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Altered 5-HT_{2A} Receptor Binding after Recovery from Bulimia-Type Anorexia Nervosa: Relationships to Harm Avoidance and Drive for Thinness

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Several lines of evidence suggest that a disturbance of serotonin neuronal pathways may contribute to the pathogenesis of anorexia nervosa (AN) and bulimia nervosa (BN). This study applied positron emission tomography (PET) to investigate the brain serotonin 2A (5-HT_{2A}) receptor, which could contribute to disturbances of appetite and behavior in AN and BN. To avoid the confounding effects of malnutrition, we studied 10 women recovered from bulimia-type AN (REC AN–BN, >1 year normal weight, regular menstrual cycles, no binging, or purging) compared with 16 healthy control women (CW) using PET imaging and a specific 5-HT_{2A} receptor antagonist, [^{18}F]altanserin. REC AN–BN women had significantly reduced [^{18}F]altanserin binding potential relative to CW in the left subgenual cingulate, the left parietal cortex, and the right occipital cortex. [^{18}F]altanserin binding potential was positively related to harm avoidance and negatively related to novelty seeking in cingulate and temporal regions only in REC AN–BN subjects. In addition, REC AN–BN had negative relationships between [^{18}F]altanserin binding potential and drive for thinness in several cortical regions. In conclusion, this study extends research suggesting that altered 5-HT neuronal system activity persists after recovery from bulimia-type AN, particularly in subgenual cingulate regions. Altered 5-HT neurotransmission after recovery also supports the possibility that this may be a trait-related disturbance that contributes to the pathophysiology of eating disorders. It is possible that subgenual cingulate findings are not specific for AN–BN, but may be related to the high incidence of lifetime major depressive disorder diagnosis in these subjects.
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INTRODUCTION

Anorexia nervosa (AN) and bulimia nervosa (BN) are disorders of unknown etiology, which invariably have their onset during adolescence in females. These disorders are characterized by the relentless pursuit of thinness, obsessive fears of being fat, and aberrant eating behaviors, such as restrictive eating, and episodes of purging and/or binge eating (American Psychiatric Association, 1994). The DSM-IV recognizes several subgroups of eating disorders which are thought to share a common vulnerability. For example, cross-over between subtypes is common (Herzog *et al*, 1996) and these subtypes are cross-transmitted in families (Kendler *et al*, 1995; Lilenfeld *et al*, 1998; Strober *et al*, 2000). Furthermore, these subtypes have similar cognitive and behavioral symptoms, such as anxiety, and obsessional, perfectionistic, and harm avoidant behaviors that occur premorbidly and persist after recovery (Bulik *et al*, 1997; Casper, 1990; Deep *et al*, 1995; Srinivasagam *et al*, 1995; Strober, 1980).

Large-scale family and twin studies suggest that heritable factors (Bulik *et al*, 1998; Klump *et al*, 2001) contribute to the susceptibility to develop an eating disorder. Several lines of evidence support the possibility that altered central nervous system serotonin (5-HT) activity contributes to the appetitive alterations found in AN (Blundell, 1984; Leibowitz and Shor-Posner, 1986). Moreover, disturbed 5-HT activity may play a role in anxious, obsessional behaviors and

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extremes of impulse control (Barr *et al*, 1992; Cloninger, 1987; Higley and Linnoila, 1997; Kaye, 1997; Lucki, 1998; Mann, 1999; Soubrie, 1986). Physiologic and pharmacologic studies show disturbances of 5-HT activity in people who are underweight with AN (Brewerton and Jimerson, 1996; Kaye *et al*, 1988, 2001a; Walsh and Devlin, 1998; Wolfe *et al*, 1997).

The nature of 5-HT disturbances in AN and BN has been poorly understood due to the inaccessibility of the central nervous system (CNS) in humans and the complexity of 5-HT neuronal activity. However, the development of new selective tracers for the 5-HT system has made *in vivo* study of 5-HT function possible with positron emission tomography (PET). This study used PET imaging with the radioligand [^{18}F]altanserin to assess CNS 5-HT$_{2A}$ receptor binding in humans. The 5-HT$_{2A}$ receptor is of interest in AN because it has been implicated in the modulation of feeding and mood, as well as SSRI response (Bonhomme and Esposito, 1998; De Vry and Schreiber, 2000; Simansky, 1996; Stockmeier, 1997). Previous studies, using other types of brain imaging technologies, have identified potential alterations in temporal, cingulate, and frontal regions in AN (Ellison and Fong, 1998; Gordon *et al*, 2001; Gordon *et al*, 1997). These regions are known to contain 5-HT$_{2A}$ postsynaptic receptors (Burnet *et al*, 1997; Saudou and Hen, 1994). These previous imaging studies guided our choices of brain regions to investigate in our recovered subjects.

This study investigated women who had recovered for one or more years from bulimia-type AN for several reasons. First, studies of women who have recovered from an eating disorder avoid the confounding effects of malnutrition on 5-HT activity. Second, some, but not all studies, showed that a disturbance of 5-HT activity persists after recovery from an eating disorder (Kaye *et al*, 1991; O'Dwyer *et al*, 1996; Ward *et al*, 1998). Finally, certain behaviors, such as anxiety, perfectionism, and obsessionality, have been found to occur premorbidly, and persist after recovery from AN (Bulik *et al*, 1997; Casper, 1990; Deep *et al*, 1995; Srinivasagam *et al*, 1995; Strober, 1980). Together these studies raise the possibility that altered 5-HT activity and these behavioral symptoms may be traits that contribute to a vulnerability to develop AN–BN and are not just secondary to malnutrition.

