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

Chelsea L. Robertson,^{1,5} Kenji Ishibashi,^{3,4} Mark A. Mandelkern,^{5,6} Amira K. Brown,³ Dara G. Ghahremani,³ Fred Sabb,³ Robert Bilder,³ Tyrone Cannon,² Jacqueline Borg,² and Edythe D. London^{1,3,4,5}

Departments of ¹Molecular and Medical Pharmacology, and ²Psychology, ³Department of Psychiatry and Biobehavioral Sciences, The Semel Institute for Neuroscience and Human Behavior at UCLA, and ⁴Brain Research Institute, University of California, Los Angeles, Los Angeles, California 90024, ⁵Veterans Administration Greater Los Angeles Healthcare System, Los Angeles, California 90073, and ⁶Department of Physics, University of California, Irvine, Irvine, California 92697

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 referred to nondisplaceable uptake (BP_{ND})], measured using positron emission tomography with [¹¹C]NNC-112 and [¹⁸F]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 striatum, but not the 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 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 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; Ramdani et al., 2014).

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Correspondence should be addressed to Edythe D. London, Semel Institute, University of California, Los Angeles, 760 Westwood Plaza, C8-831, Los Angeles, CA 90024. E-mail: elondon@mednet.ucla.edu.

K. Ishibashi's present address: Tokyo Metropolitan Institute of Gerontology, Tokyo 173-0022, Japan.

A.K. Brown's present address: Life Sciences Institute, Charles R. Drew University of Medicine and Science, Los Angeles, CA 90059.

F. Sabb's present address: Research Team for Neuroimaging, Lewis Center for Neuroimaging, University of Oregon, Eugene, OR 97403.

R. Borg's present address: Department of Clinical Neuroscience, Karolinska Institute, 171 77 Stockholm, Sweden.

T. Cannon's present address: Departments of Psychology and Psychiatry, Yale University, New Haven, CT 06520.

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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, 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, the 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 [¹¹C]NNC-112 and [¹⁸F]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 [binding potential referred to as 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 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) 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 systematic 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., 1989) 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 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 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 presented at random, 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 D₁-type dopamine receptor availability (D₁-type BP_{ND}); 24 participants with D₂-type BP_{ND}; and 19 participants with both. Performance data from the CPT were used to calculate 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. D₁-type BP_{ND} was assayed using [¹¹C]NNC-112, a high-affinity ligand for D₁-type receptors (Andersen et al., 1992; Ekelund et al., 2007) in 26 subjects (14 females). Dopamine D₂-type BP_{ND} was assayed on a different day using [¹⁸F]fallypride, a high-affinity radioligand for D₂-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 mm³). 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; 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' (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_{ND} 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' / k_{2a}.

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; Buckholz 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 among BP_{ND}, 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 BP_{ND} with SST and CPT performance included a voxelwise 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 the 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 with the BP_{ND} value of the ventral striatum.

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

The relationships of receptor BP_{ND} 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

Table 1. Performance variables for the stop-signal task and the continuous performance task

	Mean	SD
Stop-signal task ($n = 27$)		
SSRT (ms)	235	37
Median GoRT (ms)	567	109
SD GoRT (ms)	112	30
Correct go responding (%)	99	0.007
Inhibition on stop-trials (%)	52	0.056
Continuous performance task ($n = 31$)		
Mean GoRT (ms)	372	45
Median GoRT (ms)	356	39
SD of GoRT (ms)	85	25
Commission errors	13	5.9

Table 2. D₁-type and D₂-type BP_{ND} in the striatum and within-region correlations

Region of interest	D ₁ -type BP _{ND}	D ₂ -type BP _{ND}	r value
Whole striatum	1.98 (0.19)	29.59 (4.68)	0.310
Limbic striatum	1.82 (0.18)	26.38 (4.26)	0.193
Associative striatum	2.02 (0.23)	29.29 (4.55)	0.259
Sensory motor striatum	2.01 (0.21)	31.87 (5.77)	0.469*

Data are reported as the mean (SD).

* $p = 0.028$; $n = 26$, 14 females; $n = 27$, 14 females; $n = 22$, 12 females.

