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Dopamine Transporters, D₂ Receptors, and Dopamine Release in Generalized Social Anxiety Disorder

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Abstract

Background—Dopamine D₂ receptor and dopamine transporter availability in the striatum have each been reported abnormal in generalized social anxiety disorder (GSAD) in studies using single photon computerized tomography (SPECT). D₂ receptors and dopamine transporters have not previously been studied within the same GSAD subjects, however, and prior GSAD studies have not assessed dopamine release or subdivided striatum into functional subregions.

Methods—Unmedicated adults with GSAD (N=17) and matched healthy comparison subjects (HC, N=13) participated in this study. Of these, 15 GSAD and 13 HC subjects completed baseline assessment of D₂ receptor availability using positron emission tomography (PET) with the radiotracer [¹¹C] raclopride. Twelve GSAD and 13 HC subjects completed a repeat scan after intravenous administration of D-amphetamine, to study dopamine release. Twelve of the GSAD subjects and 10 of the HC subjects also completed SPECT with the radiotracer [¹²³I] methyl 3β-(4-iodophenyl) tropane-2β-carboxylate ([¹²³I] β-CIT) to assess dopamine transporter availability.

Results—GSAD and HC groups did not differ significantly in striatal dopamine transporter availability, overall striatal or striatal subregion D₂ receptor availability at baseline, or change in D₂ receptor availability after D-amphetamine. Receptor availability and change after D-amphetamine were not significantly associated with severity of social anxiety or trait detachment.

Conclusions—These findings do not replicate previous findings of altered striatal dopamine transporter and D₂ receptor availability in GSAD subjects assessed with SPECT. The differences from results of prior studies may be due to differences in imaging methods or characteristics of samples.

Keywords

social phobia; raclopride; imaging; SPECT; PET

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Introduction

Evidence from neuroreceptor imaging and pharmacological studies has suggested that the generalized type of social anxiety disorder (GSAD, also known as generalized social phobia) may be associated with abnormal central dopamine function. Using single photon emission computerized tomography (SPECT) neuroreceptor imaging, Tiihonen et al [1] reported low striatal dopamine transporter binding, a presynaptic measure of dopaminergic innervation. Van der Wee et al [2], however, found the same measure to be increased in GSAD. Schneier et al [3,4] reported low availability of striatal D₂ receptors, a primarily postsynaptic measure, in GSAD and in GSAD comorbid with OCD. Striatal function also has been shown to be abnormal in GSAD during cognitive tasks [5].

In pharmacological studies, D₂ receptor antagonist medications have been reported to precipitate social anxiety symptoms in patients with Tourette's syndrome and psychotic disorders [6-8], although pilot studies have suggested that second generation antipsychotics may also be therapeutic in GSAD [9-11]. Some medications with dopaminergic activity, such as MAOIs, have appeared particularly effective as treatments for GSAD [12].

The dopamine system findings for GSAD are supported by similar associations with personality traits that are common in GSAD [13]. Low extraversion in depressed patients was associated with lower levels of dopamine metabolite homovanillic acid (HVA) in the cerebrospinal fluid (CSF) [14], and trait detachment has been associated with lower striatal D₂ receptor and dopamine transporter availability in healthy subjects studied with positron emission tomography (PET) [15-17]. In nonhuman primates, PET studies have found decreased striatal D₂ binding to be associated with subordinate social status [18], a condition that shares features with human GSAD [19].

We hypothesized that GSAD is heterogeneous in respect to DA system dysfunction and that either presynaptic, postsynaptic or both abnormalities may be present. This study assessed presynaptic and postsynaptic receptors in the same groups of GSAD and healthy comparison subjects. Presynaptic function was assessed using SPECT with the ligand [¹²³I]β-CIT to assess DA transporter availability, and PET to assess D-amphetamine-induced change in [¹¹C]raclopride binding. D-amphetamine administration reduces [¹¹C]raclopride binding in proportion to the increase in extracellular dopamine [20]. Postsynaptic function was assessed with the baseline PET with [¹¹C]raclopride.

