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Modulation of striatal dopamine D1 binding by cognitive processing

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ABSTRACT

There is strong evidence that dopamine (DA) is implicated in higher-order cognitive functioning, but it remains controversial whether D1 receptor binding can be modified by cognitive activity. We examined striatal D1 binding potential (BP) in 20 younger (22–30 years) and 20 older (65–75 years) persons who underwent two [^{11}C] SCH 23390 PET measurements, one while resting and one while performing a cognitive task taxing inhibitory functioning. The younger persons showed significant task-related BP reductions in sensorimotor, limbic, and associative striatum during cognitive activity compared to rest. Older persons showed no reliable BP reductions in any striatal subregion. These findings demonstrate that D1 receptor binding can be modified by cognitive activity in younger persons, but also provide novel evidence for the notion that human aging is associated not only with lower DA receptor density but also with altered modifiability of the DA system.

Introduction

Converging evidence indicates that dopamine (DA) is implicated in higher-order cognitive functions (Bäckman et al., 2006; Cropley et al., 2006). Molecular imaging studies using radioligands for both D1 (Bäckman et al., 1997; Wang et al., 1998) and D2 (Volkow et al., 1998; Bäckman et al., 2000) receptors show that lower DA receptor binding is associated with poorer cognitive performance. In these studies, DA receptor binding during resting state was related to performance in cognitive tasks administered at a separate occasion.

A more direct way to assess the link between DA function and cognitive performance is to compare DA binding during actual cognitive task performance with binding at resting state. Given that DA is linked to cognition, radioligand binding should be altered while engaging in a cognitive task compared to rest. Specifically, to the extent that DA release is increased during cognitive performance, ligand receptor binding should be reduced during cognitive activity, because of competition with endogenous DA (Laruelle, 2000). Reduced D2 binding potential (BP) has been reported during motor tasks (Koepp et al., 1998; Ouchi et al., 2002; Pappata et al., 2002; Badgaiyan et al., 2008) as well as cognitive tasks (Aalto et al., 2005; Christian et al., 2006; Ko et al., 2009; Monchi et al., 2006; Sawamoto et al., 2008). No previous study has examined potential alterations in D1 receptor binding induced by cognitive demands, although D1 receptors are strongly implicated in higher-order cognitive functioning (Sawaguchi and Goldman-Rakic, 1991; Williams and Goldman-Rakic, 1995; Wang et al., 1998; Vijayraghavan et al., 2007). In addition, altered prefrontal and parietal D1 receptor density was recently demonstrated during resting state after five weeks of cognitive training (MacNab et al., 2009), which justifies examining direct effects of cognitive activity on D1 receptor binding.

There are age-related losses of both D1 (Suhara et al., 1991; Wang et al., 1998) and D2 (Nordström et al., 1992; Ichise et al., 1998) receptor densities (Bäckman et al., 2006 for review). In age-comparative molecular imaging work, strong relationships have consistently been found between D1 or D2 markers and cognitive performance (Wang et al., 1998; Volkow et al., 1998; Bäckman et al., 2000; Reeves et al., 2005), indicating that age-related DA losses contribute to cognitive deficits in late life (Bäckman and Farde, 2004; Bäckman et al., 2006). A recent study comparing D2 binding during a spatial working-memory task and a visuomotor task reported that patients with Parkinson's disease, unlike controls, did not exhibit decreased striatal D2 binding during the cognitive task (Sawamoto et al., 2008). The fact that aging is associated with a severely compromised striatal DA system (Bäckman and Farde, 2004; Reeves et al., 2005) opens up for the possibility that older persons may not release DA to the same extent as younger persons in response to a cognitive challenge.

Here we examined whether striatal D1 receptor binding can be modified by cognitive processing relative to rest in younger and older

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adults, using the Multi-Source Interference Task (MSIT), which involves trials that tax the ability to suppress irrelevant information as well as control trials (Bush et al., 2003). The striatum was operationally divided into three different compartments: sensorimotor, associative, and limbic striatum (Martinez et al., 2003; Cervenka et al., 2008). PET and the radioligand [^{11}C] SCH23390 were used to determine D1 binding (Farde et al., 1987).

Methods

Participants

Twenty young (mean age = 25.2 years, range = 22–30; 10 male, 10 female) and 20 old (mean age = 70.3 years, range = 65–75; 10 male, 10 female) persons were recruited through a newspaper advertisement. Mean years of education was 14.67 for the young (SD = 1.97) and 14.30 for the old (SD = 2.96, p > .70). Exclusion criteria included mental disorders, brain damage, other significant medical conditions, actual or previous drug or alcohol abuse, nicotine use, and hormone therapy. Cognitive testing outside the PET system revealed that the two samples were highly representative of their birth cohorts: There was a clear advantage of the young in tests of episodic memory and perceptual speed (Free recall of words: M_{young} = 11.90 [SD = 2.31], M_{old} = 9.60 [SD = 2.46], t = 3.05, p < .01; Digit symbol: M_{young} = 35.75 [SD = 13.90], M_{old} = 20.30 [SD = 5.90], t = 4.57, p < .01). By contrast, the old outperformed the young in tests of crystallized intelligence (Vocabulary: M_{young} = 29.30 [SD = 2.49], M_{old} = 33.30 [SD = 2.00], t = 5.59, p < .01; General knowledge: M_{young} = 23.20 [SD = 2.28], M_{old} = 25.30 [SD = 3.08], t = 2.45, p = .02). Written informed consent was obtained from all participants, and the study was approved by the Ethics and Radiation Safety Committees of the Karolinska Hospital, Stockholm, Sweden.

