Psychiatry Research: Neuroimaging 211 (2013) 160–168

Contents lists available at SciVerse ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Interaction between serotonin transporter and dopamine D2/D3 receptor radioligand measures is associated with harm avoidant symptoms in anorexia and bulimia nervosa

Ursula F. Bailer[a,b], Guido K. Frank[c,d], Julie C. Price[e], Carolyn C. Meltzer[e,f,g], Carl Becker[e], Chester A. Mathis[e], Angela Wagner[a], Nicole C. Barbarich-Marsteller[h], Cinnamon S. Bloss[i], Karen Putnam[j], Nicholas J. Schork[k], Anthony Gamst[l], Walter H. Kaye[a,*]

[a] University of California San Diego, UCSD Department of Psychiatry, 8950 Villa La Jolla Drive, La Jolla, CA 92037, USA
[b] Medical University of Vienna, Department of Psychiatry and Psychotherapy, Division of Biological Psychiatry, Vienna, Austria
[c] Department of Psychiatry, University of Colorado Denver, Children's Hospital Colorado, Aurora, CO, USA
[d] Department of Neuroscience, University of Colorado Denver; Anschutz Medical Campus, Aurora, CO, USA
[e] University of Pittsburgh, School of Medicine, Department of Radiology, Presbyterian University Hospital, Pittsburgh, PA, USA
[f] University of Pittsburgh, School of Medicine, Department of Psychiatry, Western Psychiatric Institute and Clinic, Pittsburgh, PA, USA
[g] Emory School of Medicine, Departments of Radiology, Neurology, and Psychiatry and Behavioral Sciences, Atlanta, GA, USA, and University of Pittsburgh School of Medicine, Pittsburgh, PA, USA
[h] Department of Psychiatry, College of Physicians and Surgeons of Columbia University, New York, NY, USA
[i] Scripps Genomic Medicine, Scripps Translational Science Institute (STSI), and Scripps Health, La Jolla, CA, USA
[j] Department of Environmental Health, Division of Epidemiology and Biostatistics, University of Cincinnati, School of Medicine, Cincinnati, OH, USA
[k] The Scripps Research Institute and the Scripps Translational Science Institute (STSI), La Jolla, CA, USA
[l] University of California San Diego, Department of Biostatistics and Bioinformatics, La Jolla, CA

ARTICLE INFO

Article history:
Received 6 June 2011
Received in revised form
25 June 2012
Accepted 29 June 2012

Keywords:
Anorexia nervosa
Bulimia nervosa
Positron emission tomography
Dopamine
Serotonin
Harm avoidance

ABSTRACT

Individuals with anorexia nervosa (AN) and bulimia nervosa (BN) have alterations of measures of serotonin (5-HT) and dopamine (DA) function, which persist after long-term recovery and are associated with elevated harm avoidance (HA), a measure of anxiety and behavioral inhibition. Based on theories that 5-HT is an aversive motivational system that may oppose a DA-related appetitive system, we explored interactions of positron emission tomography (PET) radioligand measures that reflect portions of these systems. Twenty-seven individuals recovered (REC) from eating disorders (EDs) (7 AN–BN, 11 AN, 9 BN) and nine control women (CW) were analyzed for correlations between [^{11}C]McN5652 and [^{11}C]raclopride binding. There was a significant positive correlation between [^{11}C]McN5652 binding potential ($BP_{non\ displaceable(ND)}$) and [^{11}C]Raclopride BP_{ND} for the dorsal caudate, antero-ventral striatum (AVS), middle caudate, and ventral and dorsal putamen. No significant correlations were found in CW. [^{11}C]Raclopride BP_{ND}, but not [^{11}C]McN5652 BP_{ND}, was significantly related to HA in REC EDs. A linear regression analysis showed that the interaction between [^{11}C]McN5652 BP_{ND} and [^{11}C]raclopride BP_{ND} in the dorsal putamen significantly predicted HA. This is the first study using PET and the radioligands [^{11}C]McN5652 and [^{11}C]raclopride to show a direct relationship between 5-HT transporter and striatal DA D2/D3 receptor binding in humans, supporting the possibility that 5-HT and DA interactions contribute to HA behaviors in EDs.

1. Introduction

Anorexia nervosa (AN) and bulimia nervosa (BN) are related disorders of unknown etiology that often emerge during adolescence in women (American Psychiatric Association, 2000). These disorders are characterized by the relentless pursuit of thinness, obsessive fears of being fat, aberrant eating behaviors, and disturbances of mood and impulse control.

Genetic, pharmacologic, and physiological data (Bergen et al., 2005; Friederich et al., 2006, Kaye, 2008; Kaye et al., 1999; Lawrence, 2003) suggest that ill and recovered (REC) AN have altered striatal dopamine (DA) function. It remains uncertain whether BN have trait-related DA disturbances because fewer DA studies have been conducted (Jimerson et al., 1992;

* Corresponding author. Tel.: +1 858 534 3951; fax: +1 858 534 6727.
E-mail address: wkaye@ucsd.edu (W.H. Kaye).

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http://dx.doi.org/10.1016/j.pscychresns.2012.06.010

Kaye et al., 1990). In terms of positron emission tomography (PET) studies, our group found that REC AN and AN–BN had increased DA D2/D3 binding (e.g., [^{11}C]raclopride binding potential (BP)) in the antero-ventral striatum (AVS) (Frank et al., 2005).

REC AN and REC BN have altered (and often different patterns of) 5-HT function (Kaye, 2008). For example, studies have shown different degrees of elevated cerebrospinal fluid (CSF) concentrations of 5-hydroxyindoleacetic acid (5-HIAA) (Kaye et al., 1991; Kaye et al., 1998) and altered behavioral responses to 5-HT challenges in these populations (Frank et al., 2001; Kaye et al., 2003; Smith et al., 1999; Ward et al., 1998). We have used PET and specific radioligands ([^{11}C]McN5652, [^{11}C]WAY100635 and [^{18}F]altanserin) to assess the BP of the 5-HT transporter (5-HTT) and the 5-HT$_{1A}$ and 5-HT$_{2A}$ receptors. In general, REC eating disorder (ED) individuals tend to have reduced 5-HT$_{2A}$ BP ([^{18}F]altanserin BP$_{\text{non displaceable (ND)}}$) (Bailer et al., 2004; Frank et al., 2002; Kaye et al., 2001) and elevated 5-HT$_{1A}$ BP ([^{11}C]WAY100635 BP$_{\text{plasma free plus protein bound (P)}}$) (Bailer et al., 2011; Bailer et al., 2005). Moreover, using PET and [^{11}C]McN5652 our group found REC AN (n=11) had increased 5-HTT BP ([^{11}C]McN5652 BP$_{ND}$) in the AVS and the dorsal raphe compared to REC AN–BN (n=7) (Bailer et al., 2007b). However, neither group was statistically different from healthy CW. In contrast, [^{11}C]McN5652 BP$_{ND}$ was normal in REC BN (n=9), whereas other imaging and peripheral platelet studies have found evidence of reduced 5-HTT in ill and REC BN individuals (Kuikka et al., 2001; Steiger et al., 2005; Tauscher et al., 2001), including a recent study from our group, using [^{11}C]DASB, a more specific radioligand for the 5-HTT (Pichika et al., 2012).

It is important to move beyond studying a single monoamine system and address the complex interactions of neural systems (for review see Tremblay and Blier, 2006) in order to better understand behavior. It has been theorized that 5-HT is the crucial substrate of an aversive motivational system that might oppose a DA-related appetitive system (Cools et al., 2008; Daw et al., 2002). Specifically, 5-HT has a critical role in the adaptation of animals to aversive events (Bari et al., 2010; Deakin and Graeff, 1991) and may mediate a negative prediction error signal for future threat and punishment (Boureau and Dayan, 2011; Cools et al., 2008; Daw et al., 2002). While DA has been associated with the expression of an appetitive reward system (Schultz, 1997), it is plausible that it works in mutual opponency with a system that signals the prediction of punishment instead of reward (Daw et al., 2002; Deakin and Graeff, 1991). From another perspective, studies suggest that 5-HT has a role in action choice by controlling the timescale of delayed rewards through differential effects on ventral and dorsal striatal circuits (McClure et al., 2004; Schweighofer et al., 2007).

We are interested in exploring how complex monoamine interactions may be related to diagnostic category (e.g., AN vs. BN), impulse control, anxiety, and other behaviors that may cut across diagnostic boundaries. In terms of the latter, our PET imaging studies show striking and consistent correlations between the BP of both 5-HT$_{1A}$ and 5-HT$_{2A}$, DA D2/D3 receptors, and harm avoidance (HA) among all subgroups of ED individuals. HA is associated with 5-HT$_{1A}$ BP$_P$ in REC AN (Bailer et al., 2005) and REC BN (Bailer et al., 2011), 5-HT$_{2A}$ BP$_{ND}$ in REC AN–BN (Bailer et al., 2004) and ill AN/AN–BN (Bailer et al., 2007a), and DA D2/D3 BP$_{ND}$ in REC AN/AN–BN (Frank et al., 2005). In addition to being a premorbid influencing factor (Anderluh et al., 2003; Lilenfeld et al., 2006; Stice, 2002), elevated HA is commonly found among all ill ED subtypes [see review by Cassin and von Ranson (2005)] and persists after recovery from AN and BN (Wagner et al., 2006). HA is a multifaceted temperament trait (Cloninger et al., 1994) that contains elements of anxiety, inhibition, and inflexibility; it reflects the construct of 'behavioral inhibition'.

