Changing perspectives using nuclear brain imaging: clinical and methodological studies

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In this thesis, clinical and methodological studies have been performed to add to the clarification of as yet insufficiently characterised neurobiological mechanisms in common neurologic and psychiatric conditions, including traumatic brain injury and its sequelae and compulsive pornography use. Traumatic brain injury (TBI) contributes to a considerable number of hospitalisations and its importance is rising as a result of an increasing worldwide incidence and associated social and economic burden. Nuclear imaging techniques have been shown to be a valuable tool to detect early and late metabolic dysfunction in TBI.

Traumatic brain injury

Results of imaging studies in TBI have been influenced by a large heterogeneity, related to patient inclusion, time elapsed until imaging, imaging analysis methods and the type of injury, which can be classified as mild, moderate or severe. Although not routinely part of the evaluation in the acute phase, the use of [^{18}F]FDG has led TBI to be metabolically associated with a triphasic temporal pattern, consisting of a hyperacute phase with increased glucose metabolism and a relatively long period with reduced metabolism, followed by a period during which glucose metabolism reaches a normal range. However, chronic regional reductions may persist and [^{18}F]FDG uptake in pericontusional areas may be heterogeneous, with both focal reductions and increases being reported. Using PET with a combination of tracers in moderate TBI, reductions of cerebral metabolic rate of glucose (CRMglc) have been shown in the grey matter remote of the lesion in the absence of cerebral blood flow changes, with higher values correlating with better clinical outcome. In white matter, a reduction of the oxygen-to-glucose ratio has been observed after moderate to severe TBI, suggesting the presence of inflammatory cells and elevated anaerobic glycolytic metabolism. The ability to simultaneously measure cerebral blood flow, the cerebral metabolic rate of oxygen and oxygen extraction fraction is an advantage of triple dynamic [^{15}O]O PET ([^{15}O]CO, [^{15}O]O_2, [^{15}O]H_2O), yet the practical implementation of triple dynamic [^{15}O]O PET is limited due to the need of an onsite cyclotron and the high production costs. In general, PET or SPECT imaging directed at cerebral glucose metabolism or perfusion may be more sensitive to detect focal lesions than conventional CT in the acute phase of TBI, especially in mild TBI, and its incremental value may be highest when conventional imaging methods are negative in the presence of post-injury neurological or psychiatric symptoms.

In the chronic phase, functional corticothalamic deficits correlating with neurological outcome have been detected using [^{18}F]FDG PET, even in the absence of structural abnormalities. In the setting of pharmacological interventions, glucose metabolism in various cortical regions has shown to be related to the outcomes of neuropsychological testing and may thus be used as a marker for treatment effectiveness. Studies using other PET tracers in chronic TBI pointed towards reduced neuronal viability and disturbances in various neurotransmitter systems.

Another cellular process which has been implicated in neurodegeneration and has attracted interest in TBI is neuroinflammation. In the acute phase microglia, astrocytes and neurons become active and synthesise inflammatory mediators and complement. This inflammatory response may persist months after the injury has occurred. In this thesis, [^{11}C]PK11195, a first generation TSPO ligand, was used in currently active kickboxers (n=11) and controls (n=11) to determine whether neuroinflammation was present as a consequence of chronic repetitive head injury. The non-displaceable binding potential (BP_{nd}) was calculated for the whole brain, as well as for subregions hypothesised to be prone to injury. Although on a group level no

significant differences in BP_{nd} between active kickboxers and controls could be detected, three individual kickboxers showed widespread increases of TSPO PET signal, with BP_{nd} exceeding typically reported normal ranges (figure 1). The observed changes could not be correlated to the performance on neurological tests or to surrogate markers of cumulative repetitive head injury (years of training, training frequency, number of bouts or number of lost bouts). The results of this study confirm that a degree of neuroinflammation may be present in currently active athletes exposed to repetitive head injury, even without the presence of neurologic complaints or measurable cognitive decline. This finding is relevant since drugs aiming to moderate microglia function and improve outcome after TBI are being investigated.

