Striatal D₁- and D₂-type Dopamine Receptors Are Linked to Motor Response Inhibition in Human Subjects

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Motor response inhibition is mediated by neural circuits involving dopaminergic transmission; however, the relative contributions of dopaminergic signaling via D₁- and D₂-type receptors are unclear. Although evidence supports dissociable contributions of D₁- and D₂-type receptors to response inhibition in rats and associations of D₂-type receptors to response inhibition in humans, the relationship between D₁-type receptors and response inhibition has not been evaluated in humans. Here, we tested whether individual differences in striatal D₁- and D₂-type receptors are related to response inhibition in human subjects, possibly in opposing ways. Thirty-one volunteers participated. Response inhibition was indexed by stop-signal reaction time on the stop-signal task and commission errors on the continuous performance task, and tested for association with striatal D₁ and D₂-type receptor availability. Stop-signal reaction time was negatively correlated with D₁-type receptor availability, measured using positron emission tomography with [¹¹C]NNC-112 and [¹⁸F]fallypride, respectively. The results indicate that dopamine D₁- and D₂-type receptors are associated with response inhibition, and identify the dorsal striatum as an important locus of dopaminergic control in stopping. Moreover, the similar contribution of both receptor subtypes suggests the importance of a relative balance between phasic and tonic dopaminergic activity subserved by D₁- and D₂-type receptors, respectively, in support of response inhibition. The results also suggest that the stop-signal task and the continuous performance task use different neurochemical mechanisms subserving motor response inhibition.

Key words: dopamine; impulsivity; PET imaging

Introduction

Impulsive actions are premature, poorly conceived, or difficult to suppress (Dalley et al., 2008), and lack of inhibitory control over impulsiveness is a hallmark of an attention deficit hyperactivity disorder (ADHD) and substance use disorders (Bari and Robbins, 2013). Impaired inhibitory control can disrupt goal-directed behavior, with negative consequences that contribute to psychological distress associated with these disorders. Clarifying the mechanisms that mediate inhibitory control, therefore, ultimately may help to guide treatment for disorders characterized by an impulsive phenotype.

Research findings have indicated a role for dopamine in impulsive behavior. Syndromes such as ADHD (Vaidya et al., 1998; Bedard et al., 2003; Senderecka et al., 2012) and addictions (Fillmore and Rush, 2002; Monterosso et al., 2005; Lane et al., 2007; Lee et al., 2009) that feature behavioral disinhibition are associated with dopaminergic dysfunction. In addition, studies of genetic polymorphisms (Colzato et al., 2010, 2013) and pharmacological manipulations (Chamberlain et al., 2006; Eagle and Baunez, 2010) have identified a role for dopaminergic signaling in motor response inhibition, an index of inhibitory control (Chamberlain et al., 2006; Eagle and Baunez, 2010). For example, methylphenidate or d-amphetamine administration improves response inhibition in ADHD patients and healthy subjects, respectively (Tannock et al., 1989; de Wit et al., 2000; Aron et al., 2003), and manipulation of dietary tyrosine (dopamine precursor) alters response inhibition (Colzato et al., 2014; Randhani et al., 2014).
Despite an evident role for dopamine, the relative contributions of dopamine signaling via dopamine D_1- and D_2-like receptor subtypes are unclear. In rats, systemic administration of dopaminergic antagonists does not affect response inhibition (Eagle et al., 2007, 2008; Bari and Robbins, 2013). However, direct infusion of the D_1-receptor antagonist SCH-23390 into the dorsal-medial striatum improves response inhibition, whereas infusion of the D_2 receptor antagonist sulpiride has the opposite effect. Similar infusions into the ventral striatum have no effect (Eagle et al., 2011). Thus, the effects of dopamine receptor subtype signaling on response inhibition appear to be regionally specific and possibly opposing. In addition, the administration of the D_2-specific agonist cabergoline improves response inhibition (Nandam et al., 2013), and striatal D_2-type receptor availability is correlated with the capacity for response inhibition and corresponding neural activation during inhibition in humans (Ghahremani et al., 2012). Nonetheless, human investigations of the role of D_1-type receptors in response inhibition and direct comparisons of D_1- vs D_2-type receptor contributions to motor response inhibition have not been performed.