The main purpose of this study was to use our previously published PET data to explore whether 5-HT and DA interactions occur in REC ED subjects, beyond diagnostic boundaries, and whether such interactions were related to HA or to other behaviors. We have not found significant relationships between [^{11}C]raclopride BP$_{ND}$ or [^{11}C]WAY100635 BP$_P$ or [^{18}F]altanserin BP$_{ND}$ (unpublished data). The only significant relationships were between [^{11}C]McN5652 BP$_{ND}$ and [^{11}C]raclopride BP$_{ND}$, indicating an interaction between 5-HTT and DA D2/D3 binding, which is the focus of this article. The [^{11}C]McN5652 BP$_{ND}$ data have been published elsewhere (Bailer et al., 2007b). The current article presents new [^{11}C]raclopride BP$_{ND}$ data on REC ED subjects and CW in order to explore these interaction findings.

2. Methods

2.1. Subjects

Forty-five women who were REC from EDs were studied with PET imaging and the radioligand [^{11}C]raclopride.. The sample consisted of 17 REC AN [4 part of (Frank et al., 2005)], 14 REC AN-BN [6 part of (Frank et al., 2005)], 14 REC BN, and 21 CW [12 part of (Frank et al., 2005)]. Out of this initial sample, a smaller sample of 27 REC EDs (11 REC AN, 7 REC AN–BN, 9 REC BN) and 9 CW were analyzed for correlations between [^{11}C]McN5652 and [^{11}C]raclopride binding, as these subjects completed both PET studies. Data on some subjects (of this smaller sample) regarding [^{11}C]McN5652 binding (11 REC AN, 7 REC AN–BN, 9 REC BN, 9 CW) and [^{11}C]raclopride binding (4 REC AN, 6 REC AN–BN, 9 CW) were recently published (Bailer et al., 2007b; Frank et al., 2005). We are presenting all of the [^{11}C]raclopride data because it would be misleading to only present the [^{11}C]raclopride data on the group who also had [^{11}C]McN5652 data.

Subjects were recruited as previously described (Wagner et al., 2006). Women between the ages of 18 and 45 years who had previously met criteria for AN or BN as defined in the 4th ed. of the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2000) were recruited. They were previously treated in the ED treatment program at Western Psychiatric Institute and Clinic (University of Pittsburgh Medical Center, Pittsburgh, PA) or were recruited nationally through advertisements. All individuals underwent four levels of screening: (a) a brief telephone screening; (b) an intensive screening process to assess psychiatric history, lifetime weight, binge eating and methods of weight loss/ control, and menstrual cycle history as well as their eating pattern for the past 12 months; (c) a comprehensive assessment using structured and semi-structured psychiatric interviews conducted by telephone or in person; and (d) a face-to-face interview and physical examination with a psychiatrist. In order to be considered REC, subjects had to: (1) maintain a weight above 90% average body weigh (Metropolitan Life Insurance Company, 1959); (2) have regular menstrual cycles; (3) not have binged, purged, or engaged in significant restrictive eating patterns, or exercised excessively; and (4) not have used psychoactive medications such as antidepressants for at least 1 year prior to the study. Also, they must not have met criteria for current alcohol or drug abuse/ dependence.

Because of the small group size, we combined all individuals who met criteria for binge/purge type AN and individuals who met lifetime criteria for both AN and BN during the course of their illness (referred to as REC AN–BN) after determining by a Mann–Whitney test that these groups did not differ on any of the dependent measures (data not shown). CW were recruited through local advertisements. They had no history of an ED or any psychiatric disorder and no serious medical or neurologic illness. They had normal menstrual cycles and had been within normal weight range since menarche ($>$90% of average body weight). This study was conducted according to the institutional review board regulations of the University of Pittsburgh, and all subjects gave written informed consent. During the screening process, current psychopathology was assessed, both in REC ED and CW, with a comprehensive battery of standardized instruments (see Wagner et al., 2006), designed to diagnose Axis I and II disorders and to assess symptoms typical in individuals with EDs. The battery included the Temperament and Character Inventory (Cloninger et al., 1994) for assessment of HA, novelty seeking (NS), reward dependence (RD) and persistence (P). Trained doctoral-level psychologists with experience in ED administered the clinical interviews.

2.2. Image acquisition

All subjects were scanned on the same ECAT HR+PET scanner (CTI PET systems, Knoxville, TN), located at the University of Pittsburgh PET Center, in three-dimensional

(3D) imaging mode during the first 10 days of the follicular phase of the menstrual cycle. All subjects also underwent magnetic resonance (MR) imaging before the PET scan on a Signa 1.5T scanner (GE Medical Systems, Milwaukee, WI) using a standard head coil. A volumetric spoiled gradient recalled (SPGR) sequence (TE=5, TR=25, flip angle=40°, NEX=1; field of view=24 cm, image matrix=256 × 192 pixels) acquired in the coronal plane was used for MR-PET image registration (to guide region of interest (ROI) placement) and for partial volume correction of the PET data. Fast spin-echo T2 and proton density weighted images were also routinely acquired to exclude significant neuropathology. Pixels that corresponded to scalp and calvarium were removed from the SPGR MR images (Sandor and Leahy, 1997). The MR-PET image alignment was performed using an automated method for centering (Minoshima et al., 1992) and alignment and reslicing (Woods et al., 1993). The PET image data were aligned to the SPGR MR data to yield registration parameters. The MR data were then resliced using the inverse transformation of the PET-to-MR alignment to match PET image space. The data were visually inspected for subject motion and inter-frame motion was corrected by applying a more extensive registration procedure on a frame-by-frame basis.

Immediately following slow bolus intravenous injection of 13.8 ± 1.8 mCi [^{11}C]McN5652, dynamic emission scanning with arterial blood sampling (input function) was performed over 90 min (Bailer et al., 2007b; Lopresti et al., 2001). Additionally, after slow bolus intravenous injection of high specific activity 10.4 ± 0.5 mCi [^{11}C]raclopride, dynamic emission scanning with arterial blood sampling (input function) was performed over 60 min, as described previously (Drevets et al., 2001; Frank et al., 2005). Whenever possible, the two PET scans were done on the same day. Only four REC EDs (two REC AN, two REC BN) and three CW had the scans on different days, ranging from 1 day to a maximum of 12 weeks interval. However, test–retest measures are high for both radioligands (Hietala et al., 1999; Kent et al., 2002; Schlosser et al., 1998; Szabo et al., 2002; Uchida et al., 2009; Volkow et al., 1993) and indicate that [^{11}C]McN5652 and [^{11}C]raclopride binding is stable when measured over weeks to months.

2.3. PET data processing

ROIs were hand drawn on the coregistered MR images, blind to subjects' diagnosis and applied to the dynamic PET data to generate time–activity curves, as described by Drevets et al. (2001): AVS, dorsal and middle caudate, dorsal and ventral putamen, and cerebellum (as a reference region) (Bailer et al., 2005; Drevets et al., 2001; Frank et al., 2005). In addition to these ROIs, the dorsal raphe nucleus was chosen. For the kinetic analyses, regional [^{11}C]McN5652 volume of distribution (V_T) was determined using a two-compartment, three-parameter tracer kinetic model (Innis et al., 2007). Specific 5-HTT binding was assessed using the BP_{ND} measure which is based upon the ratio of each ROI V_T to the cerebellar volume of distribution (V_{ND}) [(V_T/V_{ND})], where $BP_{ND}=(V_T-V_{ND})/V_{ND}$ (Parsey et al., 2000). Due to the fact that arterial blood sampling was not available in all subjects, the Reference Tissue Model (Lammertsma and Hume, 1996) was applied for the imaging data analysis of [^{11}C]raclopride, which has been shown to be an appropriate and robust model for quantifying [^{11}C]raclopride (Drevets et al., 2001; Frank et al., 2005). Here, the [^{11}C]raclopride BP_{ND} was derived from the kinetic rate constant $k3/k4$, which is equivalent to $(V_T-V_{ND})/V_{ND}$ (Innis et al., 2007).

An MR-based partial volume (PV) effect correction method was applied to correct the PET data for the dilutional effect of expanded CSF spaces accompanying normal aging and disease-related cerebral atrophy (Meltzer et al., 1996, 1999).

2.4. Statistical analysis

Correlations were examined with Pearson correlation coefficients, demographics and assessments between groups were compared with a one-way analysis of variance (ANOVA). We used Troendle's method (Troendle, 1995) to adjust for the multiple correlations between [^{11}C]McN5652 BP_{ND} and [^{11}C]raclopride BP_{ND}. This resampling method for multiple hypothesis testing is designed to deal with the fact that multiple test statistics computed over a single dataset will tend to be dependent. It determines the appropriate correction directly from the data, as follows. First, the raw test statistics are computed and the hypothesis corresponding to the largest of these is noted. Then, resampling is applied to the dataset to determine the null distribution of the maximum test statistic. The largest observed test statistic is compared to this null distribution and the corresponding null hypothesis is rejected if the p-value is below the desired family-wise error rate (set to 0.05). If this hypothesis is not rejected, the procedure stops and no null hypotheses are rejected. On the other hand, if it is rejected, that hypothesis is removed from the list of those to be tested and the procedure starts again with the new list, repeating until we fail to reject the remaining null hypotheses. [^{11}C]raclopride BP_{ND} was regressed on age and t-tests of age-adjusted values within the General Linear model in the statistical computing environment R version 2.9.0 (2009-04-17) (R Development Core Team, 2011) were used to compare [^{11}C]raclopride BP_{ND} between CW and REC AN, REC BN, REC AN–BN, respectively. Additional linear regression analyses that included an interaction term were used to assess the extent to which the interaction between [^{11}C]McN5652 BP_{ND} and [^{11}C]raclopride BP_{ND} predicted HA. Prior to performing the regression analyses, assessment of possible outliers showed one individual who displayed a [^{11}C]McN5652 BP_{ND} value that was more than 3 standard deviations above the mean; this individual was removed from the analysis.

