Amphetamine Induced Dopamine Release Increases Anxiety in Individuals Recovered from Anorexia Nervosa

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ABSTRACT

Objective: Genetic, pharmacologic, and physiological data suggest that individuals with anorexia nervosa (AN) have altered striatal dopamine (DA) function.

Method: We used an amphetamine challenge and positron emission tomography [^{11}C]raclopride paradigm to explore DA striatal transmission in 10 recovered (REC) AN compared with 9 control women (CW).

Results: REC AN and CW were similar for baseline, postamphetamine [^{11}C]raclopride binding potential (BP_{ND}) and change (Δ) in BP_{ND} for all regions. In CW, ventral striatum Δ BP_{ND} was associated with euphoria ($r = -0.76$; $p = 0.03$), which was not found for REC AN. Instead, REC AN showed a significant relationship between anxiety and Δ BP_{ND} in the precommissural dorsal caudate ($r = -0.62$, $p = 0.05$).

Discussion: REC AN have a positive association between endogenous DA release and anxiety in the dorsal caudate. This finding could explain why food-related DA release produces anxiety in AN, whereas feeding is pleasurable in healthy participants.

Keywords: anorexia nervosa; amphetamine; dopamine; anxiety; positron emission tomography

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Introduction

Anorexia nervosa (AN) is a disorder of unknown etiology, which invariably has an onset during adolescence in women.[1] AN is characterized by the relentless pursuit of thinness, substantial weight loss, obsessive fears of being fat, aberrant eating behaviors, disturbances of mood, and frenetic exercise.[1] Large-scale community-based twin studies have shown that 50 to 80% of the variance in eating disorders (EDs)[2–4] can be accounted for by genetic factors. Considerable evidence suggests that AN personality and temperament traits, such as anxiety, harm avoidance, perfectionism, and obsessionality, are heritable and confer liability to the development of AN. Such traits occur in childhood before the onset of AN, persist after recovery, and are elevated in unaffected family members.[5–8]

Genetic, pharmacologic, and physiological data[9] suggest that individuals with AN have altered striatal dopamine (DA) function which, in theory, may play

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a role in symptoms, such as altered feeding behavior, anhedonia, dysphoric mood, and increased motor activity.[10,11] It is important to emphasize that DA disturbances may be traits that contribute to a vulnerability to AN, rather than simply emerging secondary to malnutrition. First, there is altered frequency of the functional polymorphisms of D2 receptor genes.[12] Underweight AN have impaired visual discrimination learning,[13] a task thought to reflect DA signaling function, and a generalized failure to activate the appetitive motivational system in a startle task.[14] DA disturbances persist after individuals recover (e.g., normal weight, nutrition, and menses) from AN. For example, recovered (REC) AN, particularly restricting type AN, have less homovanillic acid (HVA), a DA metabolite, in cerebrospinal fluid (CSF) than control women (CW).[15]

Recent advances in imaging technology permit a more direct examination of DA function in humans. Specifically, positron emission tomography (PET) and the radioligand [^{11}C]raclopride can be used to assess striatal DA D2/D3 receptor binding. Studies of REC AN have found increased binding of DA D2/D3 receptors at baseline in the anterior ventral striatum,[16,17] a region that contributes to optimal responses to reward stimuli.[18–20] Moreover, indices of greater anxiety were associated with baseline dorsal caudate and dorsal putamen [^{11}C]raclopride binding.[16,17]

[^{11}C]raclopride binding is influenced by endogenous DA; therefore, elevated anterior ventral striatum [^{11}C]raclopride binding could indicate either an elevation of the density and/or affinity of the D2/D3 receptors or a reduction in intrasynaptic DA concentrations. One way to further characterize endogenous DA function is to assess the decrease in striatal [^{11}C]raclopride binding that occurs after administration of drugs, such as amphetamine, that stimulates DA release. It has been shown that the decrease of [^{11}C]raclopride binding following amphetamine-induced DA release is a reliable measure of endogenous DA transmission[21,22] in striatal subdivisions (limbic, associative, and sensorimotor striatum)[23,24] and can be used as a noninvasive measure of the change in DA induced by the challenge. Thus, the amphetamine challenge PET [^{11}C]raclopride paradigm was used to further explore altered DA striatal transmission in REC AN compared with CW.

