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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

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Abstract

Objective—Because altered serotonin (5-HT) function appears to persist after recovery from bulimia nervosa (RBN), we investigated the 5-HT$_{1A}$ receptor, which could contribute to regulation of appetite, mood, impulse control, or the response to antidepressants.

Method—Thirteen RBN individuals were compared to 21 healthy control women (CW) using positron emission tomography and [carbonyl-^{11}C]WAY100635 ([^{11}C]WAY).

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Results—RBN had a 23–34% elevation of [^{11}C]WAY binding potential $(BP)_P$ in subgenual cingulate, mesial temporal, and parietal regions after adjustments for multiple comparisons. For CW, [^{11}C]WAY BP_P was related negatively to novelty seeking, whereas for RBN, [^{11}C]WAY BP_P was related positively to harm avoidance and negatively related to sensation seeking.

Discussion—Alterations of 5-HT_{1A} receptor function may provide new insight into efficacy of 5-HT medication in BN, as well as symptoms such as the ability to inhibit or self-control the expression of behaviors related to stimulus seeking, aggression, and impulsivity.

Keywords

bulimia nervosa; 5-HT_{1A} receptor; positron emission tomography; behavioral inhibition; subgenual cingulate; mesial temporal cortex

Introduction

Bulimia nervosa (BN) is a disorder of unknown etiology that tends to occur in adolescent and young adult women.[1] Individuals with this illness suffer from cycles of binge eating, usually followed by self-induced vomiting or other purging behaviors, as well as disturbances of mood and impulse control.

Considerable physiologic and pharmacologic data show that disturbances of serotonin (5-HT) function occur in individuals with eating disorders.[2,3] The 5-HT_{1A} receptor is of interest in eating disorders because it has been implicated in the modulation[4,5] of mood, impulse control, and appetite as well as the response to antidepressant medication.[6] Positron emission tomography (PET) and the ligand [carbonyl-^{11}C]WAY100635 ([^{11}C]WAY) can be used to investigate the binding potential (BP) of this receptor. The 5-HT_{1A} autoreceptor is located presynaptically on 5-HT somatodendritic cell bodies in the raphe nuclei, where it functions to decrease 5-HT neurotransmission.[4] High densities of postsynaptic 5-HT_{1A} exist in the hippocampus, septum, amygdala, and entorhinal and frontal cortices, where they serve to mediate the effects of released 5-HT.

Despite differences in BP measurements [for a definition of BPs see consensus nomenclature for in vivo imaging for reversibly binding radioligands[7]] and radioligands used, studies have tended to show elevated binding of the 5-HT_{1A} receptor[2,3] in individuals with eating disorders, and some relationship between 5-HT_{1A} receptor binding and measures of harm avoidance (HA). Specifically, individuals ill with BN had elevated [^{11}C]WAY BP_P,[8] previous studies from our group found[9] that women ill with anorexia nervosa (AN) had a highly significant (30–70%) increase in [^{11}C]WAY BP_P, whether they were restrictive or bulimic-type AN. Finally, our group[10] found that women recovered from bulimic-type AN had a persistent 22% to 43% increase in [^{11}C]WAY BP_P. While women recovered from restrictive-type AN had normal [^{11}C]WAY BP_P,[10] [^{11}C]WAY BP_P values were markedly elevated in some participants and were most recently found to be significantly increased in lean and recovered restricting-type AN individuals (using the radioligand [^{18}F]MPPF and BP_{ND})[11]

This is the first study to investigate 5-HT_{1A} receptor binding in recovered BN (RBN) individuals who have never had AN. It is not known whether extremes of dietary intake, or other factors related to the ill state, are a cause or consequence of abnormal 5-HT function. To avoid these possible confounding effects, we studied RBN, and compared them to age- and weight-matched control women (CW). More than 50% of individuals who have BN recover (i.e., their binge and purge symptoms disappear). Nonetheless, these individuals often continue to have persistent dysphoric mood, obsessional thoughts, and body image concerns that are modest compared to the ill state.[12] Such behavioral symptoms are present in childhood, before the onset of BN. Thus, they may reflect traits that contribute to a vulnerability to develop BN. It should be emphasized that other 5-HT system abnormalities in recovered BN are profound, including approximately a 50% elevation of cerebrospinal fluid hydroxyindoleacetic acid (CSF 5-HIAA) (the major metabolite of brain 5-HT),[13] reduced 5-HT_{2A} receptor binding in frontal regions,[14] altered mood response to 5-HT agents,[13,15] and evidence of reduced 5-HT transporter function in RBN[16] and ILL BN.[17] Together, these findings support the hypothesis that a substantial dysregulation of serotonergic neuronal circuits occurs in BN.