3. Results

3.1. Demographics and assessments

Demographics and assessments, shown in Table 1, are displayed for the entire sample (n=66) of REC ED and CW for the [^{11}C]raclopride BP_{ND}, and for the smaller sample (n=36) for the correlational analysis between [^{11}C]raclopride BP_{ND} and [^{11}C]McN5652 BP_{ND}. Neither a lifetime history of major depressive disorder nor the number of previous depressive episodes were related to [^{11}C]McN5652 BP_{ND} (n=16; 5 REC AN, 4 REC AN–BN, and 7 REC BN, Bailer et al., 2007b) or to [^{11}C]raclopride BP_{ND} (n=34; 10 REC AN, 11 REC AN–BN; 13 REC BN).

3.2. [^{11}C]Raclopride BP_{ND}

[^{11}C]Raclopride BP_{ND} in the AVS differed significantly between CW and REC AN women (t [36]=2.148, p=0.036) (Fig. 1) after adjusting for the effects of age. However, this significance would not survive a correction for multiple comparisons. Otherwise, there were no significant differences between REC ED groups and CW for the AVS or any of the other regions (Table 2).

Table 1
Demographic values and assessments between groups.

Entire sample for [^{11}C]raclopride BP_{ND}							
	CW (n=21)[1]	REC AN (n=17)[2]	REC AN-BN (n=14)[3]	REC BN (n=14)[4]	F [df]	Sig.	Group diff.
Age (years)	27.7 (7.1)	25.6 (6.4)	28.1 (7.2)	26.3 (7.2)	0.46 [3,62]	0.71	
Current BMI (kg/m^2)	22.51 (2.26)	20.69 (2.00)	22.85 (2.82)	22.81 (2.34)	3.17 [3,62]	0.04	2 < 3*
Harm avoidance	10.30 (5.27)#	18.69 (7.36)#	16.43 (8.05)	19.35 (7.61)	6.27 [3,60]	0.001	1 < 2, 4
Sample for relationships between [^{11}C]raclopride BP_{ND} and [^{11}C]McN5652 BP_{ND}							
	CW (n=9)[1]	REC AN (n=11)[2]	REC AN-BN (n=7)[3]	REC BN (n=9)[4]	F [df]	Sig.	Group diff.
Age (years)	27.0 (6.4)	24.7 (5.5)	23.7 (4.2)	24.4 (5.3)	0.60 [3,32]	0.62	
Current BMI (kg/m^2)	22.45 (2.04)	20.74 (2.44)	21.75 (2.27)	23.24 (2.76)	3.16 [3,32]	0.04	2 < 4
Age of onset (years of age)	–	15.9 (3.2)	15.8 (1.9)#	17.4 (4.7)#	0.49 [2,22]	0.62	
Length of recovery (months)	–	43.4 (49.5)	12.0 (13.6) #	17.1 (10.2)#	2.13 [2,22]	0.14	
Harm avoidance	7.78 (3.96)	16.18 (7.97)	12.86 (10.78)	19.88 (6.28)	4.31 [3,32]	0.01	1 < 4
Novelty seeking	21.00 (5.27)	17.00 (7.51)	21.71 (8.50)	20.32 (8.28)	0.77 [3,32]	0.52	
Reward dependence	19.22 (2.95)	16.73 (3.90)	18.80 (2.36)	19.38 (2.74)	1.58 [3,32]	0.21	
Persistence	4.56 (1.42)	6.91 (1.51)	6.86 (1.35)	6.00 (1.73)	4.72 [3,32]	0.01	1 < 2, 3

Sig., significance; CW, control women; REC, recovered; AN, anorexia nervosa, restricting type AN; AN-BN, bulimic type AN; BN, bulimia nervosa;
*at a trend level (p=0.07); #one missing value.

3.3. Relationship of [^{11}C]McN5652 BP_{ND} and [^{11}C]raclopride BP_{ND}

In the sample of 27 REC EDs there was a positive correlation between [^{11}C]McN5652 BP_{ND} and [^{11}C]raclopride BP_{ND} for the dorsal caudate ($r(27)=0.62$; $p<0.001$) (Fig. 2A), AVS ($r(27)=0.55$, $p=0.003$) (Fig. 2B), middle caudate ($r(27)=0.68$; $p<0.001$), ventral putamen ($r(27)=0.64$; $p<0.001$) and dorsal putamen ($r(27)=0.42$; $p=0.03$). The correlation between [^{11}C]McN5652 BP_{ND} in the dorsal raphe and [^{11}C]raclopride BP_{ND} in the AVS was trending in the positive direction ($r(27)=0.35$; $p=0.07$). After correction using Troendle's (1995) method, the correlations within the dorsal caudate ($p_{adjusted}=0.026$), AVS ($p_{adjusted}=0.047$), middle caudate ($p_{adjusted}=0.004$), and ventral putamen ($p_{adjusted}=0.010$) remained significant. No significant correlations were found within individual ED subgroups (REC AN, REC AN–BN, REC BN) between [^{11}C]raclopride BP_{ND} and [^{11}C]McN5652 BP_{ND}. In the small sample of only nine CW who completed both [^{11}C]McN5652 and [^{11}C]raclopride PET studies, no significant correlations were found between [^{11}C]McN5652 BP_{ND} and [^{11}C]raclopride BP_{ND}.

When using PV-uncorrected values for both [^{11}C]raclopride and [^{11}C]McN5652 BP_{ND} in the sample of 27 REC EDs, there was a positive correlation between [^{11}C]McN5652 BP_{ND} and [^{11}C]raclopride BP_{ND} for the dorsal caudate ($r(27)=0.62$; $p=0.001$), AVS ($r(27)=0.56$, $p=0.002$), middle caudate ($r(27)=0.66$; $p<0.001$), ventral putamen ($r(27)=0.60$; $p=0.001$) and dorsal putamen ($r(27)=0.42$; $p=0.03$). This is quite similar to what we found with the PV corrected values (see above). In addition, there were significant correlations between [^{11}C]McN5652 BP_{ND} in the dorsal raphe and [^{11}C]raclopride BP_{ND} in the AVS ($r(27)=0.52$; $p=0.006$), dorsal caudate ($r(27)=0.40$; $p=0.04$), dorsal putamen ($r(27)=0.39$; $p=0.05$), middle caudate ($r(27)=0.58$; $p=0.002$) and ventral putamen ($r(27)=0.60$; $p=0.001$). No significant correlations were found within each individual ED subgroup (REC AN, REC AN–BN, REC BN) between [^{11}C]raclopride BP_{ND} and [^{11}C]McN5652 BP_{ND}. In the small sample of only nine CW who completed both [^{11}C]McN5652 and [^{11}C]raclopride PET studies, no significant correlations were found between [^{11}C]McN5652 BP_{ND} and [^{11}C]raclopride BP_{ND}, when using PV-uncorrected values.

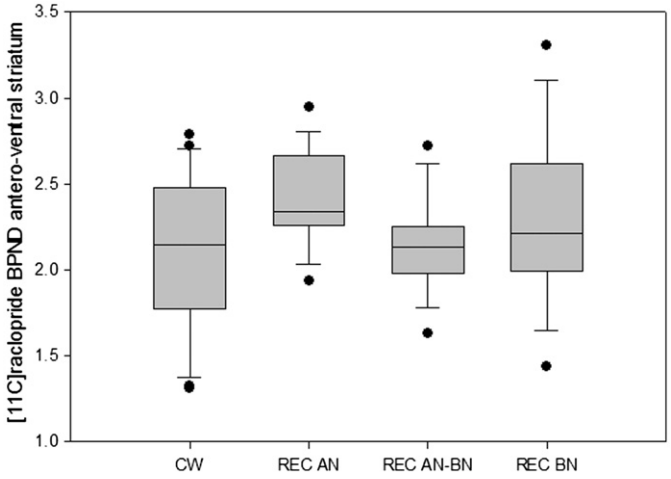

Fig. 1. Comparison of [^{11}C]raclopride BP_{ND} in the antero-ventral striatum between groups; CW, control women; REC, recovered; AN, anorexia nervosa, restricting type AN; AN-BN, bulimic type AN; BN, bulimia nervosa.

3.4. Relationship of [^{11}C]McN5652 BP_{ND} and [^{11}C]raclopride BP_{ND} and HA

REC EDs showed positive correlations between [^{11}C]raclopride BP_{ND} and HA in the dorsal caudate, ($r(27)=0.48$; $p=0.01$) (Fig. 3A) and dorsal putamen ($r(27)=0.42$; $p=0.03$) (Fig. 3B). There was no

Table 2
Regional [^{11}C]raclopride BP_{ND} between groups.

