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Brief report

Association of harm avoidance with dopamine $D_{2/3}$ receptor availability in striatal subdivisions: A high resolution PET study

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ABSTRACT

We examined the relationship between the personality trait of harm avoidance (HA) and the dopamine $D_{2/3}$ receptor availability in striatal subdivisions using high resolution positron emission tomography (PET) with [^{11}C]raclopride. Twenty-one healthy subjects completed 3 T magnetic resonance imaging and high resolution PET scans with [^{11}C]raclopride in order to measure $D_{2/3}$ receptor availability in subregions of the striatum. The $D_{2/3}$ receptor availability was obtained on the basis of the Logan graphical method. The Temperament and Character Inventory was used to measure the biogenetic temperament of HA. The analysis revealed that the HA score had significant negative correlations with $D_{2/3}$ receptor availability in the pre-commissural dorsal caudate and post-commissural putamen, suggesting that HA is associated with $D_{2/3}$ receptor availability in the associative and sensorimotor subdivisions of the striatum, which are mainly involved in cognition and locomotion. Further research is required to determine if pathological states have similar dopaminergic mechanisms in specific striatal subdivisions.

1. Introduction

Several lines of evidence implicate dopamine in the personality trait of harm avoidance (HA), which is defined as a tendency to respond intensely to previously established aversive stimuli signals and to learn to passively avoid punishment, novelty, and frustrating non-reward (Montag et al., 2010; Cloninger et al., 1993). HA is also associated with ruminating about future outcomes, shyness, and being careful in uncertain situations (Cloninger et al., 1993; Pud et al., 2004). Two previous positron emission tomography (PET) studies using [^{11}C]FLB457 and [^{18}F]DOPA reported that HA was related to dopamine transmitter parameters in normal subjects and in patients with Parkinson's disease (Yasuno et al., 2001; Kaasinen et al., 2001). Yasuno et al. (2001) reported a significant negative relationship between HA and dopamine D_2 receptor binding with [^{11}C]FLB457 in normal subjects, while Kaasinen et al. (2001) reported that HA score showed a significant positive correlation with [^{18}F]DOPA uptake in the caudate nucleus of the patients with Parkinson's disease. There was also a report that anxiety-related personality traits were associated with low striatal presynaptic dopamine synthesis capacity in normal subjects (Laakso et al., 2003). Considering the complex role of dopamine within the striatum, a heterogeneous structure that includes several anatomic and functional subdivisions (Mawlawi et al., 2001; Martinez et al., 2003), it is hypothesized that HA may be associated with specific striatal subdivisions subserving cognitive processing. Hence, in the present study, we examined the relationship between HA and dopamine $D_{2/3}$ receptor availability in striatal subdivisions in healthy normal subjects using high resolution PET instrumentation with [^{11}C]raclopride in order to better characterize the role of dopamine in this core personality trait.

2. Experimental procedures

The study protocol was approved by the Institutional Review Board of the Gachon University of Medicine and Science, and all procedures used in the study were conducted in accordance with international ethical standard, Declaration of Helsinki. Participants were recruited through local advertisements. After giving their written informed consent, 21 healthy normal subjects (8 men, 13 women; mean age: 34.6 ± 8.8) participated in the study. Table 1 shows the demographic characteristics of the subjects. Subjects underwent complete medical, neurological, and psychiatric examinations in order to ensure the absence of disease. The psychiatric evaluation included lifetime and current DSM-IV axis I diagnoses that were determined by the Structured Clinical Interview for Axis I DSM-IV Disorders (SCID) (First et al., 1996). Exclusion criteria included a past or present psychiatric or neurological disorder, alcohol or substance abuse, medical conditions such as immunologic, metabolic, and cardiovascular disorders, and a history of head trauma with loss of consciousness. None of the subjects were taking any medication known to affect dopaminergic neurotransmission. All subjects had normal 3 T magnetic resonance imaging (MRI) scans as evaluated by a radiologist.