A limitation of prior SPECT studies of striatal DA dysregulation is that they lacked resolution to assess receptor availability in functional subregions of striatum. We hypothesized that dysregulation of the ventral striatum, which includes the nucleus accumbens and is the subregion most associated with motivational and reward functions, including social reward [21,22], would be specifically associated with social dysfunction in GSAD. This study utilized high resolution PET with [¹¹C]raclopride, which permits discrimination of striatal subregions in the imaging of D₂ receptors. Because adequate PET ligands for the DA transporter were not available at the time of this study, we utilized SPECT with [¹²³I]β-CIT to image DA transporter binding in the striatum as a whole.

Specific goals of this study were to assess in GSAD and healthy comparison (HC) subjects:

1. Dopamine D₂ receptor availability in the striatum and in striatal subregions.
2. D-amphetamine-induced decrease in D₂ receptor availability in the striatum and striatal subregions.
3. Dopamine transporter availability in the striatum.

4. The relationship of imaging outcome measures to clinical severity of GSAD and trait detachment.

Methods and Materials

Subjects

Subjects with a principal diagnosis of GSAD and HC subjects with no psychiatric diagnoses were recruited by media notices or referral by clinicians. HC subjects were selected to match the GSAD group in respect to age and sex. Diagnoses were made by interview with a clinician and independently confirmed by a semi-structured interview by another trained clinician using the Structured Clinical Interview for DSM-IV (SCID-IV) [23]. All subjects were aged 18-55, physically healthy as confirmed by physical and laboratory examination including urine toxicology and pregnancy test, and had not taken psychoactive medications within the past month. Subjects had no current psychotic disorders, mood disorders (other than dysthymia), somatoform disorders, eating disorders, panic disorder, or posttraumatic stress disorder, and no history of a substance use disorder. Written informed consent was obtained, and subjects received financial compensation for completing study procedures. This study was approved by the Institutional Review Board of New York State Psychiatric Institute.

Overview of Assessments

GSAD and HC subjects completed a β -CIT SPECT scan to assess dopamine transporter availability, followed approximately one week later by raclopride PET scans before and after D-amphetamine challenge to assess D_2 receptor availability and D-amphetamine-induced dopamine release. An MRI was obtained for PET coregistration. Clinical features assessed as potential correlates of dopamine system indices included social anxiety (Liebowitz Social Anxiety Scale) [24] and trait detachment (Karolinska Scales of Personality [25]). Four items (happiness, restlessness, energy and anxiety) from the Amphetamine Interview Rating Scale (AIRS) [26] were self-rated during the 60 minutes following D-amphetamine injection, and maximal scores for each item were analyzed.

[123 I] β -CIT SPECT

[123 I] β -CIT was prepared from the corresponding trimethylstannyl precursor as previously described [27]. Because of the slow uptake and slow peripheral clearance of the tracer, a state of sustained equilibrium is reached approximately 15 hours after injection [28]. This state of equilibrium allows reliable quantification of DAT density at 24 hours post injection. Equilibrium analysis performed at 24 hours provided results similar to those of kinetic analysis of data acquired on the day of injection [29]. One 24-min scan was obtained approximately 24 hours (1483 min, SD = 51) after injection of [123 I] β -CIT (5.8 mCi, SD = 1.2). SPECT data were acquired on the PRISM 3000 (*Picker, Cleveland, OH*) with high-resolution fan beam collimators (resolution of 11-9 mm full width half maximum).

Data analysis—Projections from photopeak window were prefiltered using a Butterworth (cutoff 0.24 Hz^{-1} , power factor = 10). Images were reconstructed with filtered backprojections using a ramp filter on a $128 \times 128 \times 64$ matrix (corresponding to a voxel volume of $2.07 \times 2.07 \times 3.56 \text{ mm}$, = 15.25 mm^3). Images were then exported to the MEDX image analysis software (*Sensor Systems, Sterling, Virginia*). Stacks of 64 images were reoriented so that the canthomeatal line, as identified by the fiducial markers, corresponded to the transaxial plane of the data set. The eight slices with highest striatal uptake, as identified in the sagittal plane, were summed to generate a summed striatal slice. The same procedure was performed using the eight slices with highest brainstem uptake. Summed slices were attenuation corrected with a Chang algorithm, assuming uniform attenuation

