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

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Abstract

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 (binding potential, \(BP_{ND}\)), measured using positron emission tomography with \(^{11}\text{C}\)NNC-112 and \(^{18}\text{F}\)fallypride, respectively. Stop-signal reaction time was negatively correlated with D1- and D2-type \(BP_{ND}\) in whole striatum, with significant relationships involving the dorsal but not ventral striatum, and no significant correlations involving the Continuous Performance Task.

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 utilize different neurochemical mechanisms subserving motor response inhibition.
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 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 guide treatment for disorders characterized by an impulsive phenotype.

Research findings have indicated a role of 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, 2005; Lane et al., 2007; Lee et al., 2009), which feature behavioral disinhibition, are associated with dopaminergic dysfunction. In addition, studies of genetic polymorphisms (Colzato et al., 2010; Colzato et al., 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; Ramdani et al., 2014).

Despite an evident role for dopamine, the relative contributions of dopamine signaling via dopamine D1- and D2-like receptor subtypes are unclear. In rats, systemic administration of dopaminergic antagonists does not affect response inhibition (Eagle et al., 2007; Eagle et al., 2008; Bari and Robbins, 2013). However, direct infusion of the D1-receptor antagonist, SCH-23390, into the dorsal-medial striatum, improves response inhibition, whereas infusion of the D2 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, administration of the D2-specific agonist, cabergoline, improves response inhibition (Nandam et al., 2013), and striatal D2-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 D1-type receptors in response inhibition
and direct comparisons of D1- vs D2-type receptor contributions to motor response inhibition have not been performed.

We used positron emission tomography (PET) with $[^{11}{\text{C}}]$NNC-112 and $[^{18}{\text{F}}]$fallypride as radioligands for dopamine D1- and D2-type receptors, respectively (Mukherjee et al., 1995; Ekelund et al., 2007), to examine the relationships of subtype-selective dopamine-receptor availability (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, but not the ventral, striatum would be linked to response-inhibition task performance, and that D1- and D2-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) Institution Review Board. Thirty-one healthy volunteers (16 female, mean age = 30.68 years, SD = 8.3), participating in the UCLA Consortium for Neuropsychiatric Phenomics (CNP; www.phenomics.ucla.edu), completing 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 approximately 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 DSM-IV 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 systematic disease; 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 Stop-Signal Task (SST) (Logan et al., 1984) and Continuous Performance Task (CPT) (Tannock et al., 1989) were administered via PC laptop (E-prime 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 equally important. The SSD was adjusted on a trial-by-trial basis according to performance; values were drawn from two interleaved ladders to ensure equal performance level across participants, producing successful inhibition on ~50% of stop trials. Participants received task training prior to 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 presented at random, each containing 20 trials at a fixed inter-trial interval (ITIs): 1000, 2000, or 4000ms. Participants received task training prior to 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 standard deviation of reaction time on go trials were calculated using all-correct go trials (GoRT). 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). Percent 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), (4) SSRT estimate that was negative or <50 ms (n=1, computer failure). SST data from 27 participants were subject to analysis: 22 with D1-type BP<sub>ND</sub>, 24 with D2-type BP<sub>ND</sub>, and 19 with both. Performance data from the CPT were used to calculate the mean and standard deviation of go-trial reaction time (GoRT) on all go trials. Commission error (CE) was calculated as the number of failed no-go trials (response to a no-go stimulus).

PET scanning

D1-type dopamine receptor availability (D1-type BP<sub>ND</sub>) was assayed using [<sup>11</sup>C]NNC-112, a high-affinity ligand for D1-type receptors (Andersen et al., 1992; Ekelund et al., 2007), in 26 subjects (14 female). Dopamine D2-type receptor availability (D2-type BP<sub>ND</sub>) was assayed on a different day using [<sup>18</sup>F]fallypride, a high affinity radioligand for D2-type receptors (Mukherjee et al., 1995) in 27 subjects (14 female). PET scanning was performed on a Philips Gemini Tru Flight PET/CT in 3D mode (Philips Electronics, Netherlands; FWHM = 5.0 mm × 4.8 mm, 90 slices, voxel size 2 mm<sup>3</sup>). A CT-transmission scan was performed to obtain data for measured
attenuation correction. After bolus injection of $^{[11]}$C]NNC-112 (~15 mCi ±5%, specific activity ≥ 1 Ci/μmol), dynamic emission data were acquired for 90 min. For $^{[18]}$F]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 (3D-RAMLA). Scatter and random corrections were applied.