Method

Subject Selection

Ten REC AN (5 restricting type AN, 5 binge-purge type AN) women were recruited. Nine healthy CW were recruited through local advertisements. REC AN had to meet the following criteria over the past year: (1) maintain a weight above 90% of average body weight; (2) have regular menstrual cycles; (3) have not binged, purged, restricted food intake or exercised excessively; (4) not used psychoactive medications, such as antidepressants; and (5) no current alcohol or drug abuse/dependence. CW had no history of any psychiatric, serious medical, or neurological illness. Details on sample selection and assessment are described elsewhere.[5,16,25–29] The PET imaging was performed during the first 10 days of the follicular phase of the menstrual cycle for all participants. All participants were allowed to eat up until 2.5 hours before the first scan and were not allowed to drink caffeinated beverages before or during the study. All participants were nonsmokers.

This study was conducted according to the institutional review board regulations of the University of Pittsburgh, and all participants gave written informed consent.

PET Protocol

The radiosynthesis of [^{11}C]raclopride for human injection was performed as previously described by Halldin et al.[30] PET outcome measures described in this article are consistent with the recommended consensus nomenclature for in vivo imaging of reversibly binding radioligands.[31]

The PET imaging was conducted on an ECAT EXACT HR+ scanner consistent with previously described image acquisition protocols.[32,33] In brief, after completion of a transmission scan (~10 min) for attenuation correction of the emission data, the first PET scan was acquired following a slow intravenous bolus administration (for 20 seconds) of [^{11}C]raclopride. On the basis of a previous report,[34] the maximal injected mass for [^{11}C]raclopride was restricted to 6 μg to be at tracer dose (less than 5% receptor occupancy). Emission data were collected in three-dimensional (3D) mode for 60 min.

Thirty minutes following the first scan with [^{11}C]raclopride, the participant received 0.5 mg kg^{-1} of oral amphetamine, as used in other PET studies.[33,35–38] The postamphetamine [^{11}C]raclopride scan was performed 3 hours after the administration of amphetamine.

In the postamphetamine condition, amphetamine plasma levels were measured in two venous samples obtained at 0 and 30 min relative to the PET scan. Assessment of behavioral responses were conducted before and after PET scans, in which participants completed a symptom-rating visual analog scale (VAS) prebaseline PET, preamphetamine, and then at 30 min intervals assessing several states: "happy," "anxious," "energetic," "restless."[39]

Image Analysis

A 3D spoiled gradient recalled sequence magnetic resonance image was acquired by using a Signa 1.5T mag-

netic resonance imaging (MRI) scanner (GE Healthcare, Little Chalfont, Buckinghamshire, UK) for coregistration of the PET data. PET data were reconstructed using filtered back-projection and standard corrections applied that included those for photon attenuation, scatter, and radioactive decay.[32,33] Reconstructed image files were then processed with MEDx image analysis software (Sensor Systems, Sterling VA) and SPM software (www.fil.ion.ucl.ac.uk/spm). Frame-to-frame motion correction for head movement and magnetic resonance-PET image alignment were performed by using a mutual information algorithm implemented in SPM software.

Time-activity curves were generated for the following regions of interest (ROIs): The striatum was divided into five anatomic ROIs and three functional subdivisions (limbic, associative, and sensorimotor) as outlined by Martinez et al.[24] The anatomic ROIs, that were traced on coronal planes of each subject's MRI, 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 (postcommisural putamen [postPU]) according to the criteria by Mawlawi et al.[34] The striatum (STR) as a whole was derived as a spatially weighted average of the five ROIs. Activity from the left and right regions were averaged. The cerebellum was subsampled in 15 consecutive coronal MRI slices caudal to the cerebellar peduncle and used as a reference region using previously described methods.[32,33] The limbic striatum (LST) comprised VST; the associative striatum (AST) comprised the spatially weighted average of the preDCA, preDPU and postCA; the sensorimotor striatum (SMST) comprised the postPU (for details see Martinez et al.[24]).