METHODS AND MATERIALS

In all, 10 women who had recovered from bulimia (binging–purging)-type anorexia nervosa (REC AN–BN) were recruited. Subjects were previously treated in the eating disorders treatment program at the Western Psychiatric Institute and Clinic (Pittsburgh, PA) or were recruited through advertisements. All subjects underwent four levels of screening: (1) a brief phone screening; (2) an intensive screening assessing psychiatric history, lifetime weight, and exercise and menstrual cycle history as well as eating pattern for the past 12 months; (3) a comprehensive assessment using structured and semistructured interviews; and (4) a face-to-face interview with a psychiatrist. To be considered 'recovered', subjects had to (1) maintain a weight above 85% average body weight (Metropolitan, 1959), (2) have regular menstrual cycles; and (3) have not binged, purged, or engaged in significant restrictive eating patterns for at least 1 year before the study. Restrictive eating pattern was defined as regularly occurring behaviors, such as restricting food intake, restricting high-caloric food, counting calories, and dieting. Additionally, subjects must not have used psychoactive medication such as antidepressants or met criteria for alcohol or drug abuse or dependence, major depressive disorder, or severe anxiety disorder within 3 months of the study. In total, 16 healthy control women (CW) were recruited through local advertisements. The CW had no history of an eating disorder or any psychiatric, medical, or neurological illness. They had no first-degree relative with an eating disorder. They had normal menstrual cycles and had been within normal weight range since menarche. CW were not on medication, including herbal supplements. Both REC AN–BN and CW were included if they were taking birth control pills. Data have previously been reported on 11 CW subjects (Frank *et al*, 2002).

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 for all subjects. The follicular phase was determined by history. Subjects were admitted to a research laboratory on the eating disorders unit of Western Psychiatric Institute and Clinic at 21:00 of the day before the PET study for adaptation to the laboratory and for psychological assessments. The PET study was done the next day. All subjects had the same standardized, monoamine controlled (low protein) breakfast on the morning of the study.

Blood was drawn for assessment of β-hydroxybutyrate (BHBA), a plasma ketone body that is relatively sensitive to reflecting the presence of starvation (Fichter *et al*, 1990), as well as for evaluation of gonadal hormone levels (estradiol, E2). The Structured Clinical Interview for DSM-IV Axis I Disorders (First *et al*, 1996) was used to assess the lifetime prevalence of Axis I psychiatric disorders, and the Structured Interview for Anorexia and Bulimia (Fichter *et al*, 1998) to assess lifetime diagnosis of an eating disorder. Current psychopathology was assessed with a battery of standardized instruments including the Beck Depression Inventory (Beck *et al*, 1961), the Spielberger-Trait Anxiety Inventory (Spielberger *et al*, 1970), the Frost Multidimensional Perfectionism Scale (Frost *et al*, 1990), the Eating Disorders Inventory (EDI-2; (Garner, 1991)), the Yale–Brown Obsessive Compulsive Scale (Y–BOCS) (Goodman *et al*, 1989a, b), the Yale–Brown–Cornell Eating Disorder Scale (YBC) (Mazure *et al*, 1994; Sunday *et al*, 1995), and the Temperament and Character Inventory (Cloninger *et al*, 1994) for assessment of harm avoidance, novelty seeking, and reward dependence.

All subjects underwent magnetic resonance (MR) imaging prior to the PET scan on a Signa 1.5 Tesla scanner (GE Medical Systems, Milwaukee, WI). A volumetric spoiled gradient recall (SPGR) sequence with parameters optimized for maximal contrast among gray matter, white matter, and CSF was acquired as previously described (Frank *et al*, 2002). The SPGR MR data were coregistered to the [^{18}F]altanserin data. The MR data were resliced to match the spatial orientation of the PET image data, based upon

previously published methods (Minoshima *et al*, 1992; Woods *et al*, 1993).

The 5-HT_{2A} receptor antagonist, [^{18}F]altanserin, was synthesized according to established methods (Lemaire *et al*, 1991; Price *et al*, 2001a, b). All subjects were scanned on a Siemens ECAT HR + PET scanner (CTI PET systems, Knoxville, TN) in two-dimensional (2D) imaging mode. The HR + acquires 63 continuous slices over a 152-mm axial field of view.

Subjects were positioned with the head oriented parallel to the canthomeatal line. A softened thermoplastic mold with generous holes for the eyes, nose, and ears was fitted closely around the head and attached to a headholder to minimize subject motion. A windowed transmission scan (10–15 min) was obtained for attenuation correction of the emission data using rotating 68Ge/68Ga rods. Prior to radiotracer injection, a 5-ml sample of arterial blood was collected and used to assess the level of [^{18}F]altanserin binding to plasma proteins, using previously published methods (f1, free fraction) (Price *et al*, 1993) .

Immediately following bolus intravenous injection of 10 mCi high-specific activity (> 1.04 Ci/μmol) [^{18}F]altanserin, dynamic emission scanning with arterial blood sampling (input function) was performed over 90 min. The arterial input function was determined from approximately 35 0.5-ml hand-drawn blood samples collected over the scanning interval (including 20 samples in the initial 2 min postinjection). Blood samples were centrifuged and the plasma radioactivity concentration measured (Cobra II, Packard Instruments, Cleveland, OH). Additionally, 3-ml blood samples were acquired at 2, 10, 30, 60, and 90 min after [^{18}F]altanserin injection and used to determine the fraction of unmetabolized [^{18}F]altanserin (of total plasma radioactivity concentration) using high-performance liquid chromatography (HPLC). Plasma data were corrected for the presence of radiolabeled metabolites of [^{18}F]altanserin using the HPLC data (Lopresti *et al*, 1998). The PET data were corrected for radioactive decay and scatter (Watson *et al*, 1995). Image reconstruction was performed using filtered back-projection (Hann filter); the final reconstructed image resolution was 6.5–7.0 mm.

The scans were visually inspected for head motion and a postprocessing correction was performed. Head motion was determined by overlaying an MR-based brain outline on each frame of the PET study. Motion was indicated when the signal clearly shifted, relative to the outline, in a manner that was not consistent with expected changes in radiotracer distribution over time; motion tended to occur at later times (> 20 min). To correct for head motion, premotion scan frames were summed, assuming no motion during the initial frames (< 1 min) as signal to noise can be poor. A reference frame was then chosen (a later premotion frame) that primarily reflected the distribution of blood flow (rather than specific binding). The summed early image and the other individual frames were individually aligned to the reference image using Automated Image Registration (AIR) techniques (Woods *et al*, 1992).