Method

Participants

We studied 13 RBN and 21 healthy CW recruited through local advertisements. None of the BN subjects had a history of AN. To be considered “recovered,” individuals had to have met the following criteria for the previous year: (1) maintain a weight above 90% of average body weight; (2) have regular menstrual cycles; (3) have not binged, purged, restricted food intake or exercised excessively; (4) not used psychoactive medications such as antidepressants; (5) no current alcohol or drug abuse/dependence. CW had no history of any psychiatric, serious medical or neurological illness. This study was conducted according to local institutional review board regulations and all subjects gave written informed consent. The PET imaging was performed during the first 10 days of the follicular phase of the menstrual cycle for all participants as the potential effect of different phases of the menstrual cycle on 5-HT_{1A} binding in some regions, e.g. the dorsal raphe, cannot be fully excluded.[18] Methods are described in detail elsewhere.[10] Mean BP_P values for 21 CW were previously reported.[9,10] Data on the 13 RBN participants have not been reported previously.

Behavioral Assessments

All participants underwent a face-to-face interview with a psychiatrist using the Structured Clinical Interview for DSM-IV Axis I Disorders[19] to assess lifetime prevalence of Axis I psychiatric disorders. Current psychopathology and personality traits (Table 1) were assessed with a battery of standardized instruments designed to characterize temperament (Temperament and Character Inventory, TCI),[20] mood (Beck Depression Inventory, BDI),[21] anxiety (Spielberger State-Trait Anxiety Inventory, STAI),[22] and impulse self-control (Barratt Impulsiveness Scale, BIS).[23] The Novelty Seeking, Harm Avoidance, and Self-Transcendence scales were used from the TCI. The value for one RBN who had a BIS self-control score over two standard deviations (SDs) below the mean was removed from the correlations.

Image Acquisition

Magnetic resonance (MR) imaging and PET imaging were performed as previously described for arterial-based dynamic imaging of [^{11}C]WAY binding to 5-HT$_{1A}$ receptors.[24] [^{11}C]WAY was synthesized according to established methods.[25] A slow bolus intravenous injection of 13.9 ± 1.9 mCi (range: 9.2–15.9; RBN: 14.2 + 1.7; CW: 13.7 + 2.9; $p = 0.5$) high-specific activity [^{11}C]WAY was administered and dynamic three-dimensional emission scanning with arterial blood sampling (34 sample input function) was performed over 60 min (a longer 90 min acquisition was collected in 9 of 13 RBN and 14 of 21 CW participants). Studies done earlier used 60 min acquisition. Later studies used 90 min acquisition to verify stability in the BP_P measures in areas such as the raphe.[26] A metabolite corrected input function was determined, as previously described.[24] The temporal stability of the outcome measures was examined in the subset of participants for which a full 90 min emission data set was available. High correlations were observed between the 60-and 90-min datasets for both the Logan cerebellar distribution volume (V_{ND}) and regional Logan BP_P measures, respectively (CW: $r = .95–.99$; RBN: $r = .96–.99$). The bias across regions of interest (ROIs) between the two measures was similar for CW (9.4% ± 4.1%) and RBN participants (8.4% ± 4.2%; $p = .71$). This observation supports the validity of the results for the 60 min interval.

PET Data Processing

The ROIs were hand-drawn on the coregistered MR images and applied to the dynamic PET data to generate time-activity curves. ROIs have been described previously.[10,24] Briefly, ROIs included the cerebellum (left and right hemispheres) as a reference region, and prefrontal, lateral orbital frontal, medial orbital frontal, parietal, mesial temporal, subgenual cingulate cortical regions, and the dorsal raphe nucleus. Because the raphe nuclei cannot be delineated on MR, this ROI was directly identified on the PET image[27] using circular fixed 6 mm radius ROIs (for all participants) placed over the area of highest radioactivity. The inferior border of the dorsal raphe nucleus was identified by the interpeduncular cistern. To reduce noise, right and left regions were combined.[25]

We denote here the outcome variables using the recently issued consensus nomenclature for in vivo imaging for reversibly binding radioligands.[7] For the arterial-based kinetic analyses, regional [^{11}C]WAY distribution volume (V_T) was determined using both the Logan graphical method[28] and three-compartment model (2-tissue compartments)[26] that included a vascular volume term. A modified Logan analysis that applied generalized linear least squares smoothing to the data prior to analysis[29] was used as this method effectively reduced noise-induced bias in the Logan V_T as previously described for other PET radiotracers.[28] The Logan analysis was performed using integrated PET data intervals that were each determined over $0 – T_i$ min after injection, where T_i ranged from 25 to 60 or 90 min, with 7 or 10 data points used for the analyses of the 60 and 90 min data sets, respectively. Our main outcome measure for this study was BP. The BP measure was determined as: $BP_P = V_T – V_{ND}$.[26] This BP_P is dependent on plasma protein binding (f_P) rather than tissue-free fraction (f_{ND}).[26] As a result, plasma protein binding was measured in all participants to determine the extent to which a group difference in [^{11}C]WAY BP_P could

be influenced by this factor. For comparison purposes, we also determined BP_{ND} as: $BP_{ND} = V_T/V_{ND} - 1$.

