries at each of the 36,000 nodes from the surface projected data were correlated with all other nodes of that same hemisphere, yielding two 36,000 by 36,000 correlation matrices for each participant's hemisphere. These were Fisher Z-transformed and then averaged per visual area (25 areas) as defined in a previously published probabilistic atlas based on retinotopy (Wang, Mruczek, Arcaro, & Kastner, 2015).

The final matrices were thus 25 × 25 sized, and for each participant four such matrices were estimated—two for each hemisphere and two for each viewing condition (2D and

3D). We used two-tailed t-tests to compare these between groups and corrected the results using false discovery rate (Benjamini & Hochberg, 1995b).

3.5 Results

3.5.1 Timeseries from mTBI patient was poorly explained by normal template

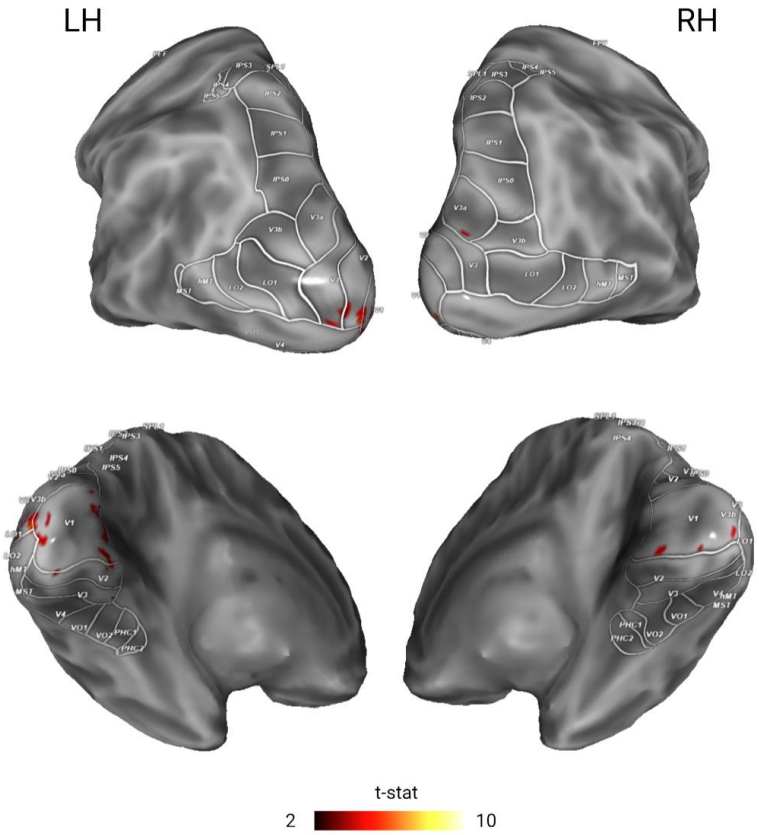

Figure 3-2 Difference of scaling factor to normal template between groups (control-mTBI) projected on a standard surface.

When comparing mTBIs with healthy controls' fit to normal templates of activity in response to our narrative-free movie stimuli, the first striking result was that most visual areas did not reveal significant differences in scaling between groups. Figure 3-2 shows only a few isolated clusters of nodes in early visual areas (V1, V2, V3, V3a, V3b) where mTBIs showed significantly smaller scaling factors for their node-wise timeseries fits to normal templates than healthy controls. We found that in these few nodes, mTBI participants' timeseries needed less scaling

than healthy controls to fit normal templates of activity, but as the differences were few and scattered, we interpret this as effectively showing no scaling difference between mTBI and controls.

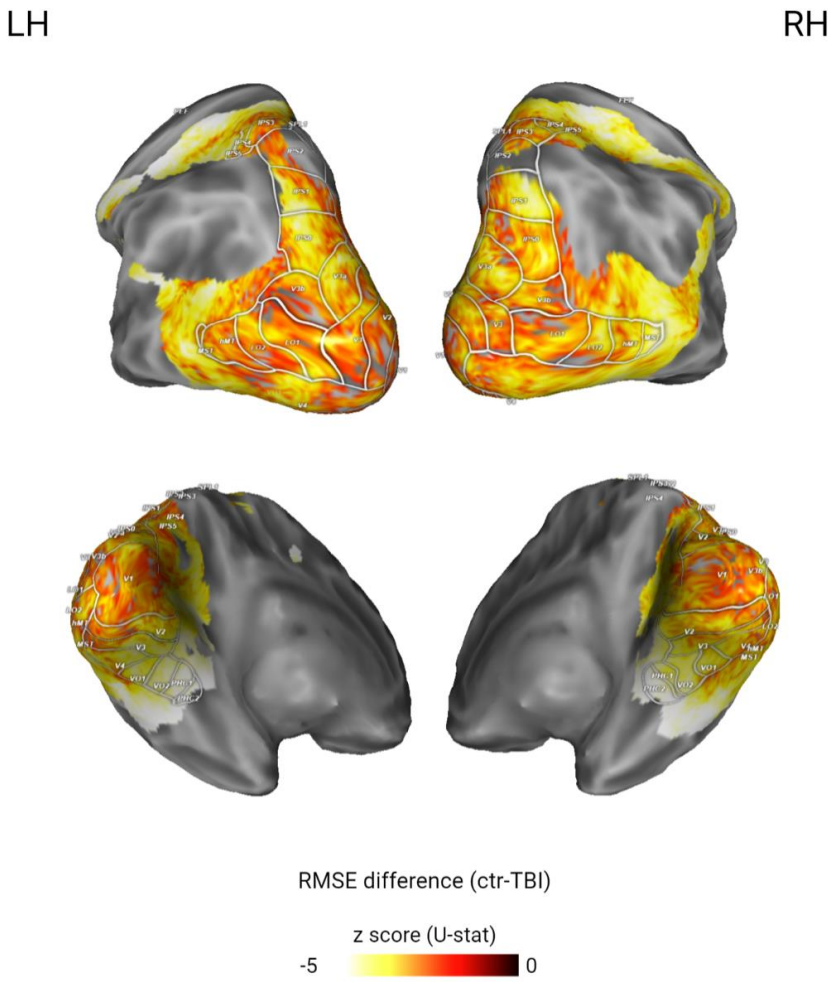

Figure 3-3 Difference in RMSE from linear fit to normal templates (control-mTBI) projected on a standard surface

The second important finding concerned the error parameter from fitting timeseries to normal templates—RMSE in the mTBI group was higher than that of healthy controls in almost all visual areas (see Figure 3-3). Thus, cortical activity of mTBI participants could not be fitted to normal templates as well as they could be in the healthy controls.

This pattern of results was repeated for the 2D viewing condition, in which the widespread increase in RMSE after mTBI showed that the fit-to-normal Templates was impaired, even in the absence of significant differences in scaling factor. Thus, the results for the 2D viewing condition mirrored that of the 3D condition.

3.5.2 ROI analysis reveals compensation by fronto-parietal areas for decreased activity in early visual areas in mTBI

We averaged scaling factors within each region of interest and found that the mTBI group showed lower betas (i.e., lower BOLD magnitude) in early visual areas (see Figure 3-4). Specifically, V1v ($t_{df=71}$= 4.07, $p_{adjusted}$< 0.005), V1d ($t_{df=71}$= 3.48, $p_{adjusted}$ < 0.01) and V2v ($t_{df=71}$ = 2.96, $p_{adjusted}$ < 0.05) showed significantly lower scaling factors in the mTBI group. In contradistinction, fronto-parietal areas showed a tendency to increased betas (i.e., greater BOLD magnitude) in the mTBI group, although that group difference was not statistically significant ($p_{adjusted}$ > 0.05). Ventral and Dorsal areas followed the trend of early visual areas as well, with a tendency towards lower betas for the mTBI group, but this did not reach significance either ($p_{adjusted}$ > 0.05).

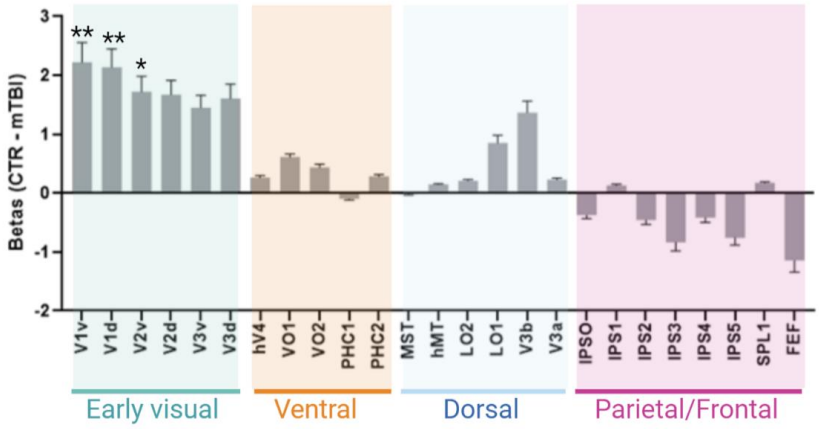

Figure 3-4 Scaling factor differences between groups (CTR-mTBI) for each Region of Intererest of the visual cortex. One star represents a significance p < 0.05, two stars p < 0.01 (after FDR correction). V1v, V1d and V2v showed decreased activation in the mTBI group.

3.5.3 Dysfunctional connectivity after mTBI

We constructed functional connectivity matrices for each subject describing the Pearson's correlation between each visual area using the averaged ROI timeseries. These were then averaged across healthy controls to obtain a single normal functional connectivity matrix illustrated in light grey in the circular graph (Figure 3-5). We compared groups by performing a t-test between all the matrices from the mTBI group and all of those from the healthy controls. We found that visual areas from the parietal and frontal regions (SPL1, IPS2,3,5) exhibited higher functional connectivity to dorsal and ventral areas after mTBI ($t_{df=71}$>3.5; p < 0.05). Two dorsal visual areas—V3A and LO—were more connected to each other and to an early visual area (V2v) as well as a ventral area (PHC1) ($t_{df=71}$>3.5; p < 0.05). Thus, functional connectivity during naturalistic movie viewing is significantly altered in select cortical networks.

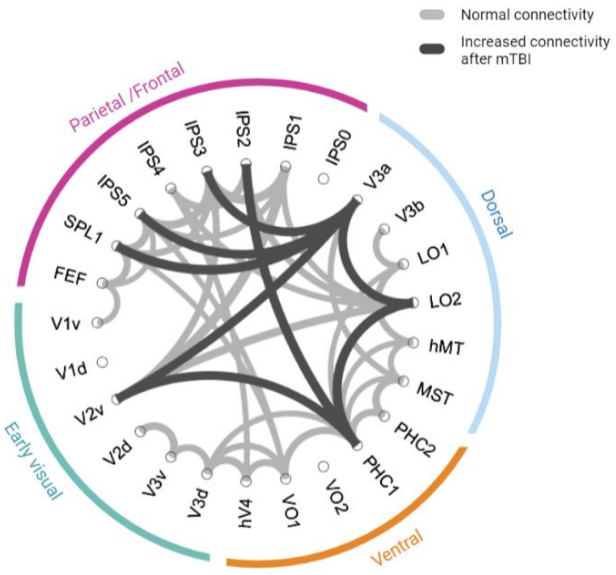

Figure 3-5 Normal functional network of Regions of Interest of the visual cortex overlayed with connections that showed increased functional connectivity in the mTBI group. The increase in connectivity was thresholded at p < 0.05 after FDR ($t_{df=71}$ > 3.5) and the normal functional connectivity was thresholded at R > 0.7.