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 BP_{ND}

Overall, BP_{ND} values for both receptor subtypes were higher in the dorsal than in ventral regions of the striatum. D₁- and D₂-type BP_{ND} values were approximately equal in the associative and sensory motor striatum, while D₂-type BP_{ND} was higher in the sensory motor than the associative striatum (Table 2; see Fig. 4). D₁-type receptor BP_{ND} and D₂-type BP_{ND} 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_{ND} and response inhibition on the SST

SSRT was negatively correlated with D₁-type BP_{ND} 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 BP_{ND} 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 BP_{ND} were examined. D₁-type BP_{ND} 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 BP_{ND} 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 ($r =$

Figure 1. Scatter plot depicting the correlation between SSRT and D₁-type BP_{ND} in the whole striatum. Table insert displays partial correlation coefficients, p values, and R^2 values for the relationship between whole striatum and associative striatum D₁-type BP_{ND} and SSRT, controlling for age and sex.

Figure 2. Scatter plot depicting the correlation between SSRT and D₂-type BP_{ND} in the whole striatum. Table insert displays partial correlation coefficients, p values, and R^2 values for the relationship between whole striatum and associative striatum D₂-type BP_{ND} and SSRT, controlling for age and sex.

−0.478, $p = 0.021$; Figs. 2, 3; Table 3). *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

Figure 3. *A, B*, Voxelwise effect size maps depicting the partial correlation coefficient (r) between individual SSRT and D₁-type (*A*) and D₂-type (*B*) receptor BP_{ND} in the striatum, controlling for the effects of age and sex.

Figure 4. Scatter plot depicting the relationship between D₂-type BP_{ND} and D₁-type BP_{ND} in the whole striatum; z-scores of BP_{ND} were used for presentation purposes. Table insert displays correlation coefficients, p values, and R^2 values for the correlations in the whole and associative striatum.

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 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 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 the effects of both D₁- and D₂-type BP_{ND} (D₁: $t = -2.506$, $p = 0.025$; D₂: $t = -2.082$, $p = 0.056$).

Table 3. Relationships of dopamine receptor binding potential (BP_{ND}) and stop-signal task performance variables

Region of interest	SSRT		GoRT	
	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>
D₁-type BP_{ND}				
Whole striatum	−0.624	0.003	−0.425	0.062
Limbic striatum	−0.342	0.139	−0.399	0.082
Associative striatum	−0.548	0.012	−0.343	0.138
Sensory motor striatum	−0.527	0.017	−0.332	0.153
Midbrain	−0.373	0.106	0.153	0.519
D₂-type BP_{ND}				
Whole striatum	−0.478	0.021	−0.035	0.875
Limbic striatum	−0.308	0.153	0.085	0.700
Associative striatum	−0.544	0.007	−0.016	0.942
Sensory motor striatum	−0.419	0.046	−0.112	0.610
Midbrain	−0.327	0.137	0.041	0.851

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 receptor 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 D₁- or D₂-type BP_{ND} in any region tested.

Neither D₁- nor D₂-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 D₁- or D₂-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 D₁- and D₂-type dopamine receptors in the dorsal striatum. D₁ and D₂ receptors are localized to striatonigral and striatopallidal neurons, respectively, with minimal colocalization (Hersch et al., 1995). Dopamine regulates striatal activation and output via D₁ receptor activation, which enhances the function of striatonigral neurons, and via D₂-receptor activation, which suppresses the function of striatopallidal 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 the 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 coadministration 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 the 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 of striatonigral and striatopallidal pathways (Logan et al., 1984; Mink, 1996; Frank, 2005; Frank et al., 2007). This model posits that D₁-expressing striatonigral neurons facilitate the “go” process and D₂-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 D₂-type BP_{ND} and SSRT is consistent with this model and corroborates findings from other human studies showing that the administration of the D₂-type receptor agonist, cabergoline, enhances stopping ability (Nandam et al., 2013), and findings 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_{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 frontostriatal function (Durstewitz and Seamans, 2008). Moreover, a new model of dopamine function in the basal ganglia posits 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 an integrated function, suggesting that there is cooperative signaling between D₁- and D₂-type receptor-mediated pathways during stopping.