It is acknowledged that [^{11}C]WAY is a radiotracer with low nondisplaceable tissue uptake and quantification of the cerebellar V_{ND} can be problematic. Complicating factors include technical issues related to PET imaging (i.e., scatter, spillover from occipital radioactivity), low levels of receptor binding in vermis, and variable sensitivity at the ends of the 3D PET field-of-view.[26,30–32] In this work, and in our previous [^{11}C]WAY studies, we carefully sought to minimize such factors through various means that included implementation of an improved scatter correction algorithm, standard subject positioning with the cerebellum within the central 7 cm of the field-of-view and cerebellar ROI placement that does not include vermis and ensures minimal contamination from occipital uptake. Parsey et al.[33] utilized cerebellar white matter to approximate the [^{11}C]WAY reference region kinetics. We also examined the use of cerebellar white matter as reference for [^{11}C]WAY and other PET neuroreceptor binding radiotracers (data not shown). The cerebellar white matter was not used because it did not appear to exhibit in vivo kinetics consistent with nondisplaceable uptake in receptor-rich areas.

Statistical Analysis

Standard statistical software packages (SAS Version 8.2, StatExact 4.0, and SPSS 14.0) were used for all analyses except the multivariate profile analysis described later. Comparisons between RBN and CW were made using Wilcoxon rank-sum tests. Exact *p*-values were computed due to the small sample sizes. Standard regression diagnostics were used to assess the sensitivity of the model to outlying and highly influential observations in the data set. Pearson correlation coefficients were also computed and exact significance levels based on Monte Carlo methods are reported. All values are expressed as mean ± SD. We applied a Sidak correction to control for Type I errors in the analysis of group differences in ROIs for BP_P and BP_{ND} (Table 2). This type of correction is more appropriate than other methods (e.g., Bonferroni) when the multiple tests performed are not independent.[34] Otherwise, we assumed a p value of $p < .05$ for declaring significance.

Multivariate distance matrix regression (MDMR)[35] was used to examine the extent to which similarity in 5-HT_{1A} receptor binding *profiles* was related to several predictor variables of interest. MDMR is an analytic method, which involves the construction of a dissimilarity or distance matrix that, in this case, reflects the correlation of study participants' profiles with respect to BP values over all of the brain regions sampled. Predictor variables, including age, BMI, and measures of behavior were then tested for association with variation in the BP_P distance matrix using the statistical program DISTLM *forward*.[36] Independent variables were tested both individually and in a forward stepwise manner, with *p*-values computed via permutation analysis. The independent variables selected are based on the highest cumulative proportion of variance in BP_P distance, explained by the inclusion of an additional variable in the regression model.

Finally, a repeated-measures ANOVA was used to explore potential group differences in radiolabeled metabolites of [^{11}C]WAY. Because sphericity tests failed, *p*-values for the within-subject effects (time and the interaction of time X group) were adjusted using the

conservative Lower Bound estimator. For the [^{11}C]WAY metabolites, only 9 of the 13 RBN and 14 of the 21 CW participants had 90-min data, therefore, the model was run both with and without the 90-min measurement.

Results

Demographic and Clinical Variables

RBN and CW participants were similar in age, body mass index (BMI, kg/m^2), plasma estradiol, and β-hydroxy-butyrate (BHBA) values. RBN women had elevated trait anxiety (STAI), depression (BDI), and Harm Avoidance (TCI) compared to CW (Table 1).

Group Comparison of [^{11}C]WAY BP_P

Using a Logan analysis (Table 2 and Fig. 1) the RBN women showed significant elevations of post-synaptic receptor BP_P, and a trend for increased autoreceptor BP_P compared to CW. After a conservative adjustment for multiple comparisons, findings persisted for the subgenual cingulate, mesial temporal, and parietal regions. Group differences for the compartmental analysis were similar, but less robust (Table 2). The Logan cerebellar V_{ND} values were higher in the RBN compared to the CW (0.85 ± 0.17 vs. 0.72 ± 0.13; $p = .03$). This difference was similar for the cerebellar V_{ND} from compartmental modeling (0.85 ± 0.19 vs. 0.53 ± 0.11; $p < .001$). There was no difference in regional [^{11}C]WAY BP_P values for RBN participants with a diagnosis of major depression ($n = 8$) or obsessive-compulsive disorder ($n = 5$).