3.6 Discussion

We have shown for the first time that naturalistic stimuli and an ecologically valid task such as movie viewing can reveal differences in visual processing following mTBI and have done so with a novel method of comparison to normative hemodynamic timeseries.

First, we have shown that data from mTBI participants poorly fit the normal template of activity when watching naturalistic movies. Interestingly, the betas—often used in GLM analysis as a proxy for magnitude of activity—were similar between both groups, but crucially we found that the RMSE was substantially higher in the mTBI group in both 2D and 3D viewing conditions. This can be a sign of greater asynchrony between mTBI patients and the normal template, increased noise in the mTBI, or both. The widespread error could be a sign of asynchrony—the temporal synchrony found between healthy controls and the normal template is diminished following mTBI. In this view, each mTBI patient's brain response is more likely to deviate from the normal template, and therefore as a group, there is greater RMSE, which is a reflection of how much error is not explained by the fit. This could be the case even when beta scores are similar, especially if the asynchrony is mild but consistent in the group. Under this Asynchrony Hypothesis, the mTBI cortex still responds in a structured fashion, but in a manner slightly different than the normal template would dictate. In contrast, it could simply be the case the mTBI cortex exhibits more noise due to computational errors. This would also result in betas comparable to the control group but increased in RMSE. Under this view, the cortex is not simply responding in a new, changed way, but expresses greater error. Our results do not distinguish between these two explanations, and both may actually be present as well.

Second, we have found that early visual areas tended to be less active (and significantly so) in the mTBI group—beta values were lower—compared to healthy controls, while parietal areas tended to exhibit slightly elevated activity compared to healthy controls, but this hyperactivity did not reach statistical significance. It is possible that while naturalistic movies reveal abnormalities in early visual areas in the form of scattered activity deficits, it is likely that these deficits were revealed *because* the task did not put large demands on the subject and thus compensatory mechanisms were not needed to be engaged. Compensatory hyperactivity has

been repeatedly associated with TBI (Caeyenberghs, Wenderoth, Smits-Engelsman, Sunaert, & Swinnen, 2009; Gooijers et al., 2016; Y.-H. Kim et al., 2008; Rasmussen et al., 2008) and meaningful for specific regions recruited by high load tasks such as during working memory (T.W. McAllister et al., 1999) or sustained attention (Wu et al., 2018).

Third, we found a marked increase in functional connectivity between all four major sets of visual areas—early, ventral, dorsal, and fronto-parietal—which denotes increased synchrony *within* individual mTBI participants. The parietal-frontal regions showed the strongest increase in connectivity to ventral and dorsal areas, but each were significantly more connected to each other and to early visual areas as well. Increased functional connectivity has been reported previously at rest in TBI patients (Muller & Virji-Babul, 2018; David J. Sharp et al., 2011) especially in fronto-parietal regions in TBI and mild TBI patients (Shumskaya et al., 2012; Stevens et al., 2012), in the visual cortex of mild TBI patients (Stevens et al., 2012) and between occipital and frontal regions in mild TBI patients (Iraji, Chen, Wiseman, Welch, et al., 2016).

Regions from the parietal-frontal set (SPL and IPS) were particularly more connected to regions from the dorsal set of visual areas (V3a), but also to one region from the ventral set (PHC1). SPL and IPS have been identified as major contributors to visual feature integration (Corbetta, Shulman, Miezin, & Petersen, 1995), attention shifts (Corbetta et al., 1998), and attentive tracking (Culham et al., 1998). Our results suggest that visual attention deficits previously found in the mTBI population (Konrad et al., 2010) could be related to increased functional connectivity even when stimuli are not particularly demanding in terms of attentional load.

Area V3a is thought to be involved in motion perception and segregation of visual scenes based on texture features (Kastner, De Weerd, & Ungerleider, 2000). More specifically, V3a has been shown to contribute to directed attention towards or away from motion defined stimuli (Seiffert, Somers, Dale, & Tootell, 2003). These functions relate to symptoms reported by mTBI—motion sensitivity and vertigo (Kapoor & Ciuffreda, 2002; Patel, Ciuffreda, Tannen, & Kapoor, 2011), and visuo-motor integration deficits (Benassi, Frattini, Bolzani, Giovagnoli, & Pansell, 2019). V3a is also involved in second order motion processing (Seiffert et al., 2003).

Interestingly, we had previously found abnormalities in contrast sensitivity of second-order motion-defined stimuli (higher cut-off spatial frequency) following mTBI (Spiegel et al., 2016). V3a was also more connected to LO2 in the mTBI group which belongs to the dorsal set as well. The lateral occipital cortex is sensitive to objects (Rafael Malach et al., 1995) especially when presented foveally (Sayres & Grill-Spector, 2008). We interpret the increased connectivity in these regions dedicated to attention shift, texture, motion and scenes, to be revealing of increased efforts of integration between these visual features to process simple narrative-free naturalistic movies in the mTBI group.

One early visual area, V2v, was more connected to PHC1 (belonging to the ventral set) and to V3a (dorsal set). V2 is anatomically divided into a ventral and a dorsal subregion, retinotopically distinct in that the former processes information from the upper visual field and the latter from the lower visual field. In our movie, the lower visual field consists mostly of seafloor. Thus, the significance of V2v's altered functional connectivity reflects more vivid and attention-grabbing elements of the stimuli located in the upper visual field. V2 is known to process simple orientation (Boynton & Finney, 2003; Montaser-Kouhsari, Landy, Heeger, & Larsson, 2007), contrast (Avidan et al., 2002) and chromatic (Engel, Zhang, & Wandell, 1997) information and as well as figure-ground segregation from stereoscopic information (Qiu & Von Der Heydt, 2005). It is most probable that the mTBI group experienced more difficulty in the latter function—figure-ground segregation—given the type of stimuli we presented. The para-hippocampal cortex (PHC) is sensitive to scenes more than object and faces (Arcaro, McMains, Singer, & Kastner, 2009) and to contextual information surrounding objects (Biederman, Mezzanotte, & Rabinowitz, 1982). Together, these regions collaborate to process colorful scenes in motion surrounded by contextual cues and increased functional connectivity between these regions denotes that complex features forming natural stimuli are more difficult to integrate following mTBI.

In conclusion, natural movie viewing revealed that although normal inter-subject synchrony was diminished after mTBI, within-subject synchrony was increased in relevant cortical areas of the

visual system, possibly as a compensatory mechanism. Our results show that important differences could be observed in mTBI without resorting to demanding tasks or simply relying on resting-state connectivity.

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Chapter 4 Graph analysis of the visual cortical network during naturalistic movie viewing reveals increased integration and decreased segregation following mild TBI

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Keywords: fMRI, graph theory, naturalistic stimulation, visual perception

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4.1 Preamble

Naturalistic movie viewing is an active task that suffices to reveal differences in visual processing after a mild TBI. We have found decreased activity in early visual areas and increased functional connectivity between fronto-parietal regions and early, ventral and dorsal regions. These functional connectivity differences hint at critical network changes that we will explore in the following chapter. We will apply graph theory to the visual cortical network activated by natural movie viewing to probe changes in natural cortical dynamics following mTBI.

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4.2 Abstract

Conventional approaches to neuroimaging of mTBI have shown critical changes in the distribution of cortical activity at rest, during high-demand tasks, and during natural visual function. Graph theoretical approaches have revealed network changes in mTBI but results are inconsistent. Findings seem to depend on the network investigated and on the level of demand of the task. We used naturalistic movie viewing to mimic mondain task demands while the participants were being scanned (fMRI). We imaged 17 mTBI participants and 54 healthy controls while they were watching an underwater movie devoid of narrative or semantic structure. The activated network was analyzed for changes in mean degree, global efficiency, modularity and clustering. All measures were significantly affected by mTBI. We found that the mTBI group showed increased mean connectivity degree, which is in line with previous literature. We also found increased efficiency and clustering, but this was not in full accordance with previous findings in mTBI. Thus, we found increased integration at a global scale and increased

specialization at the local scale. We attribute our results to the stimuli we used, arguing that our low-demand task—natural movie viewing—recruits networks that are actively engaged in visual processing and display a functional architecture that reflects the need for organized integration of information but does not overload the system. In contrast, we found decreased modularity in the mTBI group, suggesting that the cortical network of mTBI participants was less functionally segregated than healthy controls at the global scale. We also analyzed subnetworks of the visual cortex and found that the combined results of increased connectivity degree and efficiency were repeated for all subnetworks except in early visual areas. Clustering only increased in dorsal and fronto-parietal subnetworks and modularity only decreased in fronto-parietal subnetworks. Regions of complex feature integration seem to be the most affected by network changes during naturalistic movie viewing but the whole visual system endures network changes following mTBI even when the task is only moderately demanding. Our results warrant the application of graph analysis of networks activated by naturalistic stimuli for other types of brain injury and disorders related to integrative dysfunction.

4.3 Introduction

Mild Traumatic Brain Injury induces long lasting and debilitating cognitive deficits that are hard to explain neurometrically in humans. Since the first fMRI study on mTBI (T.W. McAllister et al., 1999), conventional approaches using General Linear Models (GLM) have been tremendously successful in identifying regions that may be implicated in the cognitive deficits associated with mTBI (McDonald, Saykin, & McAllister, 2012). A sizeable list of such cortical regions include prefrontal (Matthews et al., 2011; Witt, Lovejoy, Pearlson, & Stevens, 2010), medial and temporal (T. W. McAllister, Flashman, McDonald, & Saykin, 2006), and the anterior cingulate (Sheth,

Rogowska, Legarreta, McGlade, & Yurgelun-Todd, 2021) cortices. Altered functional connectivity in the visual network were correlated with visuo-spatial and cognitive dysfunction in a mild TBI group (Li, Lu, Shang, Hu, et al., 2020).

The emergent model is that the multiple regions implicated likely form multiple networks—interconnected regions that share information and depend on one another. Whereas detecting activity differences with GLM can be straightforward, detecting network changes is quite complex because networks can change by adding/subtracting nodes, or connections, and by adjusting the magnitude of node response. These alterations combine to essentially modify the topology of the network. Thus, making inferences about network changes requires a mathematically rigorous framework that captures network shape changes, which is found in graph theory (Caeyenberghs et al., 2012; Messé et al., 2013).

Network graphs are inferred from node-based functional connectivity matrices. After traditional processing of BOLD signal, the classic functional connectivity matrix (correlation of timeseries from each pair of voxels or voxel clusters or areas) can be translated into graph networks in one of two ways. Thresholding is applied to categorize connections between functionally significant and irrelevant processes, and correlation values can be kept reflecting connection strength (weighted graph) or simply discarded (binary graph). Parameters describing such networks thus fully depend on the brain state activating that network. Graph network analysis provides key insight into whether new connections are formed and whether they are random, which allows for comparison between clinical and healthy populations.