Analysis of the PET data was performed using the simplified reference tissue method[40] using the cerebellum time activity curve as an input function. This reference tissue method has been shown to be an appropriate model for quantifying [^{11}C]raclopride data in humans without arterial input function. The outcome measure derived from this analysis is binding potential (BP) $_{\text{Nondisplaceable tissue uptake (ND)}}$. BP_{ND} (unitless) is equal to $f_{ND}B_{avail}/K_D$ where B_{avail} is D2 receptor density available to bind radioligand in vivo, K_D is the in vivo affinity of [^{11}C]raclopride for D2 receptors, and f_{ND} is the free fraction in nondisplaceable compartment.[31]

Statistical Analysis

The primary outcome measure of this study was change (Δ) in BP_{ND} (defined as the difference between the [^{11}C]raclopride BP_{ND} at baseline and postamphetamine treatment normalized to the baseline BP_{ND} and expressed as a percentage). Differences between groups were assessed via unpaired *t* test, with diagnosis group as the independent factor and regional Δ BP_{ND} as dependent variable. Effect sizes, using Cohen's d,[41] were calculated. Relationships between the PET data and behavioral responses [peak and maximum change (between baseline and peak) of VAS variables were chosen respectively] of REC AN and CW women were analyzed with Pearson Product-Moment correlation coefficient. A repeated measures (RM) analysis of variance (ANOVA) was used for the behavioral changes over time after the amphetamine challenge. A two-tailed probability value of $p < 0.05$ was chosen as level of significance for all statistical tests.

Results

Demographics

CW and REC AN were similar in age (CW: 28.2 ± 4.6; REC AN: 26.3 ± 5.5; $p = 0.45$).

However, REC AN had lower current BMI compared with CW (CW: 22.6 kg m^{-2} ± 2.0; REC AN: 20.9 kg m^{-2} ± 1.0; $p = 0.04$).

Baseline Scan Parameters

The mean injected dose, mass, and specific activity at the time of injection for the baseline and postamphetamine condition for CW and REC AN are shown in **Table 1**. No significant differences were observed between the baseline and postamphetamine condition in injected radiation dose in REC AN and CW. In REC AN only, injected mass for [^{11}C]raclopride in the postamphetamine condition was significantly higher compared with the baseline condition, whereas the specific activity was lower in the postamphetamine condition compared with the baseline condition.

Amphetamine Plasma Analysis

No significant differences in the plasma amphetamine levels were observed between REC AN and CW (**Table 1**). The amphetamine plasma levels were relatively stable throughout the duration of the postamphetamine scan.

ROI Analysis: Binding Potential BP_{ND}

Groups were similar for baseline and postamphetamine measures of BP_{ND} in the VST, preDCA, postCA, preDPU, and postPU (**Table 2**). For the VST, REC AN had less Δ BP_{ND} (9.4 ± 5.8) than did CW (12.4 ± 3.9). Four of the 10 REC AN had values below the range of CW. However, this finding was not significant ($t = 1.30$, $p = 0.21$). Restricting type and binge-purge type AN were similar for baseline,

TABLE 1. Baseline scan parameters and plasma analysis

	CW ($n = 9$)		REC AN ($n = 10$)	
	Baseline	Postamphetamine	Baseline	Postamphetamine
Injected dose (mCi)	10.2 ± 0.7	10.3 ± 0.6	10.2 ± 0.6	10.4 ± 0.5
Specific activity (Ci/mmol)	1483.3 ± 516.0	1152.2 ± 326.2	1709.0 ± 273.8*	1166.0 ± 356.6*
Injected mass (μg)	2.6 ± 0.8	3.4 ± 1.3	2.1 ± 0.4*	3.42 ± 1.2*
Plasma amphetamine (0 min, ng × ml^{-1})	–	65.4 ± 7.7 (6)	–	57.3 ± 8.6 (8)
Plasma amphetamine (30 min, ng × ml^{-1})	–	59.1 ± 7.2 (7)	–	55.8 ± 6.3 (8)

*$p < 0.05$, unpaired t test, baseline compared with postamphetamine condition; plasma amphetamine levels are relative to the postamphetamine scan; the numbers in parentheses show the number of available data.

