MR-DTI and PET multimodal imaging of dopamine release within subdivisions of basal ganglia

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Abstract. The basal ganglia is a group of anatomical nuclei, functionally organised into limbic, associative and sensorimotor regions, which plays a central role in dopamine related neurological and psychiatric disorders. In this study, we combine two imaging modalities to enable the measurement of dopamine release in functionally related subdivisions of the basal ganglia. $^{[11C]}$-$(+)$-PHNO Positron Emission Tomography (PET) measurements in the living human brain pre- and post-administration of amphetamine allow for the estimation of regional dopamine release. Combined Magnetic Resonance Diffusion Tensor Imaging (MR-DTI) data allows for the definition of functional territories of the basal ganglia from connectivity information. The results suggest that there is a difference in dopamine release among the connectivity derived functional subdivisions. Dopamine release is highest in the limbic area followed by the sensorimotor and then the associative area with this pattern reflected in both striatum and pallidum.

1. Introduction

Dopamine is a neurotransmitter which enables the transmission of signals in the brain. Its abundance or insufficient formation can impair motor, cognitive and emotional functions such as in Schizophrenia and Parkinson’s diseases.

In such neurological and psychiatric diseases, unbalanced dopamine formation or release is observed in the basal ganglia, a group of anatomical nuclei whose role has not yet been fully elucidated due to their complex neuropathological mechanisms. Anatomically, basal ganglia consist of: striatum, which is further sub-divided into caudate, putamen and ventral striatum; pallidum which is subdivided into globus pallidus external, globus pallidus internal and ventral pallidum; substantia nigra and the subthalamic nuclei. Basal ganglia are functionally organised into limbic, associative and sensorimotor areas [1]. However, the boundaries of these regions are not defined from anatomical information.

In order to understand the role of dopamine in neurological and psychiatric disorders, several PET studies have measured dopamine release in the brain following the administration of amphetamine. In these studies dopamine release has been measured in anatomical subdivisions of the basal ganglia. Here we propose a multimodal approach and in particular a combined DTI-PET method to measure
dopamine release in the functional areas of the basal ganglia (specifically in the striatum and pallidum). Probabilistic tractography methods are applied to obtain connectivity based functional subdivisions of the brain for application to \[^{11}\text{C}-(+)-\text{PHNO}\] PET data. \[^{11}\text{C}-(+)-\text{PHNO}\] is an agonist radioligand which binds to the Dopamine D2/D3 receptors and has preferential affinity for the D3 receptors. Due to its agonist profile and its selectivity for the D3 receptors, it has a higher sensitivity to detect dopamine release in comparison to other antagonist radioligands.

2. Methods

2.1. Data acquisition

A total of eleven healthy volunteers were recruited and underwent two \[^{11}\text{C}-(+)-\text{PHNO}\] PET scans at baseline conditions and after the oral administration of the dopamine releasing agent amphetamine (oral dose 0.3 mg/kg). Furthermore DTI data of 32 directions blip-up and blip-down were acquired for each subject. The study was approved by Essex 1 Research Ethics Committee and the Administration of Radioactive Substances Advisory Committee (ARSAC). All PET and MRI scans were performed at the Clinical Imaging Centre, Hammersmith Hospital, London.

2.2. DTI analysis

DTI data were corrected for motion, eddy-currents and distortions using FSL (FMRIB Software Library, University of Oxford). Subsequently FSL probabilistic tractography, a method that can delineate the neuronal tracts and hence define the probability of connection between brain regions, was applied to derive the connectivity defined functional subdivision (conFROI) of striatum and pallidum. conFROIs were defined using the following projections (a) Limbic: the medial orbital cortex, amygdala and hippocampus are connected to the limbic striatum whose limbbic area then projects to the limbic pallidum, (b) Associative: dorsolateral prefrontal cortex projects to the associative striatum which subsequently projects to the associative pallidum (c) Sensorimotor: the primary, premotor and SMA cortices project to the sensorimotor striatum which then projects to the sensorimotor pallidum. The probabilistic tractography took place in each subject’s space (diffusion space) and the results were non-linearly registered to the MNI space using the non-linear deformation algorithm FNIRT [2]. The CIC neuroanatomical atlas [3] was used for the definition of the cortical, striatal and pallidal masks.

2.3. PET analysis

PET images were corrected for motion by realigning each frame to a reference frame using mutual information as the cost function. The basis-function implementation of SRTM was applied to the dynamic PET data to derive parametric images of the binding potential (\(BP_{ND}\)) which reflects the receptor availability [4]. conFROIs were then applied to the parametric \(BP_{ND}\) images to derive the conFROIs \(BP_{ND}\) estimates.

2.4. Dopamine release measurements

For each conFROI dopamine release was calculated as the percent change in \(BP_{ND}\) elicited by amphetamine (\(\Delta BP_{ND}\)),

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\Delta BP_{ND} = \frac{BP_{ND}^{\text{amph}} - BP_{ND}^{\text{Base}}}{BP_{ND}^{\text{Base}}} \times 100 \% \quad (1)
\]

where \(BP_{ND}^{\text{Base}}\) is the \(BP_{ND}\) in the baseline condition and \(BP_{ND}^{\text{amph}}\) is the \(BP_{ND}\) in the amphetamine condition.
3. Results
Across subjects, a topographically consistent subdivision of the basal ganglia was achieved. The in-vivo human connectivity derived functional subdivisions demonstrated a functional organisation similar to that obtained in post-mortem non-human primate tracing studies [1], shown in figure 1. The dopamine release estimates in the conFROIs of striatum and pallidum are presented in figure 2.

![Functional subdivisions (conFROIs) of the BG for a representative subject defined using structural connectivity information from DTI.](image)

**Figure 1.** Functional subdivisions (conFROIs) of the BG for a representative subject defined using structural connectivity information from DTI.

![The percentage BPND change elicited by amphetamine administration.](image)

**Figure 2.** The percentage BPND change elicited by amphetamine administration.

4. Conclusions
The anatomical connectivity data from DTI were able to produce robust subdivision of the BG that corresponded well to post-mortem data. Dopamine release was highest in the limbic area followed by the sensorimotor and then the associative area with this pattern reflected in both striatum and pallidum.

References
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