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

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A B S T R A C T

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 [11C]McN5652 and [ 11C ]raclopride binding. There was a significant positive correlation between [11C]McN5652 binding potential (BPnon displaceable (ND)) and [11C]Raclopride BPND for the dorsal caudate, antero-ventral striatum (AVS), middle caudate, and ventral and dorsal putamen. No significant correlations were found in CW. [11C]Raclopride BPND, but not [11C]McN5652 BPND, was significantly related to HA in REC EDs. A linear regression analysis showed that the interaction between [11C]McN5652 BPND and [11C]raclopride BPND for the dorsal putamen significantly predicted HA. This is the first study using PET and the radioligands [11C]McN5652 and [11C]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.

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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;
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., [11C]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 ([11C]MCn5652, [11C]WAY100635 and [18F]altanserin) to assess the BP of the 5-HT transporter (5-HTT) and the 5-HT1A and 5-HT2A receptors. In general, REC eating disorder (ED) individuals tend to have reduced 5-HT2A BP ([18F]altanserin BP

potential (BP)) in the antero-ventral striatum (AVS) (Frank et al., 2005). In addition to D2/D3 BPND in REC AN/AN–BN (Frank et al., 2007). The current article presents new [11C]raclopride BP 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 [11C]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)]. 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 [11C]MCn5652 and [11C]raclopride binding, as these subjects completed both PET studies. Data on some subjects of this smaller sample regarding [11C]MCn5652 binding (11 REC AN, 7 REC AN–BN, 9 REC BN, 9 CW) and [11C]raclopride binding (4 REC AN, 6 REC AN–BN, 9 REC BN) were recently published (Bailer et al., 2007b; Frank et al., 2005). We are presenting all of the [11C]raclopride data because it would be misleading to only present the [11C]raclopride data on the group who also had [11C]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 weight (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 independence (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...
PET image space. The data were visually inspected for subject motion and inter-frame alignment and reslicing (Woods et al., 1993). The PET image data were aligned using the center of mass (Minoshima et al., 1992) and alignment and reslicing (Woods et al., 1993). The PET 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 ± 0.5 mCi [11C]McN5652, dynamic emission scanning with arterial blood sampling (input function) was performed over 60 min (Bailer et al., 2007b, Lopresti et al., 2001). Additionally, after slow bolus intravenous injection of high specific activity 10.4 ± 0.5 mCi [11C]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 acquired on the same day. Only on 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; Schlosler et al., 1998; Szabo et al., 2002; Uchida et al., 2009; Volkow et al., 1993) and indicate that [11C]McN5652 and [11C]raclopride binding is stable when measured over weeks to months.

2.3. PET data processing

ROIs were hand-drawn on the co-registered 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 [11C]McN5652 volume of distribution (Vr) was determined using a two-compartment, three-parameter tracer kinetic model (Innis et al., 2007). Specific 5-HTT binding was assessed using the BPND measure which is based upon the ratio of each ROI Vr to the cerebellar volume of distribution (Vref) (Vr/Vref), where BPND = (Vr − Vref)/Vref (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 [11C]raclopride, which has been shown to be an appropriate and robust model for quantifying [11C]raclopride (Drevets et al., 2001; Frank et al., 2005). Here, the [11C]raclopride BPND was derived from the kinetic constant k3/k4, which is equivalent to (Vr − Vref)/Vref (Innis et al., 2007). An MR-based partial volume (PV) effect correction method was applied to the dynamic PET data to generate time-activity curves, as described by Uchida et al. (2009), Volkow et al. (1993), and indicate that [11C]McN5652 and [11C]raclopride binding is stable when measured over weeks to months.

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 [11C]raclopride BPND, and for the smaller sample (n = 36) for the correlational analysis between [11C]raclopride BPND and [11C]McN5652 BPND. Neither a lifetime history of major depressive disorder nor the number of previous depressive episodes were related to [11C]McN5652 BPND (n = 16; 5 REC AN, 4 REC AN–BN, and 7 REC BN, Bailer et al., 2007b) or to [11C]raclopride BPND (n = 34; 10 REC AN, 11 REC AN–BN; 13 REC BN).