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Table 1
Demographic characteristics of the subjects ($N = 21$).

Variables	Mean ± SD/number (percentage)
Age (years)	34.6 ± 8.8
Gender	
Male	8 (38%)
Female	13 (62%)
Education (years)	14.8 ± 1.5
Marital status	
Single	11 (52.0%)
Married	10 (48.0%)
Smoking status	
Nonsmoking	17 (81%)
Smoking	4 (19%)

SD, standard deviation.

The Temperament and Character Inventory (TCI) (Cloninger et al., 1993) was used to measure the biogenetic temperament of HA. All subjects completed PET scanning using the High Resolution Research Tomograph (HRRT) system (Siemens Molecular Imaging, Knoxville, Tennessee). Emission data were collected as listmode data in the 3-dimensional mode during 60 min after [^{11}C]raclopride injection. The tracer [^{11}C]raclopride was synthesized as previously described by methylation of the desmethyl precursor using [^{11}C]iodomethane (Wilson et al., 2000; Fei et al., 2004). A saline solution of 527.25 (SD = 37.00) MBq [^{11}C]raclopride with a specific activity at time of injection of 62.16 (SD = 24.42) GBq/μmol was injected as a bolus into an intravenous line. Transmission scans using ^{137}Cs were used to correct for attenuation of the emission scans. The 3D ordinary Poisson ordered-subset expectation maximization algorithm accelerated by the parallelized computations (Hong et al., 2007) was used for the reconstruction. The 19 frames (2×30 s, 4×60 s, 2×90 s, 2×210 s, 9×300 s) were reconstructed from the listmode data. The 207 planes covering an axial field of view of 25.2 cm (axial sampling of 1.22 mm) were generated for each time frame. The in-plane and axial resolutions were 2.52 and 2.57 mm full-width half-maximum at the center of the field of view, respectively. Attenuation, scatter, and decay time correction were estimated and applied for each frame.

To permit accurate delineation of the brain regions for data analysis, each subject underwent an MRI scan using a 3 T scanner (Magnetom Verio; Siemens, Germany). A magnetization-prepared rapid acquisition gradient echo 3D T1-weighted sequence with 1 mm thickness was performed. The MRI scan of each subject was coregistered to his or her PET scan using statistical parameter mapping software (SPM8). The spatial normalization of the coregistered MRI images of each subject was performed on the Montreal Neurological Institute template using SPM8 and the estimated transform was applied to the corresponding PET images. Regions of interest (ROIs) were drawn on each individual's MRI. ROIs were manually drawn tightly on the boundary of the structure to minimize the partial volume effect. The striatum was divided into 5 anatomic ROIs, including the ventral striatum (VST), the pre-commissural dorsal caudate (preDCA), the pre-commissural dorsal putamen (preDPU), the post-commissural caudate (postCA), and the post-commissural putamen (postPU), following the guidelines specified in the studies by Mawlawi et al. (2001) and Martinez et al. (2003). Fig. 1 shows representative MRI and PET images indicating the precise location of the striatal ROIs. The cerebellum was used as the region of reference for the analysis without arterial blood sampling. Time–activity curves were generated for each ROI by averaging the dynamic PET images, which were coregistered to the corresponding MRI images. Activities from left and right regions were averaged. The distribution volume ratio (DVR) for [^{11}C]raclopride was obtained on the basis of the Logan graphical method (Logan et al., 1996).

To evaluate the relationship between HA and dopamine $D_{2/3}$ receptor availability in striatal subdivisions, Pearson's product–moment correlations were calculated between HA score and dopamine $D_{2/3}$ receptor availability in subregions of the striatum. The level of statistical significance was defined as $p < 0.05$ (two-tailed).

Table 2
[^{11}C]Raclopride DVRs in subregions of the striatum.