Four commonly-reported parameters of network restructuring are (1) network connectivity degree (the average number of significantly correlated connections per

node), (2) efficiency (the inverse of the shortest path between two nodes), (3) modularity (connections pertaining to a functional module in a case-network compared to the total number of edges in the graph) and (4) clustering (the abundance of interconnected node trios) (Rubinov & Sporns, 2010). These parameters are biologically meaningful as they quantify synchrony of processing across the cortical network (connectivity degree), the availability of local information—the tightness of connectivity in trade-off with redundancy (efficiency), the functional segregation in the architecture of a cortical network (related to modularity; See Wig (2017) for a review), and the level of local cohesiveness (clustering; see Wasserman and Faust (1994)). Their interpretation thus includes integration and segregation of processing on top of simple connection density when taken together.

These four parameters have been valuable in understanding functional network restructuring and have been related to abnormal cognitive function that TBI patients experience (A. Fornito et al., 2015; David J. Sharp et al., 2014). To only cite a few examples, connectivity degree was correlated with motor-cognitive contralateral disruptions in TBI and not in heathy controls (Caeyenberghs et al., 2012). Raizman et al. (2020) reported a correlation between efficiency and nonverbal abstract reasoning in a group of healthy controls but not in the TBI group. On the other hand, cognitive training was found to reorganize network modularity in TBI (Han, Chapman, & Krawczyk, 2020) and training was predictive of modularity in another study (Arnemann, Chen, Novakovic-Agopian, Gratton, Nomura, & D'Esposito, 2015). In a resting state study, mild TBI was associated with increased clustering which was negatively correlated with post concussive symptoms (Zhou, 2017).

Ideally, network descriptors should add value to our general understanding of cortical changes after mTBI and consider the dynamic aspect of cortical function. The rapid

cortical responses to internal demands or external factors, however, are overlooked when network behaviour is deemed constant, as for example, when network organization is inferred from resting state data (David J. Sharp et al., 2014).

While the studies above looked at network architecture in relation with the performance of cognitive tasks, others have assessed baseline changes that are manifest in resting state—when a patient lies quietly in the scanner while their brains are scanned (Biswal, Yetkin, Haughton, & Hyde, 1995). Han, Chapman, and Krawczyk (2016) analyzed resting-state data of 40 TBI patients suffering from chronic symptoms (8 years after injury on average) using network analytic approaches and reported increased connectivity and decreased efficiency, which they took to implicate weaker integration and thus poorer information flow. Results from studies of Acquired Brain Injury (Nomura et al., 2010) and TBI patients of various severity (Pandit et al., 2013) have been understood similarly—after acquired damage to the cortical network, integration is compromised. Thus, TBI may impair cortical integration even at rest.

Resting state connectivity is clearly informative of *baseline* changes, but they do not directly predict *functional* network changes, while classic cognitive tasks pose problems for ecological validity. This is especially true in the context of mTBI. The healthy brain can be comprehended as fluctuating between intense functional states demanded by difficult tasks and resting state (Biswal et al., 1995). However, we have no certitude that injury affects these brain states equally or even proportionately. It is likely that mTBI causes the cortical system to behave as if it were constantly under load because patients experience cognitive fatigue from completing usual tasks (Kohl et al., 2009). Patients struggle with cognitive fatigue in the absence of excessive demands, so results from demanding tasks might place them in an uncharacteristic state of functional activity

(Shumskaya et al., 2012) or misrepresent their cognitive function because they could be at floor performance.

This presents us with a conundrum, whereby we cannot fully infer mTBI dysfunction from resting-state changes (because they could be well compensated during natural activity) and we cannot do this from targeted tasks (because they may represent "lab" behaviour and are often more difficult than real-world tasks). To overcome this conundrum and carry out a network analysis of mTBI changes during an ecologically valid task, we opted for a visually-complex, narrative-free movie scenes to achieve a level of engagement consistent with familiar, everyday activity.

We predict the mTBI group to exhibit higher connectivity degree than the healthy controls as this had already been demonstrated during fMRI and attributed to compensation (Iraji, Chen, Wiseman, Welch, et al., 2016; Mayer et al., 2011). Efficiency is predicted to be higher in the mTBI group if the increased degree is not random but caused by purposeful compensatory mechanisms instead (Han, Chapman, & Krawczyk, 2019). This parameter reflects the integrative capabilities of the system and describes how well information travels from one cortical area to another. In contrast, the tightness and segregation of processing is reflected by the modularity of the graph. In the mTBI group, modularity is expected to be decreased as compared to healthy controls because the boundaries between functional modules are blurred by active degeneracy and the connections are less specialized (Finger et al., 2004) . We expect clustering to be increased in the mTBI group as a marker for strengthened local cohesiveness and specialization (Imms et al., 2019). We thus expected stronger connections between modules and better long-range integration combined with short-range specialization, all while actively being engaged in a natural viewing task.

4.4 Methods

4.4.1 Participants

All participants gave their informed consent prior to taking part in the experiment. All procedures were in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and were approved by the Research Ethics Board of the McGill University Health Center.

All participants were screened for anomalous vision loss or vision disorders (glaucoma, retinal detachment, macular degeneration, etc.). They had normal or corrected to normal visual acuity (wore their usual refractive correction if lenses). The average age of the participants was 36. years old (SD = 10. years, n=17) in the mTBI group and 26 years old (SD = 6 years, n=54) in the control group.

TBI participants

Participants were recruited through the McGill University Health Center out-patient TBI clinic. The diagnostic criteria for mild TBI were: Glasgow Coma Scale score between 13 and 15, less than 30 minutes of loss of consciousness, and less than 24 hours of amnesia regarding events immediately before or after the accident. Patients with mild TBI who gave their authorization to be contacted went through a phone screening interview. The exclusion criteria were (1) family history of epilepsy or seizure, or the administration of prescription medication with increased risk of seizure, (2) severe tremors or involuntary movements, (3) general anesthesia in the past 6 months, (4) mTBI occurred less than 1 month ago or more than 2 years ago, (5) a history of multiple brain injury. Following our previous publication, participants filled a questionnaire adapted from Assessment with Mild Traumatic Brain Injury for the

Defense Centers of Excellence for Psychological Health and Traumatic Brain Injury (Spiegel et al., 2016) investigating blurred vision, migraines, behavioral change to palliate visual discomfort etc. None of our self-reported and neuropsychological measures (clock drawing test, trail making test, bells test) correlated with any of our neuroimaging results. The final sample size of tested mTBI participants was 17, (9 females).

Control participants

Healthy participants were recruited through public announcements in the Montreal General Hospital and on social media. Exclusion criteria included conditions 1-4 outlined above, and no history of any acquired brain injury. The control group was comprised of 54 individuals (28 females).

3.4.2 Stimuli and procedure

Stimuli were presented using MATLAB® (2014b, The Math Works Inc., Natick, Massachusetts) and synchronised with acquisition start time by Sterescopic Player (http://www.3dtv.at) and ActiveX connection using a 10-bit graphics card (Nvidia Quadro 2000) on a gamma-calibrated 3-D LCD BOLD screen reflected by a mirror above the participants' head. They were placed at a 170 cm viewing distance from the monitor, spanning 9.4 by 17 degrees of visual angle at a pixel resolution of 1920 by 1080. Participants were scanned while watching two five minutes movie clips twice, once in 2D, and once in 3D (using polarized glasses), cut from the movie "Under the Sea 3-D: IMAX" (Hall, 2009). Whether participants did see two of the four clips in 3D was verified after each the scanning session. Scenes included marine fauna and flora, constituting naturalistic stimuli with no human made object or other element that could have biased representation depending on culture, gender or age. Participants were

instructed to fixate on the center of the screen (white fixation cross present for the entirety of the stimuli), and a blank screen with fixation cross was presented before each clip for four seconds.

Data acquisition

Data was acquired on a 3T Siemens TIM Trio scanner (TR=2000ms, Resolution $3mm^3$, TE=30ms, flip angle=76, matrix size=64x64, Field of View=192x192mm, number of slices=37) at the Montreal Neurological Institute (McGill University Health Center). Anatomical data was acquired first (see parameters from Zhang and Farivar (2020), followed by functional imaging.

3.4.3 Data processing

Preprocessing

fMRI data was preprocessed with Analysis of Functional NeuroImages (AFNI) (Cox, 1996). To minimize spatial blurring, we applied all spatial transformations in a single step following slice-time correction. Motion and distortion corrections, and anatomical registration were concatenated to have a single estimate of spatial transformation for each volume. Temporal denoising and detrending were carried out using ANATICOR (Jo et al., 2010).

Surface-based analysis

After pre-processing, all data were projected onto cortical surface meshes for the group analysis. Cortical surfaces were first extracted for each subject using their T1-weighted image, using the Freesurfer package (http://surfer.nmr.mgh.harvard.edu/), and corrected errors after visual inspection. The Freesurfer surfaces were then converted to SUMA (Saad, Reynolds, Argall, Japee, & Cox, 2004) using a standard mesh model with 32,000 nodes (ld40; (Argall, Saad, & Beauchamp, 2006)). We selected a mesh of 32,000

nodes (per hemisphere) to maximize resolution and optimize graph computation power Statistical analysis was performed on surface-projected data because they preserve individual subjects' topology and allow for better domain-matching across subjects, which strengthens statistical power compared to voxel-based analysis (Saad & Reynolds, 2012). In this scheme, each node from one subject corresponded to the same node from other subjects, which allows for inter-subject comparisons.

Graph Comparisons

To find global and local differences in functional connectivity (FC) between groups, we computed multiple measures of network topologies on thresholded FC in mTBI participants and healthy controls.

Functional connectivity matrices were calculated as correlation matrices (Pearson) between pairs of timeseries for each of the 32,000 nodes for each subject and each movie clip. We then thresholded the 32k x 32k correlation matrix using false-discovery rate (FDR) correction controlled at q*=0.001 (Benjamini & Hochberg, 1995a). On average, 5 to 10% of correlations were maintained. Correlation matrices were thus converted into cortical network graphs.

Thresholded FC matrices induce an undirected, unweighted network structure. An undirected unweighted network (graph) is a set of vertices $V = (v_1, v_2, v_3, \dots, v_n)$ and edge connections between pairs of vertices $E = (e_1, e_2, e_3, \dots, e_k)$. In our example, the nodes in V will represent a node in the cortical mesh models and edges E represent pairs of cortical nodes whose functional correlation values survived the thresholding.

We hypothesized that TBIs have reduced segregation and increased integration, due to compensation by their unaffected pathways and circuitry. To test this hypothesis, we

computed four measures of how well information is communicated globally and locally in graphs: (1) mean degree of nodes, (2) global efficiency (3) modularity, and (4) clustering. These were calculated in R (R Core Team, 2013). For a graphic illustration of the network measures explored, see Figure 4-1.