3.2. [11C]Raclopride BPND

[11C]Raclopride BPND 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).
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 ($p_{\text{adjusted}} = 0.026$), AVS ($p_{\text{adjusted}} = 0.047$), middle caudate ($p_{\text{adjusted}} = 0.004$), and ventral putamen ($p_{\text{adjusted}} = 0.010$) 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.

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

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**Table 2**

Regional $[^{11}C]raclopride\ BP_{ND}$ between groups.

<table>
<thead>
<tr>
<th>ROI</th>
<th>CW (n = 21)$^a$</th>
<th>REC AN (n = 17)$^b$</th>
<th>REC AN–BN (n = 14)$^a$</th>
<th>REC BN (n = 14)$^a$</th>
<th>2 vs. 1 $P$</th>
<th>3 vs. 1 $P$</th>
<th>4 vs. 1 $P$</th>
<th>$T$ [df]</th>
<th>$T$ [df]</th>
<th>$T$ [df]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antero-ventral striatum</td>
<td>2.120 0.436</td>
<td>2.404 0.268</td>
<td>2.147 0.262</td>
<td>2.299 0.473</td>
<td>0.036</td>
<td>0.246</td>
<td>0.807</td>
<td>1.281 [33]</td>
<td>0.205</td>
<td></td>
</tr>
<tr>
<td>Dorsal caudate</td>
<td>2.622 0.365</td>
<td>2.541 0.345</td>
<td>2.328 0.367</td>
<td>2.729 0.351</td>
<td>-0.711</td>
<td>0.480</td>
<td>0.750</td>
<td>0.456</td>
<td>0.845</td>
<td>0.402</td>
</tr>
<tr>
<td>Dorsal putamen</td>
<td>2.921 0.579</td>
<td>2.965 0.328</td>
<td>2.838 0.253</td>
<td>3.087 0.338</td>
<td>0.168</td>
<td>0.867</td>
<td>-0.553</td>
<td>0.582</td>
<td>1.059</td>
<td>0.294</td>
</tr>
<tr>
<td>Ventral putamen</td>
<td>2.841 0.506</td>
<td>3.018 0.288</td>
<td>2.867 0.242</td>
<td>3.086 0.431</td>
<td>1.194</td>
<td>0.237</td>
<td>0.230</td>
<td>0.819</td>
<td>1.698</td>
<td>0.095</td>
</tr>
<tr>
<td>Middle caudate</td>
<td>2.516 0.293</td>
<td>2.617 0.342</td>
<td>2.450 0.224</td>
<td>2.658 0.391</td>
<td>0.668</td>
<td>0.506</td>
<td>-0.576</td>
<td>0.567</td>
<td>1.154</td>
<td>0.253</td>
</tr>
</tbody>
</table>

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

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**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.

**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 $[^{11}\text{C}]\text{McN5652 BP}_{\text{ND}}$ and HA in any of the ROIs; however, linear regression analysis revealed that the interaction between $[^{11}\text{C}]\text{McN5652 BP}_{\text{ND}}$ and $[^{11}\text{C}]\text{raclopride BP}_{\text{ND}}$ 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 $[^{11}\text{C}]\text{raclopride BP}_{\text{ND}}$ and HA, $[^{11}\text{C}]\text{McN5652 BP}_{\text{ND}}$ 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 $[^{11}\text{C}]\text{McN5652 BP}_{\text{ND}}$ and $[^{11}\text{C}]\text{raclopride BP}_{\text{ND}}$ in the dorsal putamen, with and without their interaction. When the interaction term was not included, neither BP$_{\text{ND}}$ were significantly predictive of HA ($b_{\text{McN}} = 11.902, \text{se} = 10.200, p = 0.252; b_{\text{rac}} = 4.755, \text{se} = 4.878, p = 0.337$). However, when the interaction term was included, both the interaction and the $[^{11}\text{C}]\text{McN5652 BP}_{\text{ND}}$ term were statistically significant ($b_{\text{McN}} = -219.92, \text{se} = 107.38, p = 0.0488; b_{\text{rac}} = -42.73, \text{se} = 22.39, p = 0.0653; b_{\text{interaction}} = 73.72, \text{se} = 34.01, p = 0.0377$). No significant correlations were found between HA and $[^{11}\text{C}]\text{McN5652 BP}_{\text{ND}}$ or $[^{11}\text{C}]\text{raclopride BP}_{\text{ND}}$ in CW. Other behaviors, body mass index, or length of recovery were not related to either $[^{11}\text{C}]\text{McN5652 BP}_{\text{ND}}$ or $[^{11}\text{C}]\text{raclopride BP}_{\text{ND}}$ or HA, NS, RD, or P.