**PET image processing**

Reconstructed $^{[11]}$C]NNC-112 PET data (1-min × 90-frames) were averaged into 23 frames, consisting of four 1-min frames, three 2-min frames and sixteen 5-min frames. Reconstructed $^{[18]}$F]fallypride PET data (2 blocks; 1-min × 80-frames) were combined into 16 frames, each consisting of the average of 10-min. PET images were motion-corrected (Jenkinson et al., 2002) then co-registered to the corresponding MRI (Jenkinson and Smith, 2001). VOI-based time/activity data were extracted for kinetic modeling using PMOD (PMOD 3.1, Zurich). Time/activity curves were fit using the simplified reference tissue model (SRTM)(Lammertsma and Hume, 1996). The cerebellum was selected as the reference region (Hall et al., 1994; Abi-Dargham et al., 2000; Ishibashi et al., 2013). A volume-weighted average of k2', 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. Binding potential referred to non-displaceable uptake (BP$_{ND}$) was calculated by subtracting 1.0 from the product of R1 and k2'/k2a.

**MRI scanning and volumes of interest (VOIs)**

MRI scanning was performed on a Siemens Trio (MPRAGE: repetition time = 1.9 sec, echo time = 2.26 msec, voxel size = 1 mm$^3$, 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 BP_{ND} with behavioral measures in striatal functional subdivisions were tested *post-hoc* if a significant relationship was found using the whole-striatum VOI. Relationships between BP_{ND}, SST, and CPT were conducted analyzed using SPSS (SPSS 22; IBM Corp., Armonk, NY). 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 BP_{ND} with SST and CPT performance included a voxel-wise analysis of correlations between cortical BP_{ND} and SSRT, GoRT or CE and VOI-based analysis using measurements of midbrain BP_{ND}.

**Relationships of regional D1-type and D2-type BP_{ND}**

Within-region correlations of D1- and D2-type BP_{ND} 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 determination of both D1- and D2-type BP_{ND}, and their data were used for this analysis.

**Dopamine receptor BP_{ND} and performance on the SST and CPT**

Relationships of striatal BP_{ND} 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 BP_{ND} versus SSRT and ventral striatum BP_{ND}. For this test, BP_{ND} values of the associative and sensory-motor regions were combined to create a BP_{ND} value for the dorsal striatum, and compared to the BP_{ND} value of the ventral striatum.
To examine the contributions of both receptor subtypes (BP<sub>ND</sub>) on SSRT, a step-wise regression analysis was used. To determine the effect of adding D2-type BP<sub>ND</sub> to a model with D1-type BP<sub>ND</sub>, the variables entered into the first step of the regression were age, sex and D1-type BP<sub>ND</sub>. D2-type BP<sub>ND</sub> was included in the second step. Next, the reverse relationship was tested, to determine the effect of adding D1-type BP<sub>ND</sub> to a model using D2-type BP<sub>ND</sub>, with D1-type BP<sub>ND</sub> included in the second step instead.

The relationships of receptor BP<sub>ND</sub> with commission errors (CE), the outcome variable reflecting response inhibition in the CPT, and GoRT were assessed using partial correlation analysis, controlling for sex and age.

To estimate effects of time lapse between neuroimaging and neurobehavioral procedures (average 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 re-testing 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 (Table 1)

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. SSRT and 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 CE (of 36 no-go trials). Mean GoRT values were similar to those reported previously (Steele et al., 2013).

Dopamine receptor BP<sub>ND</sub> (Table 2, Figure 4)

Overall, BP<sub>ND</sub> values for both receptor subtypes were higher in the dorsal than in ventral regions of the striatum. D1- and D2-type BP<sub>ND</sub> values were approximately equal in the associative and sensory-motor striatum, while D2-type BP<sub>ND</sub> was higher in the sensory-motor than the associative striatum. D1-type receptor BP<sub>ND</sub> and D2-type BP<sub>ND</sub> 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 BP<sub>ND</sub> and response inhibition on the SST (Table 3)