The degree of a node v_i, $d(v_i)$, is the number of edges connected to v_i. As such, the mean degree of the whole network $D(G)$ is the mean of all nodal degrees and measures average local connectivity across the whole graph.

The global efficiency of a graph G was measured as the average of reciprocal distances—the minimum number of edges needed to walk between two nodes, denoted by $d_{i,j}$—between all pairs of distinct nodes v_i, v_j where $i \neq j$: $E_{global}(G) = \frac{1}{n(n-1)} \sum_{i \neq j} \frac{1}{d_{i,j}}$ (Latora & Marchiori, 2001). The fraction before the summation accounts for the number of pairs of vertices in the graph. Intuitively, $E_{global}(G)$ is large when many distances are small, which is when most nodes are separated by short walks in the graph, which in effect is a measure of integration in the network.

Given a parcellation of nodes into functional areas (i.e. assigning a functionally relevant (L. Wang et al., 2015) label such as "primary visual cortex", V2, V3, etc., to each node in the graph), we can ask how modular the network is with regard to that parcellation. Intuitively, modularity relates to how specialized/segregated different regions of the brain (graph) are in processing information. We can quantify this notion in the graph by $Q(G) = \frac{1}{2k} \sum_{i,j} \left[1 - \frac{\deg(v_i) * \deg(v_j)}{2k}\right] * \delta(r_i, r_j)$, where r_i is the region label of vertex v_i and $\delta(r_i, r_j)$ is 1 if its two inputs are the same and is 0 otherwise (Clauset, Newman, & Moore, 2004). In essence, modularity grows as the number of edges within a defined region grows.

Finally, the clustering coefficient can be understood as a resiliency marker for a given network. When two nodes are connected to each other, whether they are both connected to the same third node or not determines the local stability of processing. Information has more paths on which it can travel between its source and destination on the local scale when edges form triangles between three nodes. The clustering coefficient C_i of a node i is the likelihood of a_{jh}=1 when $a_{ij} = a_{ih} = 1$, defined as

$C_i = \frac{1}{k_i(k_i-1)} \Sigma_{i \neq h \in v} a_{ij} a_{ih} a_{hj}$ where k_i is the number of neighbors of i defined as

$k_i = \Sigma_{j \in v} a_{ij}$ (Barrat, Barthelemy, Pastor-Satorras, & Vespignani, 2004). The clustering of a graph is simply the average of all node-specific clustering coefficients.

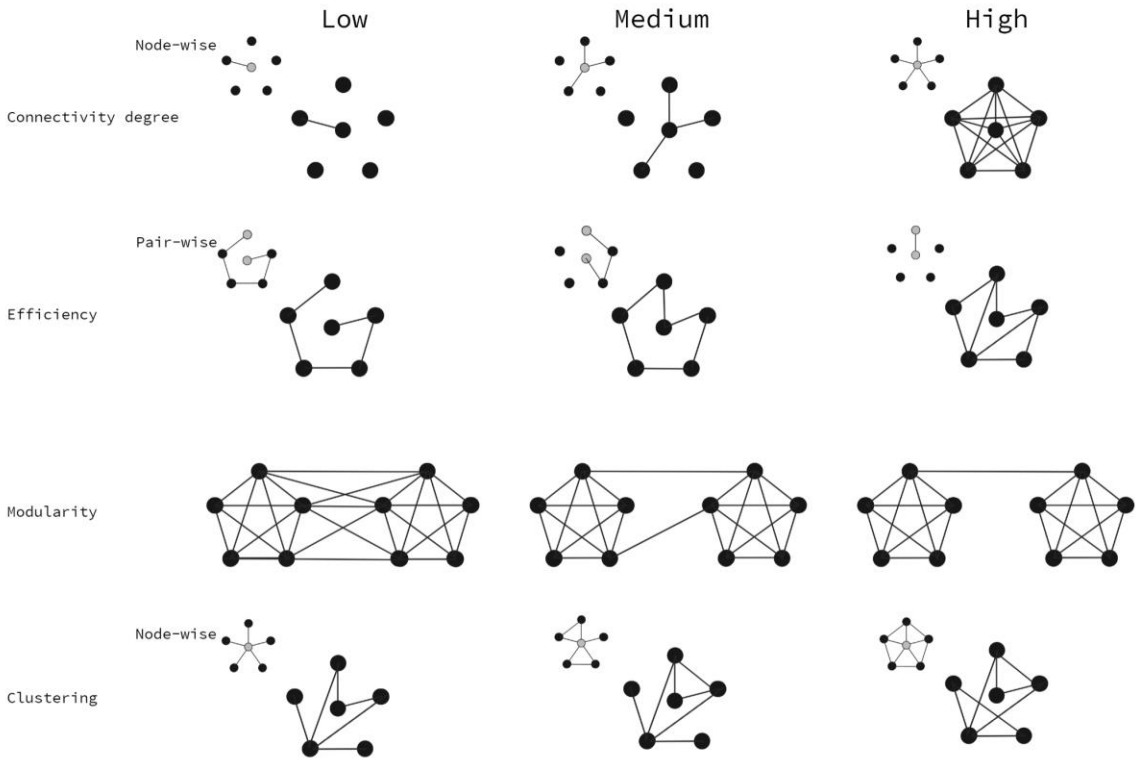

Figure 4-1 Measures of network organisation. Schematic illustration of increasing levels of connectivity degree, efficiency and modularity. Nodes represented as dots, edges as lines connecting the nodes. The number of nodes represented is arbitrary. Number and position of edges determine network organisation. Connectivity degree, efficiency and clustering are calculated throughout the network as averages so Node-wise (number of edges connected

to single grey node) and Pairwise (number of edges taken as steps between two grey nodes) illustrations are added to describe a single item in the global average. The networks made of all-black nodes illustrate the measures of network organisation when all nodes and edges are taken into account.

Whole-brain networks and regional sub-networks

We also sought to study graph structures in sub-networks in addition to whole-brain networks (as above). For sub-network analyses, we divided the cortex into early, dorsal, ventral and fronto-parietal regions as defined by a large-scale atlas (L. Wang et al., 2015). We defined a subnetwork as a subset of the vertices of the graph, $V' \subseteq V$ and the edges of the subnetwork are the edges of the full graph which connect vertices in V'. Because modularity is not meaningful within a sub-network, we only calculated mean degree, efficiency and clustering of the subnetwork graph of each functional region in the parcellation. All graph analytic estimates were carried out using the igraph (version 1.2.5) and brainGraph (version 2.7.3) packages in the R (version 3.6.3) programming language.

To estimate the effects of mTBI on the various network measures outlined above, we computed a mixed model factorial ANOVA with Group (mTBI vs. Controls) x Movie (3D vs 2D) for each measure of network organisation (mean degree, efficiency, and modularity).

For stream subgraphs and region subgraphs there was a separate model for each of the early, dorsal, ventral and fronto-parietal subnetworks and regions respectively. The significance and sign (positive or negative) of the β_{tbi} were the focus of our results, however the interaction terms including tbi effects were also examined.

For thorough introductions to graph theory for neuroscience, see Rubinov and Sporns (2010) and A. Fornito et al. (2015).

4.5 Results

We first consider the linear effects of traumatic brain injury on (1) mean degree, (2) efficiency, (3) modularity, and (4) clustering coefficient in thresholded FC graphs in sub-networks or the full visual cortex. In all models there were no meaningful interactions, suggesting that the stimulus (2D/3D) did not alter the effect of mTBI on FC architecture. However, the stimulus condition had a main effect on connectivity degree: 3D yielded higher connectivity than 2D ($\beta = 24.4$, $p < 0.05$). We related all our findings with our visual symptom questionnaire and found no correlation between with each question nor with the total score.

No change in static architecture of natural viewing network after mTBI

There was no major restructuring of the visual cortex network engaged in natural movie viewing between groups—the regions of interest engaged in the control group were the same in the mTBI group and they were connected in a similar network. The dynamic aspect of these connections however—the degree, efficiency, modularity, and clustering ruling their interaction—was altered.

Global network changes in the visual cortex in the mTBI group:

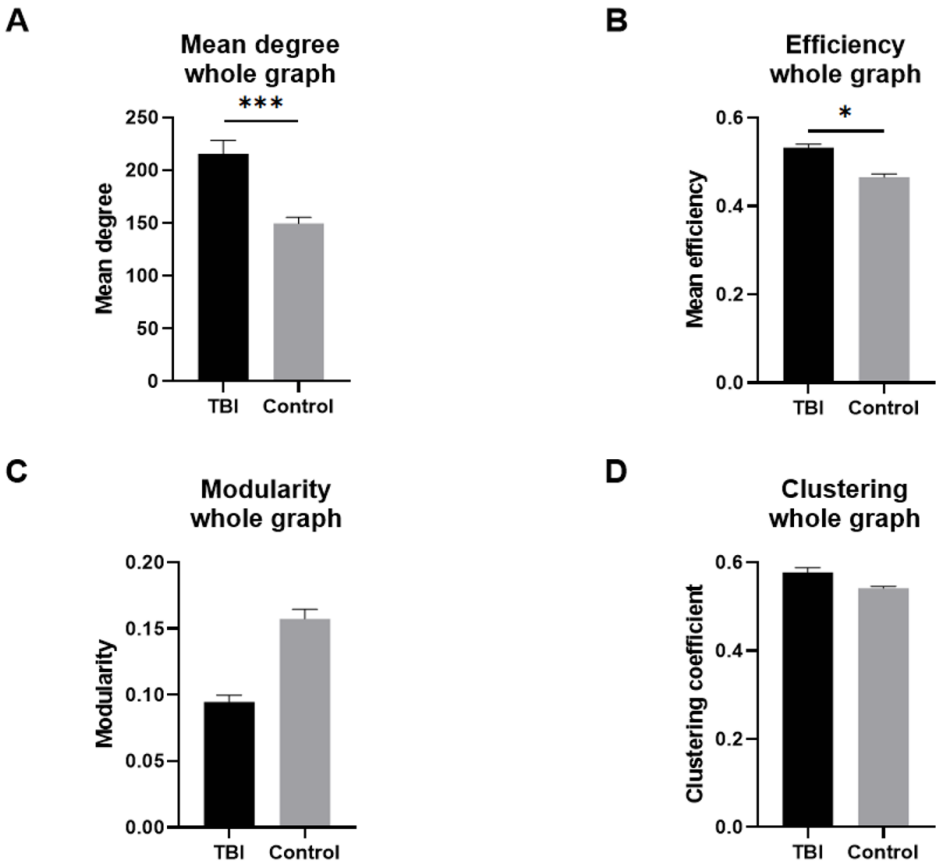

Figure 4-2 Global network measures of the visual cortex during naturalistic viewing in mTBI participants and healthy controls. All measures reached statistically significant differences between the two groups.

In the full-graph models (all nodes from the visual cortex), mTBI had significant effects on all metrics: mean degree ($\beta = 88.4, p = 1.30E-06$), efficiency ($\beta = 0.08,\ p = 4.28E-05$), clustering ($\beta = 0.04,\ p = 0.001$), and modularity ($\beta = -0.07,\ p = 0.0002$).