The effect of D₂-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 D₁-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 D₁ receptors enhances motor activity (Kreitzer and Berke, 2011). D₁-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 D₂-type BP_{ND} and fMRI activation during stopping was found in dorsal striatum, but not in ventral striatum (Ghahremani et al., 2012). Last, although D₂-type BP_{ND} in the midbrain has been associated with self-reports of impulsivity and novelty seeking (Zald et al., 2008; Buckholz et al.,

2010), there were no significant relationships between behavioral performance measures and D₂-type BP_{ND} 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 D₁-type over 5HT_{2A} 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 5HT_{2A} binding. Although contamination of the D₁ receptor signal with 5HT_{2A} 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, BP_{ND} 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 (D_{2S} and D_{2L}); therefore, BP_{ND} 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 BP_{ND} 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 D₁- and D₂-type BP_{ND} 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 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

- Abi-Dargham A, Martinez D, Mawlawi O, Simpson N, Hwang DR, Slifstein M, Anjilvel S, Pidcock J, Guo NN, Lombardo I, Mann JJ, Van Heertum R, Foted C, Halldin C, Laruelle M (2000) Measurement of striatal and extrastriatal dopamine D₁ receptor binding potential with [¹¹C]NNC 112 in humans: validation and reproducibility. *J Cereb Blood Flow Metab* 20:225–243. [CrossRef Medline](#)
- Alexander GE, Crutcher MD (1990) Functional architecture of basal ganglia circuits: neural substrates of parallel processing. *Trends Neurosci* 13:266–271. [CrossRef Medline](#)
- Andersen PH, Grønvald FC, Hohlweg R, Hansen LB, Guddal E, Braestrup C, Nielsen EB (1992) NNC-112, NNC-687 and NNC-756, new selective and highly potent dopamine D₁ receptor antagonists. *Eur J Pharmacol* 219:45–52. [CrossRef Medline](#)
- Aron AR, Dowson JH, Sahakian BJ, Robbins TW (2003) Methylphenidate improves response inhibition in adults with attention-deficit/hyperactivity disorder. *Biol Psychiatry* 54:1465–1468. [CrossRef Medline](#)
- Aron AR, Robbins TW, Poldrack RA (2014) Inhibition and the right inferior frontal cortex: one decade on. *Trends Cogn Sci* 18:177–185. [CrossRef Medline](#)
- Band GP, van der Molen MW, Logan GD (2003) Horse-race model simulations of the stop-signal procedure. *Acta Psychol (Amst)* 112:105–142. [CrossRef](#)
- 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. [CrossRef Medline](#)
- Bedard AC, Ickowicz A, Logan GD, Hogg-Johnson S, Schachar R, Tannock R (2003) Selective inhibition in children with attention-deficit hyperactivity disorder off and on stimulant medication. *J Abnorm Child Psychol* 31:315–327. [CrossRef Medline](#)
- Bilder RM, Sabb FW, Cannon TD, London ED, Jentsch JD, Parker DS, Poldrack RA, Evans C, Freimer NB (2009) Phenomics: the systematic study of phenotypes on a genome-wide scale. *Neuroscience* 164:30–42. [CrossRef Medline](#)
- Boehler CN, Appelbaum LG, Krebs RM, Hopf JM, Woldorff MG (2010) Pinning down response inhibition in the brain—conjunction analyses of the stop-signal task. *Neuroimage* 52:1621–1632. [CrossRef Medline](#)
- Broos N, Schmaal L, Wiskerke J, Kostelijk L, Lam T, Stoop N, Weierink L, Ham J, de Geus EJ, Schoffeleer AN, van den Brink W, Veltman DJ, de Vries TJ, Pattij T, Goudriaan AE (2012) The relationship between impulsive choice and impulsive action: a cross-species translational study. *PLoS One* 7:e36781. [CrossRef Medline](#)