within an ellipse drawn around the skull and using an attenuation coefficient value 0.12 cm^{-1} . A standard region of interest (ROI) was used. The same ROI profile was used for each subject, and the placement of the ROI was optimized for each subject as to be centered on the striatal activity distribution. Right and left striatal ROIs and occipital region were positioned on the summed striatal slice. The occipital region was selected as the background region because, in primates, no displaceable binding was observed in the occipital region following injection of unlabelled β -CIT [30].

Specific binding was calculated as the difference between total striatal and occipital activity. Because [^{123}I] β -CIT uptake is near equilibrium at 24 hours post injection, a simple ratio of specific to nonspecific activities measured at 24 hours provides BP_{ND} , the equilibrium specific to nonspecific partition coefficient [26].

$$BP_{ND} = \frac{BP_p}{V_2} = \frac{B_{\max}}{K_D * V_2}$$

[^{11}C]Raclopride PET

Each subject was scanned before and after intravenous administration of D-amphetamine (0.3mg/kg). [^{11}C]raclopride was administered as a bolus, followed by constant infusion (Kbol of 105 min) as described previously [31,32]. Emission data were collected as eight frames of 5 min each at 40-80 min after the start of infusion. The second [^{11}C]raclopride administration was started 2 min following the D-amphetamine administration, with ongoing cardiovascular monitoring. Four venous samples were collected (at 40, 50, 60 and 70 min) to measure plasma concentration of [^{11}C]raclopride and the free fraction (f_1). Another venous sample was obtained at 40 min to measure amphetamine levels. An MRI was acquired on a GE 1.5-T Signa Advantage system.

Image analysis was performed in MEDx (*Sensor Systems, Sterling, Virginia*) as described previously [31]. ROIs were drawn on each individual's MRI and applied to the coregistered PET images. The striatum was divided into five anatomic ROIs and three functional subdivisions: limbic striatum (LST), associative striatum (AST) and sensorimotor striatum (SMST) as described previously [32]. The anatomic ROIs included the ventral striatum (VST), the dorsal caudate rostral to the anterior commissure (AC; precommissural dorsal caudate, preDCA), the dorsal putamen rostral to the AC (precommissural dorsal putamen, preDPU), the caudate caudal to the AC (postcommissural caudate, postCA), and the putamen caudal to the AC (postcommissural putamen, postPU). Based on their cortical and subcortical connections, the preDCA, preDPU, and postCA ROIs were functionally classified as the AST, the VST as the LST, and the postPU as the SMST [for reviews, see 33,34]. Activities from the left and right regions were averaged.

PET outcomes are reported for 1) [^{11}C]raclopride binding potential (BP_p , mL/g), calculated as the ratio of striatal specific binding (i.e. striatal minus cerebellar activities) over plasma free metabolite-corrected steady-state tracer concentration measured during the same interval; and 2) BP_{ND} (specific to nonspecific equilibrium partition coefficient, unitless), calculated as the ratio of BP_p to nonspecific distribution volume [35]. Both outcome measures were obtained using an equilibrium analysis. Cerebellar activity is assumed to be equal to nonspecific activity, because the concentration of D_2 receptors in the cerebellum is negligible [36]. We will use the term " D_2 receptors" to denote both D_2 and D_3 receptors, because [^{11}C]raclopride has similar affinity for both [37]. The BP_p and BP_{ND} for the AST were calculated as the weighted average of the ROIs that make up this subdivision (weighted by size of the ROI), and BP_p and BP_{ND} for the striatum (STR) were calculated as

the weighted average of all five ROIs. BP_p was used to assess between-subject comparisons, and BP_{ND} was used for within-subject calculation of change in binding post-amphetamine.

Because the activity measured in each ROI includes spillover of activity from adjacent regions, a partial volume effects (PVE) correction was performed as previously described [31].

