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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

images in normal space. Images were spatially normalized to the MNI template in SPM2 and smoothed using a 12 mm filter.

Statistical analysis

Group comparisons on the behavioral data were analyzed with *t*-tests, with the alpha level set to .05.

For the associations between baseline BP and performance on the MSIT, as well as those between the reduction of BP and MSIT performance, product–moment correlations were calculated. One-tailed tests of significance were used, because previous research unequivocally demonstrates positive correlations between BP and cognitive performance (e.g., Bäckman et al., 2006; Cervenka et al., 2008; Cropley et al., 2006; Erixon-Lindroth et al., 2005). The alpha level was set to .05 here too. For the correlations between reduction in BP and MSIT performance, a Bonferroni correction for the three compartments was made in order to adjust for multiple comparisons.

Group differences in the reduction of BP between baseline and cognitive activation were analyzed using a mixed age group (young, old) × striatal region (sensorimotor, associative, limbic) × condition (rest, cognitive activity) multivariate analysis of variance (MANOVA), with repeated measures on the last two factors. MANOVAs were conducted for both ROI-based and SPM-based BP values.

A median-split (high versus low baseline D1 BP in the three striatal compartments) was performed in both age groups. ANOVAs (BP: high, low) × (condition: rest, cognitive activity) were then conducted within age groups for the three subregions.

In the SPM analyses, masks were created including BP values above .85 for the younger participants and BP values above .60 for the older participants. These values were found to restrict the analyses to the striatum. BP values from the parametric images were extracted from a spherical region of interest (radius = 4 mm) centred at the *x*, *y*, and *z* coordinates of the peak. Paired *t*-tests were used to examine BP reductions in the ROI-based as well as in the SPM-based analyses.

Results

Cognitive performance

Both younger and older participants performed at a high level (accuracy > 90%) on the MSIT for both control and interference items (Fig. 1). There was no significant age difference on control item accuracy (young = 99.3%, old 99.0%, $p = .40$), although the young outperformed the old on interference items (young = 96.1%, old 90.2%, $p = .05$). Further, the young had shorter latencies on control items (young: $M = 588$ ms, $SD = 79$; old $M = 633$ ms, $SD = 46$; $p = .04$), and this age difference was magnified for interference items (young: $M = 927$ ms, $SD = 114$; old $M = 1021$ ms, $SD = 91$; $p = .01$). Critically, all participants managed to maintain task performance across all trials. There were no training-related gains on accuracy or for latencies over time ($ps > .18$), except that older persons became significantly faster at responding to control items across trials ($p < .01$). These data confirm that the MSIT engages participants over an extended time period and is therefore suitable for imaging approaches requiring long acquisition times (Bush et al., 2003).

Baseline D1 binding

Analyses of ROI-based values showed that, in younger persons, mean baseline BP was highest in sensorimotor striatum ($M = 1.77$, $SD = .31$), followed by associative ($M = 1.52$, $SD = .25$), and limbic ($M = 1.27$, $SD = .27$) striatum. This rank order is in accordance with previous studies on D2 receptor binding in the striatal compartments (Cervenka et al., 2008). Older persons displayed the same pattern with highest mean BP in sensorimotor striatum ($M = 1.35$, $SD = .20$), followed by associative ($M = 1.13$, $SD = .17$) and limbic ($M = 1.06$, $SD = .18$) striatum.

Younger participants had significantly higher baseline BP than older participants in all striatal compartments, with the largest difference observed in associative striatum (25.7%), followed by the sensorimotor (24.3%) and limbic (16.5%) regions. All these age differences were statistically reliable ($p < .01$).

Associations between baseline D1 binding and cognitive performance

Of the cognitive measures (i.e., interference and control item accuracy, and latencies for interference and control items), interference item accuracy on the MSIT was positively related to baseline BP in all three striatal compartments (sensorimotor: $r = .40$, $p = .04$; associative: $r = .52$, $p = .01$; and limbic $r = .43$, $p = .03$) for younger persons (Fig. 2), whereas no reliable correlations were observed for control item accuracy or the latency measures. For the older persons,

