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Quantification of receptor–ligand binding potential in sub-striatal domains using probabilistic and template regions of interest

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ABSTRACT

Sub-striatal regions of interest (ROIs) are widely used in PET studies to investigate the role of dopamine in the modulation of neural networks implicated in emotion, cognition and motor function. One common approach is that of Mawlawi et al. (2001) and Martinez et al. (2003), where each striatum is divided into five sub-regions. This study focuses on the use of two spatial normalization-based alternatives to manual sub-striatal ROI delineation per subject: manual ROI delineation on a template brain and the production of probabilistic ROIs from a set of subject-specific manually delineated ROIs. Two spatial normalization algorithms were compared: SPM5 unified segmentation and ART. The ability of these methods to quantify sub-striatal regional non-displaceable binding potential (BP_{ND}) and BP_{ND} % change (following methylphenidate) was tested on 32 subjects (16 controls and 16 ADHD patients) scanned with the dopamine D_2/D_3 ligand [^{18}F]fallypride. Probabilistic ROIs produced by ART provided the best results, with similarity index values against subject-specific manual ROIs of 0.75–0.89 (mean 0.84) compared to 0.70–0.85 (mean 0.79) for template ROIs. Correlations (r) for BP_{ND} and BP_{ND} % change between subject-specific manual ROIs and these probabilistic ROIs of 0.90–0.98 (mean 0.95) and 0.98–1.00 (mean 0.99) respectively were superior overall to those obtained with template ROIs, although only marginally so for BP_{ND} % change. The significance of relationships between BP_{ND} measures and both behavioural tasks and methylphenidate plasma levels was preserved with ART combined with both probabilistic and template ROIs. SPM5 virtually matched the performance of ART for BP_{ND} % change estimation but was inferior for BP_{ND} estimation in caudate sub-regions. ART spatial normalization combined with probabilistic ROIs and to a lesser extent template ROIs provides an efficient and accurate alternative to time-consuming manual sub-striatal ROI delineation per subject, especially when the parameter of interest is BP_{ND} % change.

Abbreviations: ADHD, attention-deficit hyperactivity disorder; ART, automatic registration toolbox; ART_H_T, ART spatial normalization of head MR to template head; ART_B_S, ART spatial normalization of brain MR to target subject brain MR; ART_B_T, ART spatial normalization of brain MR to template brain; ASRS, adult ADHD self-rating scale; AST, associative striatum; A_S, subjective alertness; BP_{ND}, non-displaceable binding potential; DA, dopamine; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition; ICC, intraclass correlation coefficient; MPH, methylphenidate; $mROI_S$, regions of interest manually delineated per subject; $mROI_T$, regions of interest manually delineated on template brain; $mROI_T^S$, regions of interest manually delineated on template brain then warped to subject brain space; $pROI_S$, probabilistic regions of interest in subject brain space; $pROI_T$, probabilistic regions of interest in template brain space; PVC, partial volume correction; ROI, region of interest; SI, similarity index; SMST, sensorimotor striatum; $SPM5\_H_T$, SPM5 unified-segmentation spatial normalization of head MR to template; $SPM5\_B_S$, spatial normalization of brain MR to target subject brain MR using SPM5 unified-segmentation; $SPM5\_B_T$, SPM5 unified-segmentation spatial normalization of brain MR to template; SRTM, simplified reference tissue model; TAC, time–activity curve; VAS, visual analogue scales; VBM, voxel-based morphometry; VST, ventral striatum.

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Introduction

The human striatum, through its connections with the frontal cortex, plays a key role in movement control and higher cognitive functioning. Inputs to the striatum from motor, associative and limbic cortices follow a ventro-medial to dorso-lateral projection pattern, giving rise to functionally distinct cortico-striatal networks (Haber, 2003; Haber et al., 2000). On the basis of their topographic organisation, these networks can be organised into the following neural circuits: (i) limbic, which connects the ventral striatum with the medial pre-frontal, orbito-frontal and anterior cingulate cortex, hippocampus and amygdala, (ii) associative, which links the dorso-lateral pre-frontal cortex with most of the caudate and the pre-commissural putamen and (iii) sensorimotor, which connects motor and pre-motor areas of the cortex with the post-commissural portion of the putamen (Joel and Weiner, 2000). This framework has served to sub-divide the striatum into the following functional modules: ventral striatum (VST), heavily implicated in emotion, motivation and reward-guided behaviours, associative striatum (AST), largely involved in cognition and sensorimotor striatum (SMST), involved in motor function. Catecholaminergic systems (e.g. dopamine) heavily innervate cortico-striatal networks, playing a key role in the modulation of neurotransmission in emotional, cognitive and motor circuits (Haber et al., 2000).

The striatum contains the highest density of dopamine (DA) D_2-type receptors in the brain. Striatal D_2/D_3 receptor availability can be quantified *in vivo* using positron emission tomography (PET) and single photon emission computed tomography (SPECT) to image radioligands such as [^{11}C]raclopride, [^{18}F]fallypride and [^{123}I]IBZM. The binding competition between D_2/D_3 radioligands and endogenous DA provides an imaging paradigm to measure DA transmission in the context of drug- and behavioural challenges through receptor availability parameters such as non-displaceable binding potential (BP_{ND}) (Innis et al., 2007).