We used positron emission tomography (PET) with [11C]NNC-112 and [18F]fallypride as radioligands for dopamine D_1- and D_2-type receptors, respectively (Mukherjee et al., 1995; Ekelund et al., 2007), to examine the relationships of subtype-selective dopamine receptor availability [binding potential referred to nondisplaceable uptake (BP_{ND})] with measures from prototypical assessments of motor response inhibition—the stop-signal task (SST) and continuous performance task (CPT) (Logan et al., 1984; Tannock et al., 1989; Aron et al., 2014). We hypothesized that dopamine receptors in the dorsal striatum, but not the ventral striatum, would be linked to response inhibition task performance, and that D_1- and D_2-type receptor contributions would be dissociable in this region, reflecting opposing actions.

**Materials and Methods**

**Research participants.** All study procedures were approved by the University of California, Los Angeles (UCLA) Institutional Review Board. Thirty-one healthy volunteers (16 females; mean age, 30.68 years; SD, 8.3 years), who were participating in the UCLA Consortium for Neuropsychiatric Phenomics (CNP; www.phenomics.ucla.edu), completed extensive neuropsychological testing, including tests of response inhibition and MRI scanning (Bilder et al., 2009). CNP participants who expressed interest in being contacted for additional studies were offered flyers or were called via telephone, and were invited to participate in this study involving PET scanning. On average, PET scanning occurred ~17 months after participation in the CNP study. Participants received a complete description of this study and provided written informed consent. Health screening was performed using the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, and a physical examination. Participants were excluded if they met the following criteria: current axis I psychiatric diagnoses other than nicotine dependence; use of psychotropic medications or substances, except marijuana or alcohol; CNS, cardiovascular, or systemic disease; or HIV-seropositive status, hepatic disease, or pregnancy. On all test days, negative urine samples for recent drug use and pregnancy (women) were required.

**Neurobehavioral tasks.** The SST (Logan et al., 1984) and CPT (Tannock et al., 1984) were administered via PC laptop (E-prime version 2.0, Psychology Software Tools). During the SST, participants viewed a series of go stimuli (left/right arrows) and were instructed to respond with corresponding left or right key presses, respectively (go trials). On some trials (stop trials, 25%), an audible tone (stop-signal) was presented after a short delay (stop-signal delay (SSD)) following the go stimulus. Participants were instructed to withhold their responses upon hearing the tone. They were instructed to respond quickly and accurately, and that stopping and going were equal importance. The SSD was adjusted on a trial-by-trial basis according to performance; values were drawn from two interleaved ladders to ensure equal performance levels across participants, producing successful inhibition on ~50% of stop trials. Participants received task training before task initiation, consisting of eight trials (three of which were stop trials).

During the CPT, participants viewed a series of go stimuli (alphabet letters, go trials) and were instructed to respond with a key press. On some trials (no-go trials, 10%), a no-go stimulus was presented (the letter “X”) in lieu of the go stimulus, and participants were instructed to withhold responding. The task comprised 18 blocks, each containing 20 trials at a fixed intertrial interval (ITI): 1000, 2000, or 4000 ms. Participants received task training before initiation, consisting of 10 trials from the 2000 ms ITI type.