TABLE 2. [^{11}C]raclopride binding potential (BP_{ND}) results

			CW ($n = 9$)		REC AN ($n = 10$)			
	ROI	Condition	Mean	SD	Mean	SD	P	Effect size Cohen's d
LST	VST	Baseline BP_{ND}	2.28	0.26	2.35	0.25	0.58	−0.28
		postamphetamine BP_{ND}	2.00	0.25	2.12	0.21	0.26	−0.52
		Δ BP_{ND}	−12.35%	3.88%	−9.38%	5.78%	0.21	−0.60
AST		Baseline BP_{ND}	2.63	0.24	2.77	0.16	0.14	−0.69
		postamphetamine BP_{ND}	2.40	0.24	2.53	0.13	0.15	−0.68
		Δ BP_{ND}	−8.48%	3.37%	−8.43%	4.30%	0.98	−0.01
–	preDCA	Baseline BP_{ND}	2.60	0.25	2.69	0.16	0.35	−0.43
		postamphetamine BP_{ND}	2.42	0.26	2.52	0.13	0.29	−0.49
		Δ BP_{ND}	−7.13%	4.31%	−6.41%	3.27%	0.69	−0.19
–	postCA	Baseline BP_{ND}	2.06	0.21	2.06	0.24	0.99	0
		postamphetamine BP_{ND}	1.87	0.24	1.83	0.24	0.75	0.17
		Δ BP_{ND}	−9.45%	3.85%	−10.66%	10.08%	0.74	0.16
–	preDPU	Baseline BP_{ND}	3.06	0.34	3.25	0.19	0.15	−0.70
		postamphetamine BP_{ND}	2.76	0.29	2.93	0.11	0.10	−0.79
		Δ BP_{ND}	−9.74%	4.64%	−9.69%	5.00%	0.98	−0.01
SMST	postPU	Baseline BP_{ND}	3.36	0.31	3.46	0.18	0.43	−0.40
		postamphetamine BP_{ND}	2.78	0.33	2.83	0.12	0.66	−0.21
		Δ BP_{ND}	−17.31%	5.44%	−17.95%	5.17%	0.80	0.12
STR		Baseline BP_{ND}	2.77	0.21	2.93	0.17	0.10	−0.84
		postamphetamine BP_{ND}	2.45	0.22	2.57	0.12	0.14	−0.69
		Δ BP_{ND}	−11.80%	4.02%	−12.08%	4.72%	0.89	0.06

CW, control women; REC AN, individuals recovered from anorexia nervosa; BP_{ND}, binding potential, ROI, region of interest; LST, limbic striatum; VST, anterior ventral striatum; AST, associative striatum; preDCA, precommissural dorsal caudate, postCA, postcommisural dorsal caudate; preDPU, precommissural dorsal putamen; postPU, postcommisural dorsal putamen, SMST, sensorimotor striatum; STR, striatum as a whole.

postamphetamine BP_{ND}, and Δ BP_{ND} for all ROIs (data not shown) and were consequently analyzed as one group. In CW and REC AN, there was no correlation between BMI and Δ BP_{ND} in any of the ROIs.

Relationship of ΔBP_{ND} With Behavioral Response to Amphetamine

For CW, VST ΔBP_{ND} was associated with peak euphoria ($r = -0.76$; $p = 0.03$) (see **Fig. 1**). This relationship was not found for REC AN. Instead, REC AN showed a significant relationship between maximum change in anxiety and ΔBP_{ND} in the preDCA ($r = -0.62$, $p = 0.05$) (see **Fig. 1**), as well as a significant increase of anxiety after amphetamine administration compared with CW [$F(1,141) = 6.51$; $p = 0.01$] (see **Fig. 2**). No significant correlations were found for the VAS variables 'energetic' and 'restless' in REC AN and CW (peak and maximum change respectively) in any of the ROIs (data not shown).