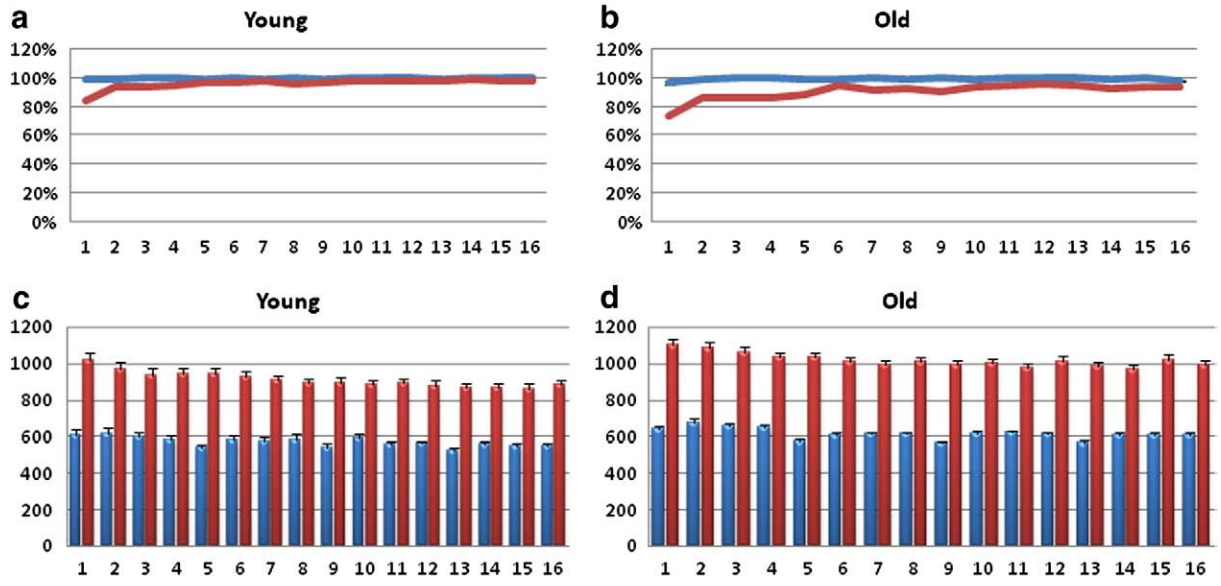

Fig. 1. Performance on the MSIT for each of the 16 blocks of trials. (a,b). Accuracy for interference (red) and control (blue) items in younger and older persons. (c, d). Latencies for interference (red) and control (blue) items in younger and older persons. Error bars indicate standard errors around the means.

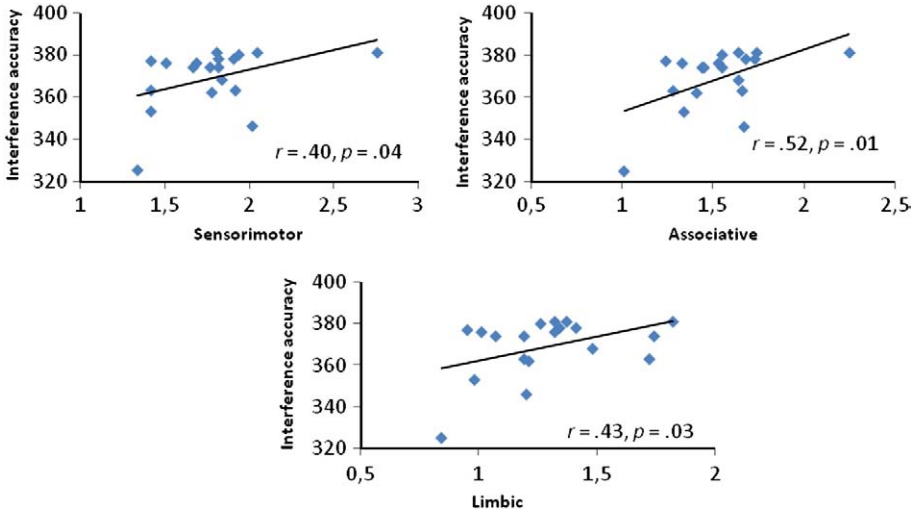

Fig. 2. Relationships of D1 binding potential during rest in sensorimotor, associative, and limbic striatum to interference item accuracy for younger persons.

no reliable correlations with D1 binding were observed for interference item accuracy (sensorimotor: $r=-.26$, $p=.13$; associative: $r=-.11$, $p=.31$; and limbic $r=.20$, $p=.20$), or for any other performance measure.