**Analysis of neurobehavioral data.** SST data were analyzed using the same methods as in a prior study of a separate sample (Ghahremani et al., 2012). The median and SD of reaction time on go trials were calculated using all-correct go trials [go trial reaction times (GoRTs)]. The average SSD was calculated using all-successful stop trials. The stop-signal reaction time (SSRT) was estimated by subtracting each participant’s average SSD from his/her median GoRT (Band et al., 2003). The percentage of inhibition on stop trials was calculated as the ratio of successful stop trials to all stop trials presented. As recommended (Congdon et al., 2012), participant data meeting the following criteria were removed from analysis: (1) <25% or >75% inhibition on stop trials (n = 3); (2) <60% correct responding on go trials (n = 0); (3) >10% direction errors on go trials (n = 0); and (4) SSRT estimate that was negative or <50 ms (n = 1, computer failure). SST data from 27 participants were subject to analysis, as follows: 22 participants with D_1-type dopamine receptor availability (D_1-type BP_{NSD}); 24 participants with D_2-type BP_{NSD}; and 19 participants with both. Performance data from the CPT were used to compute the mean and SD of the GoRT on all go trials. The commission error (CE) was calculated as the number of failed no-go trials (response to a no-go stimulus).

**PET scanning.** D_1-type BP_{NSD} was assayed using [11C]NNC-112, a high-affinity ligand for D_1-type receptors (Andersen et al., 1992; Ekelund et al., 2007) in 26 subjects (14 females). Dopamine D_2-type BP_{NSD} was assayed on a different day using [18F]fallypride, a high-affinity radioligand for D_2-type receptors (Mukherjee et al., 1995) in 27 subjects (14 females). PET scanning was performed on a Philips Gemini Tru Flight PET/CT scanner in 3D mode (FWHM = 5.0 mm × 4.8 mm; 90 slices; voxel size, 2 mm^3). A CT transmission scan was performed to obtain data for measured attenuation correction. After a bolus injection of [11C]NNC-112 (~15 mCi ±5%; specific activity, ≥1 Ci/μmol), dynamic emission data were acquired for 90 min. For [18F]fallypride (~5 mCi ±5%; specific activity ≥1 Ci/μmol), data were acquired in two scanning blocks of 80 min each, with a short break between blocks. Data were reconstructed using the 3D row action maximum likelihood algorithm. Scatter and random corrections were applied.

**PET image processing.** Reconstructed [11C]NNC-112 PET data (1 min × 90 frames) were averaged into 23 frames consisting of 4 1 min frames, 3 2 min frames, and 16 5 min frames. Reconstructed [18F]fallypride PET data (2 blocks; 1 min × 80 frames) were combined into 16 frames, each consisting of an average of 10 min. PET images were motion corrected (Jenkinson et al., 2002) then coregistered to the corresponding MRI (Jenkinson and Smith, 2001). Volume of interest (VOI)-based time activity data were extracted for kinetic modeling using PMOD Version 3.1. Time–activity curves were fit using the simplified reference tissue model (SRTM; Lammertma and Hume, 1996). The cerebellum was selected as the reference region (Hall et al., 1999; Abi-Dargham et al., 2000; Ishibashi et al., 2013). A volume-weighted average of k2* (clearance rate of the radiotracer from the reference region tissue), estimated from high-activity regions (caudate and putamen), was computed. Time–activity curves were then refit using SRTM2 (Wu and Carson, 2002), applying the computed k2* values to all VOIs. BP_{NSD} was calculated by subtracting 1.0 from the product of R1 (ratio of radiotracer delivery in the target region tissue relative to that of the reference region tissue) and k2*/k2a.

**MRI scanning and volumes of interest.** MRI scanning was performed on a Siemens Trio scanner (MPRAGE: repetition time, 1.9 s; echo time, 2.26
ms; voxel size, 1 mm³; 176 slices), and processed using the FMRIB Software Library (FSL; http://www.fmrib.ox.ac.uk/fsl/index.html; Oxford University).

Selected VOIs included the whole striatum and functional striatal subdivisions: limbic striatum, associative striatum, and sensory–motor striatum. A VOI for the whole striatum was created by combining anatomically defined VOIs for the caudate, putamen, and nucleus accumbens using the FSL software package (Patenaude et al., 2011). Functional subdivisions of the striatum (Mawlawi et al., 2001) and the midbrain region (Zald et al., 2010) were defined as described previously. The cerebellum VOI was drawn manually in standard space and transformed to each subject’s MRI.