Discussion

The major finding in this study was that DA release in the preDCA in REC AN was associated with greater anxiety. It is important to emphasize that this finding was different than in CW who had a stimulant induced euphoria associated with endogenous VST DA release. Moreover, the CW response to amphetamine is similar to other studies in controls that have found relationships between stimulant-induced striatal ΔBP_{ND} and euphoria, particularly for the VST.[24,42,43] For example, Drevets et al.,[44] using a similar PET [^{11}C]raclopride amphetamine paradigm, found VST ΔBP_{ND} correlated with

FIGURE 1. Relationships between (left panel) change in [^{11}C]raclopride binding potential (BP_{ND}) for CW in the ventral striatum (VST) and peak euphoria; and change in [^{11}C]raclopride BP_{ND} for REC AN in the precommissural dorsal caudate (preDCA) and maximum change anxiety (change between baseline and peak) (right panel); VAS, visual analog scale.

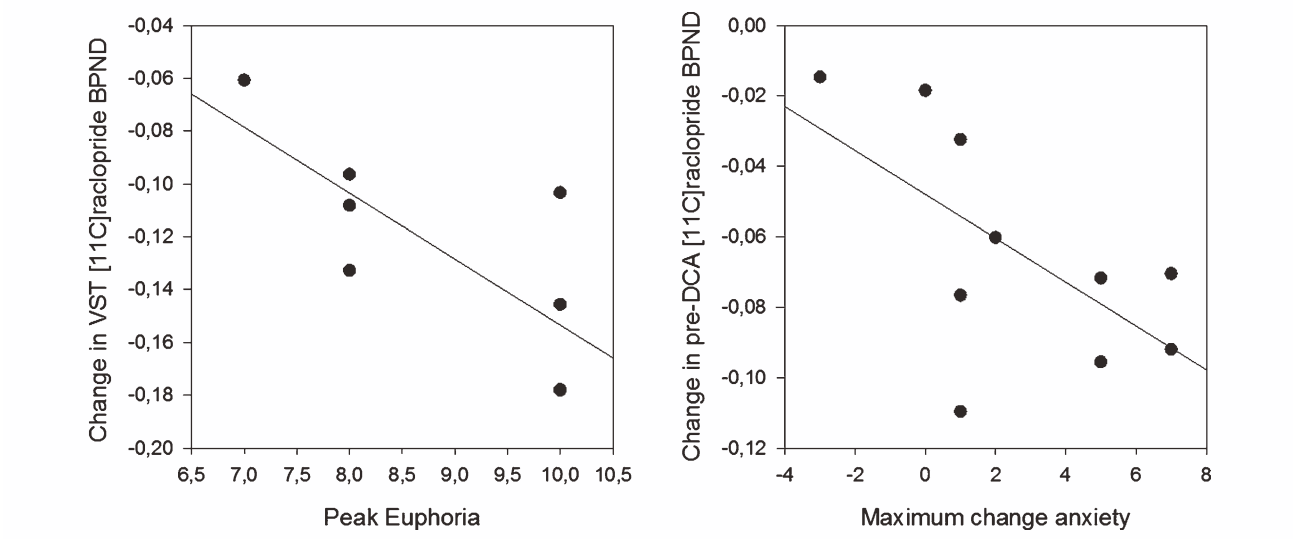
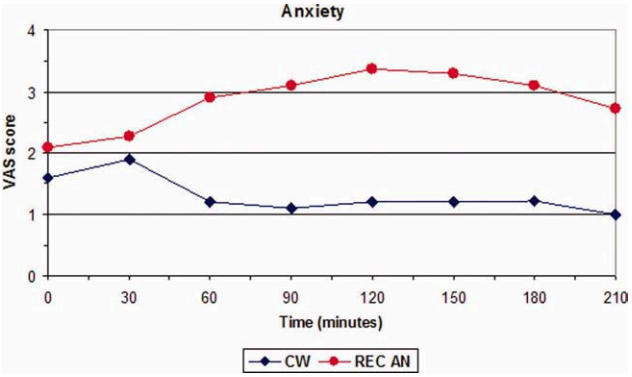