ROI	CW ($n=21$)[1]		REC AN ($n=17$)[2]		REC AN-BN ($n=14$)[3]		REC BN ($n=14$)[4]		2 vs. 1	P	3 vs. 1	p	4 vs. 1	p
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	T [df]		T [df]		T [df]	
Antero-ventral striatum	2.120	0.436	2.404	0.268	2.147	0.262	2.299	0.473	2.148 [36]	0.036	0.246 [33]	0.807	1.281 [33]	0.205
Dorsal caudate	2.622	0.365	2.541	0.345	2.528	0.367	2.729	0.351	−0.711 [36]	0.480	−0.750 [33]	0.456	0.845 [33]	0.402
Dorsal putamen	2.921	0.579	2.965	0.328	2.838	0.253	3.087	0.338	0.168 [36]	0.867	−0.553 [33]	0.582	1.059 [33]	0.294
Ventral putamen	2.841	0.506	3.018	0.288	2.867	0.242	3.086	0.431	1.194 [36]	0.237	0.230 [33]	0.819	1.698 [33]	0.095
Middle caudate	2.516	0.293	2.617	0.342	2.450	0.224	2.658	0.391	0.668 [36]	0.506	−0.576 [33]	0.567	1.154 [33]	0.253

ROI, region of interest; CW, control women; REC, recovered; AN, anorexia nervosa, restricting type AN; AN–BN, bulimic type AN; BN, bulimia nervosa.

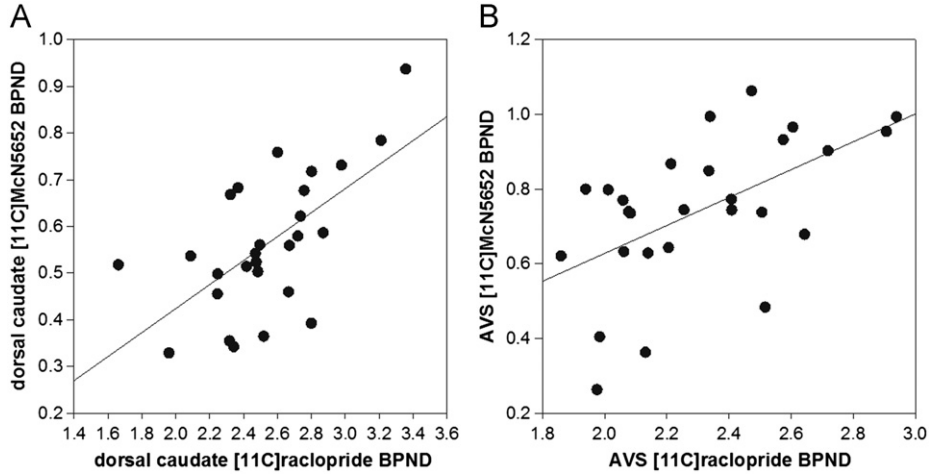

Fig. 2. Correlation of [^{11}C]McN5652 BP_{ND} and [^{11}C]raclopride BP_{ND} in the dorsal caudate (Panel A) and antero-ventral striatum (AVS) (Panel B) in the REC ED sample.

significant correlation between [^{11}C]McN5652 BP_{ND} and HA in any of the ROIs; however, linear regression analysis revealed that the interaction between [^{11}C]McN5652 BP_{ND} and [^{11}C]raclopride BP_{ND} in the dorsal putamen was significantly associated with HA ($b=140.04$; t (22)$=2.21$; $p=0.04$) (Fig. 4A). In the dorsal caudate, the same interaction approached significance ($b=-60.43$; t (22)$=-1.725$; $p=0.10$) (Fig. 4B). The AICs for each of the three models in the dorsal putamen (association between [^{11}C]raclopride BP_{ND} and HA, [^{11}C]McN5652 BP_{ND} and HA, the interaction term and HA) were 258.716, 258.282 and 256.327, respectively. The model with the interaction term had the lowest AIC and was selected as most predictive using this approach. More precisely, HA was regressed on [^{11}C]McN5652 BP_{ND}, and [^{11}C]raclopride BP_{ND}, in the dorsal putamen, with and without their interaction. When the interaction term was not included, neither BP_{ND} were significantly predictive of HA (b-McN$=11.902$, se$=10.200$, $p=0.252$; b-rac$=4.755$, se$=4.878$, $p=0.337$). However, when the interaction term was included, both the interaction and the [^{11}C]McN5652 BP_{ND} term were statistically significant (b-McN$=-219.92$, se$=107.38$, $p=0.0488$; b-rac$=-42.73$, se$=22.39$, $p=0.0653$; b-interaction$=73.72$, se$=34.01$, $p=0.0377$). No significant correlations were found between HA and [^{11}C]McN5652 BP_{ND} or [^{11}C]raclopride BP_{ND} in CW. Other behaviors, body mass index, or length of recovery were not related to either [^{11}C]McN5652 BP_{ND} or [^{11}C]raclopride BP_{ND} or HA, NS, RD, or P.

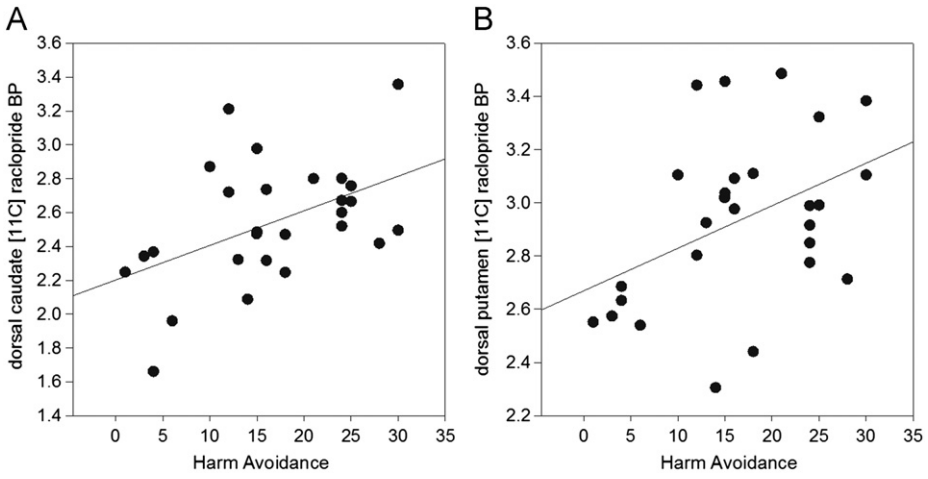

Fig. 3. REC ED showed positive correlations between [^{11}C]raclopride BP_{ND} and harm avoidance in the dorsal caudate ($r(27)=0.48$; $p=0.01$) (Panel A) and dorsal putamen ($r(27)=0.42$; $p=0.03$) (Panel B).

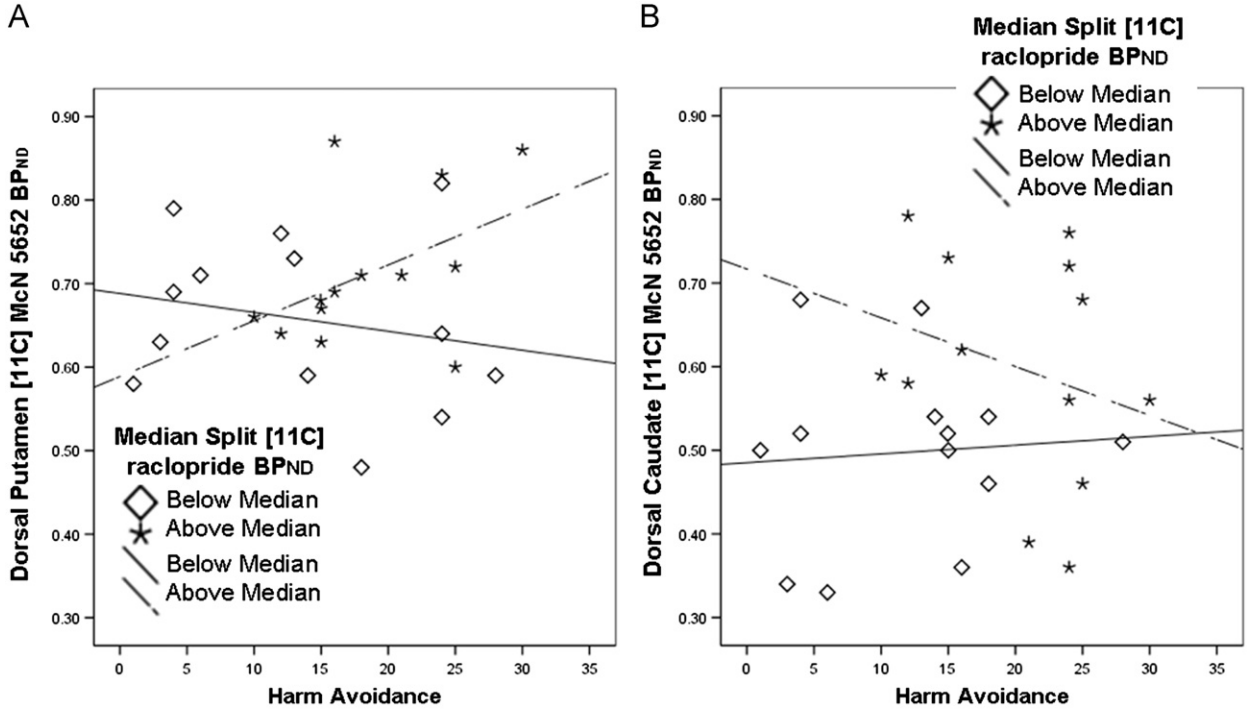

Fig. 4. For each region, scatterplots of [^{11}C]McN5652 BP_{ND} (y-axis) versus harm avoidance (x-axis), with each individual coded with a symbol based on a median split of [^{11}C]raclopride BP_{ND}, depict the relationship between these three continuous variables. Panel A: In the dorsal putamen, women with [^{11}C]raclopride BP_{ND} values below the median show a negative relationship between [^{11}C]McN5652 BP_{ND} and harm avoidance, while those with [^{11}C]raclopride BP_{ND} values above the median show a positive relationship between [^{11}C]McN5652 BP_{ND} and harm avoidance. Panel B: In the dorsal caudate, women with [^{11}C]raclopride BP_{ND} values below the median show a slight positive relationship between [^{11}C]McN5652 BP_{ND} and harm avoidance, while those with [^{11}C]raclopride BP_{ND} values above the median show a negative relationship between [^{11}C]McN5652 BP_{ND} and harm avoidance.