Experimental design

All participants were included in a larger study with several examinations including 1) health screening and cognitive testing, 2) resting state PET measurement, 3) PET measurement during the MSIT, 4) fMRI measurement, 5) fMRI measurement with a DA antagonist (younger persons only), and 6) pharmacological PET measurement (5 younger participants only), all performed on separate occasions. The whole study protocol was completed within 2 months. Participants were paid 4000–6000 SEK for their participation depending on which measurements they took part in. This study includes data from measurements 1, 2 and, 3 (see above). Each participant underwent two [^{11}C] SCH23390 PET measurements. During the first measurement, participants were instructed to rest and were free to keep their eyes open or closed. During the second measurement, they performed the MSIT. In 10 younger and 13 older persons, both PET measurements were performed on the same day; in the others, the PET measurements were performed on separate days. All PET measurements were performed in the afternoon.

Cognitive task

The MSIT is an interference task involving a combination of Stroop, Flanker and Simon-type tasks (Bush et al., 2003). Participants were shown stimuli with three figures, using the numbers 0, 1, 2, 3 (e.g., $002; 010; 131, 221$). For each stimulus they were to indicate, as quickly and accurately as possible, which figure was different from the other two. This was done using a keypad with three buttons representing the numbers 1, 2, and 3 from left to right. The task included 384 control trials and 384 interference trials. In the control trials, the distracters were always the number "0", the target was always larger than the distracters, and always presented congruently with the button press position. In the interference trials, both the target and distracters were numbers, the target number could be larger or smaller than the distracters, and the target was always presented incongruently with the button press position. Trials were presented in 16 blocks with 24 control trials and 24 interference trials in each block. Each trial lasted 2s. After blocks four and eight, there was a 90 s break. The cognitive task started simultaneously with the PET measurement and lasted for approximately 30 min. Accuracy and response latencies were calculated separately for control versus interference trials. One young subject had missing data on the MSIT, because of problems with the response pad. Excluding her imaging data did not alter the results, and thus, her data were included in the imaging analysis.

Positron Emission Tomography and Magnetic Resonance Imaging

Two PET measurements on separate occasions were obtained with an ECAT Exact HR 47 system (CTI/Siemens, Knoxville, TN) run in 3D mode. The transaxial resolution is 3.8 mm full width at half maximum (FWHM) at the centre of the field of view and 4.5 mm FWHM tangentially and 7.4 mm radially at 20 cm from the centre. Prior to each emission measurement, a transmission measurement of 10 min was performed using three rotating 68Ge–68Ga sources. The information was used for attenuation correction. [^{11}C] SCH23390 was prepared as described previously (Halldin et al., 1986) and injected into the left antecubital vein as a rapid bolus injection. Emission data were acquired over a period of 51 min in 13 frames of progressively increasing duration.

T1-weighted images were acquired with a 1.5-T GE Signa Scanner. Images were reconstructed into a $256 \times 256 \times 156$ matrix, with a resolution of $1.02 \times 1.02 \times 1$ mm^3. The MRI images were spatially normalized using the SPM2 software (Wellcome Department of Cognitive Neurology, UK). The line defined by the anterior and posterior commissures was parallel to the horizontal plane, and the inter-hemispheric plane was parallel to the sagittal plane.

Regions of interest

[^{11}C] SCH23390 BP was calculated for three striatal regions of interest (ROIs): sensorimotor, limbic, and associative striatum. These subregions of the striatum have been described previously (Martinez et al., 2003; Cervenka et al., 2008). Briefly, the sensorimotor striatum corresponds to the post-commissural part of dorsal putamen, the limbic striatum includes the ventral portion of the striatal complex, and the associative striatum is defined as the precommissural putamen and dorsal caudate nucleus. The cerebellum, where dopamine D1 receptor density is negligible, served as the reference region (Hall et al., 1998).

The ROIs were manually delineated on each individual MR image using the Human Brain Atlas software (Roland et al., 1994). The PET images were coregistered to the MRI images and re-sliced to a voxel size of $2 \times 2 \times 2$ mm. The MRI-defined ROIs were displayed on the corresponding PET images. To obtain time–activity curves, regional radioactivity was calculated for each frame, corrected for decay and plotted versus time. BP for [^{11}C] SCH23390 was calculated according to the Simplified Reference Tissue model (Gunn et al., 1997), separately for both hemispheres as well as pooled across hemispheres.

Statistical parametric mapping

Voxelwise [^{11}C] SCH23390 binding was calculated using the wavelet approach (Cselenyi et al., 2006). Images were transformed into wavelet space using a 3D wavelet transform. The kernel length was 26 and the depth of composition was 1. The resulting parameters were analyzed using the reference region version of Logan's linear graphical estimation, with the cerebellum as reference region (Logan et al., 1996). The resulting parametric transform describing pixel by pixel distribution volume ratio (DVR) -1 of [11C]SCH23390, defined as the D1-receptor binding potential (BP), was reconstructed into 3D BP