Task-related reduction in D1 binding

We adopted two different data-analytic procedures for the D1 binding data; one involving quantification of binding in manually defined regions and one involving voxelwise analysis using statistical parametric mapping (SPM).

Younger adults demonstrated lower D1 BP in striatal regions for ROI-based as well as SPM-based analyses during the MSIT relative to rest. In the ROI-based analyses, a 3.9% decrease was seen in left associative striatum. The difference between resting BP ($M=1.55$, $SD=.27$) and cognitive activation ($M=1.49$, $SD=.29$) was significant ($t=2.46$; $p=.02$). Similar trends were observed for left sensorimotor (4.6%, $p=.07$) and right limbic (6.0%, $p=.06$) striatum. The older adults demonstrated no significant reductions in any of the striatal compartments.

In the SPM analysis, the younger participants showed reliable reductions in D1 BP for all three striatal regions during cognitive activity compared to rest (Fig. 3). The largest cluster of voxels was seen in left sensorimotor striatum ($t=4.47$, cluster size = 116 voxels), with a peak at coordinates $x=-34$, $y=-8$, $z=0$. The reduction in this cluster was 10.4%. The difference in BP between resting state ($M=1.05$, $SD=.22$) and cognitive activation ($M=.93$, $SD=.18$) was significant ($t=4.40$, $p<.01$). There was also a significant BP reduction in right limbic striatum ($t=3.19$, cluster size = 71 voxels) at coordinates $x=22$, $y=6$, $z=-8$. Here, the reduction was 9.5%. Mean BP was 1.02 ($SD=.19$) at resting state and .91 ($SD=.16$) during cognitive activity ($t=3.14$, $p<.01$). Finally, there was a smaller but significant cluster ($t=3.45$, cluster size = 15 voxels) in left associative striatum at coordinates $x=-12$, $y=8$, $z=8$, showing a 7.0% reduction during the MSIT. The difference in BP at resting state ($M=1.02$, $SD=.23$) and cognitive activity ($M=.94$, $SD=.22$) was again significant ($t=3.22$, $p<.01$; Fig. 4).

For the younger persons, some significant BP decreases during the MSIT relative to rest in areas outside the striatum were observed in the SPM-based analyses. These include bilateral cuneus (BA 17; coordinates right: $x=2$, $y=-78$, $z=12$; left: $x=-2$, $y=-78$, $z=10$), bilateral cingulate gurus (BA 24; coordinates right: $x=6$, $y=4$, $z=42$; left: $x=-6$, $y=-8$, $z=44$), left amygdala (coordinates: $x=-24$, $y=-6$, $z=-18$), and right insula (coordinates: $x=38$, $y=18$, $z=4$). However, none of these reductions were observed in the ROI-based analyses and, therefore, the effects should be treated with caution. The elderly persons showed no significant decreases in any parts of the striatum or in extrastriatal areas in the SPM-based analyses either (Fig. 4).

Next, we performed MANOVAs using both ROI-based and SPM-based values extracted from 4 mm spheres around the peaks where younger persons displayed significant BP reductions. As expected, both analyses yielded significant main effects of age group (ROI analysis: $F(3,36)=6.92$, $p<.01$; SPM analysis: $F(3,36)=18,74$, $p<.01$). There were no significant main effects of condition. Most importantly, there was an overall significant age by condition

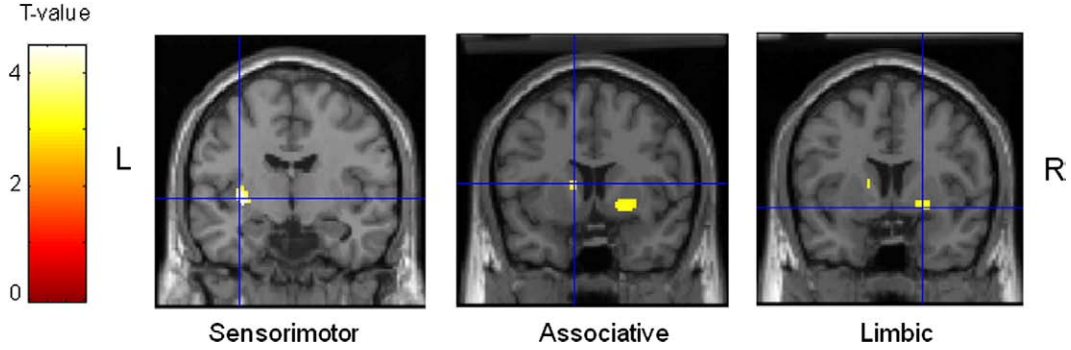

Fig. 3. Map of *t*-values showing voxels with decreases of D1 binding potential in younger persons during the MSIT ($p<.005$, ≥ 10 voxels).