The regions of interest (ROI) were hand drawn on the coregistered MR images and applied to the dynamic PET data to generate time–activity curves. The following ROIs were selected: prefrontal cortex (Brodmann's area [BA] 10), medial orbital frontal cortex (BA 11), lateral orbital frontal cortex (BA 47), mesial–temporal cortex (amygdala–hippocampal complex), lateral temporal cortex (BA 21), supragenual cingulate (BA 24/32, five planes superior to anterior most part of genu corporis callosi), pregenual cingulate (BA 24/32, anterior to anterior most part of genu of the corpus callosum), and subgenual cingulate (BA 25, inferior to the genu of the corpus callosum), parietal cortex (BA 7), and occipital cortex (BA17). We also performed ROI sampling of the cerebellum, and this was used as the reference region because of the low concentration of 5-HT_{2A} receptors (Pazos *et al*, 1987). The cerebellar reference region data were assumed to be representative of the free and nonspecifically bound radioactivity concentrations, in all regions (Price *et al*, 2001a, b). The ROIs were expressed as left and right (lateralized) values for each region, as well as the mean of left and right values. Figure 1 shows examples of MR and PET image data acquired at the levels of the parietal cortex and subgenual cingulate cortex (Figure 1a) and the corresponding PET time–activity data (Figure 1b).

For the kinetic analyses, the Logan graphical method was applied to the sampled ROI data from 12 to 90 min (10 data points) using the arterial input function. The regression slope value ([^{18}F]altanserin distribution volume, DV) for each ROI was calculated (Logan *et al*, 1990). Specific 5-HT_{2A} receptor binding was assessed using the binding potential (BP) measure. The BP measure is based upon the ratio of each ROI DV value to the cerebellar DV value (DV_{ROI}/$DV_{CER} = DV_{RATIO}$, DVR), where BP = DVR - 1 (Lammertsma, 2002). Although the concentration of cerebellar 5-HT_{2A} receptors is low, an influence on ROI-specific binding could not be excluded. We therefore also compared the cerebellar DV between groups.

An MR-based partial volume correction method is routinely applied in our laboratory to correct the PET data for the dilutional effect of expanded CSF spaces accompanying normal aging and disease-related cerebral atrophy (Meltzer *et al*, 1999, 1996). This method was applied to the SPGR MR data, in the present study, to investigate whether group differences exist in regional atrophy. Each subject's SPGR MR image set was segmented and used to generate binary images with pixels that corresponded to brain (1) and nonbrain (0) (Meltzer *et al*, 1999). The binary images were smoothed (point-spread-function of the PET scanner) and the smoothed data were sampled on a ROI basis to generate regional atrophy correction factors (0–1).

Standard statistical software packages (SAS Version 8.2 and SPSS Version 10.0) were used for all other analyses. Comparisons between CW and recovered REC AN–BN were made using Wilcoxon rank-sum tests with the exact significance levels reported. The exact levels were used due to the small sample sizes. To explore the effect of age on the results, we also tested for group differences while adjusting for age. This analysis was done using a linear model with the binding potential value as the outcome and age and group membership as predictors. Standard regression diagnostics were used to assess the sensitivity of the model to any observation in the data set. To account for the fact that the age relationship differed between groups for some of the BP values, linear models including a main effect for group, a main effect for age and an interaction between age and group were fit separately for each region. The interaction term was retained for the supragenual cingulate,

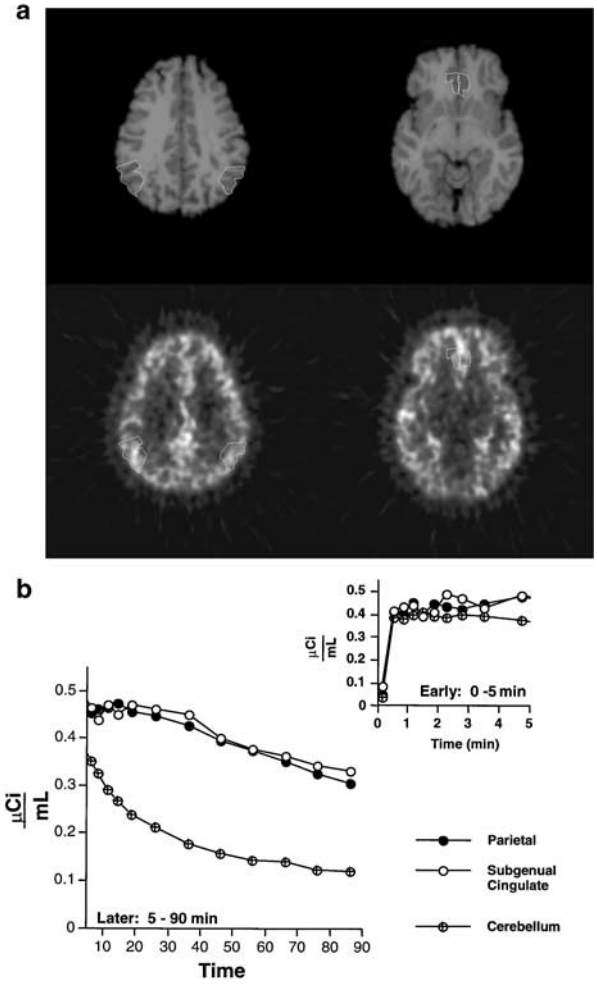

Figure 1 (a) Horizontal sections from coregistered SPGR magnetic resonance (upper panel) and positron emission tomography (PET; lower panel) images of a typical subject recovered from anorexia nervosa, bulimic type. The PET images are summations of dynamic data acquired over 12–90 min after [^{18}F]altanserin injection. The PET and MR imaging sections on the left include the left and right parietal cortex (BA 7), whereas those on the right include the subgenual cingulate (BA 25, inferior to the genu of the corpus callosum). Also shown are examples of the regions-of-interest that were used to generate the PET time–activity data. (b) Examples of the [^{18}F]altanserin PET time–activity data that were generated for the parietal and subgenual cingulate cortices and cerebellum of the subject described above (a). The inset graph shows the early kinetics of the time–activity data (0–5 min postinjection). Similar curve shapes were observed for the two cortical regions-of-interest, whereas lower uptake and rapid clearance was observed in the cerebellum.

right supragenual cingulate, lateral temporal cortex, right lateral temporal cortex, and right parietal cortex. For all other regions, a linear model was fit with age and group as the main effect. Pearson's correlation coefficients were also computed and exact significance levels based on Monte Carlo methods are reported.