SSRT was negatively correlated with D1-type BP<sub>ND</sub> in the whole striatum, controlling for the effects of age and sex (r = -0.624, p = 0.003)(Figure 1). 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 BP<sub>ND</sub> in the dorsal vs. 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 BP<sub>ND</sub> were examined. D1-type BP<sub>ND</sub> in the whole striatum showed a trend towards negative correlation with GoRT (r=-0.425, p = 0.062). We therefore conducted post-hoc analysis of the functional subdivisions, and found that the correlation involving D1-type BP<sub>ND</sub> 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 $BP_{ND}$ in the whole striatum, controlling for the effects of age and sex ($r = -0.478$, $p = 0.021$) (Figure 1). *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 D2-type $BP_{ND}$ in the dorsal versus ventral regions of striatum differed significantly from one another ($p = 0.039$), suggesting that the correlation of D2-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 D1-type $BP_{ND}$ in the associative striatum was present at trend-level when controlling for D2-type $BP_{ND}$ ($r = -0.473$, $p = 0.064$). SSRT was negatively correlated with D2-type $BP_{ND}$ in associative striatum when controlling for D1-type $BP_{ND}$ ($r = -0.599$, $p = 0.014$).

To examine the effect both receptor $BP_{ND}$ 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 D1-type $BP_{ND}$ to predict SST performance was improved by adding D2-type $BP_{ND}$ to the model ($D1: F_{3,18} = 2.937$, $p=0.067$) ($D1+D2: F_{4,18} = 3.776$, $p=0.028$). In the reverse analysis, adding D1-type $BP_{ND}$ to a model of SST performance using D2-type $BP_{ND}$ also improved the model ($D2: F_{3,18} = 2.176$, $p=0.133$) ($D1+D2: F_{4,18} = 3.776$, $p=0.028$). The model including both receptors showed effects of both D1- and D2-type $BP_{ND}$ ($D1: t= -2.506$, $p = 0.025$; $D2: t= -2.082$, $p = 0.056$).

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

Tests of the correlations between dopamine receptor subtype $BP_{ND}$ and commission error (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 D1- or D2-type BP<sub>ND</sub> in any region tested.

Neither D1- nor D2-type BP<sub>ND</sub> in the cortex showed a significant correlation with SSRT, GoRT or CE in a voxel-wise analysis, using a liberal threshold (p < 0.05, uncorrected). Analysis of D1- or D2-type BP<sub>ND</sub> in the midbrain showed no significant correlations with SSRT, GoRT or CE.

Repeated measures of neurobehaviorial task performance

Task-performance variables showed a high degree of test-retest reliability over an average elapsed time of 40 months. Average percent change in CE and SSRT was small (8%, 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 involvement of both D1- and D2-type dopamine receptors in the dorsal striatum. D1 and D2 receptors are localized to striato-nigral and striato-pallidal neurons, respectively, with minimal co-localization (Hersch et al., 1995). Dopamine regulates striatal activation and output via D1-receptor activation, which enhances the function of striato-nigral neurons, and via D2-receptor activation, which suppresses function of striato-pallidal neurons (Creese et al., 1983; Surmeier et al., 2007; Gerfen and Surmeier, 2011). Dopamine binds both D1- and D2-type receptors, but the relative activation of either subtype depends on intrasynaptic dopamine concentration and the respective affinities of the receptors for the neurotransmitter. D2-type receptors, which have higher affinity than D1-type receptors for dopamine, mediate tonic dopaminergic signaling. D1-type receptors are activated at high dopamine concentrations, during phasic increases in extracellular dopamine (Dreyer et al., 2010). D1- and D2-type receptor signaling can have synergistic effects, as shown by the observation that co-administration of D1- and D2-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 D1- and D2-modulated pathways may govern performance on the SST.

The results obtained here align with a model of striatal motor control of response inhibition in which D1- and D2-type receptors support competing processes via the modulation striato-nigral and striato-pallidal pathways (Logan et al., 1984; Mink, 1996; Frank, 2005; Frank et al., 2007). This model posits that D1-expressing striato-nigral neurons facilitate the “go” process and D2-expressing striato-pallidal neurons facilitate the “stop” process (Alexander and Crutcher, 1990; Surmeier et al., 2007; Gerfen and Surmeier, 2011). The negative correlation observed here between D2-type BP\(_{ND}\) and SSRT is consistent with this model and corroborates findings from other human studies showing that administration of the D2-type receptor agonist, carbergoline, enhances stopping ability (Nandam et al., 2013) and from neuroimaging results showing that striatal D2-type BP\(_{ND}\) is correlated with SSRT and inhibition-related striatal neural activity (Ghahremani et al., 2012).
Several studies have described opposing contributions of D1- and D2-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 D1- and D2-type BP\textsubscript{ND} values, respectively (Cox et al., 2015). A theory of prefrontal dopamine function describes a balance between D1- and D2-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 D1 receptor activation prepares a set of possible responses, then D2 receptor activation functions in selecting the final response (Keeler et al., 2014). The present findings are consistent with such integrated function, suggesting that there is cooperative signaling between D1- and D2-type receptor-mediated pathways during stopping.