Group Comparison of [^{11}C]WAY BP_{ND}

Similar to BP_P, the RBN women (Table 2) showed significant elevations of [^{11}C]WAY BP_{ND} in the mesial temporal cortex and a trend for increased [^{11}C]WAY BP_{ND} in prefrontal and parietal regions compared to CW (Logan analysis). However, after a conservative adjustment for multiple comparisons, findings did not persist. Group differences for the compartmental analysis were similar, but less robust (Table 2).

Relationship of [^{11}C]WAY BP_P to Behavior

RBN participants showed significant positive relationships between Logan regional [^{11}C]WAY BP_P and HA for the lateral orbital frontal ($r = .76$, $p = .002$), orbital frontal ($r = .57$, $p = .04$), parietal ($r = .68$, $p = .01$), and trends for the prefrontal regions ($r = .53$, $p = .06$). In addition, the BIS sensation seeking scale[23] was negatively related to [^{11}C]WAY BP_P for the lateral orbital frontal ($r = -.67$, $p = .02$), prefrontal ($r = -.61$, $p = .02$), mesial temporal ($r = -.63$, $p = .02$) and parietal ($r = -.58$, $p = .02$) BP_P, with trends for the orbital frontal BP_P ($r = -.51$, $p = .07$). In comparison, for CW, Logan regional [^{11}C]WAY BP_P was significantly negatively related to novelty seeking[20] for all ROIs surveyed (Fig. 2). These findings were the most robust for the pre-frontal cortex ($r = -.73$, $p = .0003$), orbital frontal cortex ($r = -.61$, $p = .005$), and parietal cortex ($r = -.65$, $p = .002$), but also were significant for the lateral orbital frontal cortex ($r = -.55$, $p = .01$), subgenual cortex ($r = -.49$, $p = .03$), mesial temporal cortex ($r = -.52$, $p = .02$), and dorsal raphe ($r = -.55$, $p = .03$). No relationship was found between regional [^{11}C]WAY BP_P or other clinical variables in Table 1 for either CW or RBN.

MDMR analysis (Table 3) revealed that for the RBN group, HA was a significant predictor (p = .030) of similarity for Logan regional [^{11}C]WAY BP_P profiles across all of the brain regions sampled. Furthermore, HA accounted for 29.5% of the variance in BP profile similarity for this group. For the CW, novelty seeking was a significant predictor (p = .005) of similarity in [^{11}C]WAY BP_P profiles and accounted for 28.6% of the variance in profile similarity for this group.

Plasma Data

The repeated-measures analysis of radiolabeled metabolites of [^{11}C]WAY showed significantly higher values in RBN relative to CW at time points 1 min (0.94 ± 0.02 vs. 0.92 + 0.04; p = .021), 2.25 min (0.65 ± 0.14 vs. 0.54 ± 0.13; p = .021), and 5 min (0.17 ± 0.05 vs. 0.14 ± 0.03; p = .011), but similar values were found at time points 10, 30, 45, and 60 min. Both the group (F [1, 32] = 5.88, p = .021) and the group × time interaction (F [1, 32] = 5.58, p = .024) effects were significant in this model. When the data were analyzed for the subset of 9 RBN and 14 CW for whom there were 90-min data available, trends in the data remained similar, but the group (F [1, 21] = 2.80, p = .109) and the group × time interaction (F [1, 21] = 2.24, p = .149) effects no longer reached significance, which is likely due to decreased statistical power. Significant differences in plasma free fraction (f_P) were found between RBN (f_P = 0.14 ± 0.05, n = 10) and CW (f_P = 0.09 ± 0.03, n = 17) (p = .008) in which these data were available.

Discussion

RBN individuals showed a significant 23–34% elevation of pre- and post-synaptic receptor [^{11}C]WAY BP_P compared to CW for subgenual cingulate, mesial temporal, and parietal cortices. Regional binding values for the RBN participants were also higher than in CW using the BP_{ND} measure (although not statistically significant). For CW, [^{11}C]WAY BP_P was related negatively to novelty seeking, whereas for RBN, [^{11}C]WAY BP_P was related positively to HA and negatively to sensation seeking. Moreover, novelty seeking and HA accounted for approximately 30% of the variance for [^{11}C]WAY BP_P in CW and RBN, respectively.

This is the first study to show that increased [^{11}C]WAY BP_P also occurs in women recovered from BN with no history of AN. These results supplement previous evidence showing that elevated binding of the 5-HT_{1A} receptor occurs in individuals with eating disorders. Several interpretations are possible, which will require further testing to confirm. First, in recovered state, increased binding of the 5-HT_{1A} receptor may be associated specifically with RBN, whether or not they have had a history of AN. RBN have been shown to have elevated cerebrospinal fluid concentrations of hydroxyindoleacetic acid (CSF 5-HIAA)[13] and evidence of reduced 5-HT transporter function,[16] consistent with increased extracellular 5-HT concentrations. Theoretically, increased postsynaptic 5-HT_{1A} receptor activity could be compensatory means of counteracting increased extracellular 5-HT.[37,38] Second, elevated 5-HT_{1A} receptor binding may be further exaggerated in the ill state of both AN and BN individuals, suggesting a possible trait phenomenon that is exacerbated by nutritional abnormalities.

