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PET Imaging of Mild Traumatic Brain Injury and Whiplash Associated Disorder

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General Introduction

"[...] the null hypothesis is never proved or established, but it is possibly disproved, in the course of experimentation. Every experiment may be said to exist only in order to give the facts a chance of disproving the null hypothesis."

Fisher, RA. The Design of Experiments, Edinburgh: Oliver and Boyd, 1935, p.18

The severity of apparently simple head injuries is frequently underestimated, not only by society but also at the clinical and scientific level. This underestimation is especially frequent for two highly common injuries, namely mild traumatic brain injury and whiplash injury. Traumatic brain injury (TBI) is the leading cause of brain trauma in our society, with an overall estimated incidence per year of 235 per 100,000 inhabitants in the European Union[1] and about 500 per 100,000 inhabitants in the United States,[2] of which approximately 80% are accounted for as mild TBI (mTBI).[2] Whiplash injury is one of the most frequent consequences of motor vehicle related accidents, affecting about 300 per 100,000 inhabitants per year in United States and Western European countries.[3] In both cases, patients suffering these injuries frequently report short-term symptoms as a consequence of the trauma, such as headache, dizziness and cognitive problems. While many recover within a few weeks, the trauma leads to persistent physical, cognitive and behavioral impairment in up to 50% of the patients.[4,5] These long-term conditions are frequently referred to as Post-Concussive Syndrome[6] and Whiplash-Associated Disorder (WAD).[7]

The main causes of TBI in general are falls and motor vehicle related accidents.[2] There are however an increasing awareness of the impact of mTBI in relation to sports and modern warfare. Over the past 10 years, the annual rate in the diagnosis of mTBI in adolescents and young adults in high school increased by 16%.[8] Moreover, in the last decade the rate of emergency department visits for sport- and recreation-related TBI rose by 57% for people aged below 19 year.[9] While previous data reported an incidence of 300,000 of such sport-related TBI occurring each year in the United States,[10] recent studies suggested that a more accurate number will be between 1.6–3.8 million per year.[11] It is important to remark that even these figures may still be low due to the tendency of people to underestimate mild injuries. People engaging in contact sports, e.g. American football, ice hockey, rugby, soccer or boxing, are especially prone to suffer from mTBI. This is sometimes influenced by the over-reliance on protective equipment, which leads athletes to downplay the consequences of physical contact on the field.[12]

As the highest rates of sport-related brain injuries occur during adolescence and young adulthood, it is important to make an effort to fully understand the consequences of these injuries. In addition, there is growing evidence

that repetitive head traumas lead to an increased risk of depression,[13] Alzheimer's disease,[14] chronic traumatic encephalopathy,[15–17] and other neurodegenerative diseases.[18] Moreover, there is an emerging area of research related to the persistent symptoms experienced by many military personnel following exposure to blast mTBI, and whether these symptoms reflect structural or functional brain damage.[19–21]

Whiplash injury is one of the most frequent motor vehicle injuries, and it has deep economic implications in developed countries. The yearly costs of this injury, including medical care, loss of work productivity, and litigation, have been estimated to be at least €10 billion in Europe,[22] and $29 billion in the United States.[23] The apparent lack of pathophysiological substrate had driven the focus of attention towards expectations, beliefs and other psychological aspects surrounding the trauma, including the possibility that some people may exaggerate their symptoms for monetary benefits. Even when there is no evidence indicating any difference in the outcome of patients that applied for compensation and those who have not,[24,25] the seed of distrust has been sown in society and healthcare.

Difficulties for a better understanding of mTBI and WAD

There are several issues that impede a better understanding of mTBI and whiplash injury and their prognosis.[26,27] Among the most important ones are the lack of uniformity in their definitions, the absence of detectable pathophysiological mechanisms to explain the symptoms using conventional clinical neuroimaging modalities (with the consequent impossibility to perform prognostic assessments), and the apparent prevalence of psychological factors.

The World Health Organization (WHO) Collaborating Centre for Neurotrauma Prevention, Management and Rehabilitation Task Force on Mild Traumatic Brain Injury (WHO Task Force) found the current literature on mTBI to be variable in quality, presenting more than 38 definitions.[28] Although most of the studies used similar criteria, including the Glasgow Coma Scale score (GCS), loss of consciousness (LOC), post-traumatic amnesia (PTA), disorientation/confusion, and neurological signs, it is still strongly recommended to unify the definition of mTBI.[27] Based on this, the WHO Task Force proposed an operational definition that reads as follows:

> *"MTBI is an acute brain injury resulting from mechanical energy to the head from external physical forces. Operational criteria for clinical identification include: (1) 1 or more of the following: confusion or disorientation, LOC for 30 minutes or less, PTA for less than 24 hours, and/or other transient neurological abnormalities such as focal signs, seizure, and intracranial lesion not requiring surgery; (2) GCS score*

of 13-15 after 30 minutes post-injury or later upon presentation for health care. (3) These manifestations of MTBI must not be due to drugs, alcohol, medications, caused by other injuries or treatment for other injuries (e.g., systemic injuries, facial injuries, or intubation), caused by other problems (e.g., psychological trauma, language barrier, or coexisting medical conditions), or caused by penetrating craniocerebral injury."[28]