Statistical Analysis

Group outcomes were compared using t tests and chi square tests. Relationships between continuous variables were analyzed using the Pearson product moment correlation coefficient. All imaging analyses were repeated with age and gender as covariates. A two-tailed probability value of .05 was selected as significance level. Effect sizes are reported as Cohen's *d* [38].

Results

Sample

Seventeen GSAD subjects and 13 HC subjects entered the study and completed at least one scan. Fifteen GSAD subjects and 12 HC subjects completed the baseline raclopride PET scan, but three GSAD subjects did not complete a post-amphetamine scan, due to either withdrawal of consent or medical contraindications to D-amphetamine (e.g. elevated blood pressure after first scan). Fifteen GSAD subjects and 13 HC subjects completed [¹²³I] β-CIT SPECT (2 GSAD subjects did not complete it due to technical problems.). Twelve GSAD subjects and 10 HC subjects completed all procedures.

There were no significant demographic differences between samples (see Table 1) or between the subsamples of GSAD and HC subjects who completed all scans. Severity of social anxiety in the GSAD group was typical of a treatment-seeking sample of GSAD patients and much greater than the low level in the comparison group (Liebowitz Social Anxiety Scale total 78.6 (SD=19.2) vs. 10.2 (SD=7.9), $t=13.3$, $df=28$, $p<.001$). Trait detachment scores were also elevated in the GSAD group (25.9 (SD=3.4) vs. 18.8 (SD=3.2), $t=5.8$, $df=28$, $p<.001$). In the GSAD group, three subjects had psychiatric comorbidity (one with generalized anxiety disorder, one with generalized anxiety disorder and dysthymia, and one with mild obsessive-compulsive disorder and dysthymia); three had prior medication treatment (SSRI or SNRI) that had been discontinued one, five, and nine months prior to the study.

[¹²³I] β-CIT SPECT

The GSAD and HC groups did not differ in striatal dopamine transporter binding (GSAD group mean $V_3'' = 7.69$, $SD = 1.12$ vs. HC $V_3'' = 7.62$, $SD = .91$, $p = .87$; Cohen's *d* = .07). Striatal dopamine transporter binding was not significantly correlated with Liebowitz Social Anxiety Scale score in the GSAD group ($r = -.23$, $p = .53$) or the HC group ($r = .15$, $p = .65$) or with trait detachment score in the GSAD group ($r = -.46$, $p = .18$) or the HC group ($r = -.42$, $p = .18$), nor were there significant correlations in the pooled sample.

[¹¹C]Raclopride PET

GSAD and HC groups did not differ in respect to injected dose of [¹¹C]raclopride at baseline (GSAD: 13.0 mCi, $SD = 3.7$; HC: 13.8 mCi, $SD = 3.2$, $p = .58$) or post-amphetamine (GSAD: 11.8 mCi, $SD = 4.1$; HC: 12.1 mCi, $SD = 3.2$, $p = .86$); specific activity at baseline (GSAD: 1239 Ci/mmol, $SD = 600$; HC: 1553 Ci/mmol, $SD = 597$, $p = .19$) or post-amphetamine (GSAD: 1241 Ci/mmol, $SD = 778$; HC: 1310 Ci/mmol, $SD = 429$, $p = .79$), injected mass at baseline (GSAD: 4.0 μg, $SD = .8$; HC: 3.3 μg, $SD = .9$, $p = .07$) or

post-amphetamine (GSAD: 3.9 μg , SD = 1.1; HC: 3.4 μg , SD = .9, $p = .25$), or cerebellar distribution volume V_2 at baseline (GSAD: .40 mLg^{-1} , SD = .06; HC: .42 mLg^{-1} , SD = .06, $p = .28$) or post-amphetamine (GSAD: .34 mLg^{-1} , SD = .07; HC: .35 mLg^{-1} , SD = .12, $p = .79$).

