Published in final edited form as:

Int J Eat Disord. 2012 March ; 45(2): 263–271. doi:10.1002/eat.20937.

Amphetamine induced dopamine release increases anxiety in individuals recovered from anorexia nervosa

Ursula F. Bailer, M.D.^{1,2}, Rajesh Narendran, M.D.^{3,4}, W. Gordon Frankle, M.D.^{3,4}, Michael L Himes, B.S.⁴, Vikas Duvvuri, M.D., Ph.D.², Chester A Mathis, Ph.D.³, and W.H. Kaye, M.D.²

¹ Medical University of Vienna, Department of Psychiatry and Psychotherapy, Division of Biological Psychiatry, Vienna, Austria

² University of California, San Diego, Department of Psychiatry, La Jolla, California

³ University of Pittsburgh, School of Medicine, Department of Radiology, Presbyterian University Hospital, Pittsburgh, Pennsylvania.

⁴ University of Pittsburgh, School of Medicine, Department of Psychiatry, Western Psychiatric Institute & Clinic, Pittsburgh, Pennsylvania.

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 [¹¹C]raclopride paradigm to explore DA striatal transmission in 10 recovered (REC) AN compared to 9 control women (CW).

Results—REC AN and CW were similar for baseline, post-amphetamine [¹¹C]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 ($r = -.76$; $p = .03$), which was not found for REC AN. Instead, REC AN showed a significant relationship between anxiety and Δ BP_{ND} in the pre-commissural dorsal caudate ($r = -.62$, $p = .05$).

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

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

Corresponding author: Walter H. Kaye, M.D. University of California, San Diego UCSD Department of Psychiatry 8950 Villa La Jolla Drive, Suite C – 207 La Jolla, California 92037 Tel. (858) 534 3951, FAX: (858) 534 6727 wkaye@ucsd.edu.

Disclosure/Conflict of Interest The remaining authors, Dr. Narendran and M. Himes declare that, except for income received from their primary employers and the above-mentioned funding, no further financial support or compensation has been received from any individual or corporate entity over the past 3 years for research or professional service and there are no personal financial holdings that could be perceived as constituting a potential conflict of interest.

genetic factors. Considerable evidence suggests that AN personality and temperament traits, such as anxiety, harm avoidance, perfectionism, and obsessiveness, 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 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 to CW.

Methods

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 and colleagues.(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 (approximately 10 minutes) 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. Based on 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 minutes.

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

In the post-amphetamine condition, amphetamine plasma levels were measured in two venous samples obtained at 0 and 30 minutes 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) pre-baseline PET, pre-amphetamine, and then at 30 minute 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 magnetic 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, Inc., 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) (pre-commissural dorsal caudate [pre-DCA]), the dorsal putamen rostral to the AC (pre-commissural dorsal putamen [pre-DPU]), the caudate caudal to the AC (post-commissural caudate [post-CA]) and the putamen caudal to the AC (post-commissural putamen [post-PU]) 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 pre-DCA, pre-DPU and post-CA; the sensorimotor striatum (SMST) comprised the post-PU (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)_{ND} Nondisplaceable tissue uptake (ND). BP_{ND} (unitless) is equal to $f_{\text{ND}}B_{\text{avail}}/K_D$ 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 post-amphetamine 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 ; $p = .45$). However, REC AN had lower current BMI compared to CW (CW: $22.6 \text{ kg/m}^2 \pm 2.0$; REC AN: $20.9 \text{ kg/m}^2 \pm 1.0$; $p = .04$).

Baseline scan parameters

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

ROI analysis: Binding Potential BP_{ND}

Groups were similar for baseline and post-amphetamine measures of BP_{ND} in the VST, pre-DCA, post-CA, pre-DPU, and post-PU (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 ($t = 1.30$, $p = .21$). Restricting type and