- Buckholtz JW, Treadway MT, Cowan RL, Woodward ND, Li R, Ansari MS, Baldwin RM, Schwartzman AN, Shelby ES, Smith CE, Kessler RM, Zald DH (2010) Dopaminergic network differences in human impulsivity. *Science* 329:532. [CrossRef Medline](#)
- Chamberlain SR, Müller U, Blackwell AD, Clark L, Robbins TW, Sahakian BJ (2006) Neurochemical modulation of response inhibition and probabilistic learning in humans. *Science* 311:861–863. [CrossRef Medline](#)
- Colzato LS, van den Wildenberg WP, Van der Does AJ, Hommel B (2010) Genetic markers of striatal dopamine predict individual differences in dysfunctional, but not functional impulsivity. *Neuroscience* 170:782–788. [CrossRef Medline](#)
- Colzato LS, van den Wildenberg WP, Hommel B (2013) The genetic impact (C957T-DRD2) on inhibitory control is magnified by aging. *Neuropsychologia* 51:1377–1381. [CrossRef Medline](#)
- Colzato LS, Jongkees BJ, Sellaro R, van den Wildenberg WP, Hommel B (2014) Eating to stop: tyrosine supplementation enhances inhibitory control but not response execution. *Neuropsychologia* 62:398–402. [CrossRef Medline](#)
- Congdon E, Mumford JA, Cohen JR, Galvan A, Canli T, Poldrack RA (2012) Measurement and reliability of response inhibition. *Front Psychol* 3:37. [CrossRef Medline](#)
- Cox SM, Frank MJ, Larcher K, Fellows LK, Clark CA, Leyton M, Dagher A (2015) Striatal D1 and D2 signaling differentially predict learning from positive and negative outcomes. *Neuroimage* 109:95–101. [CrossRef Medline](#)
- Creese I, Sibley DR, Hamblin MW, Leff SE (1983) The classification of dopamine receptors: relationship to radioligand binding. *Annu Rev Neurosci* 6:43–71. [CrossRef Medline](#)
- Dalley JW, Mar AC, Economidou D, Robbins TW (2008) Neurobehavioral mechanisms of impulsivity: fronto-striatal systems and functional neurochemistry. *Pharmacol Biochem Behav* 90:250–260. [CrossRef Medline](#)
- de Wit H, Crean J, Richards JB (2000) Effects of d-amphetamine and ethanol on a measure of behavioral inhibition in humans. *Behav Neurosci* 114:830–837. [CrossRef Medline](#)
- Dreyer JK, Herrik KF, Berg RW, Hounsgaard JD (2010) Influence of phasic and tonic dopamine release on receptor activation. *J Neurosci* 30:14273–14283. [CrossRef Medline](#)
- Dunn JT, Clark-Papasavas C, Marsden P, Baker S, Cleij M, Kapur S, Kessler R, Howard R, Reeves SJ (2013) Establishing test-retest reliability of an adapted [(18)F]fallypride imaging protocol in older people. *J Cereb Blood Flow Metab* 33:1098–1103. [CrossRef Medline](#)
- Durstewitz D, Seamans JK (2008) The dual-state theory of prefrontal cortex dopamine function with relevance to catechol-o-methyltransferase genotypes and schizophrenia. *Biol Psychiatry* 64:739–749. [CrossRef Medline](#)
- Eagle DM, Baunez C (2010) Is there an inhibitory-response-control system in the rat? Evidence from anatomical and pharmacological studies of behavioral inhibition. *Neurosci Biobehav Rev* 34:50–72. [CrossRef Medline](#)
- 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](#)
- Eagle DM, Robbins TW (2003b) Inhibitory control in rats performing a stop-signal reaction-time task: effects of lesions of the medial striatum and d-amphetamine. *Behav Neurosci* 117:1302–1317. [CrossRef Medline](#)
- Eagle DM, Tuft MR, Goodchild HL, Robbins TW (2007) Differential effects of modafinil and methylphenidate on stop-signal reaction time task performance in the rat, and interactions with the dopamine receptor antagonist cis-flupenthixol. *Psychopharmacology (Berl)* 192:193–206. [CrossRef Medline](#)
- Eagle DM, Bari A, Robbins TW (2008) The neuropsychopharmacology of action inhibition: cross-species translation of the stop-signal and go/no-go tasks. *Psychopharmacology (Berl)* 199:439–456. [CrossRef Medline](#)
- Eagle DM, Wong JC, Allan ME, Mar AC, Theobald DE, Robbins TW (2011) Contrasting roles for dopamine D₁ and D₂ receptor subtypes in the dorsomedial striatum but not the nucleus accumbens core during behavioral inhibition in the stop-signal task in rats. *J Neurosci* 31:7349–7356. [CrossRef Medline](#)
- Ekelund J, Slifstein M, Narendran R, Guillain O, Belani H, Guo NN, Hwang Y, Hwang DR, Abi-Dargham A, Laruelle M (2007) In vivo DA D(1) receptor selectivity of NNC 112 and SCH 23390. *Mol Imaging Biol* 9:117–125. [CrossRef Medline](#)
- Fields S, Collins C, Leraas K, Reynolds B (2009) Dimensions of impulsive behavior in adolescent smokers and nonsmokers. *Exp Clin Psychopharmacol* 17:302–311. [CrossRef Medline](#)