There were no significant group differences in D_2 receptor binding potential (BP_p) or amphetamine-induced decrease in D_2 receptor binding (ΔBP_{ND}) in the striatum overall or within each functional subregion of striatum (VST, AST, SM). (See Tables 2 and 3). Effect sizes (Cohen's d) were 0.32 for D_2 receptor BP_p and 0.59 for amphetamine-induced decrease in D_2 receptor binding in the striatum overall. Corrections for age, gender, and for partial volume effects did not significantly change any of the [^{11}C]raclopride PET results (these analyses are available from the authors on request). Self-reported mood scores after d-amphetamine did not differ between groups: happiness 6.5 (SD=2.3) for GSAD vs. 7.6 (SD=1.4) for HC, $t=1.3$, $df=20$, $p=.20$; restlessness 7.3 (SD=2.1) vs. 6.2 (SD=2.1), $t=1.6$, $df=20$, $p=.13$; energy 7.0 (SD=2.3) vs. 7.1 (SD=2.0), $t=0.1$, $df=20$, $p=.92$; anxiety 6.6 (SD=2.2) vs. 5.1 (SD=2.6), $t=1.5$, $df=19$, $p=.16$.

Regional D_2 receptor binding potentials were not significantly associated with scores on the Liebowitz Social Anxiety Scale within the GSAD group ($r = .12$, $p = .68$ for overall striatum) or the HC group ($r = -.10$, $p = .76$ for overall striatum). They also were not significantly associated with scores on the Detachment Scale within the GSAD group ($r = .14$, $p = .61$ for overall striatum) or within the HC group ($r = .13$, $p = .68$ for overall striatum). Correlations were also nonsignificant for the pooled sample.

D-amphetamine-induced decreases in D_2 receptor binding in overall striatum and striatal subregions were also not significantly associated with Liebowitz Social Anxiety Scale scores at baseline within the GSAD group ($r = -.09$, $p = .78$ for overall striatum) or the HC group ($r = -.42$, $p = .17$ for overall striatum). They also were not significantly associated with scores at baseline on the Detachment Scale within the GSAD group ($r = -.30$, $p = .35$ for overall striatum) or within the HC group ($r = .09$, $p = .79$ for overall striatum). Correlations were also nonsignificant for the pooled sample. Self-reported mood scores after d-amphetamine were not significantly correlated with decreases in D_2 receptor binding in overall striatum and striatal subregions, with the exception of greater decrease in D_2 receptor binding in the ventral striatum being correlated with restlessness in the GSP group only ($r = .68$, $p = .015$).

Discussion

These findings do not confirm prior reports of an association of GSAD with dysfunction of striatal dopamine. D_2 receptor binding was non-significantly lower in the GSAD group, in the same direction as prior significant findings but with lesser magnitude of effect. Amphetamine-induced change in D_2 receptor binding did not differ significantly between groups. Dopamine transporter binding also did not differ between groups, unlike prior [^{123}I] β -CIT SPECT studies with conflicting findings of decreased [1] and increased [2] binding in SAD (see Table 4 for summary of prior studies). None of the dopamine measures were significantly associated with severity of social anxiety in this study, and the assessment of functional subregions of striatum did not yield specific associations with GSAD or social anxiety.

Similar to a prior report [13], trait detachment was elevated in patients with GSAD. Prior findings of an association of trait detachment with D_2 receptor [4,15,16] and dopamine transporter binding [17], however, were not confirmed in this sample (see Table 4 for

summary of prior studies). Dopamine measures were not associated with trait detachment in either the GSAD or HC group.

The discrepancies between studies could be due to small samples sizes. Although this study utilized a sample size similar to prior studies of DA transporters [1,2] and D₂ receptors in GSAD [3,4], power was inadequate to reliably detect group differences smaller than the large-sized effects (Cohen's $d = 1.2 - 1.5$) reported in the prior studies. Between-group effect sizes for key outcome measures in the overall striatum in this study ranged from small (for DA transporters and D₂ receptors) to medium for decrease in D₂ receptor binding post-amphetamine (.07 - .59). Small sample sizes also increase the possibility that findings of the prior studies could represent false positives.