binge-purge type AN were similar for baseline, post-amphetamine BP_{ND} , and ΔBP_{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 ΔBP_{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 ($r = -.76$; $p = .03$) (Figure 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 pre-DCA ($r = -.62$, $p = .05$) (Figure 1), as well as a significant increase of anxiety after amphetamine administration compared to CW [$F(1,141) = 6.51$; $p = 0.01$] (Figure 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 pre-DCA 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 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 non-choosers 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%), non-choosers (30%) or as neithers (participants who chose inconsistently) (32%).(47) Non-treatment 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. That is, 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 towards 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 than hedonic, it may explain their pursuit of starvation, since it may be an effective means of diminishing such feelings in AN individuals. While 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. Due to funding constraints, sample size was small and may have lacked power to show differences. The present 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 to CW.(51) Compared to 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 to 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 to CW. We have not observed a difference in VST [^{11}C]raclopride BP_{ND} in REC binge-purge type AN compared to CW. Similarly, only REC restricting type AN (and not REC binge-purge type AN) had diminished CSF HVA compared to 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 $\Delta \text{BP}_{\text{ND}}$ between REC AN and CW. However, a comparison between the two subtypes of AN for baseline BP_{ND} and $\Delta \text{BP}_{\text{ND}}$ in this study showed similar results, and did not differ from CW, respectively.

In terms of the pre-DCA, we found no difference between REC AN and CW for baseline or $\Delta \text{BP}_{\text{ND}}$ values which is in line with our previous studies(16, 17) regarding baseline BP_{ND}

in the dorsal caudate. Non-human 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 to 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 than 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 $\Delta \text{BP}_{\text{ND}}$.(24)

In terms of limitations, we used oral amphetamine in a dose of $0.5 \text{ mg} \times \text{kg}^{-1}$. 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 $f_{\text{ND}}\text{B}_{\text{avail}}/\text{K}_{\text{D}}$,(31) to changes in receptor parameters ($\text{B}_{\text{avail}}/\text{K}_{\text{D}}$), implies that nondisplaceable free fraction in the brain (f_{ND}) is not affected by the experimental factors under study,(33, 63) 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 pre-DCA. This finding could shed light on why food-related release of DA produces anxiety in AN, whereas feeding is pleasurable in healthy individuals.

Acknowledgments

The authors want to thank the UPMC PET Laboratory staff for their invaluable contribution to this study and Eva Gerardi for the manuscript preparation. The authors are indebted to the participating participants for their contribution of time and effort in support of this study.

Funding for this work was provided by the National Institute of Mental Health (NIMH) MH046001, MH004298, K05-MH001894, and the Price Foundation. Dr Kaye has received salary support from the University of Pittsburgh and the University of California, San Diego; Research funding/support from the NIMH; Research funding for an investigator initiated treatment study from Astra-Zeneca and consulting fees from Lundbeck and Merck and the Eating Disorder Center of Denver. In addition, there are honoraria for presentations from academic institutions and meetings, and compensation for grant review activities from the National Institutes of Health. Dr Bailer has received salary support from the Hilda & Preston Davis Foundation and the Price Foundation. Dr. Mathis has received royalty payments for licensed technology from GE Healthcare and Neuroptix as well as research grant support from Neuroptix. Dr. Mathis also served as a consultant for Janssen/Elan, Wyeth/Pfizer, and Novartis over the past three years. Dr. Frankle has received salary support from the University of Pittsburgh, research funding/support from the NIMH and NIDA as well as research funding and consulting fees from Sepracor, Inc. Dr. Duvvuri has received salary support from a Hilda & Preston Davis Foundation Fellowship in Eating Disorders Research and from a NIMH T32 fellowship.

References

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition). 2000 Text Revision (DSM-IV-TR).