- Fillmore MT, Rush CR (2002) Impaired inhibitory control of behavior in chronic cocaine users. *Drug Alcohol Depend* 66:265–273. [CrossRef Medline](#)
- Frank MJ (2005) Dynamic dopamine modulation in the basal ganglia: a neurocomputational account of cognitive deficits in medicated and non-medicated Parkinsonism. *J Cogn Neurosci* 17:51–72. [CrossRef Medline](#)
- Frank MJ, Santamaria A, O'Reilly RC, Willcutt E (2007) Testing computational models of dopamine and noradrenaline dysfunction in attention deficit/hyperactivity disorder. *Neuropsychopharmacology* 32:1583–1599. [CrossRef Medline](#)
- Fujita M, Cropley V, Nathan P, Brown A, Sangare J, Ryu Y, Sprague K, Berman K, Pike V, Innis R (2006) Test retest reproducibility and influence of dopamine levels on [(18)F]fallypride PET quantification. *J Nucl Med* 47 [Suppl 1]:282P.
- Gerfen CR, Surmeier DJ (2011) Modulation of striatal projection systems by dopamine. *Annu Rev Neurosci* 34:441–466. [CrossRef Medline](#)
- Ghahremani DG, Lee B, Robertson CL, Tabibnia G, Morgan AT, De Shetler N, Brown AK, Monterosso JR, Aron AR, Mandelkern MA, Poldrack RA, London ED (2012) Striatal dopamine D₂/D₃ receptors mediate response inhibition and related activity in frontostriatal neural circuitry in humans. *J Neurosci* 32:7316–7324. [CrossRef Medline](#)
- Hall H, Sedvall G, Magnusson O, Kopp J, Halldin C, Farde L (1994) Distribution of D1- and D2-dopamine receptors, and dopamine and its metabolites in the human brain. *Neuropsychopharmacology* 11:245–256. [CrossRef Medline](#)
- Hersch SM, Ciliax BJ, Gutekunst CA, Rees HD, Heilman CJ, Yung KK, Bolam JP, Ince E, Yi H, Levey AI (1995) Electron microscopic analysis of D₁ and D₂ dopamine receptor proteins in the dorsal striatum and their synaptic relationships with motor corticostriatal afferents. *J Neurosci* 15:5222–5237. [Medline](#)
- Ishibashi K, Robertson CL, Mandelkern MA, Morgan AT, London ED (2013) The simplified reference tissue model with 18F-fallypride positron emission tomography: choice of reference region. *Mol Imaging* 12:1536–1541. [CrossRef Medline](#)
- Jenkinson M, Smith S (2001) A global optimisation method for robust affine registration of brain images. *Med Image Anal* 5:143–156. [CrossRef Medline](#)
- Jenkinson M, Bannister P, Brady M, Smith S (2002) Improved optimization for the robust and accurate linear registration and motion correction of brain images. *Neuroimage* 17:825–841. [CrossRef Medline](#)
- Jentsch JD, Ashenhurst JR, Cervantes MC, Groman SM, James AS, Pennington ZT (2014) Dissecting impulsivity and its relationships to drug addiction. *Ann N Y Acad Sci* 1327:1–26. [CrossRef Medline](#)
- Keeler JF, Pletsell DO, Robbins TW (2014) Functional implications of dopamine D₁ vs. D₂ receptors: a “prepare and select” model of the striatal direct vs. indirect pathways. *Neuroscience* 282C:156–175. [CrossRef Medline](#)
- Kreitzer AC, Berke JD (2011) Investigating striatal function through cell-type-specific manipulations. *Neuroscience* 198:19–26. [CrossRef Medline](#)
- Lammertsma AA, Hume SP (1996) Simplified reference tissue model for PET receptor studies. *Neuroimage* 4:153–158. [CrossRef Medline](#)
- Lane SD, Moeller FG, Steinberg JL, Buzby M, Kosten TR (2007) Performance of cocaine dependent individuals and controls on a response inhibition task with varying levels of difficulty. *Am J Drug Alcohol Abuse* 33:717–726. [CrossRef Medline](#)
- Lee B, London ED, Poldrack RA, Farahi J, Nacca A, Monterosso JR, Mumford JA, Bokarius AV, Dahlbom M, Mukherjee J, Bilder RM, Brody AL, Mandelkern MA (2009) Striatal dopamine D₂/D₃ receptor availability is reduced in methamphetamine dependence and is linked to impulsivity. *J Neurosci* 29:14734–14740. [CrossRef Medline](#)
- Logan GD, Cowan WB, Davis KA (1984) On the ability to inhibit simple and choice reaction time responses: a model and a method. *J Exp Psychol Hum Percept Perform* 10:276–291. [CrossRef Medline](#)
- Mawlawi O, Martinez D, Slifstein M, Broft A, Chatterjee R, Hwang DR, Huang Y, Simpson N, Ngo K, Van Heertum R, Laruelle M (2001) Imaging human mesolimbic dopamine transmission with positron emission tomography: I. Accuracy and precision of D(2) receptor parameter measurements in ventral striatum. *J Cereb Blood Flow Metab* 21:1034–1057. [CrossRef Medline](#)