The increased mean degree and efficiency support the hypothesis of overcompensation in mTBI, however in different ways. An increase in mean degree reflects a global increase in connectivity, which agrees with known results of increased functional connectivity in mTBI subjects, whereas an increase in graph efficiency points to greater

structured reorganization of key connections in the visual cortex (Alex Fornito, Zalesky, & Bullmore, 2016).

Network changes in subnetworks of the visual cortex in the mTBI group

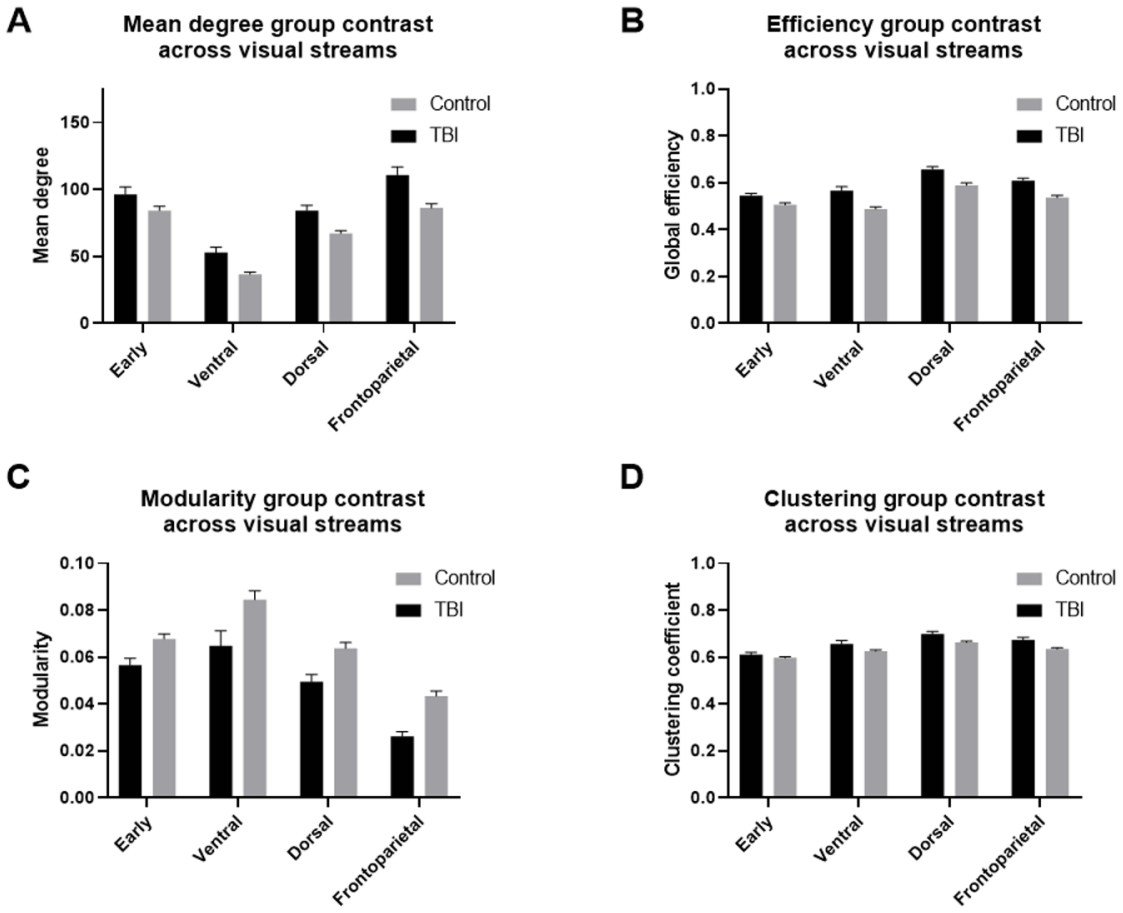

Figure 4-3 Measures of subnetwork organization during naturalistic viewing in mTBI and healthy control participants.

In the sub-networks, efficiency was significantly impacted by mTBI in the ventral subnetwork ($\beta = 0.1,\ p_{adjusted} = 0.004$), in the dorsal subnetwork ($\beta = 0.08,\ p_{adjusted} = 0.01$), and in the fronto-parietal subnetwork ($\beta = 0.09,\ p_{adjusted} = 0.005$). Mean degree was also altered in the mTBI group in the ventral subnetwork ($\beta = 21,\ p_{adjusted} = 0.0005$), in the dorsal subnetwork ($\beta = 23,\ p_{adjusted} = 0.004$), and in the

fronto-parietal subnetwork ($\beta = 38,\ p_{adjusted} = 0.002$). The combined increase in mean degree and efficiency in the ventral, dorsal and fronto-parietal but not in the early visual areas provides evidence that these particular sub-networks drive the global structured alteration following mTBI reported above. If mean degree was increased alone, and efficiency was not different, the increase in connectivity would have been diffuse and unstructured. Interestingly, efficiency was increased evenly across subnetworks, but mean degree showed a two-fold stronger increase in the fronto-parietal subnetwork.

Clustering was increased in the dorsal subnetwork ($\beta = 0.05,\ p_{adjusted} = 0.02$), and in the fronto-parietal subnetwork ($\beta = 0.06,\ p_{adjusted} = 0.004$).

Modularity was decreased only in the fronto-parietal stream ($\beta = -0.02,\ p_{adjusted} = 0.004$). We expected that any effect of TBI on modularity would be a negative one, reflecting decreased segregation of processing, and that was confirmed in our analysis.

Increased efficiency in specific regions of interest in the mTBI group

The within-region analysis only looked for effects on efficiency in subgraphs, and the regions which showed strong effect of TBI were VO2 ($\beta = 0.12,\ p_{adjusted} = 0.004$), PHC ($\beta = 0.09,\ p_{adjusted} = 0.008$), V3a ($\beta = 0.08,\ p_{adjusted} = 0.03$), IPS0 ($\beta = 0.09,\ p_{adjusted} = 0.02$), IPS1-2 ($\beta = 0.08,\ p_{adjusted} = 0.05$). All other visual areas did not show any difference in efficiency between the two groups.

4.6 Discussion

For the first time, we have shown that natural movie viewing is a powerful paradigm for revealing network changes in mTBI with ecologically-valid levels of demand on the patient, and with this paradigm we have provided evidence for the idea that injury alters

the cortical networks. Overall, our results point towards two strategies of connectivity change in mTBI patients powered by an increase in connectivity. The increase in integration (efficiency and mean degree) is counterbalanced by a decrease in segregation (modularity) at the macro scale, but at the micro scale, specialization is increased (clustering).

Higher mean connectivity degree

First, we found a significant global increase in connectivity throughout the visual cortex (whole graph) in the mTBI group. This finding was repeated specifically in regions of the visual cortex dedicated to complex processing of information—cortical regions beyond V4 in the visual system hierarchy, pertaining to both the ventral and the dorsal streams as well as the fronto-parietal region. Mean connectivity degree when calculated from binary graphs can be understood as equivalent to the significance of the functional connectivity analysis. Our results thus corroborate previous evidence of increased functional connectivity after mTBI (Iraji, Chen, Wiseman, Welch, et al., 2016; Muller & Virji-Babul, 2018). An increase in functional connectivity, or in mean connectivity degree, does not inform us about the changes to the *structure* of cortical networks after injury. For this reason, we compared other measures of network organisation between healthy controls and mTBI participants as an investigation of network reorganisation following mTBI.

Higher global efficiency

Second, we found a significant increase in global efficiency throughout the visual cortex, and within regions dedicated to complex processing of visual information (beyond V4) as well. The global graph of the visual cortex and within the ventral, dorsal and fronto-parietal subgraphs, nodes were generally less functionally distant to other nodes in the

mTBI group than they were in healthy controls—there were less edge-bridges to take between two nodes. Another way to appreciate increased efficiency is to understand it as greater integration in the mTBI group. This finding needs to be interpreted in parallel with the first one because they complement one another—the increase in connectivity degree could have been diffuse, if not for the increase in efficiency and clustering without an increase in interregional connections—and this is discussed further below. Interestingly, both parameters were increased both in the whole visual system network but also in the same specific subnetworks. Together, these two findings show a purposeful increase in connectivity towards better global integration which suggests compensatory mechanisms are involved in network reorganization following mTBI.

Lower modularity

Our third finding was that of a decreased modularity after mTBI in the whole visual cortical network as well as within the fronto-parietal subnetwork. This subnetwork is particularly important for the integration of complex visual features [more than 1 ref] (Corbetta et al., 1995) that occur in scenes in motion. A decrease in modularity in this subnetwork suggests higher co-recruitment of modules to process feature integration in the mTBI group. Decreased modularity combined with an increase in efficiency reflects an increase in functional segregation. These two parameters' changes overlapped in the complete visual cortex network and in the fronto-parietal subnetwork, suggesting that segregation is affected by mTBI specifically at high level of processing. We should note that based solely on the connectivity results, we would have expected an increase in modularity. The fact that modularity was decreased in the mTBI group is a strong indicator that the network changes were not diffuse, and the change had a functional purpose.

Higher clustering

We found increased clustering in the mTBI group in the whole visual network and within the dorsal and fronto-parietal subnetworks. Thus, these two subnetworks drove the global results and there are specific areas where there were more interconnected triplets of nodes in the mTBI group than in healthy controls. Our results are in line with previous publications using graph analysis of neuroimaging data from mTBI patients (Tsirka et al., 2011; Yuan, Wade, & Babcock, 2015; Yuan et al., 2017) and moderate to severe TBI patients (Verhelst, Vander Linden, De Pauw, Vingerhoets, & Caeyenberghs, 2018). A high clustering coefficient reflects a network with many cliques of nodes. The strategic accumulation of clusters increases segregation for local specialization (Imms et al., 2019). Functional specialization at the local scale was increased. Higher clustering might be in line with an adaptative or compensatory reorganization of the visual network following mTBI, however it can be a costly one—it supposes an increase in the number of steps needed to go from one node to another (Alex Fornito et al., 2016). This is corroborated by findings of increased path length following mTBI (Imms et al., 2019) but it is not in contradiction with the increase in efficiency that reflects a decrease in steps needed to join two nodes at a global scale. Two distant nodes tended to be functionally closer in the mTBI group than in healthy controls but two closely-linked nodes tended to be functionally further away in the mTBI group.

Taken together, these findings reflect a functionally relevant reorganization in the topology of long-range connections, which facilitates inter-regional communication for complex processing of visual information. It suggests as well that regions functionally defined via probabilistic methods in healthy controls might be working together following mTBI to solve processing problems usually handled by single modules in healthy controls. Finally, the increase in local specialization contrasts with the decrease

in global specialization, and these effects were overlapping locally only in the fronto-parietal subnetwork.