These data may provide insight into pharmaceutical treatments for BN. Although numerous controlled trials have shown some efficacy for a variety of antidepressant medications in BN, relatively few individuals achieve abstinence on medication, as most continue to binge and purge. For example, a large-scale controlled trial of fluoxetine, which showed that a relatively high dose of 60 mg/day was superior to 20 mg/day for BN,[39] had a 1-year remission rate of only 17.7%. Many participants remained symptomatic on medication and there was a worsening on all measures of efficacy over time. This result is consistent with other clinical observations[40] that suggest limited improvement and considerable relapse with long-term antidepressant treatment in BN. An important mechanism thought to contribute to the action of SSRIs is the desensitization of the somatodendritic 5-HT_{1A} autoreceptor on the raphe neurons.[6] Highly elevated 5-HT_{1A} receptor activity in BN raises the question of whether BN individuals have difficulty in achieving SSRI-induced 5-HT_{1A} autoreceptor desensitization. Such a difficulty could explain the need for higher doses of fluoxetine as well as partial response to drugs. Perhaps higher doses of SSRIs or the addition of 5-HT_{1A} specific agents may prove useful in BN.

The RBN individuals continued to have mild to moderate levels of depressive and anxiety symptoms. However, while individuals with eating disorders tend to have elevated [^{11}C]WAY BP_P, reduced binding of 5-HT_{1A} receptor ligands has been found in most [for review see Refs. 41 and 42], but not all studies of major depression (BP_F).[43] In addition, reduced binding of 5-HT_{1A} receptor ligands has been found in social phobia (BP_{ND})[44] and panic disorder ([^{18}F]FCWAY V_T and BP_{ND}[45] and [^{11}C]WAY BP_{ND}[46]). Thus, it can be argued that these disorders may differ in etiology.

For CW, [^{11}C]WAY BP_P was diminished in those who were high in novelty seeking. For RBN, [^{11}C]WAY BP_P increased in relationship to HA and diminished in those who were sensation seeking. Moreover, novelty seeking and HA accounted for approximately 30% of the variance for the [^{11}C]WAY BP_P in CW and RBN, respectively. The instruments used to assess behavior in humans tend to assess complex phenomena that are likely to be a composite of many traits, therefore confounding the understanding of how behaviors might be associated with a 5-HT receptor. For example, HA measures anxiety and behavioral inhibition, whereas novelty seeking measures exploration and impulsivity.[20] Similarly, assessment of behavior in animals is complex. Thus, while considerable studies in animals associate 5-HT_{1A} receptor function with anxiety, most tests of anxiety in rodents are based in part on the approach/avoidance conflict between the innate tendency of an animal to explore a novel place and the tendency to avoid novel stimuli or environments.[5]

Studies of male and female healthy controls using PET and [^{11}C]WAY BP have found negative relationships in frontal, temporal, and cingulate regions with self-transcendence (BP_{ND}),[47] and negative (BP_F)[48] as well as positive (BP_{ND})[49] correlations with aggression. In individuals with major depression, [^{11}C]WAY BP_F was correlated negatively with somatic anxiety and positively with psychic anxiety in cingulate and frontal regions.[50] The BP_{ND} measure in 5-HT_{1A} receptor binding studies has been associated negatively with the neuroticism facet of anxiety on the NEO[17] in healthy controls. Similar to RBN, [^{11}C]WAY BP_P was associated with HA in recovered restrictive-type AN.[10]

There is an extensive literature associating the serotonergic system and 5-HT_{1A} receptor activity with fundamental aspects of behavioral inhibition.[51] 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.[52] Activation of brainstem 5-HT_{1A} receptors inhibits stress-induced sympathetic activity and fight-or-flight behavioral responses.[53] 5-HT_{1A} receptors modulate impulse control through effects on catecholamine systems[54] and blunted 5-HT_{1A} receptor number or function is associated with increased aggression.[55] Taken together, these data raise the possibility that 5-HT_{1A} receptor may contribute to the emergent ability to inhibit or self-control the expression of a number of behaviors related to stimulus seeking, anxiety, aggression and impulsivity. Within the context of eating behavior, it is important to note that both AN and BN tend to restrict their eating and lose normal meal patterns[56] and show high harm avoidance, a measure of anxiety and inhibition. However, AN can maintain this inhibition continuously, whereas BN have periodic disinhibition and loss of self-control. 5-HT_{1A} functional activity reflects one part of a complex system of 14 or more receptors and many other components that modulate metabolism, firing rate, neuronal cascades, etc. For example, we find recovered restrictive-type and bulimic-type AN have differences in 5-HTT function[57] which might explain why these subtypes have differences in impulse control or inhibition. Thus, an understanding of the complexities of 5-HT function will likely be needed to truly understand the relationship of this system to behavior.