2. Kendler KS, MacLean C, Neale M, Kessler R, Heath A, Eaves L. The genetic epidemiology of bulimia nervosa. *Am J Psychiatry*. Dec 1; 1991 148(12):1627–37. [PubMed: 1842216]
3. Berrettini W. Genetics of psychiatric disease. *Annu Rev Med*. 2000; 51:465–79. [PubMed: 10774477]
4. Bulik C, Sullivan PF, Tozzi F, Furberg H, Lichtenstein P, Pedersen NL. Prevalence, heritability and prospective risk factors for anorexia nervosa. *Archives of General Psychiatry*. 2006; 63(3):305–12. [PubMed: 16520436]
5. Wagner A, Barbarich N, Frank G, Bailer U, Weissfeld L, Henry S, et al. Personality traits after recovery from eating disorders: Do subtypes differ? *Int J Eat Disord*. 2006; 39(4):276–84. [PubMed: 16528697]
6. Klump K, Strober M, Johnson C, Thornton L, Bulik C, Devlin B, et al. Personality characteristics of women before and after recovery from an eating disorder. *Psych Med*. 2004; 34(8):1407–18.
7. Lilenfeld L, Wonderlich S, Riso LP, Crosby R, Mitchell J. Eating disorders and personality: a methodological and empirical review. *Clin Psychol Rev*. 2006; 26(3):299–320. [PubMed: 16330138]
8. Bulik C, Tozzi F, Anderson C, Mazzeo S, Aggen S, Sullivan P. The relation between eating disorders and components of perfectionism. *Am J Psychiatry*. 2003; 160(2):366–8. [PubMed: 12562586]
9. Kaye W. Neurobiology of anorexia and bulimia nervosa. *Physiol Behav*. 2008; 94:121–35. [PubMed: 18164737]
10. Halford J, Cooper G, Dovey T. The pharmacology of human appetite expression. *Curr Drug Targets*. 2004; 5:221–40. [PubMed: 15058309]
11. Volkow ND, Wang G, Fowler J, Logan J, Jayne M, Franceschi D, et al. “Nonhedonic” food motivation in humans involves dopamine in the dorsal striatum and methylephenidate amplifies this effect. *Synapse*. 2002; 44:175–80. [PubMed: 11954049]
12. Bergen A, Yeager M, Welch R, Haque K, Ganjei JK, Mazzanti C, et al. Association of multiple DRD2 polymorphisms with anorexia nervosa. *Neuropsychopharm*. 2005; 30(9):1703–10.
13. Lawrence A. Impaired visual discrimination learning in anorexia nervosa. *Appetite*. 2003; 20:85–9. [PubMed: 12631509]
14. Friederich HC, Kumari V, Uher R, Riga M, Schmidt U, Campbell IC, et al. Differential motivational responses to food and pleasurable cues in anorexia and bulimia nervosa: a startle reflex paradigm. *Psychol Med*. 2006; 36(9):1327–35. [PubMed: 16790080]
15. Kaye WH, Frank GK, McConaha C. Altered dopamine activity after recovery from restricting-type anorexia nervosa. *Neuropsychopharm*. Oct 1; 1999 21(4):503–6.
16. Frank G, Bailer UF, Henry S, Drevets W, Meltzer CC, Price JC, et al. Increased dopamine D2/D3 receptor binding after recovery from anorexia nervosa measured by positron emission tomography and [¹¹C]raclopride. *Biol Psychiatry*. 2005; 58(11):908–12. [PubMed: 15992780]
17. Bailer, UF.; Frank, G.; Price, J.; Meltzer, C.; Becker, CM.; C, A.; Wagner, A.; Barbarich-Marsteller, NC.; Bloss, CP.; C; Kaye, WH. Relationship of serotonin transporter and dopamine D2/D3 receptor binding after recovery from eating disorders. Submitted
18. Delgado M, Nystrom L, Fissel C, Noll D, Fiez J. Tracking the hemodynamic responses to reward and punishment in the striatum. *J Neurophysiol*. 2000; 84:3072–7. [PubMed: 11110834]
19. Montague R, Hyman S, Cohen J. Computational roles for dopamine in behavioural control. *Nature*. 2004; 431:760–7. [PubMed: 15483596]
20. Schultz W. Neural coding of basic reward terms of animal learning theory, game theory, microeconomics and behavioural ecology. *Science*. 2004; 14:139–47.
21. Breier A, Su TP, Saunders R, Carson RE, Kolachana BS, de Bartolomeis A, et al. Schizophrenia is associated with elevated amphetamine-induced synaptic dopamine concentrations: evidence from a novel positron emission tomography method. *Proc Natl Acad Sci USA*. Mar 18; 1997 94(6):2569–74. [PubMed: 9122236]
22. Laruelle M, Iyer R, Al-Tikriti M, Zea-Ponce Y, Malison R, Zoghbi S. Microdialysis and SPECT measurements of amphetamine-induced dopamine release in nonhuman primates. *Synapse*. 1997; 25:1–14. [PubMed: 8987142]