Fig. 3. REC ED showed positive correlations between $[^{11}\text{C}]\text{raclopride BP}_{\text{ND}}$ 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 $[^{11}\text{C}]\text{McN5652 BP}_{\text{ND}}$ (y-axis) versus harm avoidance (x-axis), with each individual coded with a symbol based on a median split of $[^{11}\text{C}]\text{raclopride BP}_{\text{ND}}$. A: In the dorsal putamen, women with $[^{11}\text{C}]\text{raclopride BP}_{\text{ND}}$ values below the median show a negative relationship between $[^{11}\text{C}]\text{McN5652 BP}_{\text{ND}}$ and harm avoidance, while those with $[^{11}\text{C}]\text{raclopride BP}_{\text{ND}}$ values above the median show a positive relationship between $[^{11}\text{C}]\text{McN5652 BP}_{\text{ND}}$ and harm avoidance. B: In the dorsal caudate, women with $[^{11}\text{C}]\text{raclopride BP}_{\text{ND}}$ values below the median show a slight positive relationship between $[^{11}\text{C}]\text{McN5652 BP}_{\text{ND}}$ and harm avoidance, while those with $[^{11}\text{C}]\text{raclopride BP}_{\text{ND}}$ values above the median show a negative relationship between $[^{11}\text{C}]\text{McN5652 BP}_{\text{ND}}$ 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 Linnola, 1997; Leibowitz and Shar-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\(_{V}\) in REC AN (Bailer et al., 2005), lateral and medial orbital frontal as well as parietal 5-HT\(_{1A}\) BP\(_{V}\) in REC BN (Bailer et al., 2011), subgenual cingulate and temporal 5-HT\(_{2A}\) BP\(_{V}\) in REC AN–BN (Bailer et al., 2004), subgenual cingulate, lateral and medial orbital frontal and parietal 5-HT\(_{2A}\) BP\(_{V}\) 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\(_{2C}\) antagonist SB 206553 increases basal DA release in the nucleus accumbens and striatum and increases basal firing rate of DA neurons in the VTA (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., 1999; 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-HTT 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 Drewets 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 be able, making it too small and underpowered to draw conclusions regarding the nature of their relationship (see Boureau and Dayan, 2011, for review). Finally, DA, and 5-HTT 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.

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References


Anderluh, M.B., Tchanturia, K., Rabe-Hesketh, S., Treasure, J., 2003. Childhood is possible that \([^{11}C]\)raclopride BPND and \([^{11}C]\)McN5652 BPND subgroup differences will need to be completed in the future. 9 REC BN). Therefore, studies with large enough samples to detect differences 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 \([^{11}C]\)MC200008 BPND and \([^{11}C]\)raclopride BPND may serve as useful “markers” of 5-HT and DA neural activity. In this regard, it is possible that \([^{11}C]\)raclopride BPND and \([^{11}C]\)MC200008 BPND interactions or \([^{11}C]\)raclopride BPND and HA relationships reflect a balance between 5-HTT 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-HTT 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).