Psychiatric disorders

In the next section, a critical analysis of hybrid imaging in psychiatric disorders is described that emphasises potential applications as well as limitations, with a focus on the combination of MRI and PET. In the brain, these modalities may be particularly complementary. MRI is capable of producing anatomical images with high soft tissue contrast and is sensitive to macroscopic changes, whereas PET is able to detect disturbances in cellular function related to glucose metabolism, perfusion or neurotransmitter functionality. Results of PET imaging in major depressive disorder point towards locally reduced serotonin synthesis. Mixed results have been reported with respect to the serotonin transporter in depression. Additional impairments related to GABA and the metabotropic glutaminergic receptor have been described. Anxiety disorders have been consistently associated with increased recruitment of the 'fear network' during fear provocation, whereas results in the resting state point towards reduced benzodiazepine receptor binding in limbic and frontal regions as well as downregulation of $5HT_{1a}$ receptors. In schizophrenia spectrum disorder,

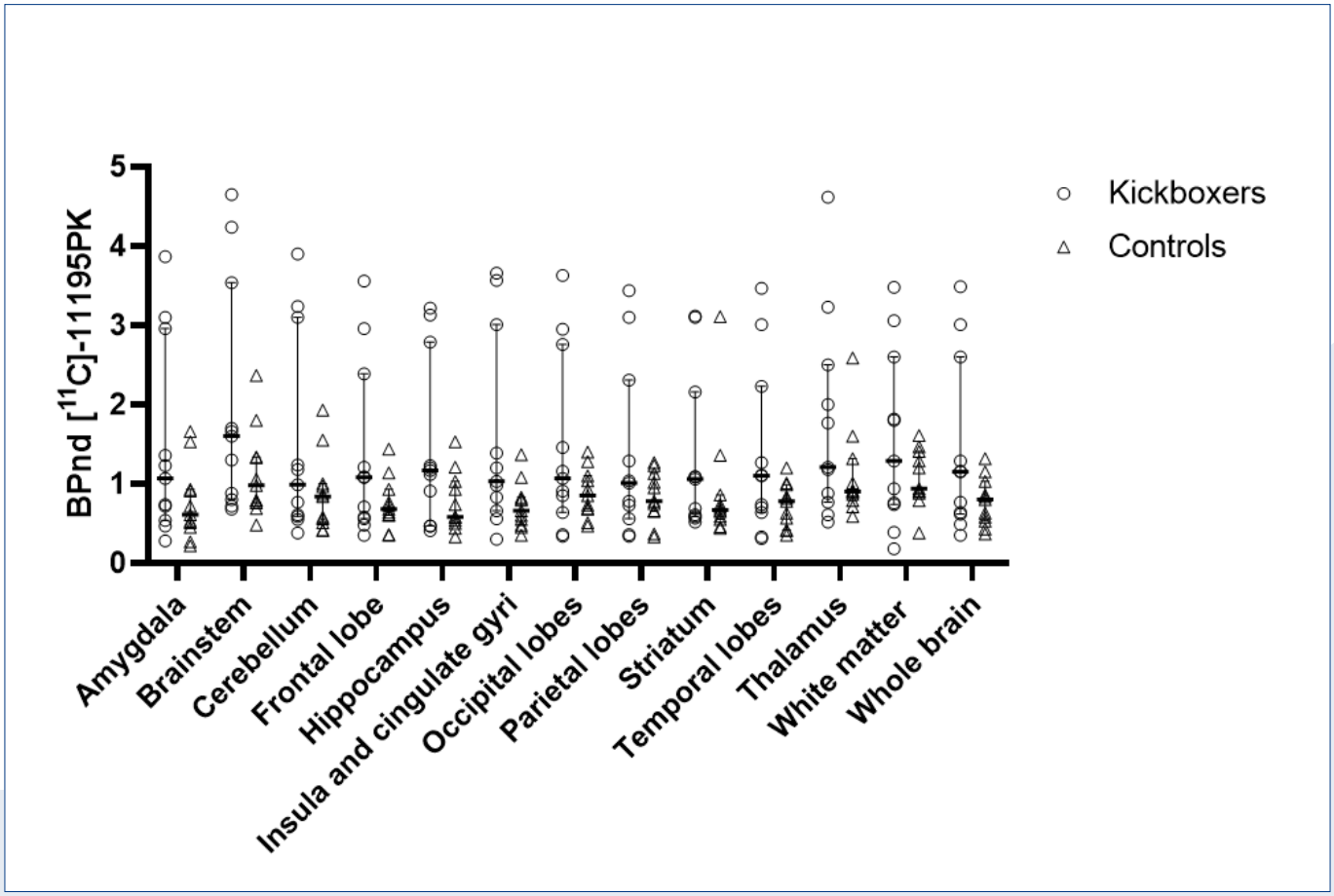

Figure 1. BP_{nd}'s of [11C]PK11195 in kickboxers (n=11) and controls (n=11). The symbols represent individual subjects. The horizontal bar reflects the median and the error bars the 1st and 3rd quartile. Three kickboxers show increased BP_{nd}'s in multiple regions of the brain.