Data analysis and statistical analysis. Striatal VOIs were selected a priori on the basis of evidence that dopaminergic transmission in these regions is important for inhibitory control (Lee et al., 2009; Buckholtz et al., 2010; Ghahremani et al., 2012). Correlations of BPND, with behavioral measures in striatal functional subdivisions were tested post hoc if a significant relationship was found using the whole-striatum VOI. Relationships among BPND, SST, and CPT were conducted analyzed using SPSS version 22 (IBM Corp.). Analyses reported here were conducted using measurements from bilateral VOIs. These correlations were nearly identical to those examined using measurements from left and right VOIs separately. Exploratory investigations of D1- and D2-type BPND with SST and CPT performance included a voxelwise analysis of correlations between cortical BPND and SSRT, GoRT, or CE, and VOI-based analysis using measurements of midbrain BPND.

Relationships of regional D1-type and D2-type BPND. Within-region correlations of D1- and D2-type BPND were performed for all striatal VOIs by Pearson correlation analysis. Of the 31 participants included in the study, 22 (12 female) underwent PET scans for the determination of both D1- and D2-type BPND and their data were used for this analysis.

Dopamine receptor BPND and performance on the SST and CPT. Relationships of striatal BPND with SSRT were tested using partial correlation analysis controlling for age and sex. Similar analyses were performed with GoRT.

The Hotelling–Williams test (Van Sickle, 2003) was used to test for equality of the correlations between SSRT and dorsal striatum BPND versus SSRT and ventral striatum BPND. For this test, BPND values of the associative and sensory motor regions were combined to create a BPND value for the dorsal striatum, and compared with the BPND value of the ventral striatum.

To examine the contributions of both receptor subtypes (BPND) on SSRT, a stepwise regression analysis was used. To determine the effect of adding D1-type BPND to a model with D2-type BPND, the variables entered into the first step of the regression were sex, age, and D1-type BPND; D2-type BPND was included in the second step. Next, the reverse relationship was tested to determine the effect of adding D2-type BPND to a model using D1-type BPND, with D1-type BPND included in the second step instead.

The relationships of BPND with CEs, the outcome variable reflecting response inhibition in the CPT, and GoRTs were assessed using partial correlation analysis, controlling for sex and age.

To estimate effects of time lapse between neuroimaging and neurobehavioral procedures (average elapsed time, 17 months), the stability of neurobehavioral task performance over time was evaluated. For this analysis, a subset of participants (n = 10) was invited to return for retesting of SST and CPT performance after an average elapsed time of 40 months. Reliability assessments were assessed using the intraclass correlation coefficient (ICC).

Results

Neurobehavioral tasks

On the stop–signal task, participants performed at a level of 99% correct on go trials and inhibited their responses on approximately half of the stop trials [mean (SD), 52% (0.056)], indicating that the adaptive staircase procedure for equating stop–trial performance across participants was successful (Table 1). SSRT values were similar to those observed in prior studies of separate samples (Boehler et al., 2010; Ghahremani et al., 2012). On the CPT, participants averaged 99% correct on go trials and averaged 13 CEs (of 36 no-go trials). Mean GoRT values were similar to those reported previously (Steele et al., 2013).

Dopamine receptor BPND

Overall, BPND values for both receptor subtypes were higher in the dorsal than in ventral regions of the striatum. D1- and D2-type BPND values were approximately equal in the associative and sensory motor striatum, while D2-type BPND was higher in the sensory motor than the associative striatum (Table 2; see Fig. 4). D1-type receptor BPND and D2-type BPND showed no significant correlation in the associative or limbic striatal subdivisions, but were significantly positively correlated in the sensory motor striatum (r = 0.469, p = 0.028).