4. Discussion

To our knowledge, this is the first imaging study to show a relationship between [^{11}C]McN5652 BP_{ND} and [^{11}C]raclopride BP_{ND} in humans. This study showed that [^{11}C]raclopride BP_{ND}, but not [^{11}C]McN5652 BP_{ND}, was significantly related to HA in REC ED. A linear regression analysis revealed that the interaction between [^{11}C]McN5652 BP_{ND} and [^{11}C]raclopride BP_{ND} in the dorsal putamen significantly predicted HA.

The physiology underlying 5-HT, DA, and HA relationships is not well understood. HA, a continuous measure of inhibition and anxiety, was thought to reflect central serotonergic turnover (Cloninger, 1988; Cloninger, 1986; Cloninger et al., 1993). There is extensive literature associating 5-HT system activity with fundamental aspects of behavioral inhibition (Geyer, 1996), e.g., reduced CSF 5-HIAA levels are associated with increased impulsivity and aggression in humans and non-human primates, whereas increased CSF 5-HIAA levels are related to behavioral inhibition (Fairbanks et al., 2001; Schweighofer et al., 2007; Westergaard et al., 2003). In fact, there is considerable evidence that 5-HT function is inhibitory of appetite and plays a role in anxious and obsessive behaviors, as well as in depression (Blundell, 1984; Cloninger, 1987; Higley and Linnoila, 1997; Leibowitz and Shor-Posner, 1986; Lucki, 1998; Mann, 1999; Soubrie, 1986).

As noted above, our previous PET imaging studies have shown consistent correlations between HA and the BP for 5-HT_{1A}, or 5-HT_{2A}, or DA D2/D3 receptors, in all subgroups of ED individuals. In specific, HA was associated with mesial temporal 5-HT_{1A} BP_P in REC AN (Bailer et al., 2005), lateral and medial orbital frontal as well as parietal 5-HT_{1A} BP_P in REC BN (Bailer et al., 2011), subgenual cinguate and temporal 5-HT_{2A} BP_{ND} in REC AN–BN (Bailer et al., 2004), subgenual cingulate, lateral and medial orbital frontal and parietal 5-HT_{2A} BP_{ND} in ill AN/AN–BN (Bailer et al., 2007a). In addition, HA has also been associated with caudate DA activity in Parkinson's disease (Kaasinen et al., 2001), and a relationship between striatal DA activity and trait anxiety has been reported in healthy controls (Laakso et al., 2003). Moreover, dorsal caudate and dorsal putamen DA D2/D3 BP_{ND} was positively associated with HA in REC AN/AN–BN (Frank et al., 2005).

Interestingly, we did not find an interaction between 5-HT_{1A} and/or 5-HT_{2A} and DA D2/D3 binding with HA (data not shown). Nor did we find a direct relationship between 5-HTT binding and HA. Rather, 5-HTT binding was associated with HA, but only in relationship to 5-HTT and DA interactions, raising the possibility that 5-HTT may have a modulatory role on DA activity, with the latter being associated with HA. In support of this idea, agents that are relatively 5-HT specific, such as psilocybin (Vollenweider et al., 1999), fenfluramine (Smith et al., 1997), and citalopram (Tiihonen et al., 1996) alter [^{11}C]raclopride binding. It is important to note that 5-HT and DA neural systems are complex. For example, the 5-HT system has 14 or more receptors and many other components that modulate metabolism, firing rate, neuronal cascades, etc. Thus it is possible that interactions between 5-HT and DA could involve elements not measured in this study, which might contribute to the paradoxical finding of interactions between 5-HTT and DA D2/D3 that showed a positive association with HA in the dorsal putamen but a negative one in the dorsal caudate. A review of the literature did not find any studies that have investigated interactions between 5-HTT and DA D2/D3 receptors. However, 5-HT_{2C} receptors tonically inhibit mesencephalic DA neurons (De Deurwaerdere et al., 2004). Administration of the selective 5-HT_{2C} agonist RO 60-0175 decreases basal DA release in the nucleus accumbens and decreases basal firing rate of DA neurons in the ventral tegmental area (VTA) (Di Matteo et al., 2000). The 5-$HT_{2C/2B}$ antagonist SB 206553 increases basal DA release in the nucleus accumbens and striatum and increases basal firing rate of DA neurons in the VTA and substantia nigra pars compacta (Di Giovanni et al., 1999).

One limitation of PET radioligand studies is that they provide a relatively narrow window into understanding complex neurotransmission function. This is an especially important consideration in our attempts to study 5-HT, as a radiotracer of equivalent value as [^{11}C]raclopride has been to dopamine has not yet been identified (for review see Paterson et al., 2010; Paterson et al., 2010). For example, [^{11}C]McN5652 BP_{ND} presumably reflects 5-HTT density and/or affinity because[^{11}C]McN5652 is not displaced from 5-HTT sites by physiologically relevant 5-HT concentrations (Hummerich et al., 2006; Meyer, 2007). Therefore, [^{11}C]McN5652 BP_{ND} appears to remain relatively unaffected by endogenous 5-HT (Hummerich et al., 2006). One model, as suggested by Meyer (2007), proposes a clearance effect of 5-HTT, with less functioning 5-HTT associated with greater extracellular 5-HT. Theoretically, individuals with greater [^{11}C]McN5652 BP_{ND} have reduced extracellular 5-HT. This is consistent with our studies of CSF 5-HIAA in REC AN and BN (Kaye et al., 1991; Kaye et al., 1998), where REC AN have relatively lower concentrations compared to REC BN, which corresponds with higher purported 5-HTT binding in REC AN compared to REC BN (Bailer et al., 2007b). One possibility, although conjectural, is that those individuals with elevated [^{11}C]McN5652 BP_{ND} have reduced extracellular 5-HT. In turn, there would be diminished 5-HT stimulation of 5-HT_{2C} post-synaptic receptors. As described, studies in animals show that 5-HT_{2C} receptors tonically inhibit mesencephalic DA neurons (De Deurwaerdere et al., 2004). Less 5-HT_{2C} inhibition might result in less inhibition of DA neurons. Sustained DA activation has been shown to be related to uncertainty (Fiorillo et al., 2003), which could be consistent with behavioral measures of elevated anxiety and inhibition – and HA – in some individuals with ED.

It has been shown in animals (Morris et al., 1999) and humans (Volkow et al., 1996; Volkow et al., 2000) that [^{11}C]raclopride BP_{ND} diminishes with age. When corrected for age, as done in other [^{11}C]raclopride PET studies (Reeves et al., 2005; Reeves et al., 2007), this study found that REC AN (but not REC AN–BN or REC BN) had increased AVS [^{11}C]raclopride BP_{ND} when compared to CW (uncorrected for multiple comparisons). This finding corresponds with our previous report of increased [^{11}C]raclopride BP_{ND} in REC AN/AN–BN, where AVS [^{11}C]raclopride BP_{ND} in REC AN tended to be higher compared to REC AN–BN (Frank et al., 2005). [^{11}C]raclopride BP_{ND} is influenced by endogenous DA; therefore, the BP_{ND} is interpreted as a measure of receptor availability, rather than absolute receptor density (see Drevets et al., 2001; Graff-Guerrero et al., 2008; Zald et al., 2010). Thus, elevated AVS [^{11}C]raclopride BP_{ND} could indicate either an elevation of the density and/or affinity of the D2/D3 receptors or a reduction in intrasynaptic DA concentrations. The latter would be consistent with our previous findings of reduced CSF homovanillic acid (HVA) concentrations in REC AN and normal CSF HVA levels for REC AN–BN and BN subjects (Kaye et al., 1999). It is important to note that DA D2/D3 receptors are just one small part of a complex DA system that involves the interaction of a number of DA receptors and other molecules. Moreover, DA D2/D3 receptors show opposite roles in subregions of the nucleus accumbens which may confound interpretation of findings (Besson et al., 2010). In addition, there are differences within striatal regions in terms of the relative balance of D2 and D3 receptors (Gurevich and Joyce, 1999), expression of the DA transporter (Martinez et al., 2003), and DA D1 receptor density (Muly et al., 2010).

