PET Imaging of Mild Traumatic Brain Injury and Whiplash Associated Disorder

Vállez García, David

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Summary

Traumatic brain injury (TBI) is the leading cause of brain trauma in our society, with an estimated incidence of 235 per 100,000 inhabitants per year in the European Union and about 500 per 100,000 inhabitants per year in the United States. About 80% of all these cases are accounted for as mild (mTBI). At the same time, whiplash-associated disorder is one of the most frequent consequences of motor vehicle related accidents, affecting about 300 per 100,000 inhabitants per year in the United States and Western European countries. Both brain injuries are frequently underestimated due to their apparent low severity, and because in many cases the symptoms disappear within a few weeks. Nevertheless, several patients develop persistent symptoms without a definitive evidence of damaged tissue resulting from the injury. This apparent lack of pathophysiological evidence had driven the interest of clinicians and researchers towards the patient expectations, beliefs and other psychological aspects surrounding the trauma.

While the role of psychological factors within these conditions is undeniable, in the absence of detectable pathophysiological mechanisms with conventional imaging studies (i.e. magnetic resonance imaging (MRI) and computed tomography (CT)) the mechanisms behind the long-term symptoms remain unknown. Therefore, it is within this frame of uncertainty that functional imaging techniques, such as positron emission tomography (PET), have the potential to provide insight into the underlying changes that arise from mild traumatic brain injury and whiplash-associated disorder, especially in the chronic stages.

The first part of this thesis was focused in the improvement of methodological aspects of small animal PET studies. **Chapter 2** investigated the use of tracer-specific templates for the registration of PET and SPECT rat brain images, together with the implementation of SAMIT, a software package that facilitates the image processing and the voxel-based analysis of the data. Studies with rodent models of human brain diseases are increasingly used by the research community. However, high resolution anatomical image data is often not available, which complicates the intra- and inter-subject comparisons. Intra-modality registration of the images to a tracer-specific template, aligned to a standardized coordinate space, was tested in this chapter. Results indicated that, in the absence of individual MRI data, the use of strain and tracer specific templates is the most appropriate approach when performing spatial normalization of PET and SPECT functional rat brain images. Additionally, it is advisable to have images with approximately the same dimensions as those of the reference template. Overall, the mean registration errors were smaller than the spatial resolution of the cameras used in the study. This procedure allows the use of advanced voxel-based analysis approaches, in which the resulting coordinates are in accordance

with a standardized atlas space. In conclusion, the methodology used for the construction and validation of the templates appears to be a reliable approach for the design of tracer specific templates. These templates can be adjusted to the particular needs of each individual research group and used in the evaluation of human brain diseases through specific rat models.

Chapter 3 evaluated the tracer [^{11}C]CB184 for the imaging and quantification of the translocator protein (TSPO) overexpression in a rat model of herpes encephalitis. TSPO is involved in a variety of cellular functions, and under physiological conditions its expression is low. In neuroinflammatory processes, TSPO expression is up-regulated in glial cells and infiltrating macrophages. [^{11}C]PK11195 has been widely used as the PET probe for *in vivo* visualization and quantification of the TSPO expression in various diseases, including glioma, stroke, Parkinson and Alzheimer's disease, multiple sclerosis and traumatic brain injury. However, [^{11}C]PK11195 suffers from several limitations, like a poor signal-to-noise ratio, highly variable kinetic behavior, and an apparent lack of sensitivity in detecting low levels of microglia activation. In the search for a better alternative, the novel imidazopyridine compound [^{11}C]CB184 was investigated in a rat model of herpes encephalitis (HSE). [^{11}C]CB184 showed a nonspecific binding to healthy tissue comparable to that observed for [^{11}C]PK11195, but displayed significantly higher specific binding in those brain regions affected by the HSE, i.e. brainstem. These results suggest that [^{11}C]CB184 PET ligand is a good alternative for the imaging of neuroinflammatory processes.

The second part of the thesis focused on TBI, with a special interest in mTBI. **Chapter 4** provides a review of the nuclear medicine neuroimaging studies performed in TBI and mTBI. Although further evidence-based imaging studies are needed, [^{18}F]FDG PET appears to be a valuable tool in studying metabolic dysfunction initiated by TBI. Evidence suggests that [^{18}F]FDG is useful for visualizing the acute phase of TBI in patients who fail to show abnormalities via conventional structural neuroimaging techniques – CT and MRI – that explain their neurological symptoms. In chronic TBI cases, most of the [^{18}F]FDG studies identify a diffuse hypometabolism that involves key brain regions related with cognitive functioning, such as the thalamus. In addition, decreased neuronal viability ([^{11}C]flumazenil) and increased neuroinflammatory response ([^{11}C]PK11195) has also been observed in the thalamus and midbrain structures of these patients. The use of other PET and SPECT radioligands, such as [^{11}C]flumazenil, [^{18}F]DOPA or [^{99m}Tc]HMPAO, as markers of specific cellular process are an attractive tool for detecting the secondary neuronal damage involved in the pathophysiology of TBI, and the evaluation of several therapeutic approaches.

Chapter 5 evaluates the consequences of mTBI in a rat model of closed head injury, over a period of three months. The presence of neuroinflammation ([^{11}C]PK11195) and changes in metabolism ([^{18}F]FDG) was explored by means of PET imaging. The mTBI rat model did not result in death, skull fracture or neurological suppression of reflexes in any of the animals. Moreover, no statistical differences were found in the behavioral tests at any time point between the healthy group and trauma group. PET imaging showed a neuroinflammatory process limited to the sub-acute phase after trauma, involving the amygdala, globus pallidus, hypothalamus, pons, striatum and thalamus. Alterations in glucose metabolism were detected in several regions over the whole period of three months, with increased regional tracer uptake located mostly in the medulla, and decreased regional tracer uptake in the amygdala, cortex, globus pallidus, striatum and thalamus. Therefore, it seems that as a consequence of the mTBI, and with the absence of detectable behavioral changes, relative brain glucose metabolism was altered in several brain regions which correspond with those presenting neuroinflammation in the sub-acute stage.

Finally, the Whiplash Associated Disorder (WAD) was discussed in the last section of the thesis. **Chapter 6** provided an overview of the scientific data regarding the presence of an injury mechanism consequence of the whiplash trauma, with special interest in the unexpectedness of the accident as an essential part in the process. In addition, a new concept is presented wherein 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 investigated the existence of alterations in the regional cerebral blood flow (rCBF) of chronic WAD female patients with [^{15}O]H_2O PET imaging. While conventional structural imaging seems to be inconclusive for the prognosis of WAD, several PET and SPECT studies in chronic WAD patients have shown the presence of hypoperfusion and hypometabolism in the posterior parietal occipital cortex, and hyperperfusion in the posterior parahippocampal region, posterior cingulate gyri, medial prefrontal gyrus and thalamus. In this study, no alterations in the rCBF of either healthy volunteers or WAD patients were measured as a result of different intensities of non-painful neck stimulations. However, WAD patients showed statistically lower tolerance to the electrical stimulation, supporting the idea of altered sensitivity thresholds related with a process of central hyperexcitability. Moreover, alteration in the rCBF was found in the superior parietal cortex, a region previously reported to be affected in chronic WAD patients. In addition, a decreased rCBF was observed in the thalamus and

insula, in support of the hypothesis put forward in chapter 5 regarding a misbalance in the interoceptive sensory system.