Dopamine receptor BPND and response inhibition on the SST

SSRT was negatively correlated with D1-type BPND in the whole striatum, controlling for the effects of age and sex (r = −0.624, p = 0.003; Figs. 1, 3; Table 3). Post hoc evaluations of data from functional subdivisions of the striatum revealed significant relationships in the dorsal regions (associative striatum: r = −0.548, p = 0.012; sensory motor striatum: r = −0.527, p = 0.017), but not in the ventral region (limbic striatum: r = −0.342, p = 0.139). A difference in correlations between SSRT and D1-type BPND in the dorsal versus ventral region of striatum was detected using the Hotelling–Williams test at a trend level (p = 0.083). To determine the specificity of the association to the stopping process, correlations between GoRT and D1-type BPND were examined. D1-type BPND in the whole striatum showed a trend toward a negative correlation with GoRT (r = −0.425, p = 0.062). We therefore conducted a post hoc analysis of the functional subdivisions and found that the correlation involving D1-type BPND in the ventral striatum reached a trend level (p = 0.082), but the Hotelling–Williams test indicated no difference in dorsal versus ventral correlations.

SSRT was negatively correlated with D2-type BPND in the whole striatum, controlling for the effects of age and sex (r =
Post hoc tests involving functional subdivisions of the striatum showed significant negative correlations in the associative striatum ($r = -0.544$, $p = 0.007$) and sensory motor striatum ($r = -0.419$, $p = 0.046$), but not in the limbic striatum ($r = -0.308$, $p = 0.153$; Table 3). The Hotelling–Williams test of equality of correlations showed that the relationships of SSRT and $D_2$-type BP$_{ND}$ in the dorsal versus ventral regions of striatum differed significantly from one another ($p = 0.039$), suggesting that the correlation of $D_2$-type BP$_{ND}$ with SSRT was specific to the dorsal striatum.

Since BP$_{ND}$ for each receptor subtype in the dorsal striatum was negatively correlated with SSRT, we tested the correlations between BP$_{ND}$ for each receptor subtype and SSRT, controlling for the effects of age, sex, and BP$_{ND}$ for the other receptor subtype. A negative correlation of SSRT with $D_1$-type BP$_{ND}$ in the associative striatum was present at trend level when controlling for $D_2$-type BP$_{ND}$ ($r = -0.473$, $p = 0.064$). SSRT was negatively correlated with $D_2$-type BP$_{ND}$ in associative striatum when controlling for $D_1$-type BP$_{ND}$ ($r = -0.599$, $p = 0.014$).

To examine the effect of both receptor BP$_{ND}$ measures on SSRT, a stepwise regression was used to determine the effect of adding additional BP$_{ND}$ measures to a model of SST performance using only one BP$_{ND}$ measure. A model using age, sex and $D_1$-type BP$_{ND}$ to predict SST performance was improved by adding $D_2$-type BP$_{ND}$ to the model ($D_1$: $F_{(3,18)} = 2.937$, $p = 0.067$; $D_1 + D_2$: $F_{(4,18)} = 3.776$, $p = 0.028$). In the reverse analysis, adding $D_1$-type BP$_{ND}$ to a model of SST performance using $D_2$-type BP$_{ND}$ also improved the model ($D_2$: $F_{(3,18)} = 2.176$, $p = 0.133$; $D_1 + D_2$: $F_{(4,18)} = 3.776$, $p = 0.028$). The model including both receptors showed the effects of both $D_1$- and $D_2$-type BP$_{ND}$ ($D_1$: $t = -2.506$, $p = 0.025$; $D_2$: $t = -2.082$, $p = 0.056$).
Table 3. Relationships of dopamine receptor binding potential (BP_{ND}) and stop-signal task performance variables