23. Martinez D, Gil R, Slifstein M, Hwang D, Huang Y, Perez A, et al. Alcohol dependence is associated with blunted dopamine transmission in the ventral striatum. *Biol Psychiatry*. 2005; 58:779–86. [PubMed: 16018986]
24. Martinez D, Slifstein M, Broft A, Mawlawi O, Hwang D, Huang Y, et al. Imaging human mesolimbic dopamine transmission with positron emission tomography. Part II: amphetamine-induced dopamine release in the functional subdivisions of the striatum. *J Cereb Blood Flow Metab*. 2003; 23:285–300. [PubMed: 12621304]
25. Frank GK, Kaye WH, Meltzer CC, Price JC, Greer P, McConaha C, et al. Reduced 5-HT_{2A} receptor binding after recovery from anorexia nervosa. *Biol Psychiatry*. 2002; 52:896–906. [PubMed: 12399143]
26. Bailer UF, Price JC, Meltzer CC, Mathis CA, Frank GK, Weissfeld L, et al. Altered 5-HT_{2A} receptor binding after recovery from bulimia-type anorexia nervosa: relationships to harm avoidance and drive for thinness. *Neuropsychopharmacology*. 2004; 29(6):1143–55. [PubMed: 15054474]
27. Bailer UF, Frank GK, Henry SE, Price JC, Meltzer CC, Weissfeld L, et al. Altered brain serotonin 5-HT_{1A} receptor binding after recovery from anorexia nervosa measured by positron emission tomography and [¹¹C]WAY100635. *Arch Gen Psychiatry*. 2005; 62(2):1032–41. [PubMed: 16143735]
28. Bailer UF, Frank G, Henry S, Price J, Meltzer C, Mathis C, et al. Exaggerated 5-HT_{1A} but normal 5-HT_{2A} receptor activity in individuals ill with anorexia nervosa. *Biol Psychiatry*. 2007; 61(9):1090–9. [PubMed: 17241616]
29. Bailer UF, Frank G, Henry S, Price J, Meltzer CC, Becker C, et al. Serotonin transporter binding after recovery from eating disorders. *Psychopharmacology*. 2007; 195(3):315–24. [PubMed: 17690869]
30. Halldin C, Farde L, Hogberg T, Hall H, Strom P, Solin O. A comparative PET-study of five carbon-11 or fluorine-18 labelled salicylamides. Preparation and in vitro dopamine D-2 receptor binding. *Int J Rad App Instrum B*. 1991; 18(8):871–81.
31. Innis R, Cunningham V, Delforge J, Fujita M, Gjedde A, Gunn R, et al. Consensus nomenclature for in vivo imaging of reversibly binding radioligands. *J Cereb Blood Flow Metab*. 2007; 27:1533–9. [PubMed: 17519979]
32. Narendran R, Frankle W, Mason N, Laymon C, Lopresti B, Price C, et al. Positron emission tomography imaging of D(2/3) agonist binding in healthy human subjects with the radiotracer [(11)C]-N-propyl-norapomorphine: preliminary evaluation and reproducibility studies. *Synapse*. 2009; 63(7):574–84. [PubMed: 19301416]
33. Narendran R, Mason N, Laymon C, Lopresti B, Velasquez N, May M, et al. A comparative evaluation of the dopamine D(2/3) agonist radiotracer [11C](–)-N-propyl-norapomorphine and antagonist [11C]raclopride to measure amphetamine-induced dopamine release in the human striatum. *J Pharmacol Exp Ther*. 2010; 333(2):533–9. [PubMed: 20103586]
34. Mawlawi O, Martinez D, Slifstein M, Broft A, Chatterjee R, Hwang D, et al. 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*. 2001; 21(9):1034–57. [PubMed: 11524609]
35. Riccardi P, Li E, Ansari M, Zald D, Park S, Dawant B, et al. Amphetamine-induced displacement of [(18)F] fallypride in striatum and extrastriatal regions in humans. *Neuropsychopharmacology*. 2005; 31(5):1016–26. Riccardi P, Li E, Ansari M, Zald D, Park S, Dawant B, Anderson S, Doop M, Woodward N, Schoenberg E, Schmitt D, Baldwin R, Kessler RC.
36. Wolkin A, Angrist B, Wolf AP, Brodie J, Wolkin B, Jaeger J, et al. Effects of amphetamine on local cerebral metabolism in normal and schizophrenic subjects as determined by positron emission tomography. *Psychopharmacology*. 1987; 92(2):241–6. [PubMed: 3110848]
37. Wolkin A, Sanfilipo M, Angrist B, Duncan E, Wieland S, Wolf A, et al. Acute d-amphetamine challenge in schizophrenia: effects on cerebral glucose utilization and clinical symptomatology. *Psychol Med*. 1994; 35:649–57.