Limitation

The interpretation of the findings in this study is complicated because of observed group differences in nonspecific factors (e.g., cerebellar V_{ND} and plasma protein binding, $1/f_P$). The receptor binding measures reflect both the concentration of available receptors (B_{avail}) and the dissociation constant (K_D), as well as nonspecific factors (i.e., $BP_P = V_T - V_{ND} = f_P B_{avail}/K_D$ and $BP_{ND} = V_T/V_{ND} - 1 = f_{ND} B_{avail}/K_D$). Therefore, we performed a secondary examination of the data to facilitate interpretation of the BP differences.

First, the cerebellar V_{ND} measure was greater for RBN participants than controls whether determined using a Logan analysis or two-tissue compartment model (i.e., $V_{ND} = K_1/k_2 \times (1 + k_3/k_4)$). The greater RBN cerebellar V_{ND} resulted more from the ($K_1/k_2 \times k_3/k_4$) term than the K_1/k_2 term that were respectively, 0.42 and 0.44, as compared to the values for control participants of 0.15 and 0.38, respectively. The greater difference observed for the compartmental V_{ND}—relative to the Logan V_{ND}—may result, in part, from variability in the kinetic parameter estimates determined in an area of low radioactivity concentration. Despite the greater RBN V_{ND} measures, significantly greater 5-HT_{1A} receptor binding was observed in multiple brain areas whether BP was determined through V_{ND} subtraction or ratio (using Logan or compartmental analysis) and the greater RBN V_{ND} measures would serve to minimize increases in either BP_P or BP_{ND} for the RBN group.

Second, the average f_P value for CW (i.e., 0.09) was consistent with [^{11}C]WAY f_P values recently reported for controls,[58,59] while the average f_P value for RBN participants (i.e., 0.14) was about 56% greater (with inversely lower protein binding of 36%) relative to CW. This f_P difference was statistically significant despite large measurement variation (~ 35%)

for both groups. The regional V_T values (Logan or compartmental analysis) for RBN participants were also significantly greater than those for CW across all regions, with the exception of the dorsal raphe. This observation could be consistent with greater radiotracer availability as a result of lower plasma protein binding in the RBN participants, but the magnitude of the V_T increases (relative to CW) varied across regions (21–32%) rather than being on the order of 56% (i.e., the group difference in f_P).

Correction of the BP_P measure for f_P yields $BP_F = B_{avail}/K_D$. A group comparison of the BP_F measures yielded a reversal of the BP_P difference, reflecting BP_F values of CW greater than those of RBN (data not shown). This difference was not statistically significant when an individual f_P correction was performed on a subject-by-subject basis, but was significant when the group f_P average values were applied. Confidence in the correction was dampened by the level of variation in f_P and the fact that f_P values were not available for all participants. Potential associations between the f_P values and use of birth control pills among participants and estradiol or BHBA levels were also examined but these results were unremarkable. Significantly lower f_P has most recently been found in remitted depressed participants compared to controls,[43] as well as nonsignificantly lower f_P among currently depressed participants compared to controls,[59] although the origin of these differences remain unclear. Paradoxical group differences for BP_P and BP_{ND} relative to those for BP_F have been noted in other [^{11}C]WAY PET investigations of neuropsychiatric disorders,[43] particularly when BP_F was determined based on the use of cerebellar white matter to approximate nondisplaceable radiotracer uptake. In this work, the cerebellar reference uptake was determined in predominantly gray matter areas (low white matter contribution) using methods that were carefully defined to minimize well-known sources of error (see Methods section).

In conclusion, the BP_P binding measure showed evidence of significantly greater 5-HT_{1A} receptor binding in subgenual cingulate, mesial temporal and parietal cortices of participants recovered from bulimia nervosa, relative to healthy controls. This work also indicated group differences in nonspecific factors that raised concern about the direction of this group difference in 5-HT_{1A} receptor binding. The BP_P measure is determined using standard methods with minimal “nonspecific” corrections. This work further highlights the importance of careful measurement and evaluation of non-specific factors in neuroreceptor binding studies including the need to verify potential plasma protein binding differences between eating disorder groups, and to address the potential nature of such f_P differences in RBN.