A multivariate analysis of variance model (MANOVA), with the left and right region BPs being the outcome variables and age and group as the predictors, was also fit to the data. The MANOVA *p*-value represents the test of equality of BPs from the left and the right region across control and REC AN–BN women. The correlation (*r*) between the left and right side is also estimated as part of this analysis and the corresponding test of statistical significance is presented. All of these analyses are age adjusted and include age as a predictor in the model.

RESULTS

Demographic Variables and Behavioral Assessments

The REC AN–BN and CW women were of similar age and had similar body mass indices (BMI) (Table 1). Subject groups had similar plasma BHBA values, a measure of ketone body metabolism, suggesting REC AN were not starving. In addition, groups had similar plasma estradiol values. The REC AN–BN subjects had significantly higher values for eating disorder-related obsessionality (YBC-EDS), higher total values for the Yale–Brown Obsessive–Compulsive Scale, higher values for the EDI-2 subscale 'drive for thinness' (EDI-DT), and nonsignificantly higher values in trait and state anxiety. (For further details see Table 1).

Plasma Data

The fraction of unmetabolized [^{18}F]altanserin in plasma was similar between control and REC AN–BN subjects, across all time points (2 min: CW: $0.95.\pm0.03$ REC AN–BN: 0.95 ± 0.02; 30 min: CW: 0.57 ± 0.08 REC AN–BN: 0.60 ± 0.07; 90 min: CW: 0.41 ± 0.10 REC AN–BN: 0.42 ± 0.06). No difference in protein binding was found between the groups ($f1 = 0.029 + 0.008$ for REC AN–BN *vs* $f1 = 0.029 + 0.010$ for control women).

ROI-Based Analysis

The [^{18}F]altanserin cerebellar DV value was similar ($p = 0.48$). for CW ($1.30 + 0.15$) and REC AN–BN ($1.32 + 0.09$). The regional [^{18}F]altanserin BP values followed the known rank order of 5-HT$_{2A}$ receptor binding as shown in Table 2 (Pazos *et al*, 1987). In terms of combined ROI, we found REC AN–BN had significantly ($p < 0.05$) reduced [^{18}F]altanserin BP in the subgenual cingulate, parietal cortex and a trend toward significant reduction in the occipital cortex compared to CW (Table 2). In terms of lateralized findings, REC AN–BN women had reduced [^{18}F]altanserin BP in the left subgenual cingulate, the left parietal cortex, and the right occipital cortex. A trend toward a reduction occurred in the left lateral temporal cortex (see Table 2 for details). The MR-based atrophy correction factors were not significantly different between CW and REC AN–BN when using Mann–Whitney U-test (data not shown). Overall, we found similar results when comparing the partial volume corrected BP values (see Table 3), showing additional significant differences in the right subgenual cingulate, lateral temporal cortex, and occipital cortex.

After correction for multiple comparisons, using the method of false discovery rate (Benjamini and Hochberg, 1995), none of our results are significant at the 0.05 level.

Table 1 Group Comparisons of Demographic Variables and Assessment Data

	CW[1] ($n=16$)		REC AN-BN[3] ($n=10$)			
	Mean	**SD**	**Mean**	**SD**	**U**	**Exact sig.**
Age (years)	23.5	3.0	25.2	3.3	57	0.24
Current BMI	21.6	1.3	20.9	2.2	67.5	0.52
AN onset (years of age)	—	—	15.2 (9)	1.6	—	—
Duration of recovery (months)	—	—	21.4 (8)	17.9	—	—
Estradiol (μmol/ml)	29.9	32.4	26.1	23.1	79.5	0.98
Beta-hydroxy-butyrate (BHBA) (mmol/l)	0.06 (15)	0.04	0.07 (8)	0.04	54	0.73
Depression (BDI)	1.6 (14)	1.6	5.6 (9)	5.8	35.5	0.08
EDI 2—Drive for Thinness ("worst ever")	0.88	1.6	15.9	4.7	0	<0.001
Novelty seeking (TCI)	21.8	4.7	21.7 (9)	6.4	69.5	0.89
Harm avoidance (TCI)	11.8	4.3	14.7 (9)	7.9	61.5	0.56
Reward dependence (TCI)	19.6	2.0	18.9 (9)	3.2	62	0.60
State anxiety (STAI)	26.0	4.1	31.9 (9)	7.5	39	0.07
Trait anxiety (STAI)	28.8	8.2	34.9 (9)	8.2	39.5	0.07
Yale–Brown Obsessive–Compulsive Scale (Y-BOCS)	1.0 (15)	2.0	8.1 (9)	9.2	26.5	0.01
Yale–Brown–Cornell Eating Disorders Scale (YBC-EDS)	0.4 (15)	0.9	5.6 (9)	6.1	31	0.03

The numbers in parentheses indicate the number of subjects with assessment. Group comparison by Mann–Whitney U-test.
CW, healthy control women; REC AN–BN, recovered anorexic women, bulimia type; BMI, body mass index; BHBA, beta-hydroxy butyric acid; TCI, Temperament and Character Inventory, BDI, Beck Depression Inventory; STAI, State and Trait Anxiety Inventory, EDI-2, Eating Disorder Inventory.

Relationship of Age With [^{18}F]Altanserin BP

Female CW in this study were 23.5 + 3.0 years old (range 18.6–28.7 years) and female REC AN–BN were 25.2 + 3.3 years old (range 19.7–30.3 years). Despite this narrow age range, female CW showed a negative relationship for each ROI for age and [^{18}F]altanserin BP (Table 4), which reached significance in the prefrontal cortex, lateral temporal cortex, left lateral orbital frontal cortex, left subgenual cingulate, and right medial orbital, mesial temporal, and parietal cortex regions. In contrast, for the REC AN–BN, few ROIs showed a negative relationship between age and [^{18}F]altanserin BP and none were significant. When slopes for these correlations were compared, there was only a significant difference in slopes for the right lateral temporal cortex. It is possible that relationships between age and [^{18}F]altanserin BP might effect the comparison of [^{18}F]altanserin BP between CW and REC AN–BN women. Thus, we tested for group differences while adjusting for age (Table 2). Overall, group differences remained similar after age correction, with the right occipital cortex moving from a significant difference to a trend, and the supragenual cingulate, lateral temporal cortex, and right lateral temporal cortex moving from a trend to a significant difference.