The initial impetus to guide the analysis of human striatal D_2/D_3 receptor imaging studies by functional rather than anatomical sub-divisions came from the demonstration that in baboons (Drevets et al., 1999) and humans (Drevets et al., 2001), intra-venous amphetamine induced greater increases of endogenous DA levels (as measured by [^{11}C]raclopride BP_{ND} change) in the antero-ventral striatum than in dorsal caudate, with DA changes in ventral but not dorsal striatum predicting hedonic responses (Drevets et al., 2001). These findings were the first *in vivo* demonstration in humans that DA transmission in the VST plays a key role in the reinforcing properties of drugs of abuse.

A well-replicated region-based approach to investigate the human striatum using D_2/D_3 receptor imaging is that described in Mawlawi et al. (2001) and Martinez et al. (2003). According to this approach, the striatum is subdivided into VST, including nucleus accumbens and antero-ventral portions of caudate and putamen, and the remaining caudate and putamen. The latter regions are further subdivided along their rostro-caudal axis into pre- and post-commissural dorsal caudate and pre- and post-commissural dorsal putamen. The post-commissural portion of the putamen represents the aforementioned SMST, whereas the aggregation of pre-commissural dorsal caudate and putamen, together with post-commissural caudate forms AST.

In as much as the projections from the frontal cortex to the basal ganglia form a functional gradient of inputs from the ventromedial sector through the dorsolateral striatum, apportioning functional roles to distinct striatal sub-regions is only an approximation. However, the wide application of this methodology has proved extremely valuable to our understanding of cortico-striatal DA neurotransmission, both in health (Cervenka et al., 2008; Lappin et al., 2009; Martinez et al., 2003) and disease (Kegeles et al., 2010; Martinez et al., 2007), contributing greatly to the characterisation of drugs acting on the DA system.

The amount of manual intervention needed for this region-based analysis represents a major limiting factor in its general application. One alternative to time-consuming manual delineation is automated/semi-automated segmentation of each scan. Chow et al. (2007) applied a semi-automated method for ROI definition for PET quantification but as the method was applied to the serotonin 1A receptor ligand [^{11}C]WAY-100635 results were not reported for the striatum, which contains a low abundance of these receptors. Fully automated segmentation has been applied for the caudate and putamen in [^{11}C]raclopride imaging (Tohka et al., 2006; Wallius et al., 2008). This approach, however, has not been attempted for sub-divisions of the caudate and putamen.

Another option is to use atlases of human neuro-anatomy in combination with spatial normalization. These approaches can be divided into those based on a single ROI set (Hammers et al., 2002; Rousset et al., 2008; Rusjan et al., 2006; Yasuno et al., 2002) and probabilistic atlases based on the fusion of multiple ROI sets (Ahsan et al., 2007; Eickhoff et al., 2005; Hammers et al., 2003; Heckemann et al., 2006; Hurlemann et al., 2005; Kang et al., 2001; Shattuck et al., 2008; Shidahara et al., 2009; Svarer et al., 2005; Wang et al., 2005). Most of these studies were aimed at automated segmentation of MR studies and none attempted segmentation of the striatum into the aforementioned sub-regions. Of those designed and tested for PET quantification (Hurlemann et al., 2005; Kang et al., 2001; Yasuno et al., 2002; Rousset et al., 2008; Rusjan et al., 2006; Shidahara et al., 2009; Svarer et al., 2005), only the last four report values for the striatum or its divisions.

Rusjan et al. (2006) defined a single set of ROIs on the International Consortium for Brain Mapping (ICBM)/Montreal Neurological Institute (MNI) ICBM/MNI152 brain template and warped the ROIs onto individual MR and hence PET images with SPM2 (www.fil.ion.ucl.ac.uk/spm). Caudate and putamen regions were tested for [^{11}C]raclopride quantification but further sub-division of these structures was not investigated. Rousset et al. (2008) also warped a single ROI set to determine ROIs for both time–activity curve generation and partial volume correction of [^{11}C]raclopride. The regions defined on the MNI305 template (Evans et al., 1993) included caudate and putamen.

Svarer et al. (2005) warped ROIs defined on multiple subjects to produce a probabilistic atlas for each subject that included caudate nucleus and a combined putamen/pallidus region. They showed that producing a probabilistic atlas from multiple subjects significantly improved overlap ratios with manually delineated ROIs compared to warping a single ROI set, consistent with the finding of Heckemann et al. (2006). The correlation between manual and probabilistic ROI determination of distribution volume for the 5HT2 ligand [^{18}F]altanserin in 20 subjects was high but individual results were not given for the striatal regions. Finally, Shidahara et al. (2009) used the probabilistic atlas of Hammers et al. (2003) to produce regional PET values, including caudate and putamen, which were used to inform a voxel-wise partial volume correction technique.

In this study, we apply four approaches for quantification in Mawlawi/Martinez sub-striatal regions based on spatial normalization: manual ROIs delineated on a template brain (ICBM152-2009a; Fonov et al., 2009) which are also warped to subject brain space and two variants of probabilistic ROIs produced by warping a set of subject-specific ROIs to either the ICBM152-2009a template brain or the brain of each subject. Data from a dual-scan protocol of attention-deficit hyperactivity disorder (ADHD) patients and controls with the D_2/D_3 ligand [^{18}F]fallypride are used to assess how well these methods quantify BP_{ND} and BP_{ND} % change.

For the spatial normalization step, two algorithms are compared: unified segmentation in SPM5 (Ashburner and Friston, 2005) and the automatic registration toolbox (ART; Ardekani et al., 2005). This SPM5 algorithm has previously been used in atlas generation (Shattuck et al., 2008) and is also included here as it is a widely used spatial