conflicting results have been reported regarding $D_{2/3}$ receptor imaging, whereas in substance-related disorders, reductions of $D_{2/3}$ receptor availability have been a consistently reported finding. In general, the reported findings in many neuroimaging studies related to psychiatry are influenced by heterogeneity in patient selection and MRI findings may help to identify subsets with more specific disturbances. Currently, most single modality studies in psychiatric disorders using MRI have focused on anatomy, white matter integrity and the tracking of neural activity (fMRI). Correlation of PET derived parameters with outcomes derived from MRI may help to integrate findings from multimodal imaging modalities. An integrated PET/MRI system might even offer additional advantages such as the possibility to achieve measurements of neuronal activity and neurotransmitter simultaneously when performing a task or a pharmacological intervention and investigate temporal relationships.

In subjects with psychiatric disorders, different neurobiological disturbances may underlie a clinically similar syndrome. The detection of specific neurobiological abnormalities in patient groups using neuroimaging may have consequences for treatment selection and disease categorisation. Currently, there is continuing debate on whether or not to include certain behavioural addictions in the DSM-V in the section 'Substance-Related and Addictive Disorders. Pornographic addiction (PA) refers to an addiction model associated with compulsive and repeated use of pornographic material. Whether the use of (internet) pornography may indeed become addictive remains a matter of debate. To this end, we investigated the striatal $D_{2/3}$ receptor availability in subjects with compulsive pornography use (CPU) using [^{11}C]raclopride PET and compared with healthy controls without CPU. MRI was used to measure regional cerebral blood flow and assess white matter tract integrity. In substance use disorders, reduced $D_{2/3}$ receptor availability is an often replicated finding. Similarly, reductions of cerebral blood flow in frontal regions have been reported, which could reflect a lack of inhibitory signalling towards the striatum. In our study we aimed to detect whether similar alterations were present in subjects with CPU. No significant differences between subjects with CPU and controls could be detected, suggesting that other neurobiological mechanisms are involved, which contrasts this form of addiction with other addictive modalities.

Methodological studies

Methodological studies in this thesis focused on applications of 6-[^{18}F] fluoro-L-3,4-dihydroxyphenylalanine (FDOPA) PET, a radioligand used to assess presynaptic dopaminergic functioning in neurodegenerative disease and for the detection and staging of neuroendocrine tumours. The University Medical Centre Groningen has extensive experience using this tracer. At our institution, [^{18}F]-FDOPA is prepared by electrophilic fluorination of the trimethylstannyl precursor with [^{18}F]fluorine gas ([^{18}F]F_2). After the installation of a Cyclone 18 twin cyclotron (IBA, Belgium), it was possible to improve the production method of [^{18}F]F_2.We investigated the effects of introducing a novel GMP compliant multi-dose production method of [^{18}F]FDOPA ([^{18}F] FDOPA-H) on the biodistribution of the radiopharmaceutical in subjects with neuro-endocrine tumours. [^{18}F]-FDOPA-H was produced from [^{18}O] O_2 via a double-shoot approach resulting in a higher activity yield, improved molar activity and a lower administered mass than the conventional method ([^{18}F]FDOPA-L). In our retrospective analysis of 49 subjects with neuro-endocrine tumours scanned using both methods, comparable or slightly higher uptake in various physiological sites was observed as well as a slightly higher uptake in tumour lesions in subjects scanned with [^{18}F]FDOPA-H. This may be relevant when performing quantitative evaluations, such as determining the striatal-to-occipital ratio in presynaptic dopaminergic imaging, and in longitudinal research studies. In day-to-day clinical practice the new production method allows for more subjects to be scanned out of a single production run with little impact on image interpretation.

Finally, we performed intrastriatal analyses of [^{18}F]FDOPA binding to differentiate between idiopathic Parkinson's disease (IPD) and atypical parkinsonian disorders (APD). In IPD, a preferential presynaptic dopaminergic decline of the posterior putamen is present as a consequence of predominantly affected ventrolateral parts of the substantia nigra and its striatal projections. Although this pattern is often observed visually when assessing [^{18}F]FDOPA PET scans, it is unclear whether additional quantification methods would be of value in the differential diagnosis. Subregional VOI analyses were performed to investigate whether this pattern contrasts with the deficits observed in APD. The results of the analyses indicate that although in both groups the posterior putamen is most affected, in APD patients the anterior putamen is spared relative to the caudate nucleus and that in patients with IPD a more linear decrease was present from the head of the caudate nucleus to the posterior putamen. ♦