<table>
<thead>
<tr>
<th>Region of interest</th>
<th>SSRT</th>
<th>GoRT</th>
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<tbody>
<tr>
<td></td>
<td>( r )</td>
<td>( p )</td>
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<tr>
<td>D_1-type BP_{ND}</td>
<td></td>
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<tr>
<td>Whole striatum</td>
<td>0.624</td>
<td>0.003</td>
</tr>
<tr>
<td>Limbic striatum</td>
<td>-0.342</td>
<td>0.139</td>
</tr>
<tr>
<td>Associative striatum</td>
<td>0.548</td>
<td>0.012</td>
</tr>
<tr>
<td>Sensory motor striatum</td>
<td>0.527</td>
<td>0.017</td>
</tr>
<tr>
<td>Midbrain</td>
<td>-0.373</td>
<td>0.106</td>
</tr>
<tr>
<td>D_2-type BP_{ND}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole striatum</td>
<td>0.478</td>
<td>0.021</td>
</tr>
<tr>
<td>Limbic striatum</td>
<td>-0.308</td>
<td>0.153</td>
</tr>
<tr>
<td>Associative striatum</td>
<td>-0.544</td>
<td>0.007</td>
</tr>
<tr>
<td>Sensory motor striatum</td>
<td>-0.419</td>
<td>0.046</td>
</tr>
<tr>
<td>Midbrain</td>
<td>-0.327</td>
<td>0.137</td>
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Partial correlation coefficients for the relationships between dopamine receptor availability (BP_{ND}) and stop-signal task performance variables, controlling for the effects of sex and age. Significant relationships are highlighted in bold.

Dopamine receptor BP_{ND} and response inhibition assessed by the CPT

Tests of the correlations between dopamine subtype BP_{ND} and CE or GoRT on the CPT showed no statistically significant relationships. Furthermore, CE was not correlated with response inhibition capacity (SSRT) on the SST. Although GoRT on the SST and GoRT on the CPT showed a significant association (\( r = 0.419, p = 0.024 \)), GoRT on the CPT did not show any significant relationship with either D_1- or D_2-type BP_{ND} in any region tested.

Neither D_1- nor D_2-type BP_{ND} in the cortex showed a significant correlation with SSRT, GoRT, or CE in a voxelwise analysis, using a liberal threshold (\( p < 0.05 \), uncorrected). Analysis of D_1- or D_2-type BP_{ND} in the midbrain showed no significant correlations with SSRT, GoRT, or CE.

Repeated measures of neurobehavioral task performance

Task performance variables showed a high degree of test–retest reliability over an average elapsed time of 40 months. The average percentage change in CE and SSRT was small (8% and 7%, respectively), and intraclass correlations were moderately high (CE: ICC = 0.913, \( p = 0.001, n = 10 \); SSRT: ICC = 0.738, \( p = 0.029, n = 10 \)). Adding the time interval between neuroimaging and neurocognitive tests as a covariate in statistical analyses did not change the results.

Discussion

This study extends evidence for a contribution of striatal dopaminergic function to motor response inhibition in humans (Ghahremani et al., 2012; Bari and Robbins, 2013; Nandam et al., 2013), demonstrating the involvement of both D_1- and D_2-type dopamine receptors in the dorsal striatum. D_1 and D_2 receptors are localized to striatonigral and striatopallidal neurons, respectively, with minimal colocalization (Hersch et al., 1995). Dopamine regulates striatal activation and output via D_1 receptor activation, which enhances the function of striatonigral neurons, and via D_2-receptor activation, which suppresses the function of striatopallidal neurons (Creese et al., 1983; Surmeier et al., 2007; Gerfen and Surmeier, 2011). Dopamine binds both D_1- and D_2-type receptors, but the relative activation of either subtype depends on the intrasynaptic dopamine concentration and the respective affinities of the receptors for the neurotransmitter. D_2-type receptors, which have higher affinity than D_1-type receptors for dopamine, mediate tonic dopaminergic signaling. D_1-type receptors are activated at high dopamine concentrations during phasic increases in extracellular dopamine (Dreyer et al., 2010). D_1- and D_2-type receptor signaling can have synergistic effects, as shown by the observation that coadministration of D_1- and D_2-type dopamine receptor agonists, at doses that are behaviorally inactive when administered alone, increases locomotor behavior in rats (Vermeulen et al., 1994). Such an interaction between striatal D_1- and D_2-modulated pathways may govern the performance on the SST.