- Mink JW (1996) The basal ganglia: focused selection and inhibition of competing motor programs. *Prog Neurobiol* 50:381–425. [CrossRef Medline](#)
- Monterosso JR, Aron AR, Cordova X, Xu J, London ED (2005) Deficits in response inhibition associated with chronic methamphetamine abuse. *Drug Alcohol Depend* 79:273–277. [CrossRef Medline](#)
- Mukherjee J, Yang ZY, Das MK, Brown T (1995) Fluorinated benzamide neuroleptics—III. Development of (S)-N-[(1-allyl-2-pyrrolidinyl)methyl]-5-(3-[18F] fluoropropyl)-2, 3-dimethoxybenzamide as an improved dopamine D-2 receptor tracer. *Nucl Med Biol* 22:283–296. [CrossRef Medline](#)
- Murray AM, Ryo HL, Gurevich E, Joyce JN (1994) Localization of dopamine D3 receptors to mesolimbic and D2 receptors to mesostriatal regions of human forebrain. *Proc Natl Acad Sci U S A* 91:11271–11275. [CrossRef Medline](#)
- Nandam LS, Hester R, Wagner J, Dean AJ, Messer C, Honeysett A, Nathan PJ, Bellgrove MA (2013) Dopamine D(2) receptor modulation of human response inhibition and error awareness. *J Cogn Neurosci* 25:649–656. [CrossRef Medline](#)
- Patenaude B, Smith SM, Kennedy DN, Jenkinson M (2011) A Bayesian model of shape and appearance for subcortical brain segmentation. *Neuroimage* 56:907–922. [CrossRef Medline](#)
- Ramdani C, Carbone L, Vidal F, Beranger C, Dagher A, Hasbroucq T (2014) Dopamine precursors depletion impairs impulse control in healthy volunteers. *Psychopharmacology (Berl)* 232:477–487. [CrossRef Medline](#)
- Reynolds B, Ortengren A, Richards JB, de Wit H (2006) Dimensions of impulsive behavior: personality and behavioral measures. *Pers Individ Dif* 40:305–315. [CrossRef](#)
- Reynolds B, Penfold RB, Patak M (2008) Dimensions of impulsive behavior in adolescents: laboratory behavioral assessments. *Exp Clin Psychopharmacol* 16:124–131. [CrossRef Medline](#)
- Robinson ES, Eagle DM, Economidou D, Theobald DE, Mar AC, Murphy ER, Robbins TW, Dalley JW (2009) Behavioural characterisation of high impulsivity on the 5-choice serial reaction time task: specific deficits in “waiting” versus “stopping.” *Behav Brain Res* 196:310–316. [CrossRef Medline](#)
- Rubia K, Russell T, Overmeyer S, Brammer MJ, Bullmore ET, Sharma T, Simmons A, Williams SC, Giampietro V, Andrew CM, Taylor E (2001) Mapping motor inhibition: conjunctive brain activations across different versions of go/no-go and stop tasks. *Neuroimage* 13:250–261. [CrossRef Medline](#)
- Senderecka M, Grabowska A, Szewczyk J, Gerc K, Chmylak R (2012) Response inhibition of children with ADHD in the stop-signal task: an event-related potential study. *Int J Psychophysiol* 85:93–105. [CrossRef Medline](#)
- Slifstein M, Hwang DR, Huang Y, Guo N, Sudo Y, Narendran R, Talbot P, Laruelle M (2004) In vivo affinity of [18F]fallypride for striatal and extrastriatal dopamine D2 receptors in nonhuman primates. *Psychopharmacology (Berl)* 175:274–286. [CrossRef Medline](#)
- Slifstein M, Kegeles LS, Gonzales R, Frankle WG, Xu X, Laruelle M, Abi-Dargham A (2007) [11C]NNC 112 selectivity for dopamine D1 and serotonin 5-HT(2A) receptors: a PET study in healthy human subjects. *J Cereb Blood Flow Metab* 27:1733–1741. [CrossRef Medline](#)
- Soreni N, Crosbie J, Ickowicz A, Schachar R (2009) Stop signal and Conners’ continuous performance tasks: test–retest reliability of two inhibition measures in ADHD children. *J Atten Disord* 13:137–143. [CrossRef Medline](#)