The effect of D2-type BP\textsubscript{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 D1-type BP\textsubscript{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 activation of D1 receptors enhances motor activity (Kreitzer and Berke, 2011). D1-type BP\textsubscript{ND}, however, was not correlated with GoRT on the CPT.

The anatomical specificity of the correlations between SSRT and BP\textsubscript{ND} corroborate findings from rodent studies (Eagle and Robbins, 2003a; Eagle et al., 2011). These studies showed that dopaminergic transmission in the dorsal 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 which D2-type BP\textsubscript{ND} and fMRI activation during stopping was found in dorsal but not ventral striatum (Ghahremani et al., 2012). Lastly, although D2-type BP\textsubscript{ND} in the midbrain has been associated with self-reports of impulsivity and novelty-seeking (Zald et al., 2008; Buckholtz et al., 2010), there were no significant relationships between behavioral performance measures and D2-type BP\textsubscript{ND} in the midbrain. This difference between findings may reflect differences between what is measured by self-reports of impulsivity as compared with neurocognitive tasks (Reynolds et al., 2006; Reynolds et al., 2008; Fields et al., 2009).
That performance on the SST but not 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 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 imperfect selectivity of the radioligands used. $^{[1]}\text{C}$NNC-112 has approximately 10-fold higher in vivo affinity for D1-type over 5HT2A receptors (Slifstein et al., 2007), and pharmacological blocking studies show that ~5% of the $^{[1]}\text{C}$NNC-112 signal in the striatum represents 5HT2A binding (Ekelund et al., 2007). Although contamination of the D1-receptor signal with 5HT2A binding is minor in the striatum, it should be acknowledged. $^{[1]}\text{F}$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, BP_{ND} measurements in the dorsal striatum primarily reflect D2 receptor availability, and those in the ventral striatum are likely a combination of signal from D2 and D3 receptors. \[^{18}\text{F}]\text{Fallypride also binds to both isoforms of the D2 receptor (D2S and D2L); therefore, BP_{ND} measurements using \[^{18}\text{F}]\text{fallypride do not distinguish between pre- and post-synaptic D2 receptors.}\]

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 BP_{ND} measurements made using \[^{11}\text{C}]\text{NNC-112 or \[^{18}\text{F}]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 D1- and D2-type BP_{ND} with aging, a decrease of only \sim 8\% with every decade of life. In addition, 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 (Wostmann 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 BP_{ND} and task performance reported here are likely to be minimal.

In summary, we present direct evidence for associations of striatal D1- and D2-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 D1- and D2-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 D1-targeted, to treat patients with neuropsychiatric disorders that are characterized by an impulsive phenotype, such as observed in ADHD and addictive disorders.
References


Bari A, Robbins TW (2013) Noradrenergic versus dopaminergic modulation of impulsivity, attention and monitoring behaviour in rats performing the stop-signal task: possible relevance to ADHD. Psychopharmacology (Berl) 230:89-111.


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.


**Figure 1:** Scatter plot depicting the correlation between stop-signal reaction time (SSRT), and D1-type receptor binding potential (D1-type BP<sub>ND</sub>) in the whole striatum. Table insert displays partial correlation coefficients, p values and R<sup>2</sup> for the relationship between whole striatum and associative striatum D1-type BP<sub>ND</sub> and SSRT, controlling for age and sex.

**Figure 2:** Scatter plot depicting the correlation between stop-signal reaction time (SSRT), and D2-type receptor binding potential (D2-type BP<sub>ND</sub>) in whole striatum. Table insert displays partial correlation coefficients, p values and R<sup>2</sup> for the relationship between whole striatum and associative striatum D2-type BP<sub>ND</sub> and SSRT, controlling for age and sex.

**Figure 3:** Voxel-wise effect size maps depicting the partial correlation coefficient (r) between individual stop-signal reaction time (SSRT) and D1-type (A) and D2-type (B) receptor binding potential (BP<sub>ND</sub>) in the striatum, controlling for the effects of age and sex.