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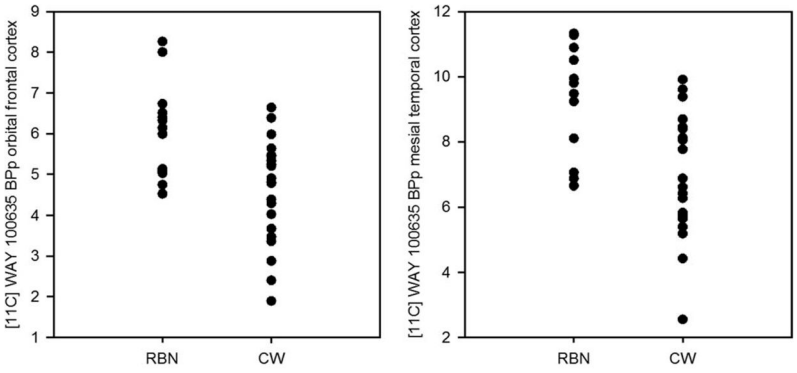

FIGURE 1.

Representational scatter plots for logan [^{11}C] WAY 100635 BP_P in the medial orbital frontal cortex (left graph) and mesial temporal cortex (right graph) in RBN and CW.

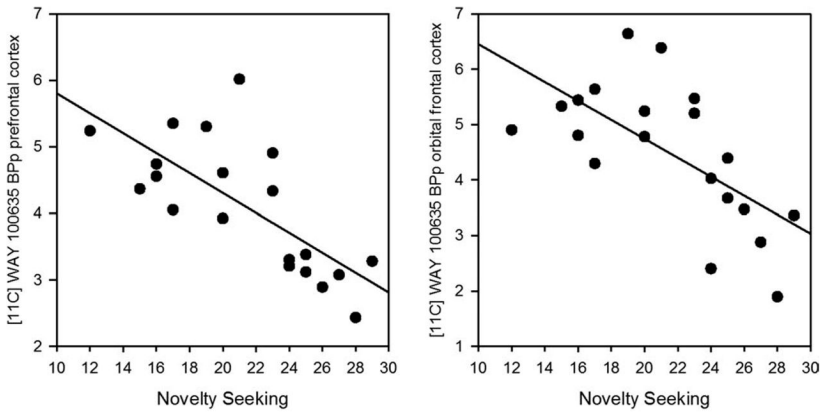

FIGURE 2.

Correlation between Novelty Seeking (NS) and logan [^{11}C] WAY 100635 BP_P for prefrontal cortex ($r = -.73$, $p = .0003$, $n = 20$*) and orbital frontal cortex ($r = -.61$, $p = .005$, $n = 20$*) in CW; * indicates that one CW did not have NS value available.

TABLE 1

Group comparisons of demographic variables and representational assessment data

	CW (*N* = 21)		RBN (*N* = 13)		CW vs. RBN
	Mean	**SD**	**Mean**	**SD**	**Exact Sig.**
Age (years)	26.2	6.7	24.7	5.8	0.60
Current BMI (kg/m^2)	22.2	1.8	23.1	2.2	0.23
BN onset (years)	—	—	16.5	3.4	—
Duration of recovery (months)	—	—	24.2	17.8	—
Estradiol (μmol/l)	53.9	57.8	72.7	88.4	0.92
Beta-hydroxy-butyrate (BHBA) (mmol/l)	0.07	0.04	0.08	0.02	0.37
Depression (BDI)	1.1	1.4	6.2	7.3	0.0002
Trait anxiety (STAI)	26.9	4.8	44.4	10.1	<0.0001
Novelty seeking (TCI)	21.4[a]	4.8	22.7	7.4	0.39
Harm avoidance (TCI)	10.0	3.3	16.2	6.4	0.0008
Self-transcendence (TCI)	13.5	5.1	17.1	6.5	0.14
Self-control (BIS)	85.5	18.5	102.7	22.2	0.02

Notes: BN, bulimia nervosa; CW, healthy control women; BDI, Beck Depression Inventory; STAI, Spielberger State-Trait Anxiety Inventory; TCI, Temperament and Character Inventory; BIS, Barratt Impulsiveness Scale.

[a]Indicates that one CW did not have a Novelty Seeking value available.

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TABLE 2

Differences between groups using Logan graphical method and compartmental modeling for BP_P (A) and BP_{ND} (B)