- Steele VR, Aharoni E, Munro GE, Calhoun VD, Nyakanti P, Stevens MC, Pearlson G, Kiehl KA (2013) A large scale (N = 102) functional neuroimaging study of response inhibition in a Go/NoGo task. *Behav Brain Res* 256:529–536. [CrossRef Medline](#)
- Surmeier DJ, Ding J, Day M, Wang Z, Shen W (2007) D1 and D2 dopamine-receptor modulation of striatal glutamatergic signaling in striatal medium spiny neurons. *Trends Neurosci* 30:228–235. [CrossRef Medline](#)
- Swick D, Ashley V, Turken U (2011) Are the neural correlates of stopping and not going identical? Quantitative meta-analysis of two response inhibition tasks. *Neuroimage* 56:1655–1665. [CrossRef Medline](#)
- Tannock R, Schachar RJ, Carr RP, Chajczyk D, Logan GD (1989) Effects of methylphenidate on inhibitory control in hyperactive children. *J Abnorm Child Psychol* 17:473–491. [CrossRef Medline](#)
- Vaidya CJ, Austin G, Kirkorian G, Ridlehuber HW, Desmond JE, Glover GH, Gabrieli JD (1998) Selective effects of methylphenidate in attention deficit hyperactivity disorder: a functional magnetic resonance study. *Proc Natl Acad Sci U S A* 95:14494–14499. [CrossRef Medline](#)
- Van Sickle J (2003) Analyzing correlations between stream and watershed attributes. *JAWRA* 39:717–726. [CrossRef](#)
- Vermeulen RJ, Drukarch B, Sahadat MC, Goosen C, Wolters EC, Stoof JC (1994) The dopamine D1 agonist SKF 81297 and the dopamine D2 agonist LY 171555 act synergistically to stimulate motor behavior of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned parkinsonian rhesus monkeys. *Mov Disord* 9:664–672. [CrossRef Medline](#)
- Weaver J, Baggott MJ, de Wit H (2013) Test-retest reliability of behavioral measures of impulsive choice, impulsive action, and inattention. *Exp Clin Psychopharmacol* 21:475–481. [CrossRef Medline](#)
- Wöstmann NM, Aichert DS, Costa A, Rubia K, Möller HJ, Ettinger U (2013) Reliability and plasticity of response inhibition and interference control. *Brain Cogn* 81:82–94. [CrossRef Medline](#)
- Wu Y, Carson RE (2002) Noise reduction in the simplified reference tissue model for neuroreceptor functional imaging. *J Cereb Blood Flow Metab* 22:1440–1452. [CrossRef Medline](#)
- Zald DH, Cowan RL, Riccardi P, Baldwin RM, Ansari MS, Li R, Shelby ES, Smith CE, McHugo M, Kessler RM (2008) Midbrain dopamine receptor availability is inversely associated with novelty-seeking traits in humans. *J Neurosci* 28:14372–14378. [CrossRef Medline](#)
- Zald DH, Woodward ND, Cowan RL, Riccardi P, Ansari MS, Baldwin RM, Cowan RL, Smith CE, Hakyemez H, Li R, Kessler RM (2010) The interrelationship of dopamine D2-like receptor availability in striatal and extrastriatal brain regions in healthy humans: a principal component analysis of [18F]fallypride binding. *Neuroimage* 51:53–62. [CrossRef Medline](#)
- Zheng D, Oka T, Bokura H, Yamaguchi S (2008) The key locus of common response inhibition network for no-go and stop signals. *J Cogn Neurosci* 20:1434–1442. [CrossRef Medline](#)
- Zheng P, Zhang XX, Bunney BS, Shi WX (1999) Opposite modulation of cortical N-methyl-D-aspartate receptor-mediated responses by low and high concentrations of dopamine. *Neuroscience* 91:527–535. [CrossRef Medline](#)