4.1. Limitations

The main focus of this article was the interaction of [^{11}C]McN5652 BP_{ND} and [^{11}C]raclopride BP_{ND} and its relationship to behavior in REC ED. First, the sample of CW that had [^{11}C]McN5652 BP_{ND} studies was

about half of the entire sample that had [^{11}C]raclopride data available, making it too small and underpowered to draw conclusions about relationships that might occur in healthy populations. Secondly, the interactions between 5-HTT, DA D2/D3 and HA would not survive a correction for multiple comparisons. Lastly, small sample sizes and insufficient power to detect differences between groups also applied to the ED subgroup samples (7 REC AN–BN, 11 REC AN, 9 REC BN). Therefore, studies with large enough samples to detect subgroup differences will need to be completed in the future.

It is unclear whether the 5-HTT is itself abnormal in ED subjects or whether disturbed 5-HTT binding may be secondary to other 5-HT disturbances (Laje et al., 2010). If so, it is possible that [^{11}C]McN5652 BP_{ND} and [^{11}C]raclopride BP_{ND} may serve as useful "markers" of 5-HT and DA neural activity. In this regard, it is possible that [^{11}C]raclopride BP_{ND} and [^{11}C]McN5652 BP_{ND} interactions or [^{11}C]raclopride BP_{ND} and HA relationships reflect a balance between 5-HT functional activity (aversive or inhibitory) and DA functional activity (reward or motivation) (Cools et al., 2008; Daw et al., 2002). However, aspects suggesting a competition or a collaboration or neither between serotonin and dopamine function are manifold, making it difficult to draw conclusions regarding the nature of their relationship (see Boureau and Dayan, 2011, for review). Finally, DA, and 5-HT systems have reciprocal interactions, making it virtually impossible to act on a specific neuronal element without a cascade effect on the other systems (Tremblay and Blier, 2006).

5. Conclusion

In summary, positive correlations between PET radioligand measures reflecting binding of the 5-HTT and DA D2/D3 receptors in the AVS and dorsal caudate were found. DA D2/D3 receptor binding in the dorsal caudate, as well as interactions between DA D2/D3 receptor and 5-HTT binding, were related to HA scores supporting the possibility that 5-HT and DA interactions contribute to HA behaviors in EDs.

Acknowledgments

Funding for this work was provided by the National Institute of Mental Health MH046001, MH04298, K05-MH01894, T32-MH18399, the Price Foundation and grant support from Erwin-Schrödinger Research Fellowship of the Austrian Science Fund (J2188 and J2359-B02) to Dr. Ursula Bailer.

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 subjects for their contribution of time and effort in support of this study.

References

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

Anderluh, M.B., Tchanturia, K., Rabe-Hesketh, S., Treasure, J., 2003. Childhood obsessive-compulsive personality traits in adult women with eating disorders: defining a broader eating disorder phenotype. American Journal of Psychiatry 160, 242–247.

Bailer, U., Bloss, C., Frank, G., Price, J., Meltzer, C., Mathis, C.A., Geyer, M.A., Wagner, A., Becker, C.R., Schork, N.J., Kaye, W.H., 2011. 5-HT_{1A} receptor binding is increased after recovery from bulimia nervosa compared to control women and is associated with behavioral inhibition in both groups. International Journal of Eating Disorders 44, 477–487.

Bailer, U.F., Price, J.C., Meltzer, C.C., Mathis, C.A., Frank, G.K., Weissfeld, L., McConaha, C.W., Henry, S.E., Brooks-Achenbach, S., Barbarich, N.C., Kaye, W.H., 2004. Altered 5-HT_{2A} receptor binding after recovery from bulimia-type anorexia nervosa: relationships to harm avoidance and drive for thinness. Neuropsychopharmacology 29, 1143–1155.

Bailer, U.F., Frank, G.K., Henry, S.E., Price, J.C., Meltzer, C.C., Weissfeld, L., Mathis, C.A., Drevets, W.C., Wagner, A., Hoge, J., Ziolko, S.K., McConaha, C.W., Kaye, W.H., 2005. Altered brain serotonin 5-HT_{1A} receptor binding after recovery from anorexia nervosa measured by positron emission tomography and [^{11}C]WAY100635. Archives of General Psychiatry 62, 1032–1041.

Bailer, U.F., Frank, G., Henry, S., Price, J., Meltzer, C.C., Mathis, C.A., Wagner, A., Thornton, L., Hoge, J., Ziolko, S.K., Becker, C.R., McConaha, C.W., Kaye, W.H., 2007a. Exaggerated 5-HT_{1A} but normal 5-HT_{2A} receptor activity in individuals ill with anorexia nervosa. Biological Psychiatry 61, 1090–1099.

Bailer, U.F., Frank, G., Henry, S., Price, J., Meltzer, C.C, Becker, C., Ziolko, S.K., Mathis, C.A., Wagner, A., Barbarich-Marsteller, N.C., Putnam, K., Kaye, W.H., 2007b. Serotonin transporter binding after recovery from eating disorders. Psychopharmacology 195, 315–324.

Bari, A., Theobald, D., Caprioli, D., Mar, A., Aidoo-Micah, A., Dalley, J., Dalley, J.W., Robbins, T.W., 2010. Serotonin modulates sensitivity to reward and negative feedback in a probabilistic reversal learnign task in rats. Neuropsychopharmacology 35, 1290–1301.

Bergen, A., Yeager, M., Welch, R., Haque, K., Ganjei, J.K., Mazzanti, C., Nardi, I., Fichter, M.M., Halmi, K.A., Kaplan, A.S., Strober, M., Treasure, J., Woodside, D.B., Bulik, C.M., Bacanu, S.A., Devlin, B., Berrettini, W.H., Goldman, D., Kaye, W.H., 2005. Association of multiple DRD2 polymorphisms with anorexia nervosa. Neuropsychopharmacology 30, 1703–1710.

Besson, M., Belin, D., McNamara, R., Theobald, D.E., Castle, A., Beckett, V.L., Crittenden, B.M., Newman, A.H., Everitt, B.J., Robbins, T.W., Dalley, J.W., 2010. Dissociable control of impulsivity in rats by dopamine D2/3 receptors in the core and shell subregions of the nucleus accumbens. Neuropsychopharmacology 35, 560–569.

Blundell, J.E., 1984. Serotonin and appetite. Neuropharmacology 23, 1537–1551.

Boureau, Y.-L., Dayan, P., 2011. Opponency revisited: competition and cooperation between dopamine and serotonin. Neuropsychopharmacology Reviews 36, 74–97.

Cassin, S., von Ranson, K., 2005. Personality and eating disorders: a decade in review. Clinical Psychology Review 25, 895–916.

Cloninger, C., 1988. A unified biosocial theory of personality and its role in the development of anxiety states: a reply to commentaries. Psychiatric Development 6, 83–100.

Cloninger, C.R., 1986. A unified biosocial theory of personality and its role in the development of anxiety states. Psychiatric Development 4, 167–226.

Cloninger, C.R., 1987. A systematic method for clinical description and classification of personality variants. A proposal. Archives of General Psychiatry 44, 573–588.

Cloninger, C.R., Svrakic, D.M., Przybeck, T.R., 1993. A psychobiological model of temperament and character. Archives of General Psychiatry 50, 975–990.

Cloninger, C.R., Przybeck, T.R., Svrakic, D.M., Wetzel, R.D., 1994. The Temperament and Character Inventory (TCI): A Guide to its Development and Use. Center for Psychobiology of Personality, Washington University, St. Louis, MO, pp. 19–28.

Cools, R., Roberts, A., Robbins, T., 2008. Serotoninergic regulation of emotional and behavioural control processes. Trends in Cognitive Sciences 12, 31–40.

Daw, N.D., Kakade, S., Dayan, P., 2002. Opponent interactions between serotonin and dopamine. Neural Networks 15, 603–616.

De Deurwaerdere, P., Navailles, S., Berg, K., Clarke, W., Spampinato, U., 2004. Constitutive activity of the serotonin2C receptor inhibits in vivo dopamine release in the rat striatum and nucleus accumbens. The Journal of Neuroscience 24, 3235–3241.

Deakin, J., Graeff, F., 1991. 5-HT and mechanisms of defense. Journal of Psychopharmacology 5, 305–315.

Di Giovanni, G., De Deurwaerdere, P., Di Mascio, M., Di Matteo, V., Esposito, E., Spampinato, U., 1999. Selective blockade of serotonin-2C/2B receptors enhances mesolimbic and mesostriatal dopaminergic function: a combined in vivo electrophysiological and microdialysis study. Neuroscience 91, 587–597.

Di Matteo, V., Di Giovanni, G., Di Mascio, M., Esposito, E., 2000. Biochemical and electrophysiological evidence that RO 60-0175 inhibits mesolimbic dopaminergic function through serotonin(2C) receptors. Brain Research 865, 85–90.

Drevets, W., Gautier, C., Price, J., Kupfer, D., Kinahan, P., Grace, A.A., Price, J.L., Mathis, C.A., 2001. Amphetamine-induced dopamine release in human ventral striatum correlates with euphoria. Biological Psychiatry 49, 81–96.

Fairbanks, L., Melega, W., Jorgensen, M., Kaplan, J., McGuire, M., 2001. Social impulsivity inversely associated with CSF 5-HIAA and fluoxetine exposure in vervet monkeys. Journal of Neuropsychopharmacology 24, 370–378.

Fiorillo, C.D., Tobler, P.N., Schultz, W., 2003. Discrete coding of reward probability and uncertainty by dopamine neurons. Science 299, 1898–1902.