	Logan [11C]WAY BP_P					Compartmental Modeling [11C]WAY BP_P				
Region of Interest	**CW (*N* = 21)**	**RBN (*N* = 13)**	**Exact. Sig**	**% Diff.**	**SIDAK[a] *p*-Value**	**CW (*N* = 20)[b]**	**RBN (*N* = 12)[b]**	**Exact. Sig**	**% Diff.**	**SIDAK[a] *p*-Value**
A										
Prefrontal cortex	4.16 (0.99)	5.14 (1.03)	0.018	24	.119	4.08 (0.97)	5.04 (1.11)	0.024	24	.156
Lat. orbital front.	3.83 (0.83)	4.72 (1.19)	0.030	23	.192	3.68 (0.80)	4.62 (1.34)	0.020	26	.132
Med. orbit. frontal	4.67 (1.25)	6.07 (1.17)	0.008	30	.055	4.53 (1.32)	5.87 (1.37)	0.032	30	.204
Subgenual cingulate	4.70 (1.22)	6.00 (1.16)	0.007	28	.048	4.61 (1.27)	5.82 (1.33)	0.017	26	.113
Mesial temporal cortex	7.05 (1.89)	9.42 (1.73)	0.001	34	.007	6.88 (2.04)	9.00 (2.02)	0.012	31	.081
Parietal cortex	3.91 (0.95)	5.09 (1.27)	0.007	30	.048	3.83 (0.94)	4.97 (1.37)	0.024	30	.156
Dorsal raphe	2.14 (0.56)	2.67 (0.81)	0.059	25	.347	2.12 (0.69)	2.63 (1.07)	0.157	24	.697
Cerebellar VND	0.72 (0.13)	0.85 (0.17)	0.030	18	n/a	0.53 (0.11)	0.85 (0.19)	<0.001	60	n/a
	Logan [11C]WAY BP_{ND}					**Compartmental Modeling [11C]WAY BP_{ND}**				
	CW (*N* = 21)	**RBN (*N* = 13)**	**Exact. Sig**	**% Diff.**	**SIDAKa *p*-Value**	**CW (*N* = 20)[b]**	**RBN (*N* = 12)[b]**	**Exact. Sig**	**% Diff.**	**SIDAKa *p*-Value**
B										
Prefrontal cortex	5.73 (0.76)	6.08 (0.59)	0.104	6	.536	7.65 (1.23)	8.28 (1.16)	0.182	8	.755
Lat. orbital front.	5.13 (0.74)	5.58 (0.89)	0.246	9	.861	6.69 (1.19)	7.55 (1.30)	0.116	13	.578
Med. orbit. frontal	6.27 (1.16)	7.23 (1.13)	0.050	15	.302	8.40 (1.82)	9.68 (1.68)	0.053	15	.317
Subgenual cingulate	6.47 (1.12)	7.19 (1.43)	0.181	11	.753	8.65 (1.91)	9.64 (1.93)	0.136	11	.640
Mesial temporal cortex	9.73 (1.97)	11.25 (1.92)	0.039	17	.243	12.81 (2.79)	14.82 (2.64)	0.053	16	.317
Parietal cortex	5.39 (0.78)	5.97 (0.74)	0.060	11	.352	7.17 (1.13)	8.13 (1.56)	0.070	13	.398
Dorsal raphe	2.97 (0.59)	3.10 (0.73)	0.863	4	.999	3.95 (0.94)	4.27 (1.69)	0.730	8	.999
Cerebellar VND	0.72 (0.13)	0.85 (0.17)	0.030	18	n/a	0.53 (0.11)	0.85 (0.19)	<0.001	60	n/a

[a] Sidak post-hoc correction for multiple testing was applied within the context of each method.

[b] Indicates deletion of a subject whose scan had a k_4 for CER <0.

TABLE 3

Results of MDMR analysis for women recovered from BN[a] and for control women[a]

Variable[b]	SS (Trace)[c]	Pseudo-F[c]	*p*[d]	PROP[e]	Cumulative[f]
BN					
Harm avoidance	24.8015	4.6085	.0300[g]	0.2953	0.2953
BMI	11.2340	2.3421	.1039	0.1337	0.4290
STAI trait anxiety	5.7743	1.2318	.2847	0.0687	0.4977
Sensation seeking	3.0812	0.6303	.5005	0.0367	0.5344
Novelty seeking	2.8643	0.5532	.5624	0.0341	0.5685
Self control	5.0555	0.9725	.3247	0.0602	0.6287
Self transcendence	2.3243	0.4026	.6643	0.0277	0.6564
Age	0.7060	0.1003	.9231	0.0084	0.6648
Control women					
Novelty seeking	39.9659	7.5909	.0050[g]	0.2855	0.2855
Sensation seeking	12.6512	2.6060	.0969	0.0904	0.3758
STAI trait anxiety	9.6369	2.1072	.1429	0.0688	0.4447
Harm avoidance	5.6214	1.2470	.2597	0.0402	0.4848
Age	3.2416	0.7059	.4775	0.2323	0.5080
Self-transcendence	3.0496	0.6485	.4905	0.0218	0.5298
Self-control	2.5960	0.5337	.5724	0.0185	0.5483
BMI	1.9940	0.3907	.7173	0.0142	0.5625

[a] Results should be interpreted as in multiple regression contexts whereby each variable in the model is effectively "accounted for" in the assessment of the others.

[b] Each variable assessed in relation to the similarity matrix.

[c] Test statistics relating each variable to variation in the similarity matrix.

[d] The *p*-value derived from permutation tests.

[e] The proportion of variation in the similarity matrix explained by a variable.

[f] The cumulative variation explained.

[g] Denotes $p < 0.05$.