The results of the MANOVA, adjusting for age and treating the left and right sides as a multivariate outcome, showed that there were group differences between CW and REC subjects for the left and right sides in the subgenual cingulate ($p=0.03$) and in the parietal cortex ($p=0.07$). The results also indicated that there was no correlation between the left and right sides in the subgenual cingulate region ($r=0.06$; $p=0.78$) and that the left and right sides were highly correlated in the parietal cortex region ($r=0.50$; $p=0.01$). Other regions that exhibited high correlation between the left and right sides include the prefrontal cortex ($r=0.86$; $p=0.0001$), the lateral orbital frontal cortex ($r=0.62$; $p=0.001$), the medial orbital frontal cortex ($r=0.48$; $p=0.02$), the mesial temporal cortex ($r=0.61$; $p=0.001$) and the occipital cortex ($r=0.64$; $p=0.001$).

Relationship of Demographic and Behavioral Data With [^{18}F]Altanserin BP

Eight subjects of the REC AN–BN had a DSM-IV (American Psychiatric Association, 1994) history of major depressive disorder (MDD) and five subjects had a history of obsessive–compulsive disorder (OCD). Additionally, one subject in the REC AN–BN group had a history of subthreshold OCD, one subject out of this group fulfilled criteria for social phobia. None of the REC subjects had a history of any psychotic disorder. Subjects with comorbid OCD did not differ in terms of [^{18}F]altanserin BP from those subjects without OCD. No relationships were found for either group between [^{18}F]altanserin BP and current BMI, plasma BHBA, or estradiol.

REC AN–BN subjects had a positive relationship between [^{18}F]altanserin BP and harm avoidance (total score) in the left subgenual cingulate (rho = 0.73; $p=0.03$), left temporal cortex (rho = 0.73; $p=0.02$), and mesial temporal cortex (rho = 0.70; $p=0.03$). Harm avoidance subscale 2 showed additional positive relationships to [^{18}F]altanserin BP in the occipital cortex (rho = 0.83; $p=0.01$) (see also Figure 2a). No significant relationship between harm avoidance (total and subscale 2) and [^{18}F]altanserin BP was found in control women. Furthermore, negative relationships between novelty seeking and [^{18}F]altanserin BP were found in REC AN–BN in the left subgenual cingulate (rho = −0.79; $p=0.01$), the pregenual cingulate (rho = −0.77; $p=0.02$) and mesial temporal cortex (rho = −0.66; $p=0.05$). REC

Table 2 Regional [^{18}F]Altanserin BP Between Groups

Region of interest		CW ($n=16$) ALT BP		REC AN-BN ($n=10$) ALT BP		Comparison of CW and REC AN–BN	Comparison of CW and REC AN–BN after age adjustment
		Mean	SD	Mean	SD	Exact sig.	Sig. level[a]
Prefrontal cortex	Combined	1.39	0.24	1.34	0.20	0.62	0.68
	Left	1.41	0.25	1.36	0.22	0.70	0.75
	Right	1.38	0.24	1.31	0.20	0.66	0.60
Lat. orbital frontal cortex	Combined	1.23	0.27	1.25	0.33	0.55	0.91
	Left	1.30	0.27	1.33	0.36	0.34	0.53
	Right	1.16	0.33	1.18	0.36	0.78	0.87
Med. orbital frontal cortex	Combined	1.49	0.29	1.42	0.24	0.45	0.75
	Left	1.52	0.32	1.50	0.33	0.78	0.86
	Right	1.45	0.30	1.38	0.30	0.55	0.66
Supragenual cingulate	Combined	1.35	0.22	1.23	0.21	0.31	**0.04***
	Left	1.35	0.26	1.34	0.31	0.82	0.86
	Right	1.32	0.28	1.12	0.34	0.24	0.06*
Subgenual cingulate	Combined	1.70	0.23	1.40	0.24	**0.01**	**0.01**
	Left	1.82	0.30	1.47	0.29	**0.01**	**0.02**
	Right	1.54	0.29	1.31	0.38	0.11	0.09
Pregenual cingulate	Combined	1.58	0.19	1.45	0.18	0.16	0.08
	Left	1.62	0.27	1.52	0.35	0.57	0.37
	Right	1.49	0.25	1.38	0.27	0.40	0.23
Lateral temporal cortex	Combined	1.61	0.23	1.45	0.20	0.12	**0.04***
	Left	1.66	0.26	1.46	0.30	**0.05**	0.16
	Right	1.56	0.24	1.44	0.27	0.36	**0.04***
Mesial temporal cortex	Combined	0.60	0.16	0.51	0.18	0.12	0.27
	Left	0.56	0.17	0.48	0.15	0.24	0.25
	Right	0.65	0.19	0.54	0.29	0.24	0.45
Parietal cortex	Combined	1.57	0.20	1.40	0.13	**0.04**	**0.05**
	Left	1.56	0.20	1.35	0.15	**0.01**	**0.02**
	Right	1.60	0.26	1.44	0.15	0.18	0.08*
Occipital cortex	Combined	1.61	0.23	1.44	0.16	0.06	0.11
	Left	1.59	0.23	1.45	0.21	0.30	0.26
	Right	1.64	0.25	1.41	0.19	**0.03**	0.06

Group comparisons by Wilcoxon rank-sum tests with exact significance levels. ALT BP, [^{18}F]altanserin BP; CW, healthy control women; REC AN–BN, recovered anorexic women, bulimia type; Sig., significance.
[a]Significance levels marked with an * were obtained from a model that included an interaction between age of subject and diagnosis category. All reported significance levels are two-sided.