38. Willeit M, Ginovart N, Graff A, Rusjan P, Vitcu I, Houle S, et al. First human evidence of d-amphetamine induced displacement of a D2/3 agonist radioligand: A [¹¹C]-(+)-PHNO positron emission tomography study. *Neuropsychopharm.* 2008; 33(2):279–89.
39. Swerdlow N, Eastvold A, Karban B, Ploum Y, Stephany N, Geyer M, et al. Dopamine agonist effects on startle and sensorimotor gating in normal male subjects: time course studies. *Psychopharm (Berl).* 2002; 161(2):189–201.
40. Lammertsma AA, Hume SP. Simplified reference tissue model for PET receptor studies. *Neuroimage.* Dec; 1996 4(3 Pt 1):153–8. [PubMed: 9345505]
41. Cohen, J. Statistical power analysis for behavioral sciences. Lawrence Erlbaum Associates, Inc; Hillsdale, NJ, US: 1988.
42. Laruelle M, Abi-Dargham A, Van Dyck C, Rosenblatt W, Zea-Ponce Y, Zoghbi S, et al. SPECT imaging of striatal dopamine release after amphetamine challenge. *J Nucl Med.* 1995; 36(7):1182–90. [PubMed: 7790942]
43. Volkow N, Wang G, Fowler J, Logan J, Gatley S, Wong C, et al. Reinforcing effects of psychostimulants in humans are associated with increases in brain dopamine and occupancy of D(2) receptors. *J Pharmacol Exp Ther.* 1999; 291:409–15. [PubMed: 10490931]
44. Drevets W, Gautier C, Price J, Kupfer D, Kinahan P, Grace A, et al. Amphetamine-induced dopamine release in human ventral striatum correlates with euphoria. *Biol Psychiatry.* 2001; 49(2): 81–96. [PubMed: 11164755]
45. Brauer L, de Wit H. Subjective responses to D-amphetamine alone and after pimozide pretreatment in normal, healthy volunteers. *Biol Psych.* 1996; 39:26–31.
46. de Wit H, Uhlenhuth E, Johanson C. Individual differences in the reinforcing and subjective effects of amphetamine and diazepam. *Drug Alcohol Depend.* 1986; 16:341–60. [PubMed: 3698813]
47. Gabbay F. Variations in affect following amphetamine and placebo: markers of stimulant drug preference. *Exp Clin Psychopharmacol.* 2003; 11:91–101. [PubMed: 12622347]
48. Mitchell S, Laurent C, de Wit H. Interaction of expectancy and the pharmacological effects of D-amphetamine: subjective effects and self-administration. *Psychopharm (Berl).* 1996; 125:371–8.
49. Hutchinson K, Wood M, Swift R. Personality factors moderate subjective and psychophysiological responses to D-amphetamine in humans. *Exp Clin Psychopharmacol.* 1999; 7:493–501. [PubMed: 10609984]
50. White TJ, AJ, de Wit H. Differential subjective effects of D-amphetamine by gender, hormone levels and menstrual cycle phase. *Pharmacol Biochem Behav.* 2002; 73:729–41. [PubMed: 12213517]
51. Wagner A, Aizenstein H, Venkatraman M, Fudge J, May J, Mazurkewicz L, et al. Altered reward processing in women recovered from anorexia nervosa. *Am J Psych.* 2007; 164(12):1842–9.
52. Kaye WH, Barbarich NC, Putnam K, Gendall KA, Fernstrom J, Fernstrom M, et al. Anxiolytic effects of acute tryptophan depletion in anorexia nervosa. *Int J Eat Disord.* 2003; 33(3):257–67. [PubMed: 12655621]
53. Strober, M. Family-genetic perspectives on anorexia nervosa and bulimia nervosa. In: Brownell, K.; Fairburn, C., editors. *Eating Disorders and Obesity-A Comprehensive Handbook*. The Guilford Press; New York: 1995. p. 212-8.
54. Vitousek K, Manke F. Personality variables and disorders in anorexia nervosa and bulimia nervosa. *J Abnorm Psychol.* 1994; 103(1):137–47. [PubMed: 8040475]
55. Bassareo V, Di Chiara G. Differential responsiveness of dopamine transmission to food-stimuli in nucleus accumbens shell/core compartments. *Neuroscience.* 1999; 89(3):637–41. [PubMed: 10199600]
56. Bissada H, Tasca G, Barber A, Bradwejn J. Olanzapine in the treatment of low body weight and obsessive thinking in women with anorexia nervosa: A randomized, double-blind, placebo-controlled trial. *Am J Psych.* 2008; 165(10):1281–8.
57. Schultz W. Predictive reward signal of dopamine neurons. *J Neurophysiol.* 1998; 80(1):1–27. [PubMed: 9658025]
58. Schott B, Muinuzzi L, Krebs R, Elmenhorst D, Lang M, Winz O, et al. Mesolimbic functional magnetic resonance imaging activations during reward anticipation correlate with reward-related ventral striatal dopamine release. *J Neuroscience.* 2008; 28(52):14311–9.