Frank, G., Bailer, U.F., Henry, S., Drevets, W., Meltzer, C.C., Price, J.C., Mathis, C.A., Wagner, A., Hoge, J., Ziolko, S., Barbarich-Marsteller, N., Weissfeld, L., Kaye, W.H., 2005. Increased dopamine D2/D3 receptor binding after recovery from anorexia nervosa measured by positron emission tomography and [^{11}C]raclopride. Biological Psychiatry 58, 908–912.

Frank, G.K., Kaye, W.H., Weltzin, T.E., Perel, J., Moss, H., McConaha, C., Pollice, C., 2001. Altered response to meta-chlorophenylpiperazine in anorexia nervosa: support for a persistent alteration of serotonin activity after short-term weight restoration. International Journal of Eating Disorders 30, 57–68.

Frank, G.K., Kaye, W.H., Meltzer, C.C., Price, J.C., Greer, P., McConaha, C., Skovira, K., 2002. Reduced 5-HT2A receptor binding after recovery from anorexia nervosa. Biological Psychiatry 52, 896–906.

Friederich, H.C., Kumari, V., Uher, R., Riga, M., Schmidt, U., Campbell, I.C., Herzog, W., Treasure, J., 2006. Differential motivational responses to food and pleasurable cues in anorexia and bulimia nervosa: a startle reflex paradigm. Psychological Medicine 36, 1327–1335.

Geyer, M.A., 1996. Serotonergic functions in arousal and motor activity. Behavioural Brain Research 73, 31.
Graff-Guerrero, A., Willeit, M., Ginovart, N., Mama, D., Mizrahi, R., Rusjan, P., Vitcu, I., Seeman, P., Wilson, A.A., Kapur, S., 2008. Brain region binding of the D2/3 agonist [11C]-(+)-PHNO and the D2/3 antagonist [11C]raclopride in healthy humans. Human Brain Mapping 29, 400–410.
Gurevich, E., Joyce, J., 1999. Distribution of dopamine D3 receptor expressing neurons in the human forebrain: comparison with D2 receptor expressing neurons. Neuropsychopharmacology 20, 60–80.
Hietala, J., Nagren, K., Lehikoinen, P., Ruotsalainen, U., Syvalahti, E., 1999. Measurement of striatal D2 dopamine receptor density and affinity with [11C]-raclopride in vivo: a test–retest analysis. Journal of Cerebral Blood Flow and Metabolism 19, 210–217.
Higley, J.D., Linnoila, M., 1997. Low central nervous system serotonergic activity is traitlike and correlates with impulsive behavior. A nonhuman primate model investigating genetic and environmental influences on neurotransmission. Annals of the New York Academy of Science 836, 39–56.
Hummerich, R., Schulze, O., Radler, T., Mikecz, P., Reimold, M., Brenner, W, 2006. Inhibition of serotonin transport by (+)McN5652 is noncompetitive. Nuclear Medicine and Biology 33, 317–323.
Innis, R., Cunningham, V., Delforge, J., Fujita, M., Gjedde, A., Gunn, R.N., Holden, J., Houle, S., Huang, S.C., Ichise, M., Iida, H., Ito, H., Kimura, Y., Koeppe, R.A., Knudsen, G.M., Knuuti, J., Lammertsma, A.A., Laruelle, M., Logan, J., Maguire, R.P., Mintun, M.A., Morris, E.D., Parsey, R., Price, J.C., Slifstein, M., Sossi, V., Suhara, T., Votaw, J.R., Wong, D.F., Carson, R.E., 2007. Consensus nomenclature for in vivo imaging of reversibly binding radioligands. Journal of Cerebral Blood Flow and Metabolism 27, 1533–1539.
Jimerson, D.C., Lesem, M.D., Kaye, W.H., Brewerton, T.D., 1992. Low serotonin and dopamine metabolite concentrations in cerebrospinal fluid from bulimic patients with frequent binge episodes. Archives of General Psychiatry 49, 132–138.
Kaasinen, V., Nurmi, E., Bergman, J., Eskola, J., Solin, O., Sonninen, P., Rinne, J.O., Sonninen, P., et al., 2001. Personality traits and brain dopaminergic function in Parkinson's disease. Proceedings of the National Academy of Science USA 98, 13272–13277.
Kaye, W., 2008. Neurobiology of anorexia and bulimia nervosa. Physiology and Behavior 94, 121–135.
Kaye, W.H., Ballenger, J.C., Lydiard, R.B., Stuart, G.W., Laraia, M.T., O'Neil, P., Fossey, M.D., Stevens, V., Lesser, S., Hsu, G., 1990. CSF monoamine levels in normal-weight bulimia: evidence for abnormal noradrenergic activity. American Journal of Psychiatry 147, 225–229.
Kaye, W.H., Gwirtsman, H.E., George, D.T., Ebert, M.H., 1991. Altered serotonin activity in anorexia nervosa after long-term weight restoration. Does elevated cerebrospinal fluid 5-hydroxyindoleacetic acid level correlate with rigid and obsessive behavior? Archives of General Psychiatry 48, 556–562.
Kaye, W.H., Greeno, C.G., Moss, H., Fernstrom, J., Fernstrom, M., Lilenfeld, L.R., Weltzin, T.E., Mann, J.J., 1998. Alterations in serotonin activity and psychiatric symptomatology after recovery from bulimia nervosa. Archives of General Psychiatry 55, 927–935.
Kaye, W.H., Frank, G.K., McConaha, C., 1999. Altered dopamine activity after recovery from restricting-type anorexia nervosa. Neuropsychopharmacology 21, 503–506.
Kaye, W.H., Frank, G.K., Meltzer, C.C., Price, J.C., McConaha, C.W., Crossan, P.J., Klump, K.L., Rhodes, L., 2001. Altered serotonin 2A receptor activity in women who have recovered from bulimia nervosa. American Journal of Psychiatry 158, 1152–1155.
Kaye, W.H., Barbarich, N.C., Putnam, K., Gendall, K.A., Fernstrom, J., Fernstrom, M., McConaha, C.W., Kishore, A., 2003. Anxiolytic effects of acute tryptophan depletion in anorexia nervosa. International Journal of Eating Disorders 33, 257–267.
Kent, J.M., Coplan, J.D., Lombardo, I., Hwang, D.R., Huang, Y., Abi-Dargham, A., Van Heertum, R.L., Gorman, J.M., Laruelle, M., 2002. Occupancy of brain serotonin transporters during treatment with paroxetine as measured with PET and [^{11}C] McN 5652. Psychopharmacology (Berlin) 164, 341–348.
Kuikka, J.T., Tammela, L., Karhunen, L., Rissanen, A., Bergström, K.A., Naukkarinen, H., Vanninen, E., Karhu, J., Lappalainen, R., Repo-Tiihonen, E., Tiihonen, J., Uusitupa, M., 2001. Reduced serotonin transporter binding in binge eating women. Psychopharmacology (Berlin) 155, 310–314.
Laakso, A., Wallius, E., Kajander, J., Bergman, J., Eskola, O., Solin, O., Ilonen, T., Salokangas, R.K., Syvälahti, E., Hietala, J., 2003. Personality traits and striatal dopamine synthesis capacity in healthy subjects. American Journal of Psychiatry 160, 904–910.
Laje, G., Cannon, D., Cannon, D., Allen, A., Klaver, J., Peck, S., 2010. Genetic variation in HTR2A influences serotonin transporter binding potential as measured using PET and [11C]DASB. International Journal of Neuropsychopharmacology 5, 1–10.
Lammertsma, A.A., Hume, S.P., 1996. Simplified reference tissue model for PET receptor studies. Neuroimage 4, 153–158.
Lawrence, A., 2003. Impaired visual discrimination learning in anorexia nervosa. Appetite 20, 85–89.
Leibowitz, S.F., Shor-Posner, G., 1986. Brain serotonin and eating behavior. Appetite 7, 1–14.
Lilenfeld, L., Wonderlich, S., Riso, L.P., Crosby, R., Mitchell, J., 2006. Eating disorders and personality: a methodological and empirical review. Clinical Psychology Review 26, 299–320.
Lopresti, B., Mathis, C., Price, J., Villemagne, V., Meltzer, C., Holt, D., et al., 2001. Serotonin transporter binding in vivo: further examination of [11C]McN5652, Molecular and Pharmacological Brain Imaging with Positron Emission Tomography. Academic Press, San Diego, pp. 265–271.
Lucki, I., 1998. The spectrum of behaviors influenced by serotonin. Biological Psychiatry 44, 151–162.
Mann, J.J., 1999. Role of the serotonergic system in the pathogenesis of major depression and suicidal behavior. Neuropsychopharmacology 21, 99S–105S.
Martinez, D., Slifstein, M., Broft, A., Mawlawi, O., Hwang, D., Huang, Y., Cooper, T., Kegeles, L., Zarahn, E., Abi-Dargham, A., Haber, S.N., Laruelle, M., 2003. Imaging human mesolimbic dopamine transmission with positron emission tomography. Part II: Amphetamine-induced dopamine release in the functional subdivisions of the striatum. Journal of Cerebral Blood Flow and Metabolism 23, 285–300.
McClure, S., Laibson, D., Loewenstein, G., Cohen, J., 2004. Separate neural systems value immediate and delayed monetary rewards. Science 306, 503–507.
Meltzer, C.C., Zubieta, J.K., Links, J.M., Brakeman, P., Stumpf, M.J., Frost, J.J., 1996. MR-based correction of brain PET measurements for heterogeneous gray matter radioactivity distribution. Journal of Cerebral Blood Flow and Metabolism 16, 650–657.
Meltzer, C.C., Kinaham, P., Nichols, T.E., Greer, P.J., Comtat, C., Cantwell, M.N., Lin, M.P., Price, J.C., 1999. Comparative evaluation of MR-based partial-volume correction schemes for PET. Journal of Nuclear Medicine 40, 2053–2065.
Metropolitan Life Insurance Company., 1959. New Weight Standards for Men and Women, pp 1–4.
Meyer, J., 2007. Imaging the serotonin transporter during major depressive disorder and antidepressant treatment. Journal of Psychiatry and Neuroscience 32, 86–102.
Minoshima, S., Berger, K.L., Lee, K.S., Mintun, M.A., 1992. An automated method for rotational correction and centering of three-dimensional functional brian images. Journal of Nuclear Medicine 33, 1579–1585.
Morris, E., Chefer, S., Lane, M., Muzic, R., Wong, D., Dannals, R.F., Matochik, J.A., Bonab, A.A., Villemagne, V.L., Grant, S.J., Ingram, D.K., Roth, G.S., London, E.D., 1999. Loss of D2 receptor binding with age in rhesus monkeys: importance of correction for differences in striatal size. Journal of Cerebral Blood Flow and Metabolism 19, 218–229.
Muly, E., Maddox, M., Khan, Z., 2010. Distribution of D(1) and D(5) dopamine receptors in the primate nucleus accumbens. Neuroscience 169, 1557–1566.
Parsey, R.V., Kegeles, L.S., Hwang, D.R., Simpson, N., Abi-Dargham, A., Mawlawi, O., Slifstein, M., Van-Heertum, R.L., Mann, J.J., Laruelle, M., 2000. In vivo quantification of brain serotonin transporters in humans using [11C]McN 5652. Journal of Nuclear Medicine 41, 1465–1477.
Paterson, L.T., Nutt, R.J., Knudsen, G.D., 2010. Measuring endogenous 5-HT release by emission tomography: promises and pitfalls. Journal of Cerebral Blood Flow and Metabolism 30, 1682–1706.
Pichika, R., Buchsbaum, M.S., Bailer, U., Hoh, C., DeCastro, A., Buchsbaum, B.R., Kay, W., 2012. Serotonin transporter binding after recovery from bulimia nervosa. International Journal of Eating Disorders 45, 345–352.
R Development Core Team., 2011. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL 〈http://www.R-project.org/〉.
Reeves, S., Cunningham, V., Grasby, P.H., Bantick, R., Asselin, A., Mehta, M., 2005. A positron emission tomography (PET) investigation of the role of striatal dopamine (D2) receptor availability in spatial cognition. Neuroimage 28, 216–226.
Reeves, S., Mehta, M., Montgomery, A., Amiras, D., Egerton, A., Howard, R.J., Grasby, P.M., 2007. Striatal dopamine (D2) receptor availability predicts socially desirable responding. Neuroimage 34, 1782–1789.
Sandor, S., Leahy, R., 1997. Surface-based labeling of cortical anatomy using a deformable atlas. Institute of Electrical and Electronics EngineersTransactions on Medical Imaging 16, 41–54.
Schlosser, R., Brodie, J.D., Alexoff, D., Wang, G., Fowler, J., Volkow, N., Logan, J., Wolf, A.P., 1998. Long-term stability of neurotransmitter activity investigated with 11C-raclopride PET. Synapse 28, 66–70.
Schultz, W., 1997. Dopamine neurons and their role in reward mechanisms. Current Opinions in Neurobiology 7, 191–197.
Schweighofer, N., Tanaka, S., Doya, K., 2007. Serotonin and the evaluation of future rewards: theory, experiments, and possible neural mechanisms. Annals of the New York Academy of Science 1104, 289–300.
Smith, G., Dewey, S.L., Brodie, J., Logan, J., Vitkun, S., Simkowitz, P., Schloesser, R., Alexoff, D.A., Hurley, A., Cooper, T., Volkow, N.D., 1997. Serotonergic modulation of dopamine measured with [^{11}C] raclopride and PET in normal human subjects. American Journal of Psychiatry 154, 490–496.
Smith, K.A., Morris, J.S., Friston, K.J., Cowen, P.J., Dolan, R.J., 1999. Brain mechanisms associated with depressive relapse and associated cognitive impairment following acute tryptophan depletion. British Journal of Psychiatry 174, 525–529.
Soubrie, P., 1986. Reconciling the role of central serotonin neurons in human and animal behavior. Behavioral and Brain Sciences 9, 319–335.
Steiger, H., Richardson, J., Israel, M., Ng Ying Kin, N., Bruce, K., Mansour, S., Marie Parent, A., 2005. Reduced density of platelet-binding sites for [3H]paroxetine in remitted bulimic women. Neuropsychopharmacology 30, 1028–1032.
Stice, E., 2002. Risk and maintenance factors for eating pathology: a meta-analytic review. Pychopharmacology Bulletin 128, 825–848.
Szabo, Z., McCann, U., Wilson, A., Scheffel, U., Owonikoko, T., Mathews, W.B., Ravert, H.T., Hilton, J., Dannals, R.F, Ricaurte, G.A., 2002. Comparison of (+)-11C-McN5652 and 11C-DASB as serotonin transporter radioligands under various experimental conditions. Journal of Nuclear Medicine 43, 678–692.