In the other hand, the Quebec Task Force on Whiplash-Associated Disorder defined WAD as:

"An acceleration-deceleration mechanism of energy transfer to the neck. It may result from rear end or side-impact motor vehicle collisions, but also occur during diving or other mishaps. The impact may result in bony or soft-tissue injuries, which may lead to a variety of clinical manifestations."[7]

Though the definition of WAD has been clearly stated since its origins, there is still an ongoing debate about its validity.[29,30]

The tissue damage consequence of the trauma can be generally divided in primary and secondary injury. Primary injuries occur at the moment of the impact and are best visualized by structural imaging techniques (i.e. magnetic resonance imaging (MRI) and computed tomography (CT)). However, the presence, or absence, of tissue damage detected by these techniques seems to be inconclusive for the prognosis of WAD and mTBI. In mild to moderate TBI about 20% of the patients without abnormalities on the admission CT have residual complains that interfere with resumption of work,[31] and even though MRI imaging is able to detect more subtle alterations than CT, these techniques cannot be used to predict neurocognitive functions at any stage of the mTBI nor its functional outcome.[32,33] Likewise, tissue damage detected by conventional imaging showed inconclusive evidence for an association with the development of WAD.[34,35] Secondary injuries are caused by a delayed non-mechanical damage and it is influenced by changes in blood flow and metabolic dysfunctions. While the neuropathology of WAD is uncertain, the complex process that follows the head trauma in mTBI patients is well known.[36] Again, conventional structural CT and MRI imaging fail to detect these metabolic alterations, as they are naturally focused on morphological features.

The lack of proof for a defined mechanism of injury should not encourage researchers and clinicians to neglect its existence. The apparent lack of physiological measures that could provide an explanation for the outcomes found in the patients with mTBI and WAD drove many researchers towards the investigation of psychological factors, such passive coping style,

depression, catastrophizing or expectations; and for many seems to be the only plausible explanation at the moment.[4,5,37–39] While the role of these psychological factors within mTBI and WAD conditions is undeniable, their existence does not exclude the pathophysiological substrate. As in the field of classical statistics, the absence of significant results in an experiment (i.e. the absence of detectable pathophysiological mechanisms) can never confirm the null hypothesis (i.e. the physiological mechanisms does not exist).

It is within this frame of uncertainty, with the absence of detectable pathophysiological mechanisms with conventional imaging studies, that "state-of-the-art" neuroimaging techniques, such as single-photon emission computed tomography (SPECT) or positron emission tomography (PET), have a great potential to provide insight into the underlying functional changes (i.e. secondary injuries) that arise from mTBI and WAD, especially in the chronic stages.

SPECT and PET imaging

PET and SPECT nuclear imaging techniques are useful tools for monitoring *in vivo* processes. The use of a wide range of radiopharmaceuticals ('tracers') enables us to image different functional processes, e.g. perfusion, glucose metabolism, and specific cellular receptor expression or enzymatic activity. Such visualizations greatly facilitate the investigation of multiple health conditions at different stages, and the evaluation of new pharmacological interventions, in single or longitudinal study designs. The tracers used for these purposes are administered to the subject under investigation. It is the distribution of this tracer in the body and its change over time that is recorded by PET and SPECT cameras. Both systems rely on detection of the γ-rays directly or indirectly emitted from the tracers for the creation of a recorded image.

SPECT cameras are equipped with a collimator that directs the γ-rays towards the detectors. In contrast to conventional planar imaging obtained with gamma cameras, the SPECT technique provides 3D images based on the acquisition of multiple projections at different angles. The radionuclides used in the labeling of SPECT tracers typically emit γ-rays between 60 and 300 keV, and present long half-lives (i.e. time in which half of the radioactivity decays) in the range of hours to days (e.g. ^{99m}Tc, ^{123}I or ^{67}Ga), which facilitates their transportation over long distances from the production site to the hospitals and/or research centers.

In contrast with SPECT, the PET cameras do not detect γ-rays directly emitted by the radionuclide. The isotopes used in PET imaging have a highly unstable nucleus, which emits positrons. These positrons are the antiparticle of the electrons and have the same mass but opposite electric charge. When the

positron is emitted by the isotope, it travels a short distance until it collides with an electron from the nearby tissue. The resulting annihilation creates two γ-rays with energy of 511 keV each that travel at almost 180° degrees of each other. These γ-rays are then detected by the PET camera, which localize their spatial source along a straight line of coincidence, in a process known as line of response. The obtained data will be used for the construction of the final 3D image. The radionuclides used in PET imaging are typically isotopes with short half-lives, from minutes to few hours (e.g. ^{15}O, ^{11}C, or ^{18}F), and generally require an on-site cyclotron for production as well as specialized personnel, which increase the cost of such PET scans. However, this technique presents some unique properties which drive the use of PET imaging as the preferred tool (e.g. highest sensitivity, lower radiation dose, and the existence of broader biologically interesting compounds).