The results obtained here align with a model of striatal motor control of response inhibition in which D_1- and D_2-type receptors support competing processes via the modulation of striatonigral and striatopallidal pathways (Logan et al., 1984; Mink, 1996; Frank, 2005; Frank et al., 2007). This model posits that D_1-expressing striatonigral neurons facilitate the “go” process and D_2-expressing striatopallidal neurons facilitate the “stop” process (Alexander and Crutcher, 1990; Surmeier et al., 2007; Gerfen and Surmeier, 2011). The negative correlation observed here between D_2-type BP_{ND} and SSRT is consistent with this model and corroborates findings from other human studies showing that the administration of the D_2-type receptor agonist, cabergoline, enhances stopping ability (Nandam et al., 2013), and findings from neuroimaging results showing that striatal D_2-type BP_{ND} is correlated with SSRT and inhibition-related striatal neural activity (Ghahremani et al., 2012).

Several studies have described opposing contributions of D_1- and D_2-mediated dopamine signaling to cognitive function and behavior. For example, individual differences in the ability to learn from positive and negative feedback are related to D_1- and D_2-type BP_{ND} values, respectively (Cox et al., 2015). A theory of prefrontal dopamine function describes a balance between D_1- and D_2-type receptor-mediated signaling in modulating fronto-striatal function (Durstewitz and Seamans, 2008). Moreover, a new model of dopamine function in the basal ganglia posit that D_2 receptor activation prepares a set of possible responses, then D_2 receptor activation functions in selecting the final response (Keeler et al., 2014). The present findings are consistent with such an integrated function, suggesting that there is cooperative signaling between D_1- and D_2-type receptor-mediated pathways during stopping.

The effect of D_2-type BP_{ND} on SSRT appears to be specific to stopping a motor response, as indicated by the lack of correlation with GoRT. In contrast, the relationship between D_1-type BP_{ND} and SSRT may reflect a general motor effect. This view is supported by the trend-level correlation found with GoRT on the SST, and by literature showing consistently that the activation of D_1 receptors enhances motor activity (Kreitzer and Berke, 2011). D_1-type BP_{ND}, however, was not correlated with GoRT on the CPT.

The anatomical specificity of the correlations between SSRT and BP_{ND} corroborate findings from rodent studies (Eagle and Robbins, 2003a; Eagle et al., 2011). These studies showed that dopaminergic transmission in the dorsal striatum, but not the ventral striatum, is necessary for SST performance. Specifically, neither excitotoxic lesions nor direct antagonist infusions into the nucleus accumbens affected SST performance in rats (Eagle and Robbins, 2003a,b; Eagle et al., 2011). Moreover, this uniquely dorsal striatal relationship with SST performance was also observed in humans in whom D_2-type BP_{ND} and fMRI activation during stopping was found in dorsal striatum, but not in ventral striatum (Ghahremani et al., 2012). Last, although D_2-type BP_{ND} in the midbrain has been associated with self-reports of impulsivity and novelty seeking (Zald et al., 2008; Buckholtz et al., 2010).
2010), there were no significant relationships between behavioral performance measures and D2-type BPND in the midbrain. This difference between findings may reflect differences between what is measured by self-reports of impulsivity compared with neurocognitive tasks (Reynolds et al., 2006, 2008; Fields et al., 2009).

That performance on the SST, but not on the CPT, was associated with dopamine receptor availability suggests that the tasks tap into different neurochemical mechanisms subserving motor response inhibition. Whereas the SST measures the ability to cancel a motor response that has been initiated, the CPT measures action restraint (i.e., not going). Brain-imaging studies have shown that these tasks engage overlapping, but distinct, neural circuits (Rubia et al., 2001; Zheng et al., 2008; Swick et al., 2011; Steele et al., 2013). If the SST and CPT were identical measures of response inhibition, they would be governed by the same neurotransmitter systems and would show comparable relationships with neurochemical markers (Jentsch et al., 2014). Our findings, however, support a functional distinction between stopping (SST) and not going (CPT) as separate constructs (Robinson et al., 2009; Swick et al., 2011) that are subserved by different neurochemical substrates (Dalley et al., 2008; Robinson et al., 2009). These results suggest that, whereas the latency of the inhibition process (SSRT) is likely influenced by dopaminergic signaling, the ability to withhold a response (CPT) is not (Eagle and Baunez, 2010). Different cognitive requirements, such as those involving attention or working memory, may influence overall task performance and links to dopamine markers. Such differences may also explain the lack of correlation between scores on the CPT and SST in both rodents and human subjects (Broos et al., 2012).