Other possible reasons for lack of replication include methodological differences, such as the use of PET to assess D₂ receptor binding in this study versus [¹²³I]IBZM SPECT used in the two prior studies of SAD. The PET methods employed here have several advantages over prior SPECT methods, such as being fully quantitative and having superior anatomic resolution. The lack of replication of studies associating trait detachment with D₂ receptor binding, [15,16] however, is not explained by imaging method differences because these studies also utilized [¹¹C]raclopride PET.

The methods for SPECT assessment of dopamine transporter binding differed, in that prior SAD studies [1,2] administered an SSRI to block [¹²³I]β-CIT from binding to serotonin transporters, used structural MRI to identify volumes of interest [2], and used different reference regions of white matter [1] and cerebellum [2]. In the striatum, however, binding of [¹²³I]β-CIT has been shown to reflect dopamine transporter density [27,30], and none of these differences in methods would predict the completely discrepant results of the three studies.

Either the GSAD or HC sample could have been atypical, although we were unable to identify meaningful deviations from prior samples in respect to demographics, severity of social anxiety, or comorbidity. Inclusion/exclusion criteria were essentially the same as those used in our prior study of D₂ receptors in GSAD [3]. The dopamine transporter study of van der Wee [2] was the only dopamine imaging SAD study limited to medication-naïve patients. Post hoc analyses excluding our three patients with prior medication exposure, two patients and two controls with tobacco use, and three patients with comorbidity each did not change the significance of group differences in outcome. We were unable to control for all potential clinical confounds that have been reported to be associated with striatal dopamine function, such as menstrual status [e.g. 39], personality traits other than detachment, such as socially desirable responding and response to pain [40,41], exposure to stressors [42], or genetic differences [43].

A strength of the current study was inclusion of assessments of both pre-synaptic and post-synaptic measures of striatal dopamine function within the same sample, which offers a more comprehensive assessment of dopamine function than a single measure alone. Other factors that may affect dopaminergic transmission and measurement of receptors, however, could not be measured in this study or the other GSAD neuroreceptor imaging studies, including the effects of baseline dopamine levels and affinity of receptors for the radiotracer. Additionally, assessment of extrastriatal dopamine receptors, which may also contribute to traits related to GSAD [44], would require use of alternative radioligands, such as [¹⁸F]fallypride and [¹¹C]FLB-457 [45,46].

Despite the discrepancies in dopamine neuroimaging findings, the greater body of evidence reviewed above continues to support an association of striatal dopamine function with SAD. Recent neurobiological study of SAD has highlighted its relationship to amygdalo-cortical

fear circuitry, with consistent findings of increased amygdala activation to social threat stimuli and fear-mediated avoidant behavior [47]. Social avoidance, however, could also be mediated by deficits in motivation needed to transcend the threat of potential negative evaluation. The mesolimbic dopamine system, and the ventral striatum in particular, are well-established modulators of such incentive function [48]. Methods of assessing social incentive and reward function need more study, as they could identify endophenotypes that map to dopamine receptor measures more directly than do social anxiety or the GSAD diagnosis. Further study with broader assessment of potential confounds such as prior medications, current nicotine use, menstrual status, stressors, personality traits, and variation in genes affecting dopamine function, along with larger sample sizes, will be needed to further elucidate the role of the mesolimbic dopamine system in SAD.

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Dr. Liebowitz reports equity ownership in ChiMatrix LLC and the Liebowitz Social Anxiety Scale (LSAS), is a consultant to Avera, Astra Zeneca, Tikvah, Wyeth Ayerst, Pherin, and Eli Lilly; has licensed LSAS software to GlaxoSmithKline, Pfizer, Avera, Tikvah, Eli Lilly, Indevus, Servier; is on the Speaker's Bureau for Wyeth Ayerst, and has received research funding from Pfizer, GlaxoSmithKline, Astra Zeneca, Forest, Tikvah, Avera, Eli Lilly, Novartis, Sepracor, Horizon, Johnson and Johnson .

Dr. Laruelle is currently employed by GlaxoSmithKline.

Dr. Hwang is currently employed by Amgen.

Drs. Martinez and Slifstein have no financial ties to disclosure.