FIGURE 2. Participants assessed by Visual Analog Scale (VAS) self-report of anxiety (0 to 10) at baseline (0) before amphetamine administration, and then at 30 min after amphetamine; CW, control women; REC AN, individuals recovered from anorexia nervosa. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]



the euphoric response to amphetamine. However, subjective variability in the mood-enhancing effects of amphetamine has been previously described.[45–47] In studies using a preference procedure, it has been observed that preference for amphetamine over placebo was associated with a unique pattern of subjective effects. After amphetamine administration, the ratings of amphetamine choosers increase on scales measuring vigor, elation, arousal, and positive mood and decrease on scales measuring fatigue and sedation.[46,47] In contrast, amphetamine nonchoosers report no effects, paradoxical sedative effects of amphetamine or increased dysphoria. The percentage of at least some positive effect versus negative only effect has been shown to be 70% versus 30%, respectively, when participants were designated as choosers (38%), nonchoosers (30%) or as neithers (participants who chose inconsistently) (32%).[47] Nontreatment oriented previous studies have attributed this variability to various factors including expectancy,[48] personality factors,[49] as well as gender, hormone levels, and menstrual cycle phase.[50]

It is possible that the anxiety in REC AN in part was related to anxious arousal at the prospect of an amphetamine ingestion in a group of subjects who are rigid and inhibited by nature. However, an association between anxiety and dorsal caudate DA function in REC AN has been previously observed by our group. A positive correlation between baseline [^{11}C]raclopride binding in the dorsal caudate and harm avoidance, a measure of anxiety and behavioral inhibition, in two studies of REC AN participants but not in CW.[16,17] In addition, using fMRI and a monetary choice task,[51] our group found positive relationships between baseline measures of trait anxiety and activation in caudate regions for both losses and wins in REC AN, but not in CW.

Considered together, these data may shed light on neural circuit dysregulation that might explain the puzzling core symptoms of AN. Individuals with AN are often anxious, inhibited, and harm avoidant. They have long been noted to be anhedonic and ascetic, able to sustain self-denial of food, as well as most comforts and pleasures in life. These data raise the provocative possibility that AN individuals have altered function of brain mechanisms that code pleasure and reward. Moreover,

they have a bias toward harm avoidant temperament and anxious response to salient stimuli, and a diminished or absent ability to experience pleasure.

Most people find food to be highly pleasurable. However, clinical observations[52–54] suggest that eating makes individuals with AN anxious, whereas dietary restraint functions to reduce anxiety in AN. Ingestion of palatable food is associated with striatal endogenous DA release.[55] If AN experience endogenous DA release as anxiogenic, rather then hedonic, it may explain their pursuit of starvation, because it may be an effective means of diminishing such feelings in AN individuals. Although conjectural, these findings may further help explain the beneficial effect of atypical antipsychotics such as olanzapine, which has DA D2 antagonistic properties, and was shown to be significantly better than placebo in terms of promoting eating and weight gain in AN in a recent controlled trial.[56]

The physiological mechanisms underlying this anxious behavior remain to be elucidated. In the past decade, considerable progress has been made in understanding mesolimbic reward processing. For example, the phasic activity of DA-releasing substantia nigra (SN)/ventral tegmental area (VTA) neurons is a response to unexpected rewards and reward-predicting cues (reward anticipation).[57] The ventral striatum/nucleus accumbens is a major target of these midbrain dopaminergic projections. In controls, a positive correlation has been shown between neural activity of the SN/VTA during reward anticipation and reward-related [^{11}C]raclopride displacement as an index of DA release in the VST.[58]