59. Zastrow A, Kaiser SS, C, Walthe S, Herzog W, Tchanturia K, Belger A, et al. Neural Correlates of Impaired Cognitive-Behavioral Flexibility in Anorexia Nervosa. *Am J Psychiatry*. 2009; 166(5): 608–16. [PubMed: 19223435]
60. Drevets WC, Price JC, Kupfer DJ, Kinahan PE, Lopresti B, Holt D, et al. PET measures of amphetamine-induced dopamine release in ventral versus dorsal striatum. *Neuropsychopharmacology*. 1999; 21(6):694–709. [PubMed: 10633475]
61. Leyton M, Boileau I, Benkelfat C, Diksic M, Baker G, Dagher A. Amphetamine-induced increases in extracellular dopamine, drug wanting, and novelty seeking: a PET/[¹¹C]raclopride study in healthy men. *Neuropsychopharmacology*. 2002; 27(6):1027–35. [PubMed: 12464459]
62. Floresco S, Tse M, Ghods-Sharifi S. Dopaminergic and glutamatergic regulation of effort- and delay-based decision making. *Neuropsychopharm*. 2008; 33(8):1966–79.
63. Innis R, Cunningham V, Delforge J, Fujita M, Gjedde A, Gunn R, et al. Consensus nomenclature for in vivo imaging of reversibly binding radioligands. *J Cereb Blood Flow Metab*. 2007; 27:1533–9. [PubMed: 17519979]

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 pre-commissural dorsal caudate (pre-DCA) 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 minutes after amphetamine; CW, control women; REC AN, individuals recovered from anorexia nervosa

Table 1

Baseline scan parameters and plasma analysis

	CW (n = 9)		REC AN (n = 10)	
	Baseline	Post amphetamine	Baseline	Post- amphetamine
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 post-amphetamine condition; plasma amphetamine levels are relative to the post-amphetamine scan; the numbers in parentheses show the number of available data

Table 2

[¹¹C]raclopride binding potential (BP_{ND}) results

	ROI	Condition	CW (n = 9)		REC AN (n=10)			Effect size Cohen's d
			Mean	SD	Mean	SD	P	
LST	VST	Baseline BP _{ND}	2.28	0.26	2.35	0.25	0.58	- 0.28
		post-amphetamine 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
		post-amphetamine 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
---	pre-DCA	Baseline BP _{ND}	2.60	0.25	2.69	0.16	0.35	- 0.43
		post-amphetamine 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
---	post-CA	Baseline BP _{ND}	2.06	0.21	2.06	0.24	0.99	0
		post-amphetamine 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
---	pre-DPU	Baseline BP _{ND}	3.06	0.34	3.25	0.19	0.15	- 0.70
		post-amphetamine 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

	ROI	Condition	CW (n = 9)		REC AN (n=10)		Effect size Cohen's d
			Mean	SD	Mean	SD	
SMST	post-PU	Baseline BP _{ND}	3.36	0.31	3.46	0.18	- 0.40
		post-amphetamine BP _{ND}	2.78	0.33	2.83	0.12	- 0.21
		Δ BP _{ND}	-17.31%	5.44%	-17.95%	5.17%	0.12
STR	---	Baseline BP _{ND}	2.77	0.21	2.93	0.17	- 0.84
		post-amphetamine BP _{ND}	2.45	0.22	2.57	0.12	- 0.69
		Δ BP _{ND}	-11.80%	4.02%	-12.08%	4.72%	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; pre-DCA, pre-commissural dorsal caudate, post-C/A, postcommissural dorsal caudate; pre-DPU, pre-commissural dorsal putamen; post-PU, post commissural dorsal putamen. SMST, sensorimotor striatum; STR, striatum as a whole.