Graph theory and mTBI

Previous studies using resting-state fMRI had reported increases (Iraji, Chen, Wiseman, Welch, et al., 2016; Kaushal et al., 2019) but also decreases (Mayer et al., 2011; Stevens et al., 2012) in functional connectivity following mTBI at rest and these changes were both paradoxically correlated with behavioral performance and mTBI symptomatology (Rigon, Voss, Turkstra, Mutlu, & Duff, 2017; Zhou, 2017). The present paper shows that connectivity degree is increased in the cortical networks engaged by natural movie viewing as well, although we could not relate our findings to visual complaints. We speculate that the decrease in activity in the early visual cortex (Ruiz et al, under submission) and the compensatory increase in mean connectivity degree throughout visual areas are maintained across very different brain states provoked by very different processing demands because the injured brain is constantly overloaded.

We are aware that our results regarding global efficiency are not in line with some of the previous literature on mTBI (Caeyenberghs et al., 2014; Zhou, 2017). However, we believe that our choice of task and stimuli (instead of using resting state) drove this difference—the increase in connectivity measured during resting-state fMRI could be unstructured and reflecting of diffuse damage to the global cortical network whereas natural viewing could recruit one or a few specific networks with tight processing within their nodes. In this scenario, natural stimuli could represent an active task that elicits efficient visual processing while resting state reflects spontaneous functional networks, meaning participants are not engaged in a common task that would grasp any particular network.

The idea that the brain is stuck in a cognitive state or experiences difficulties switching between a state and another has been previously discussed but has yet to be related to network measures. For example, concussed adolescents were found to be "stuck" in one of the three cognitive states investigated in a pilot study by Muller and Virji-Babul (2018) with the "stuck" state being one that specifically recruited attentional networks. In the perspective of network control theory, the architecture of a network constrains which transitions are easy to execute and which states are easy to maintain (J. Z. Kim et al., 2018). Mathematically, greater modularity makes it is easier to transition between states and to keep a given state (J. Z. Kim et al., 2018). Much like a pure conceptual network in physics, the human brain can be conceived as a complex system which can be manipulated into a cognitive state by changing excitatory and inhibitory input it receives as "cognitive control" (Gu et al., 2015). This could mean that the less modular a cortical network becomes following an mTBI, the more difficulties experienced by the patient in terms of state switching and maintain a state (i.e., for sustained attention). Although we did not find a relationship between visual complaints and modularity, others have shown that cognitive training was limited by decreased modularity (Arnemann, Chen, Novakovic-Agopian, Gratton, Nomura, & Esposito, 2015).

Recent studies investigating the balance in connectivity within and between networks following mTBI have not reached a consensus, possibly because functional segregation and integration might be task and network dependant. Using resting-state fMRI for a connectome-wide investigation of the cortical network following TBI, connectivity was reportedly increased within networks and decreased between networks (Iraji, Chen, Wiseman, Zhang, et al., 2016). This imbalance would support the idea that injury increases segregation.

In contrast, graph analysis of cortical networks estimated from fMRI during an N-back memory task revealed decreased segregation between task-positive networks and the Default Mode Network (DMN), and increased connectivity within the DMN but not task-positive networks specifically during the more cognitively demanding condition in the mTBI group (Sours, Kinnison, Padmala, Gullapalli, & Pessoa, 2018). It is possible that our results denote a cognitive state between these two levels of demands. At low levels of cognitive load, another study using an easier N-back task reported no change in segregation between task-relevant networks but found increased connectivity within networks as we did, but in our case using naturalistic viewing (Bernier et al., 2017).

Limitations

The present paper relies on a novel application of complex network theory to analyze stimulus-driven functional connectivity and has revealed three important new findings—when watching a naturalistic movie, the visual cortex is (1) more connected, (2) more efficient, and (3) less modular after mTBI. To draw robust conclusions about whether connectivity changes following mTBI are structured or unstructured, we would like to compare our results of increased efficiency and clustering with a rewired null model—where edges are shuffled to see whether architectural descriptors were mainly driven by the increase in connectivity degree or whether the changes were structured. Although our results are based on high-resolution graphs (32,000 nodes per hemisphere), nodes cannot be understood as neurons and edges cannot be understood as axons. Ideally, we consider the neuron to be the smallest processing unit, but it is not currently possible to evaluate them individually in humans, especially not in the context of network science. For this reason, it is noteworthy that the activity of the nodes on which functional connectivity was based and thus the graphs were constructed, is an average of all BOLD activity in these nodes. On another level, the graphs analyzed here

were binary—non-weighted—and so we have not looked at inhibitory or excitatory interactions although these might be relevant to understand mTBI (Carron et al., 2016; Hunt et al., 2011; Krivitzky et al., 2011; Spiegel et al., 2015).

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Chapter 5 Discussion and Future Directions

5.1 Summary of novel contributions

In this thesis, I have shown that mTBI induces long lasting changes in cortical processing of simple visual stimuli by using non-invasive methods and modelling.

The elementary building blocks of visual perception are processed similarly in the mTBI population except for the fact that irrelevant activity clouds their integration more than it does in healthy controls. Internal noise is increased although efficiency of contour integration is maintained, which supposes a compensation to achieve normal levels of visual performance. Interestingly, although patients report visual complaints frequently and for long periods of time following injury, it is not common or easy for clinicians to find behavioral evidence of visual dysfunctions. My first novel finding shows that simple behavioral measures can be enough to reveal critical deficits in visual processing when coupled with mechanistic models. Until now, only performance, sensitivity and capacity measures had been used, which were limited in their interpretation as they only reflected the visual system's integrative power and not its internal noise limitations.

Although isolating visual functions is a powerful mechanistic approach, it is difficult to relate results from highly specific tasks to common visual complaints of mTBI patients. My second novel contribution was to show that naturalistic movie viewing is a low-demanding task that is engaging enough to show major cortical abnormalities following mTBI. My results show that mTBI affects the synchrony between participants—timeseries of the mTBI group do not fit my normative models of cortical activity—and the synchrony of cortical activity within participants. I found that cortical activity was decreased in early visual areas and possibly increased in fronto-parietal regions as

compensation. I also found that functional connectivity between visual regions of interest was affected by mTBI, and that the fronto-parietal regions were particularly more connected to early, ventral and dorsal regions. The specific regions that showed enhanced connectivity are related to common deficits found in mTBI participants but could not be correlated with our measures of visual complaints.

Lastly, I applied a graph theoretical approach to investigate the architecture of the functional network activated by naturalistic stimuli. Movie viewing has been shown to elicit common temporal patterns among healthy controls, but I have shown that they are enough to reveal network changes in mTBI participants for the first time. The particular changes that I found were in alignment with some but not all previous literature as certain parameters show inconsistent changes depending on which network is investigated and the energy demands of the task used by the authors. I have found evidence for increased local specialization but decreased global segregation. I also found increased integration at the global scale. mTBI network investigations have mostly focused on resting-state data and the few active-task studies have used conventional block designs that could force results to be biased because of particularly demanding tasks.

5.2 Noisy cortical integration: implications and considerations

Systemic implications of noisy visual integration

Although the significant role of the visual cortex in contour representation is indisputable, other areas could potentially be crucial. We assume that the sources of noise in contour integration would be within the visual cortices, most probably V4 because contrast noise does not affect performance at the task, but what if the source of

noise was from somewhere not yet considered? Or alternatively, what if the noise in V4 or V1 circuits is modulated by a more distal brain region?

Attention may modulate orientation responses as early as the lateral geniculate nucleus (Ling, Pratte, & Tong, 2015). Top-down expectations have a facilitative effect on visual interpretation (Bar, 2004), and the dynamics of bottom-up interactions in predictive coding (Friston, 2005) stipulates that high-level predictions act on errors specifically (Rao & Ballard, 1999). The neural correlates of this effect have been measured in V1, showing increased performance and informational improvement of the representation in area V1, while decreasing BOLD-related signal (Kok, Jehee, & de Lange, 2012). Attention is not a unidirectional modulator of visual cortical responses—in a discrimination task, attention modulated V4 neurons differentially, by either increasing or decreasing spike count correlations between pairs of neurons depending on the coherence between the neuron and the perceptual decision (Ruff & Cohen, 2014).

The neural mechanisms underlying spatial attention arise from the prefrontal cortex, likely through the dopamine-mediated modulation of long-range connections between the FEF and the visual cortex (Noudoost & Moore, 2011). The disruption of cortical signal through Transcranial Magnetic Stimulation (TMS) noise induction in V5/MT is compensated by drug enhancement of dopamine activation, meaning that frontal dopamine improves SNR by reducing noise in the visual cortex (Yousif et al., 2016). Dopamine has also been shown to enhance SNR by reducing noise within prefrontal areas, both in the normal (Yousif et al., 2016) and in the diseased brain (Georg Winterer & Weinberger, 2004). The long-range control of cortical visual noise is further supported by the evidence of decreased BOLD-related activity and increased

metabolic demands (cerebral blood flow) following dopamine agonist injections (Zaldivar, Rauch, Whittingstall, Logothetis, & Goense, 2014).

Implications of the Linear Amplifier Model

Another approach to the equivalent noise method is that of the Perceptual template Model (PTM). It considers multiplicative internal noise in addition to the classic LAM additive internal noise. Multiplicative noise is not invariant to the signal's properties—it is proportional to the signal strength instead (Z. L. Lu & Dosher, 1998, 1999). This model allows for three independent predictions of discriminability modulation mechanisms—signal enhancement (additive internal noise reduction), distractor exclusion (narrowing of template filter), or internal noise reduction (multiplicative noise reduction). Lu & Dosher's findings suggest attentional mechanisms reflects reduction in internal additive noise (see Figure 5-1). Increase in additive internal noise, in contrast, may underlie saccadic suppression. Saccadic suppression refers to the loss of detectability of a stimulus presented during an eye movement or right before. In an equivalent noise study of saccadic suppression using the PTM, additive noise increase was shown as the underlying mechanism here as well (Watson & Krekelberg, 2011).