Aim of this thesis

As mentioned before, conventional structural imaging studies with CT and MRI do not correctly assess the outcome or provide a clear evidence of a lesion-based model in mTBI and WAD. However, neuroimaging using nuclear medicine techniques has greater potential in the identification of altered functional mechanisms and may serve as a guide to evaluate different therapeutic approaches.

The aim of this thesis was to contribute to a better understanding of the long-term functional changes underlying the pathophysiology of mTBI and WAD, by means of nuclear medicine techniques. In this context, the thesis is divided in three parts: the first part of the thesis focuses on methodological aspects related to the acquisition and processing of the images, the second part addresses TBI with a special focus on mild TBI cases, and the third part was organized around WAD.

Methodology:

Chapter 2: Nuclear medicine imaging techniques are increasingly used for the study of rodent models of a variety of human brain diseases. However, high resolution anatomical image data in preclinical brain PET and SPECT studies is often unavailable, complicating the intra- and inter-subject comparisons and the application of predefined reference masks or atlas structures. Intra-modality registration of the images to a tracer-specific template, aligned to a standard coordinate space, has been proposed as a good approach for the registration of these images. The aim of this chapter was to standardized the methodology used for the construction of rat PET and SPECT tracer-specific templates, and the evaluation of different factors that may affect the registration process (such as animal strain, tracer characteristics, or image size).

Chapter 3: One of the strengths of PET techniques is the variety of existent tracers that can be used to explore different biological functions. In this context, the evaluation of the translocator protein (TSPO) overexpression is considered an attractive research tool for monitoring neuroinflammation in several neurological and psychiatric disorders. [^{11}C]PK11195 PET tracer has been widely used for this purpose. However, it suffers from several limitations, including a poor signal-to-noise ratio (mainly due to its low binding potential to TSPO and high level of non-specific binding), highly variable kinetic behavior, and apparent lack of sensitivity to detect low levels of neuroinflammation. For that reason, the recently developed [^{11}C]CB184 tracer was evaluated as a potential more sensitive PET tracer for the TSPO.

Traumatic Brain Injury (TBI):

Chapter 4: This chapter provides a review of neuroimaging in TBI using nuclear medicine techniques, with a special focus on the mild injuries. With about 80% of the TBI diagnosed as mild, and a high incidence in adolescence and young adulthood, the consequences at short and long term of these injuries must be better understood. With little contribution of conventional structural imaging (i.e. CT and MRI) to the evaluation of mild TBI, nuclear imaging techniques such as PET and SPECT are in a favorable position to provide reliable tools for a better understanding of the pathophysiology.

Chapter 5: The neuropathology of mTBI seems to be the results of a complex neurometabolic cascade that follows the head trauma, involving different mechanisms. Two of these mechanisms have received particular attention in the recent years: metabolic alterations and neuroinflammation. However, more experiments are required to better understand the neuronal mechanisms underlying mTBI, especially including longitudinal studies under controlled conditions. This chapter aims to evaluate the consequences of a mild TBI over a period of 3 months, by exploring changes in the neuroinflammatory state ([^{11}C]PK11195 PET scans), metabolic function ([^{18}F]FDG PET scans) and animal behavior. For this purpose, a closed head injury model in rats was used to reproduce the pathological features seen in human mTBI, where most of the patients do no experience skull fracture or visible alterations in conventional CT.

Whiplash Associated Disorder (WAD):

Chapter 6: WAD describes a heterogeneous group of symptoms that develop frequently after unexpected rear-end car collision at low velocities. In some of the patients suffering from the so called whiplash injury, the symptoms may persist for years. However, there is an ongoing scientific debate about the existence of tissue injury to support this disorder. This chapter aims to (i) give an overview of the scientific data regarding the presence of an

injury mechanism as a consequence of the whiplash trauma, (ii) remark the unexpectedness of an accident as essential, and (iii) present a new concept according to which WAD symptoms are the result of a mismatch between aberrant information from the cervical spinal cord and the information from the vestibular and visual systems, all of which are integrated in the mesencephalic periaqueductal gray and adjoining regions.

Chapter 7: While radiography, CT and MRI seem to be inconclusive for the prognosis of WAD, several PET and SPECT studies in chronic WAD patients have shown the existence of hypoperfusion and hypometabolism in the posterior parietal occipital cortex, and hyperperfusion in the posterior parahippocampal, posterior cingulate gyri, medial prefrontal gyrus and thalamus. This chapter addresses three main objectives: First, replication of previous results that reported alterations of the cerebral blood flow; secondly, exploration of the hypothesis presented in chapter 6; third, testing if non-painful stimuli in the neck region of WAD patients were altered due to an ongoing process of central hyperexcitability.

Chapter 8 presents a correspondence letter, where we defended that in WAD "any treatment concept must be a trial-and-error process as long as the mechanism of action is not understood".

Finally, in **chapter 9** a summary of the results is given as well as an integrated discussion about the major finding of this thesis and future perspectives.

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