**Figure 4:** Scatter plot depicting the relationship between D2-type receptor binding potential (D2-type BP<sub>ND</sub>) and D1-type receptor binding potential (D1-type BP<sub>ND</sub>) in whole striatum, z-scores of BP<sub>ND</sub> were used for presentation purposes. Table insert displays correlation coefficients, p-values and R<sup>2</sup> for the correlations in the whole and associative striatum.
Table 1: Performance variables for the Stop-Signal Task and the Continuous Performance Task.

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stop-Signal Task</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSRT (ms)</td>
<td>235</td>
<td>37</td>
</tr>
<tr>
<td>Median GoRT (ms)</td>
<td>567</td>
<td>109</td>
</tr>
<tr>
<td>SD GoRT (ms)</td>
<td>112</td>
<td>30</td>
</tr>
<tr>
<td>Inhibition on Stop-trials, %</td>
<td>52</td>
<td>56</td>
</tr>
<tr>
<td>Correct Go Responding, %</td>
<td>99</td>
<td>0.0</td>
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<td></td>
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<td></td>
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<tr>
<td><strong>Continuous Performance Task</strong></td>
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<td></td>
</tr>
<tr>
<td>Mean GoRT (ms)</td>
<td>372</td>
<td>45</td>
</tr>
<tr>
<td>Median GoRT (ms)</td>
<td>356</td>
<td>39</td>
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<tr>
<td>SD of GoRT (ms)</td>
<td>85</td>
<td>25</td>
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<tr>
<td>Comission errors</td>
<td>13</td>
<td>5.9</td>
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</table>

n=27

n=31
Table 2: Means and standard deviations of D1-type and D2-type binding potential ($BP_{ND}$) in the striatum and within-region correlations.

<table>
<thead>
<tr>
<th>Region of Interest</th>
<th>D1-type $BP_{ND}$ mean (SD)</th>
<th>D2-type $BP_{ND}$ mean (SD)</th>
<th>Correlation $r$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole Striatum</td>
<td>1.98 (0.19)</td>
<td>29.59 (4.68)</td>
<td>0.310</td>
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<tr>
<td>Limbic Striatum</td>
<td>1.82 (0.18)</td>
<td>26.38 (4.26)</td>
<td>0.193</td>
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<tr>
<td>Associative Striatum</td>
<td>2.02 (0.23)</td>
<td>29.29 (4.55)</td>
<td>0.259</td>
</tr>
<tr>
<td>Sensory-Motor Striatum</td>
<td>2.01 (0.21)</td>
<td>31.87 (5.77)</td>
<td>0.469*</td>
</tr>
</tbody>
</table>

* $p = 0.028$

$n=26$ (14F)  $n=27$ (14F)  $n=22$ (12F)
Table 3: Correlation coefficients and p-values for the relationships of dopamine receptor binding potential (BP\textsubscript{ND}) and Stop-Signal Task performance variables.

<table>
<thead>
<tr>
<th>Region of Interest</th>
<th>SSRT</th>
<th>GoRT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>p</td>
</tr>
<tr>
<td>D1-type BP\textsubscript{ND}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>whole striatum</td>
<td>-0.624</td>
<td>0.003</td>
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<tr>
<td>limbic</td>
<td>-0.342</td>
<td>0.139</td>
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<tr>
<td>associative</td>
<td>-0.548</td>
<td>0.012</td>
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<td>sensory-motor</td>
<td>-0.527</td>
<td>0.017</td>
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<tr>
<td>midbrain</td>
<td>-0.373</td>
<td>0.106</td>
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<tr>
<td>D2-type BP\textsubscript{ND}</td>
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<td></td>
</tr>
<tr>
<td>whole striatum</td>
<td>-0.478</td>
<td>0.021</td>
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<tr>
<td>limbic</td>
<td>-0.308</td>
<td>0.153</td>
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<tr>
<td>associative</td>
<td>-0.544</td>
<td>0.007</td>
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<tr>
<td>sensory-motor</td>
<td>-0.419</td>
<td>0.046</td>
</tr>
<tr>
<td>midbrain</td>
<td>-0.327</td>
<td>0.137</td>
</tr>
</tbody>
</table>

Partial correlation coefficients for the relationships between dopamine receptor availability (BP\textsubscript{ND}) and Stop-Signal Task performance variables, controlling for the effect of sex and age. SSRT: Stop-signal reaction time. GoRT: mean reaction time on all go trials. Significant relationships are highlighted in bold font.