Striatal subdivisions	Mean (SD)	Range
VST	3.64 (0.19)	3.34–4.16
preDCA	4.09 (0.19)	3.75–4.39
preDPU	4.45 (0.25)	3.94–4.89
postCA	3.62 (0.35)	2.98–4.42
postPU	4.78 (0.29)	4.36–5.41

SD, standard deviation; DVR, distribution volume ratio; VST, ventral striatum; preDCA, pre-commissural dorsal caudate; preDPU, pre-commissural dorsal putamen; postCA, post-commissural caudate; postPU, post-commissural putamen.

3. Results

The mean HA score was 48.9 (SD = 12.7, range 27–70) and the [^{11}C]raclopride DVR ranged from 2.98 to 5.41. Table 2 shows the [^{11}C]raclopride DVR in each subregion of the striatum. Correlation coefficients showing the relationship between the DVR values in the striatal subregions are presented in Table 3. Regarding the relationship between demographic variables and

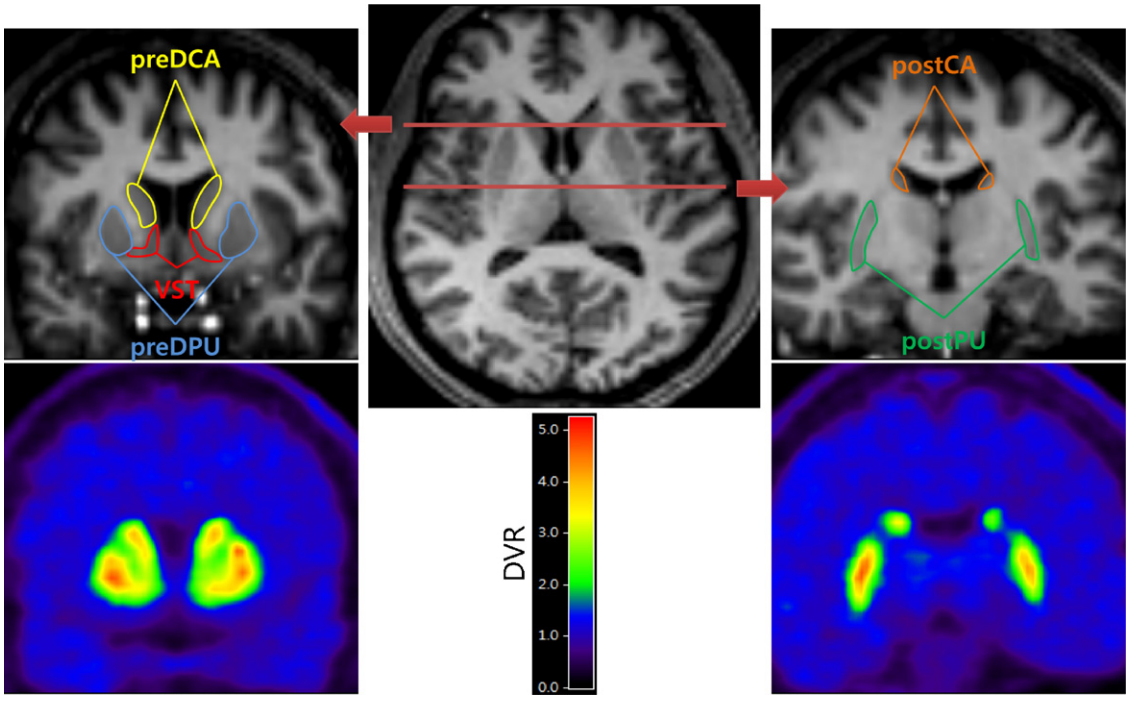

Fig. 1. Representative magnetic resonance imaging (MRI) and positron emission tomography (PET) images showing the precise location of the striatal regions of interest (ROIs), i.e., the pre-commissural dorsal caudate (preDCA), the pre-commissural dorsal putamen (preDPU), the ventral striatum (VST), the post-commissural caudate (postCA), and the post-commissural putamen (postPU). ROIs were manually drawn tightly on the boundary of the structure. Averaged distribution volume ratios (DVRs) within the ROIs were obtained for use in data analysis.