AN–BN had a negative relationship between the EDI-DT subscale and [^{18}F]altanserin BP in the right subgenual cingulate (rho $=-0.79$; $p=0.01$), right pregenual cingulate (rho $=-0.79$; $p=0.01$), the lateral temporal cortex (rho $=-0.73$; $p=0.03$), the left parietal cortex (rho $=-0.69$; $p=0.04$) and the prefrontal cortex (rho $=-0.74$; $p=0.02$) (see also Figure 2b).

DISCUSSION

These data replicate and extend previous studies suggesting that a disturbance of brain 5-HT neuronal function persists after recovery from AN. Specifically, this study suggests that REC AN–BN women have reduced 5-HT$_{2A}$ receptor activity in the left subgenual cingulate as well as in the left parietal and the right occipital cortex.

Other studies from our group have previously reported reduced [^{18}F]altanserin binding in subjects recovered from BN (Kaye *et al*, 2001b) and in subjects recovered from AN, restricting type (Frank *et al*, 2002). The subjects in this current paper have recovered from bulimia-type AN and were not subjects or an ED subgroup reported in the previous two papers. Our rationale for subdividing REC ED subjects into three groups (AN, AN–BN, and BN) is based on the DSM-IV categorization. In previous papers, we reported on combined L and R regions. When [^{18}F]altanserin BP of combined regions is compared between subgroups, both AN and AN–BN have reductions in the subgenual cingulate, parietal, and occipital cortex. Moreover, recent data from our group on a larger sample shows that REC BN also have reduced [^{18}F]altanserin BP in the subgenual cingulate (unpublished data). In comparison,

Table 3 Regional [^{18}F]Altanserin BP Between Groups After Partial Volume Correction

Region of interest		CW ($n=16$) ALT BP		REC AN–BN ($n=10$) ALT BP		Comparison of CW and REC AN–BN
		Mean	SD	Mean	SD	Exact sig.
Prefrontal cortex	Combined	1.89	0.32	1.60	0.49	0.20
	Left	1.93	0.33	1.68	0.44	0.22
	Right	1.86	0.34	1.53	0.54	0.24
Lat. orbital frontal cortex	Combined	1.62	0.29	1.50	0.36	0.52
	Left	1.72	0.30	1.66	0.40	0.90
	Right	1.51	0.37	1.37	0.42	0.45
Med. orbital frontal cortex	Combined	1.76	0.28	1.64	0.40	0.55
	Left	1.80	0.30	1.75	0.46	0.74
	Right	1.71	0.31	1.56	0.48	0.59
Supragenual cingulate	Combined	1.44	0.23	1.26	0.26	0.08
	Left	1.43	0.25	1.38	0.35	0.98
	Right	1.42	0.32	1.14	0.38	0.07
Subgenual cingulate	Combined	1.77	0.25	1.32	0.51	**0.01**
	Left	1.90	0.31	1.42	0.56	**0.01**
	Right	1.61	0.31	1.22	0.58	**0.04**
Pregenual cingulate	Combined	1.67	0.19	1.50	0.29	0.16
	Left	1.72	0.24	1.57	0.38	0.34
	Right	1.59	0.28	1.42	0.40	0.50
Lateral temporal cortex	Combined	1.95	0.24	1.70	0.27	**0.04**
	Left	2.04	0.30	1.78	0.33	**0.05**
	Right	1.87	0.26	1.62	0.37	0.11
Mesial temporal cortex	Combined	0.70	0.18	0.54	0.26	**0.05**
	Left	0.65	0.19	0.48	0.24	0.07
	Right	0.75	0.19	0.60	0.33	0.17
Parietal cortex	Combined	1.87	0.29	1.60	0.30	**0.04**
	Left	1.86	0.29	1.60	0.17	**0.02**
	Right	1.88	0.34	1.60	0.44	0.22
Occipital cortex	Combined	1.82	0.24	1.49	0.38	**0.01**
	Left	1.79	0.27	1.50	0.44	0.12
	Right	1.85	0.25	1.44	0.34	**0.003**

Group comparisons by Wilcoxon rank-sum tests with exact significance levels. ALT BP, [^{18}F]altanserin BP; CW, healthy control women; REC AN–BN, recovered anorexic women, bulimia type; sig., significance.

only REC AN have reduced [^{18}F]altanserin BP of the mesial temporal region and pregenual cingulate (Frank *et al*, 2002) and only REC BN have reductions of the medial orbital frontal cortex (Kaye *et al*, 2001b), which we have replicated in a larger sample (unpublished data). A recent investigation of ill, underweight AN used SPECT with a 5-HT$_{2A}$ receptor antagonist (Audenaert *et al*, 2003). They reported that ill AN had a significant reduction of 5-HT$_{2A}$ receptor activity in the left frontal cortex, the left and right parietal cortex, and the left and right occipital cortex. It is not certain whether the cingulate regions were investigated or whether ill AN subjects were pure restrictors or included any AN–BN subtypes. In summary, studies of REC and ill AN and/or BN subjects point to a consistent reduction of 5-HT$_{2A}$ activity.

Few other imaging studies of REC AN/AN–BN have been done, and subgroups have not been well defined. Single photon computed tomography (SPECT) studies found temporal lobe asymmetry (Chowdhury *et al*, 2001) as well as hypoperfusion of bilateral temporal, parietal, occipital, and orbitofrontal regions (Rastam *et al*, 2001) in weight recovered AN.

Other studies, using PET with (18-F)-fluorodeoxyglucose (FDG) (Delvenne *et al*, 1995) or SPECT (Chowdhury *et al*, 2003; Gordon *et al*, 1997; Kuruoĝlu *et al*, 1998; Nozoe *et al*, 1995; Rastam *et al*, 2001; Takano *et al*, 2001) have investigated 'baseline' brain metabolism in ill AN and reported parietal, temporal, and frontal lobe changes in ill AN. When both regions were investigated, both tended to be involved. Together, brain metabolism studies strongly support the presence of abnormal regional brain activity in ill and recovered AN subjects.