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Table 1

Demographic Features

	GSAD	HC
	N=17	N=13
Age, years	31.1 (SD=6.6)	30.9 (SD=8.1)
% male	64.7%	53.8%
% nonsmokers	88.2%	84.6%
% Hispanic	11.8%	0%
Not Hispanic	88.2%	100%
%Asian	17.6%	23.1%
Black	23.5%	15.4%
White	58.9%	61.5%

GSAD=generalized social anxiety disorder subjects; HC=healthy control subjects; SD=standard deviation

Table 2

[¹¹C]Raclopride binding potential (BP_p, in mL g⁻¹, mean (SD)) in GSAD and HC groups by striatal subregions.

Functional Subregions	GSAD		HC		%difference	t	df	p
	N=15		N=12					
LST	0.89 (.19)		0.93 (.15)		-4.3	0.62	25	.54
AST	1.05 (.19)		1.10 (.19)		-4.5	0.74	25	.47
SMST	1.23 (.24)		1.29 (.21)		-4.7	0.74	25	.47
Striatum, overall	1.07 (.20)		1.13 (.18)		-5.3	0.80	25	.43

BP_p=binding potential; mL g⁻¹=milliliters per gram; GSAD=generalized social anxiety disorder subjects; HC=healthy control subjects; LST=limbic striatum; AST=associative striatum; SMST=sensorimotor striatum

Table 3

D-amphetamine-induced change (% (SD)) in [¹¹C]raclopride binding in GSAD and HC groups by striatal subregions

Functional Subregions	GSAD		HC		t	df	p
	N=12	N=12	N=12	N=12			
LST	-12.23 (6.80)	-13.06 (7.04)	-6.4	0.29	22	.77	
AST	-8.58 (6.10)	-5.15 (4.61)	+66.6	1.56	22	.13	
SMST	-18.07 (3.31)	-15.78 (6.21)	+14.5	1.13	22	.27	
Striatum, overall	-11.81 (4.71)	-9.05 (4.66)	+30.5	1.44	22	.16	

GSAD=generalized social anxiety disorder subjects; HC=healthy control subjects; LST=limbic striatum; AST=associative striatum; SMST=sensorimotor striatum

Table 4

Prior studies of the association of D2 receptors and dopamine transporters with social anxiety disorder and trait detachment

Author	Method	Sample Size	Regions of Interest	Principal Findings
Tiihonen et al., 1997	[¹²³ I] β-CIT SPECT after SSRI	11 GSAD; 11 HC	Striatum/White matter	Decreased DAT binding in GSAD, $t=5.41$, $p<.001$
Schneier et al., 2000	[¹²³ I]IBZM SPECT	10 GSAD; 10 HC	Striatum/Occipital Cortex	Decreased D ₂ receptor binding in GSAD, $t=2.6$, $p=0.02$
van der Wee et al., 2008	[¹²³ I] β-CIT SPECT after SSRI; MRI	12 Medicationnaive GSAD; 12 HC	Striatum/Cerebellum	Increased DAT binding in GSAD, $p=0.011$
Schneier et al., 2008	[¹²³ I]IBZM SPECT	7 GSAD with OCD; 7 HC	Striatum/Occipital Cortex	Decreased D ₂ receptor binding in GSAD with OCD, $Z=2.24$, $p=0.025$
Farde et al., 1997	[¹¹ C]raclopride PET, Scatchard procedure	24 HC	Putamen	D ₂ receptor density correlated with detachment, $r=-0.68$, $P<0.001$
Breier et al., 1998	[¹¹ C]raclopride PET	18 HC	Striatum/Cerebellum	D ₂ receptor binding correlated with detachment, $r=-0.49$, $p=0.04$
Laakso et al., 2000	[¹⁸ F]CFT PET	18 HC	Putamen, Caudate/Cerebellum	DAT binding in putamen, but not caudate, correlated with detachment, $r=-0.45$, $p<0.04$

GSAD=generalized social anxiety disorder subjects; HC=healthy control subjects; OCD = obsessive-compulsive disorder; DAT = dopamine transporter