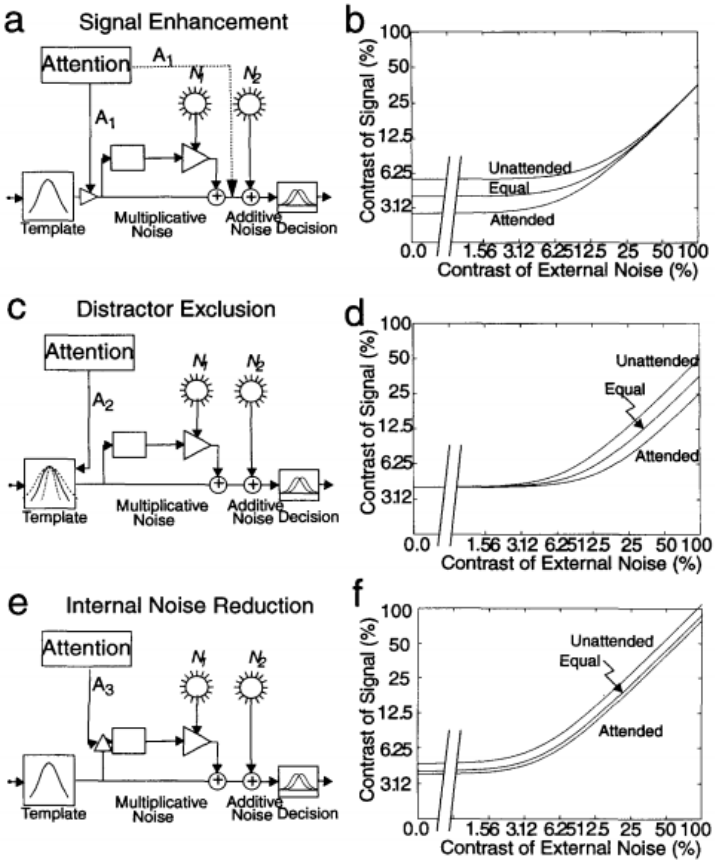

Figure 5-1: a, c, e: diagrams showing the potential targets of attention in the PTM, illustrated respectively in b, d, f: thresholds against external noise functions, modelled by the PTM, revealing changes b: at low levels- d: at high levels- f: across levels- of external noise (adapted from Z. L. Lu & Dosher, 1998)

Refining their findings obtained with the LAM model, Cavanaugh et. al. used the PTM to demonstrate that lesion-related cortical blindness recovery and residual perceptual deficits in intact cortical regions were limited by internal noise, more specifically, additive internal noise (Cavanaugh et al., 2015).

Noise in other clinical conditions with impaired cortical integration

The characterization of clinical populations such as schizophrenia and autism have contributed to shaping the concept of noise. In schizophrenia, event-related EEG recorded during an oddball task showed a different noise pattern in patients compared to normals, both spatially throughout brain regions, and spectrally throughout frequency bands. Patients exhibited increased broadband background noise, marked frontally, and so did their siblings in a lesser degree (G. Winterer et al., 2004). More generally, a recent review about abnormal oscillations and synchrony in schizophrenia (Uhlhaas & Singer, 2010) highlighted multiple studies, relying on a broad range of

methods such as EEG (Kwon et al., 1999; Light et al., 2006) and DTI (Rotarska-Jagiela et al., 2008), showing impairments in the integrity of signalling but also in the overall relative distribution of activity. Thus, the relative abnormality and localization of fluctuations seem to become more informative than the absolute amount of noise.

Increased intra-individual variability, "wobble", or "lability" has been reported both in behavioral responses (MacDonald, Nyberg, & Bäckman, 2006) and in neuroimaging (Rubenstein & Merzenich, 2003) in the autism spectrum disorder (ASD). Even in high-functioning adults on the autism spectrum, and despite exhibiting normal behavioral responses to a one-back task to sensory stimuli, BOLD-related activity variability within subjects was still higher than controls (Haigh et al., 2015). In children with ASD, evoked EEG variability was found to be greater than neuro-typical controls suggesting an impaired synchronization of activity and increased neural noise in ASD (Milne, 2011). Modelling of internal noise on psychophysical data as an estimation of neural noise using the equivalent noise method revealed higher internal noise in ASD that correlated with autistic traits (Vilidaite et al., 2017) allowing for a very relevant conceptualization of noise. Recent advancements in modelling and methodology have allowed us to operationalize neural noise as a biomarker for cognitive disorders, but we still lack in depth understanding of the mechanisms underlying noise control.

5.3 Functional changes after mTBI: mechanisms of recovery

Three main opposing views regarding the changes in the neural organization following mTBI have been proposed to explain the findings from functional imaging of the injured brain (the definitions here are a synthesis of multiple reviews including A. Fornito et al. (2015) and Medaglia et al. (2012)):

(1) Reorganization: instantiation of novel neural networks via permanent rewiring, supposing a change in the neural substrate without which cognitive performance would decline;
(2) Compensation: activation and recruitment of specific brain regions while cognitive performance is maintained, with no relevance given to the permanence or transience of the mechanism, nor to its structural correlate (ie. Diffuse axonal injury);
(3) Latent processes: the challenged system focuses metabolism onto attentional resources and cognitive control to meet task demands, causing distributed changes of altered functional engagement akin to DAI;

Importantly, the latent hypothesis implies that brain activity that was heightened by trauma is reduced by training and successful recovery (restored performance), virtually bringing behavior "back to normal" in parallel with its neural substrate. Even the activation of brain areas in both the clinical and non-clinical cohorts without significantly showing hyperactivity in the clinical group can be interpreted as latent processes when their activation is behaviorally relevant at lower levels of task difficulty.

For compensatory recruitment to occur, a system necessarily needs to show functional overlap between two regions of the network, but two subsystems can be sufficient on their own to carry out a task. That capability is referred to as degeneracy and a system that has that characteristic doesn't necessarily compensate with higher levels of activity in one area if the functionally overlapping area is compromised as long as it is sufficient to carry out a task alone (A. Fornito et al., 2015). Furthermore, compensation can occur even if degeneracy is partial or incomplete, particularly when there is evidence of hyperactivity.

Evidence supporting the reorganization theory:

Patients suffering from post concussive syndrome showed hyperactivity and additional recruitment of brain regions of the attentional and working memory networks while performing an n-back and a counting stroop task (Smits et al., 2009). Because they did not find a relationship between time since injury and this reorganization, it can be interpreted as a permanent rewiring change.

In what could be seen as an attempt to distance themselves from the latent theory, Rasmussen et al. (2008) investigated motor and visual dysfunctions in the TBI population within a varying processing load paradigm. Participants performed a single task at a time, and then both at the same time. They found that although the cortical activity was reduced in the single task condition, it was increased in the dual task condition, and that the latter also induced additional recruitment. The increase in activity in the regions recruited by the single tasks (a motor task and a visual search task) was accompanied by an increase in a region that was not recruited by the single task for that group: the bilateral medial superior frontal gyrus and left cingulate sulcus. These are extended visual search networks (Kübler, Dixon, & Garavan, 2006) that were not used by the controls suggesting a shift from the efficient automatic parallel strategy of visual search to a more effortful serial method, which is utilized in healthy controls during more difficult visual tasks (Treisman, 1991). That last detail could reverse the support of these findings and instead put them in the perspective of the latent theory.

Contralesional excitability was increased in the forelimb motor cortex of the rat after controlled cortical impact injury, accompanied with reduced sensory evoked potential latency but not by BOLD until much later than the 3-day post injury mark (Verley et al., 2018). Contralesional cortices seemed to undergo an early stage of

hyperexcitability, followed by a return to normal and then again, a late stage of hyperexcitability. The authors speculate that the excitability of the remote cortex inhibits ipsilesional activation to restore balance between excitation and inhibition.

Evidence supporting the compensation theory:

While some cortical regions showed a reduction in activity (the left inferior parietal gyrus), others significantly increased (that of the right inferior frontal gyrus) in TBI patients compared to controls while the participants were performing a working memory task (Maki Kasahara et al., 2011), combined with a compromised functional connectivity between the two, their data suggests a compensatory recruitment of an otherwise functionally overlapping area.

In the TBI group (although formed of only five patients), performance at a Stroop task and patterns of brain activity were similar to those of controls but activation of the was diminished in the anterior cingulate cortex (ACC) as compared to the control group (Soeda et al., 2005), akin to patients dealing with attention deficit/hyperactivity disorder whose performance was lower than controls (Bush et al., 1999), reflecting failure of network recruitment (Edward Bullmore et al., 1999).

Lower performance was correlated with lower brain activation measured with functional near-infrared spectroscopy in patients following mTBI during neuropsychological testing focused on word memory, spatial design memory, digit-symbol substitution (symbol matching), and working memory (Kontos et al., 2014).

A pediatric cohort of TBI patients was selected in a study evaluating motor dysfunction by tasking them to perform cyclical movements of their hand and foot in an iso and non-iso direction in the scanner (Caeyenberghs et al., 2009). The performance in the two groups were similar which allowed the team to interpret brain activation

differences as compensatory mechanisms: the medial and anterior parietal areas as well as the posterior cerebellum showed hyperactivity compared to controls meaning that the recruitment of neural resources for attentional and somatosensory processes was increased.

Interestingly, when looking at the effects of visuospatial training on functional connectivity during a visual attention task (Y.-H. Kim et al., 2008), the pattern of results can be partially interpreted as subserving both the compensatory theory and the latent theory. Behavioral performance was worse in the TBI group at first (both in terms of visual attention and in terms of reaction time) and improved after training. These cognitive improvements were accompanied by changes in the attentional network activation. In support of the compensatory theory, Y.-H. Kim et al. (2008) found that the activity of the ACC and the precuneus nucleus increased after training.

With no influence on performance at a task of executive control (working memory and inhibitory control), an mTBI group of children showed increased activity in the posterior cerebellum with the addition of a demand for inhibitory control which was correlated with self-reported post-concussive symptoms (Krivitzky et al., 2011).

TBIs presented a positive correlation between performance at an n-back task and letter-number sequencing subtest and activation of the prefrontal cortex but a positive one with the right parietal and left parahippocampus for the low and high working memory loads respectively (Sánchez-Carrión et al., 2008). Patients showed less activation than controls in the fronto-parietal regions which was positively associated with performance, so this article supports the compensation hypothesis.

With comparable task performance at a working memory, a TBI group with no focal lesion but with evidence of diffuse axonal injury with chronic symptoms showed

enhanced recruitment of the prefrontal cortex (middle frontal gyrus and right ventrolateral inferior frontal gyrus) and posterior cortices (posterior parietal and left temporo-occipital junction) (G. R. Turner & Levine, 2008). These disturbances were not attributable to load factor (task difficulty) nor to processing speed (response time), instead, the authors speculate that efficiency of processing was limited by diffuse injury.

Evidence supporting the latent theory:

However, in the same study (Y.-H. Kim et al., 2008) found a decrease in frontal activity after training. This suggests a negative relationship between that region's activity and behavioral performance, and thus supporting the latent theory instead.

In this perspective, an increase in brain activity is a sign of "computational over-heating", marked neural effort and disproportionate usage of resources. Cognitive fatigue can be experienced by patients sentiently and is part of the common self-reported complaints. While healthy controls showed decreased activity in the middle frontal gyrus, superior parietal cortex, basal ganglia and anterior cingulate, TBI participants showed an increase instead, during a symbol digit modality task (Kohl et al., 2009), in support of the latent theory.

In an investigation of the functional changes endured after a TBI and their effect on working memory, G. Turner, McIntosh, and Levine (2011) found that cortical areas pertaining to the prefrontal cortex were activated in both the TBI and the heathy control groups but were functionally relevant at an earlier stage of difficulty for the TBI group, showing altered functional engagement.

At a classic working memory task—the n-back—practice reduced activation of the PFC and the ACC as novelty and difficulty decreased (Medaglia et al., 2012). Although the area seemed to be dedicated to a similar function of support in the TBI group as it

did in healthy controls under higher task load, it was evident at lower threshold of difficulty.

A bimanual coordination task showed overactivation of the fronto-parietal areas during movement execution which Chen et al. (2008) interpreted as an increase in sensory integration, but underactivation during preparation in the TBI group compared to controls (Gooijers et al., 2016). There was more overlap between the two functional patterns (execution- and preparation-related) in the TBI group, suggesting a decrease in neural differentiation. Because the performance in the TBI group was poorer as well, reflecting a negative link between activity and performance, providing evidence for the latent hypothesis.