Postmortem human studies and PET imaging with 5-HT ligands show a strong inverse correlation between binding of cortical 5-HT$_{2A}$ receptors and age (Cheetham *et al*, 1988; Gross-Isseroff *et al*, 1990; Marcusson *et al*, 1984; Meltzer *et al*, 1998; Shih and Young, 1978). In our sample of normal

Table 4 Regional [^{18}F]Altanserin BP and Correlation With Age

		CW ($n=16$)		REC AN-BN ($n=10$)		Group comparisons*	
Region of interest		**Rho**	**P**	**Rho**	**P**	**F**	**P**
Prefrontal cortex	Combined	0.55	**0.03**	−0.07	0.86	1.91	0.18
	Left	0.56	**0.02**	−0.03	0.94	2.26	0.15
	Right	0.51	**0.05**	−0.09	0.80	1.48	0.24
Lat. orbital frontal cortex	Combined	0.39	0.13	0.16	0.66	1.70	0.21
	Left	0.54	**0.03**	−0.12	0.73	0.78	0.39
	Right	0.18	0.50	0.36	0.30	1.69	0.21
Medial orbital frontal cortex	Combined	0.38	0.02	−0.18	0.63	1.71	0.20
	Left	0.48	0.06	−0.45	0.20	0.02	0.90
	Right	0.59	**0.02**	− 0.01	0.99	2.44	0.13
Supragenual cingulate	Combined	0.38	0.15	0.27	0.45	2.50	0.13
	Left	0.50	**0.05**	− 0.25	0.49	0.27	0.61
	Right	0.12	0.66	0.46	0.18	2.20	0.15
Subgenual cingulate	Combined	0.43	0.10	0.27	0.45	3.02	0.10
	Left	0.59	**0.02**	−0.06	0.87	2.07	0.16
	Right	0.07	0.78	0.19	0.60	0.42	0.52
Pregenual cingulate	Combined	0.36	0.18	0.28	0.44	2.40	0.14
	Left	0.30	0.28	−0.04	0.91	0.30	0.59
	Right	0.23	0.39	0.33	0.36	1.77	0.20
Lateral temporal cortex	Combined	0.51	**0.05**	0.28	0.43	4.14	**0.05**
	Left	0.53	**0.03**	−0.06	0.86	1.28	0.27
	Right	0.42	0.11	0.42	0.23	4.54	**0.04**
Mesial temporal cortex	Combined	0.38	0.14	−0.08	0.84	0.52	0.48
	Left	0.15	0.57	0.28	0.44	0.92	0.35
	Right	0.54	**0.03**	− 0.29	0.41	0.10	0.76
Parietal cortex	Combined	0.48	0.06	0.19	0.59	3.22	0.09
	Left	0.28	0.29	0.19	0.60	1.23	0.28
	Right	0.56	**0.03**	0.12	0.74	3.82	0.06
Occipital cortex	Combined	0.35	0.19	−0.17	0.66	0.28	0.60
	Left	0.28	0.30	− 0.25	0.51	0.01	0.92
	Right	0.35	0.18	−0.10	0.78	0.42	0.52

CW, healthy control women; REC AN–BN, recovered anorexic women, bulimia type; rho, Pearson's correlation coefficient, exact significance levels based on Monte Carlo methods are reported.
*Comparison of the slope of the regional [^{18}F] altanserin BP and age correlation between groups (analysis of variance).

controls, we found this inverse relationship, despite the narrow age range (range 18.6–28.7 years old). Importantly, the REC AN–BN in this study and the REC BN in our previous study (Kaye *et al*, 2001b) fail to show age-dependent relationships with [^{18}F]altanserin binding. In comparison, REC AN showed some modest relationships between age and [^{18}F]altanserin binding (Frank *et al*, 2002). AN and BN are gender-specific disorders that invariably begin within a narrow postpubertal age range. These data raise the question of whether 5-HT activity in AN and BN is dissociated from normal age-associated changes, a finding that may offer new clues into the pathophysiologic mechanisms contributing to eating disorders. Whether the 5-HT system becomes free-running and insensitive to normal developmental mechanisms remains to be explored.

AN and BN are thought to share some common etiologic factors (Klump *et al*, 2000). Still, a number of factors distinguish the subgroups, such as extremes of eating behavior and impulse control. Our studies raise the possibility that AN and BN may share a disturbance of 5-HT_{2A} receptor activity of the subgenual cingulate function, whereas regional differences in 5-HT_{2A} receptor activity may distinguish eating disorder subgroups after recovery. The subgenual cingulate is thought to have a role in emotional and autonomic response (Freedman *et al*, 2000) and a disturbance of this region has been implicated in mood disorders (Buchsbaum *et al*, 1997; Drevets *et al*, 1997, 1999; George *et al*, 1995; Mayberg *et al*, 2000, 2002; Osuch *et al*, 2000; Skaf *et al*, 2002). Mood disturbances are common in AN and BN, although it has been controversial as to whether eating disorders and mood disorders are independently or commonly transmitted in families (Lilenfeld *et al*, 1998). Interestingly, subjects with AN and BN have disturbances of energy metabolism when ill (see de Zwaan *et al* (2002) for review) and persistent but mild sympathetic alterations after recovery. Recent demonstration