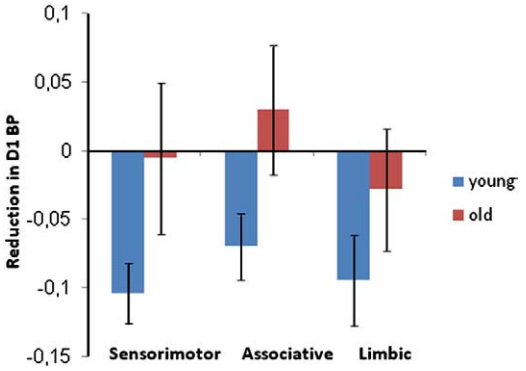

Fig. 4. Reductions in D1 binding potential in younger, but not older, persons during the MSIT in sensorimotor, associative, and limbic striatum. Data are extracted from SPM-based analyses. Error bars indicate standard errors around the means.

interaction in the ROI analysis ($F(3,36) = 9.67$, $p < .01$), and a tendency toward such an interaction in the SPM-based analysis ($F(3,36) = 1.98$, $p = .13$). Univariate ANOVAs showed that the age by condition interactions were significant in left sensorimotor striatum (ROI: $F(1,38) = 12.75$, $p < .01$; SPM: $F(1,38) = 5.26$, $p < .03$) and the associative striatum (ROI: $F(1,38) = 2.31$, $p < .01$; SPM: $F(1,38) = 4.98$, $p < .04$), but not in limbic striatum (ROI: $F(1,38) = .66$, $p = .42$; SPM: $F(1,38) = 2.39$, $p = .13$), demonstrating that BP in younger persons decreased more between baseline and cognitive activation as compared to the older persons. Although there was no significant interaction in the limbic striatum, younger, but not older, persons showed a decrease of BP under cognitive activity also in this region.

In order to verify that higher baseline BP was not the reason for the age × condition interaction effect, we performed a median-split (high versus low baseline BP in the three striatal subregions). Then, baseline BP level (high, low) × condition ANOVAs were conducted within age groups for the three striatal compartments. Critically, in these analyses, the BP level × condition interactions were non-significant in all striatal compartments in the younger (sensorimotor $p = .34$; associative $p = .90$; limbic $p = .10$) and older (sensorimotor $p = .36$; associative $p = .78$; limbic $p = .23$) age group.

Functional relationship between task-related reduction in D1 binding and cognitive performance

To determine the functional effects of the observed BP reductions during cognitive activity in the young, Bonferroni-corrected correlations were computed between the relative differences in BP during rest and MSIT (rest BP − MSIT BP)/rest BP) and interference item accuracy. The magnitude of reduction in D1 binding in limbic striatum during the MSIT was related to interference item accuracy (ROI-based values: $r = .61$, $p = .01$; Fig. 5). A similar relationship was observed for reduction in D1 binding in associative striatum (SPM-based values, $r = .55$, $p = .02$), but not for sensorimotor striatum ($ps > .30$). In both cases, greater decrease in BP during the MSIT was associated with higher cognitive performance.

Discussion

We demonstrate that striatal DA D1 receptor binding can be modified by cognitive activity in younger, but not older, persons. For younger persons, D1 binding was reduced in three striatal compartments during the MSIT compared to rest. Specifically, SPM analyses showed BP decreases in voxels corresponding to left sensorimotor, left associative, and right limbic striatum, and ROI-based analyses yielded significant reductions in left associative striatum, with left sensorimotor and right limbic striatum showing the same tendency. A similar left-lateralized DA binding reduction in associative and sensorimotor striatum was demonstrated by Lappin et al. (2009) in response to both a motor control and a motor learning task. The magnitude of the observed reductions varied between 7 and 10% in the SPM-based analyses. These reductions are comparable to those observed for D2 binding in the striatum during cognitive performance (Monchi et al., 2006).