Another investigation of cognitive control revealed increased activation within the left precentral gyrus and bilateral cingulate, the medial frontal, middle frontal and superior frontal gyri, in the TBI group which was specific to a condition of stimulus-response spatial incompatibility), while performance was similar between groups (Scheibel et al., 2007).

Working memory load has been shown to be correlated with increased activation of memory networks (E. E. Smith, Jonides, Marshuetz, & Koeppe, 1998) but in an auditory n-back task, T.W. McAllister et al. (1999) found an increase between the 0-back and the 1-back but not the 2-back in the control group while the TBI group continued to show an increase in activation as the task difficulty went on. This increase was not concomitant with a performance drop however, so the authors attributed it to compensation and not task difficulty because the latter would have caused a large increase between the 1-back and 2-back conditions (much harder) and a diminished performance as well. Importantly, I classified their findings within the latent processing

framework because I believe that their results resonate with the theory in the fact that the areas of increased activation were not recruited in addition to the normal pattern of activation, and because that hyperactivity was tightly related to processing load. The TBI group did show some activation during the low processing load level of difficulty but that significantly increased in the high load condition compared to controls who barely showed an increase there. The authors speculate that the subjective feeling of memory problems in the TBI group could be due to the fact they are aware of having to work harder than normal to attain a basic level of capability, even thought performance was not different. They propose to go deeper in that direction and to present TBI patients with tasks of even higher levels of processing load.

> *"the differences seen between control subjects and this group of very mild TBI patients appear to have more to do with the timing, allocation, and modulation of processing resources than an actual decrement in available resources"*
>
> *(T.W. McAllister et al., 1999)*

In the same vein, the default mode network (DMN) showed a greater deactivation in the TBI group during a choice-reaction task (David J. Sharp et al., 2011) meaning inhibition was increased when the system was faced with a more consequent cognitive load.

For example, working memory was diminished by TBI but impairments at a theory of mind task were no longer apparent when working memory load was controlled (Honan, McDonald, Gowland, Fisher, & Randall, 2015).

In an overview of the opposing views discussed in this section, namely the latent, reorganization and cognitive control theories, Hillary (2008) argues that hyperactivation of the prefrontal cortex during working memory is not due to compensation nor reorganization. Cortical regions that anatomically belong to areas of "support" in healthy controls and that hyperactivate in clinical populations in a load-dependant fashion are not evidence enough to claim network reorganization (Hillary, 2008).

In this thesis, we have not designed our experiments to disentangle whether cortical changes following mTBI were attributable to one of these explanations. We speculate that our Chapter 3 results can be due to compensation, possibly from latent processes given that the regions involved in the cortical response are similar in both groups. However, we can't interpret these results in terms of clear compensatory mechanisms.

5.4 From compensatory connectivity for cortical deficits to network changes following mTBI

In the third chapter we have shown that cortical activity of early visual areas is impaired even during natural vision, and that functional connectivity between most visual regions is increased. These two results can be understood as increased asynchrony between participants and increased synchrony within participants following mTBI. Asynchrony from normative cortical activity is a sign of pathology. The fact that participants who had sustained an mTBI were found to be less synchronous in their processing of naturalistic movies as a group is revealing of a deviation from the norm. The synchrony of processing found using naturalistic movies in healthy controls is interpreted as a common substrate, meaning that holistic stimuli elicit similar temporal patterns across individuals. By understanding what is common between individuals, we

can get closer to understanding brain function—and dysfunction. People who have suffered from a mild TBI are still able to see the world, perceive it and interact with it. In other words, their cortical performance is sufficient to respond to daily demands, but the way their visual system handles these demands is shifted. Understanding such shifts brings us closer to designing training paradigms and treatments in hopes of normalizing processing and healing dysfunctional patterns that might contribute to cognitive fatigue.

Beyond diffuse white matter damage and the initial theories of disconnection to explain cognitive deficits in TBI, recent technical and technological advances have made it possible to incorporate hyperconnectivity and hyperactivity in our understanding of brain damage and brain disorders (Marco Catani & ffytche, 2005). Investigating network dynamics will help determine whether different regions are involved in dysfunctional processing, or whether the same regions are organised differently following mTBI.

In a study linking structural network descriptors to performance at neuropsychological tests, van der Horn et al. (2017) found that clustering was inversely correlated with processing speed, and that symptomatic mTBI participants tended to have higher processing speed than non-symptomatic participants. However, the authors did not find that clustering was increased nor decreased as compared to healthy controls. If we look at our results from chapter 4, lower clustering could be a “more normal” local connectivity organization, and thus, local connectivity change (towards an increase in clustering) would be correlated positively with cognitive performance in the case of Horn et al’s study. This would support the idea of a compensatory mechanism where performance would decrease in the absence of cortical network change.

This thesis explored the cortical processing of vastly different visual stimuli: refined elementary visual integration and complete natural vision. Conclusions from these experiments can be taken as descriptions of the cortical deficits following mTBI from two ends of the complexity spectrum. Simplistic stimuli such as contours evoke abnormal cortical dynamics in mTBI participants, marked with increased internal noise as modelled by the equivalent noise method. In this paradigm, internal noise during contour integration reflects neural noise at the level of early cortical columns that laterally interact to integrate Gabor elements. Complex and natural movies on the other hand, evoke abnormal cortical dynamics marked with asynchrony between individuals—which can be understood as group variability and thus another concept of noise. We also found synchrony within individuals—which we speculate could be an increase in redundancy, yet another conceptualization of noise. Early visual areas tended to be less signal-driven which in a sense is another evidence of abnormal cortical noise levels. Network changes in response to natural stimuli have revealed a surprising reorganization whereby the connectivity increase was accompanied with efficiency and clustering increases. This reflects back to within-subject redundancy. Internal noise as a very concrete mechanistic element is distinct from redundancy of cortical signalling as the former does not contribute to meaningful processing. However, the latter could support signal transmission as a confirmation, validation, or repetition, aimed at strengthening the fragilized cortical system and prevent signal loss by having multiple back-up messages. In this view of mTBI, local errors—noise—are compensated for by increased integrative power and redundancy at a larger scale—integration. This contributes to disproportionate resource consumption and possibly cognitive fatigue.

5.5 Clinical and social considerations

The DSM-5 (released in May 2014) does not include post-concussion syndrome as a separate diagnostic entity. As a major change, clinicians are now instructed to diagnose “major or mild neurocognitive disorder due to traumatic brain injury” depending on the severity of cognitive deficits and functional disability present, regardless of initial injury severity (e.g., whether a patient's initial GCS score was 13–15 or below 8) (Mayer et al., 2017).

Fortunately, the disrespectful opinion that patients might be exaggerating psychological symptoms and morphing them into neuro-cognitive impairments is no longer a trend among researchers or clinicians. The neurobiological substrates of PCS have been under serious investigation since then. The importance of the structural and functional neurological aspect of the neuropsychological symptoms burdening the clinical population as been reaffirmed (Erin D. Bigler, 2003). It is now accepted that 15 to 30% of mild TBI patients suffer from long term symptoms (Alexander, 1995; Bazarian et al., 1999; Erin D Bigler, 2008; Rimel, Giordani, Barth, Boll, & Jane, 1981; Vanderploeg, Curtiss, Luis, & Salazar, 2007).

The total sample of mTBI patients who participated in the experiments presented in this thesis was comprised mostly of women (51 women and 21 males). Most studies focus on sport related concussion and or military/blast related concussions, so samples tend to include more men than women (Merritt, Padgett, & Jak, 2019). However, mTBI prevalence is higher in women who also report more symptoms and tend to have weaker performance at visual memory tasks (Merritt et al., 2019). Although we did not find an effect of sex on any of our behavioral or neuroimaging measures, it is important to consider sex in mTBI studies. For example, women tend to have a higher increase in

cortical thickness than men after a concussion, and also to score higher on a posttraumatic stress scale, and these two measures are correlated (Shao et al., 2018). It is possible that the pathophysiology of mTBI is different between sex, or gender, even though to our knowledge, gender is not a common reported characteristic of participants.

We did not include ethnicity in our demographic reports, but emerging evidence suggests that people of color tend to show higher prevalence of concussion than white people and receive less care for concussion management which would affect post-concussive symptoms and increase the risk of worse injuries (Brenner et al., 2020). These findings show a difference in incidence and treatment between ethnicities but representation in experimental studies matters even without differences in pathophysiology.

5.6 Final conclusion and future directions

This thesis has brought forth evidence for altered cortical dynamics in the visual processing of simple and natural stimuli following mild Traumatic Brain Injury. We have applied methods from the field of physics to complex neuroscience questions, approaching the perceptual system as a signal amplifier and as a network of connected nodes. We found increased levels of internal noise in the processing of contours, and a relationship between contour integration efficiency and changes in visual habits. We found that natural vision revealed deficits of activity in the early visual cortex and compensatory tendencies in fronto-parietal areas. Natural movies also showed that mTBI participants tended to have increased functional connectivity throughout the visual cortex and particularly in fronto-parietal areas. The novel application of graph theoretical analysis of the mTBI cortical network activated by natural vision confirmed a

general connectivity degree increase and revealed increased global efficiency, increased clustering and decreased modularity throughout the visual cortex. Similar findings were repeated in subnetworks of visual cortices, with an emphasis on complex processing areas. Findings from natural vision did not correlate with self-reported visual symptoms nor with our neuropsychology measures, which supports the idea that mTBI alters cortical dynamics regardless of behavior.

Future studies would benefit from strong collaborative designs involving clinicians and researcher because subtle behavioral dysfunctions require rigorous and expert-driven investigation. For example, a more detailed visual complaint questionnaire could have revealed crucial relationships with our cortical modelling—internal noise in good continuity perception, synchrony with normative timeseries models of cortical response to naturalistic movies, and network changes. Without such relationships, we are still advancing in the dark and unable to properly relate patient experience to neuroscientific findings regarding abnormal cortical processing. This is necessary if we want to build treatment to address chronic symptoms of mTBI because we need to know whether normalizing cortical activity benefits the patient first and foremost.

In our fourth chapter we have found evidence of macro scale and local scale reorganization of connectivity in mTBI. However, the increase in efficiency and clustering could be a consequence of sheer mean degree increase. Thus, mathematically shuffling connections in each participants' network to essentially create null models could rule out degree as a confounding variable. This could show that network changes in mTBI are structured by design and not simply by collateral chance. In any case, our results show that the cortical network activated by naturalistic movie viewing is altered

by mTBI, and these changes affect connectivity within and between subnetwork, their global efficiency, modularity, and clustering.

Advances in computational capacities have allowed researchers to handle unprecedented quantities of brain data and take impressive leaps for our understanding of brain function and disorder, but future studies should focus on relating these findings back to the patients, their symptoms, their experience, and their demographic background and environmental factors that could potentially affect their impairments and ultimately their recovery.

5.7 References

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