Finally, while dopamine receptors were the main focus of this study, contributions of other neurotransmitter systems cannot be overlooked, as there is substantial evidence for a role of noradrenergic and other transmitter systems in the striatal control of response inhibition (Zheng et al., 1999; Eagle et al., 2011; Bari and Robbins, 2013).

This study has limitations. Among them are its correlative design, which cannot inform on causal relationships between dopamine receptor subtype signaling and motor response inhibition, and the relatively small sample size. Another is the imperfect selectivity of the radioligands used. [11C]NNC-112 has an ∼10-fold higher in vivo affinity for D2-type over 5HT2A receptors (Slifstein et al., 2007), and pharmacological blocking studies (Ekelund et al., 2007) show that ∼5% of the [11C]NNC-112 signal in the striatum represents 5HT2A binding. Although contamination of the D1 receptor signal with 5HT2A binding is minor in the striatum, it should be acknowledged. [18F]Fallypride has nearly equal affinity for D2 and D3 dopamine receptors in vivo (Slifstein et al., 2004) and cannot distinguish between them; however, D2-type receptors in the dorsal striatum are almost exclusively D2 receptors with very low D3 expression (Murray et al., 1994). Thus, BPND measurements in the dorsal striatum primarily reflect D2 receptor availability, and those in the ventral striatum are likely a combination of signals from D2 and D3 receptors. [18F]Fallypride also binds to both isoforms of the D2 receptor (D2S and D2L); therefore, BPND measurements using [18F]fallypride do not distinguish between presynaptic and postsynaptic D2 receptors.

Another limitation is the time interval between the behavioral and PET assessments, which was 17 months on average. Of relevance is the low test–retest variation in BPND measurements made using [11C]NNC-112 or [18F]fallypride, which has been determined in previous studies to be 5–10% (Abi-Dargham et al., 2000; Fujita et al., 2006; Dunn et al., 2013), and the small change in D2- and D3-type BPND with aging, a decrease of only ∼8% with every decade of life. In addition, the test–retest reliability of the SST and CPT performance variables is well established, showing high reliability over several weeks (Soreni et al., 2009; Weafer et al., 2013; but also see Wöstmann et al., 2013) and high reliability of performance on both of the neurobehavioral tasks, with an average elapsed time of 40 months between assessments. Adding the time interval between neuroimaging and neurocognitive tests as a covariate in statistical analyses did not change the results, suggesting that the time-related influences on the relationships between dopamine receptor BPND and task performance reported here are likely to be minimal.

In summary, we present direct evidence for associations of striatal D2- and D3-type receptor availability with capacity for response inhibition on the SST in humans. These relationships were specific to the dorsal striatum, identifying this region as an important locus for differential dopaminergic control of motor response inhibition. The results support the notion that the balance between D2- and D3-type receptor-mediated signaling is important for motor response inhibition. The findings represent an important advance as the understanding of dopaminergic signaling in the human brain has implications for the development of specific agents, possibly D2-targeted, to treat patients with neuropsychiatric disorders that are characterized by an impulsive phenotype, such as observed in ADHD and addictive disorders.

References


Eagle DM, Robbins TW (2003a) Lesions of the medial prefrontal cortex or nucleus accumbens core do not impair inhibitory control in rats performing a stop-signal reaction time task. Behav Brain Res 146:131–144. CrossRef Medline


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