Tauscher, J., Pirker, W., Willeit, M., de Zwaan, M., Bailer, U., Neumeister, A., Asenbaum, S., Lennkh, C., Praschak-Rieder, N., Brücke, T., Kasper, S., 2001. [^{123}I]beta-CIT and single photon emission computed tomography reveal reduced brain serotonin transporter availability in bulimia nervosa. Biological Psychiatry 49, 326–332.

Tiihonen, J., Kuoppamaki, M., Nagren, K., Bergman, J., Eronen, E., Syvälahti, E., Hietala, J., 1996. Serotonergic modulation of striatal D2 dopamine receptor binding in humans measured with positron emission tomography. Psychopharmacology Bulletin 126, 277–280.

Tremblay, P., Blier, P., 2006. Catecholaminergic strategies for the treatment of major depression. Current Drug Targets 7, 149–158.

Troendle, J., 1995. A stepwise resampling method of multiple hypothesis testing. Journal of the American Statistical Association 90, 370–378.

Uchida, H., Graff-Guerrero, A., Mulsant, B., Pollock, B., 2009. Long-term stability of measuring D(2) receptors in schizophrenia patients treated with antipsychotics. Schizophrenia Research 109, 130–133.

Volkow, N., Wang, G., Fowler, J., Logan, J., Gatley, S., MacGregor, R.R., Schlyer, D.J., Hitzemann, R., Wolf, A.P., 1996. Measuring age-related changes in dopamine D2 receptors with 11C-raclopride and 18F-N-methylspiroperidol. Psychiatry Research 67, 11–16.

Volkow, N., Logan, J., Fowler, J., Wang, G., Gur, R., Wong, C., 2000. Association between age-related decline in brain dopamine activity and impairment in frontal and cingulate metabolism. American Journal of Psychiatry 157, 75–80.

Volkow, N.D., Fowler, J.S., Wang, G.J., Dewey, S.L., Schlyer, D., MacGregor, R., Logan, J., Alexoff, D., Shea, C., Hitzemann, R., Angrist, B., Wolf, A.P., 1993. Reproducibility of repeated measures of carbon-11-raclopride binding in the human brain [published erratum appears in Journal of Nuclear Medicine 1993 May;34(5):838]. Journal of Nuclear Medicine 34, 609–613.

Vollenweider, F., Vontobel, P., Hell, D., Leenders, K., 1999. 5-HT modulation of dopamine release in basal ganglia in psilocybin-induced psychosis in man—a PET study with [^{11}C]raclopride. Neuropsychopharmacology 20, 424–433.

Wagner, A., Barbarich, N., Frank, G., Bailer, U., Weissfeld, L., Henry, S.E., Vogel, V., Plotnicov, K., McConaha, C., Kaye, W.H., 2006. Personality traits after recovery from eating disorders: do subtypes differ? International Journal of Eating Disorders 39, 276–284.

Ward, A., Brown, N., Lightman, S., Campbell, I.C., Treasure, J., 1998. Neuroendocrine, appetitive and behavioural responses to d-fenfluramine in women recovered from anorexia nervosa. British Journal of Psychiatry 172, 351–358.

Westergaard, G., Suomi, S., Chavanne, T., Houser, L., Hurley, A., Cleveland, A., Snoy, P.J., Higley, J.D., 2003. Physiological correlates of aggression and impulsivity in free-ranging female primates. Neuropsychopharmacology 28, 1045–1055.

Woods, R.P., Mazziotta, J.C., Cherry, S.R., 1993. MRI-PET registration with automated algorithm. Journal of Computer Assisted Tomography 17, 536–546.

Zald, D., Woodward, N., Cowan, R., Riccardi, P., Ansari, M., Baldwin, R.M., Cowan, R.L., Smith, C.E., Hakyemez, H., Li, R., Kessler, R.M., 2010. The interrelationship of dopamine D2-like receptor availability in striatal and extrastriatal brain regions in healthy humans: a principal component analysis of [18F]fallypride binding. Neuroimage 51, 53–62.