This is the first study to use the amphetamine challenge paradigm and [^{11}C]raclopride PET in AN. This study did not find a difference in [^{11}C]raclopride displacement, as a measure of DA release, between REC AN and CW. Because of funding constraints, sample size was small and may have lacked power to show differences. This study was completed to establish feasibility. Previous data from our group has shown that REC AN have a disturbed function of VST and dorsal caudate regions compared with CW.[51] Compared with CW, the REC AN women showed impaired VST discrimination of positive and negative monetary feedback, suggesting they cannot code or distinguish salient feedback. Moreover, compared with CW, the REC AN group generated a large activation in the dorsal striatum/dorsal caudate, and in the 'cognitive' cortical projection regions, specifically the dorsal lateral prefrontal cortex (DLPFC) and the parietal cortex, that was associated with baseline anxious mood. Importantly, a recent fMRI study using a set-shifting task, showed relatively similar findings among underweight AN. That is, impaired behavioral response shifting was associated with hypoactivation in the ventral anterior cingulate-VST-thalamic loop, but a predominant activation of frontoparietal networks, suggesting increased effortful and supervisory cognitive control.[59]

Several studies from our group have shown that it is mainly the restricting type AN that have increased baseline VST [^{11}C]raclopride BP_{ND}[16,17] compared with CW. We have not observed a difference in VST [^{11}C]raclopride BP_{ND} in REC binge-purge type AN when compared with CW. Similarly, only REC restricting type AN (and not REC binge-purge type AN) had diminished CSF HVA compared with CW.[15] Together, these data suggest that only the restricting type AN has altered VST DA function. As noted, the sample size of REC AN and CW was small and possibly underpowered. Importantly, this study of REC AN consisted of both AN subtypes, restricting and binge-purge type, which could have masked underlying differences regarding baseline VST BP_{ND} and Δ BP_{ND} between REC AN and CW. However, a comparison between the two subtypes of AN for baseline BP_{ND} and ΔBP_{ND} in this study showed similar results, and did not differ from CW, respectively.

In terms of the preDCA, we found no difference between REC AN and CW for baseline or Δ BP_{ND} values which is in line with our previous studies[16,17] regarding baseline BP_{ND} in the dorsal caudate. Nonhuman primate studies have shown that the magnitude of reduction in [^{11}C]raclopride binding, following amphetamine administration, was two-fold greater in the VST compared with the dorsal caudate.[60] The preferential sensitivity of the VST to the DA releasing effects of amphetamine has been confirmed in humans.[24,44,61] Thus, the amphetamine challenge paradigm may not be able to characterize differences in DA function in the dorsal caudate. Several mechanisms may account for VST and dorsal caudate regional differences.[24] For instance, the VST and dorsal caudate differ as to the relative balance of D2 and D3 receptors (the affinity of DA for D3 receptors is higher then D2 receptors) and differ in DA transporter expression. The amphetamine challenge does not directly measure DA release but rather its impact on [^{11}C]raclopride binding. Regional differences in the potency of DA to reduce [^{11}C]raclopride binding (postsynaptic factors) or regional differences in amphetamine-induced DA release (presynaptic

factors) potentially account for regional differences in Δ BP_{ND}.[24]

In terms of limitations, we used oral amphetamine in a dose of 0.5 mg kg^{-1}. At this dose, the prominent effect of amphetamine is a substantial release of DA,[38] although effects on other monoamine neurotransmitters (e.g. norepinephrine, serotonin) occur as well.[62] The mean displacement of [^{11}C]raclopride BP_{ND} in CW in our study is consistent with that reported in previous studies that have used the same paradigm (for review see[33]). As we did not use an arterial line and used a reference tissue method without a plasma input function for PET analysis, we are limited to presenting BP_{ND} as the sole outcome measure. To exclusively ascribe changes in BP_{ND}, which is equal of $f_{ND}B_{avail}/K_D$,[31] to changes in receptor parameters (B_{avail}/K_D), implies that nondisplaceable free fraction in the brain (f_{ND}) is not affected by the experimental factors under study,[31,33] which is a reasonable assumption in a within-subject design.

In summary, the role that DA neurotransmission plays in many pathological behaviors associated with food intake, reinforcement, reward, and hyperactivity in REC AN participants is not yet well understood. This study showed for the first time, that REC AN have a positive association between endogenous DA release and anxiety in the preDCA. This finding could shed light on why food-related release of DA produces anxiety in AN, whereas feeding is pleasurable in healthy individuals.

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