Reductions in D2 receptor binding during cognitive challenges have previously been demonstrated in younger persons using [^{11}C] FLB457 (Aalto et al., 2005; Ko et al., 2009), [^{11}C] raclopride (Monchi et al., 2006; Sawamoto et al., 2008), and fallypride (Christian et al., 2006) in both striatum (Monchi et al., 2006; Sawamoto et al., 2008) and in extrastriatal areas (Aalto et al., 2005; Ko et al., 2009; Sawamoto et al., 2008). These reductions in binding are interpreted to reflect increased DA release as a function of the cognitive demands. Similarly, the present findings could reflect changes in endogenous DA release. Previous research aimed at pharmacologically challenging endogenous DA levels have failed to show effects on D1 receptor binding in animal studies (Abi-Dhargam et al., 1999; Chou et al., 1999). This has led to the belief that D1 receptor radioligands are unsuitable for measuring changes in the concentration of endogenous DA. However, other research has demonstrated that electrical stimulation of DA receptors in rat brain slices affected the binding of a D1 radioligand even more so than for a D2 ligand (Gifford et al., 1996). Furthermore, a recent study showed that D1 receptor binding in prefrontal and parietal regions was altered after extensive working-memory training (MacNab et al., 2009). These observations support the interpretation that the current finding of altered D1 receptor binding during an acute cognitive challenge reflects enhanced endogenous DA release.

The elderly persons showed no significant reductions in BP during cognitive activity in any part of the striatum. The representative nature of the older sample is evidenced by the fact that they outperformed the young in tests of crystallized intelligence, although they showed deficits in tests of fluid abilities (see Methods). Critically, the younger adults outperformed the older on the more cognitively challenging interference trials in the MSIT, and for response latencies on both interference and control trials. This pattern is consistent with previous data suggesting that the frontostriatal circuitry is compromised in aging (for review, see Bäckman et al., 2006). Further, in accordance with previous studies (Wang et al., 1998; Volkow et al., 1998), the older persons had lower D1 BP values at baseline. Most important, the present findings provide novel information demonstrating that older adults not only have a reduced number of D1 receptors, but also a D1 system that is less responsive in face of a cognitive challenge. Note that the age-group differences in D1 binding reductions were not an effect of baseline differences, as median-split analyses demonstrated no influences of baseline D1 levels on changes between rest and the MSIT. One caveat in comparing PET imaging data of younger and older adults is that aging is associated with decreases in brain volumes, which may influence BP. However, the

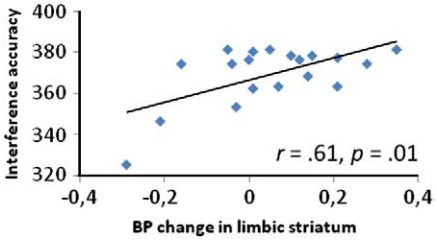

Fig. 5. Relationship between change in D1 binding potential (rest minus MSIT/rest) in limbic striatum and interference item accuracy for younger persons.

fact that the focus of analysis was intra-individual change in BP between conditions should minimize the influence of partial-volume effects.

In the young, reductions in BP during cognitive activity were seen in all three striatal regions. These regions are thought to be functionally different, with the sensorimotor compartment primarily involved in motor functions, the associative striatum involved in cognitive processing, and the limbic compartment implicated in drive and motivation (Martinez et al., 2003). In addition, recent studies indicate that the limbic striatum is involved in memory and executive performance (Adcock et al., 2006; Cervenka et al., 2008). In the present study, baseline BP in young persons was related to MSIT performance in all three compartments for the cognitively more demanding task (interference item accuracy). However, only BP reductions in limbic striatum and associative striatum were functionally linked to task performance, with greater decreases during the MSIT being related to higher scores on the interference task. This pattern of data suggests that increased DA release during task performance reflects the motivational and cognitive demands of the task, rather than the sensorimotor requirements (i.e., responding with a finger press).

To our knowledge, this is the first study to demonstrate reductions in D1 receptor binding in direct response to a cognitive challenge. Thus, our findings provide strong support for a critical role of DA D1 receptors in cognitive performance (Sawaguchi and Goldman-Rakic, 1991; Williams and Goldman-Rakic, 1995; Vijayraghavan et al., 2007), and for age-related deficits in modulating DA activity in response to cognitive demands (Bäckman and Farde, 2004; Reeves et al., 2005; Bäckman et al., 2006).

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