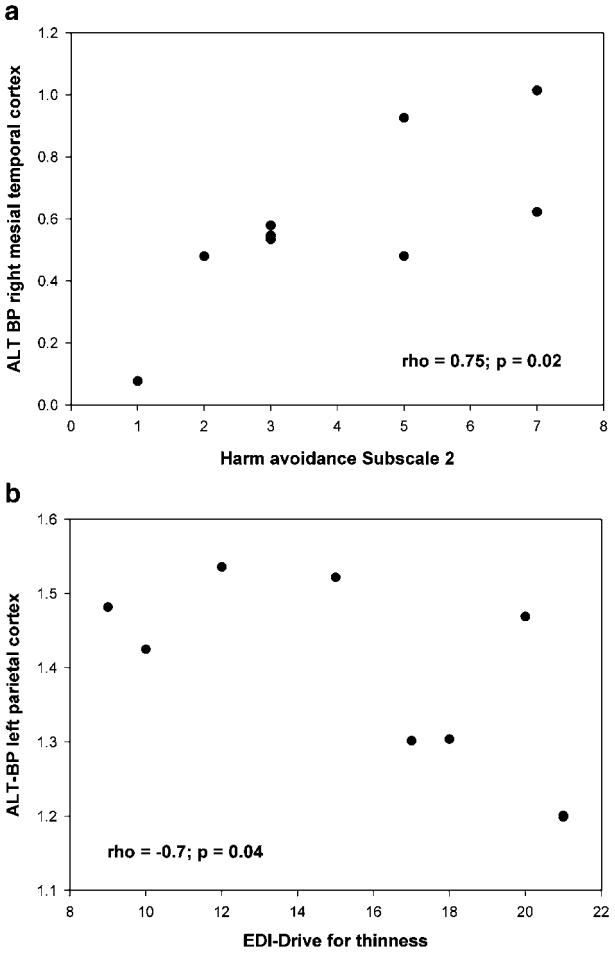

Figure 2 (a) Correlation of Harm avoidance, subscale 2, and [^{18}F]altanserin binding potential (ALT BP) in the right mesial temporal cortex. rho, Pearson's correlation coefficient. (b) Correlation of Eating Disorder Inventory-2 (EDI-2), subscale 'drive for thinness' and [^{18}F]altanserin binding potential (ALT BP) in the left parietal cortex. rho, Pearson's correlation coefficient.

of dense projections from the subgenual cingulate cortex (area 25) to the dorsal raphe (Freedman *et al*, 2000) raises the tantalizing possibility that the subgenual cortex plays some role in regulating overall serotonergic activity. In fact, in CW the subgenual cingulate has the highest density of [^{18}F]altanserin binding (Table 2) of any region. Together these data raise the possibility that some factor related to subgenual cingulate function creates a vulnerability for AN and BN, perhaps related to mood and autonomic modulation.

We found negative relationships between [^{18}F]altanserin BP and the EDI-DT subscale in several regions, for example, the left parietal cortex. Recently, Wagner *et al* (2003) found a hyper-responsiveness in the parietal lobule in AN subjects, when confronted with their own digitally distorted body images using a computer-based video technique and functional magnetic resonance imaging. Moreover, neuropsychologic studies are consistent with disturbances of parietal function in AN (Horne *et al*, 1991; Palazidou *et al*, 1990; Mathias and Kent, 1998; Szmukler *et al*, 1992; Hamsher *et al*, 1981). Mesulam (1999) describes a network involving parietal, frontal, cingulate, and limbic pathways that modulate spatial attention. It is well known that lesions in the right parietal cortex may not only result in denial of illness or anosognosia, but may also produce experiences of disorientation of body parts and body image distortion (Critchley, 1953). Kinsbourne and Bemporad (1984) hypothesized that a dysfunction of the right hemisphere of the brain, especially of the right parietal cortex, is evident in patients with AN. Alternatively, our data raise the intriguing possibility that L hemisphere parietal disturbances are related to body image distortion.

The mechanism responsible for decreased 5-HT$_{2A}$ activity in REC AN–BN is unknown. Still, evidence from other studies raises the possibility that reduced activity of 5-HT$_{2A}$ receptor could be an expected compensatory downregulation for increased extracellular 5-HT concentration. Elevated cerebrospinal fluid 5-hydroxyindoleacetic acid (CSF 5-HIAA) levels were found in subjects recovered from AN (Kaye *et al*, 1991) and from BN (Kaye *et al*, 1998), raising the possibility that they have increased 5-HT activity with increased extracellular 5-HT concentration. Furthermore, studies in animals confirm that reduced 5-HT$_{2A}$ receptor density occurs in response to increased intrasynaptic 5-HT (Rioux *et al*, 1999; Saucier *et al*, 1998) or 5-HT agonists (Eison and Mullins, 1996).

A number of authors (Cloninger 1987; Soubrie, 1986; Spoont, 1992) have suggested that increased 5-HT functional activity is inhibitory of behavior and may be related to harm avoidance. Most recently, 5-HT$_{2A}$ receptor binding and harm avoidance were shown to be negatively correlated in the frontal cortex in healthy subjects (Moresco *et al*, 2002) and in the prefrontal cortex in patients that attempted suicide (van Heeringen *et al*, 2003). We found [^{18}F]altanserin BP was positively related to harm avoidance and negatively related to novelty seeking in REC AN–BN. In particular, we found relationships with the Harm Avoidance subscale 2, which particularly assesses fear of uncertainty (Cloninger *et al*, 1994), in temporal and other regions. Our data are consistent with the literature that implicates that 5-HT activity is related to anxiety and impulsivity in ill BN subjects (Steiger *et al*, 2001a, b, c) and to impulsive, aggressive behaviors in men (Arango *et al*, 1997; Coccaro *et al*, 1997; New *et al*, 1997; Siever and Trestman, 1993).

Our method of partial volume correction, applied in this study, is a two-compartment method that does correct for spillover between brain and CSF but not between gray and white matter. While it is well known that ill AN subjects have reduced cortical volume (Ellison and Fong, 1998) and increased ventricular volume (Golden *et al*, 1996; Swayze *et al*, 1996; Katzman *et al*, 1996), it remains uncertain whether such brain volume reductions and enlargement of CSF spaces persist in the recovered state (Artmann *et al*, 1985; Swayze *et al*, 2003). Some studies showed that weight-recovered AN have significantly greater CSF volumes and smaller gray matter volumes than healthy control women (Lambe *et al*, 1997; Katzman *et al*, 1997, Krieg *et al*, 1988). In this study, no group differences were detected between the atrophy correction factors, across ROIs.

Several limitations of the study should be raised. We rely upon subject self-report of recovered status. Normal plasma BHBA and E2 values in REC AN–BN support the probability that they have normal nutritional and gonadal status. Studies in animals (Cyr *et al*, 1998; Summer and Fink, 1995)

and humans (Moses *et al*, 2000) suggest that E2 can alter 5-HT_{2A} receptor activity. However, our study did not find any relationships between [^{18}F]altanserin BP and E2 plasma levels. *In vivo* studies in people with major depression have found both reduced (Biver *et al*, 1997; Attar-Levy *et al*, 1999; Yatham *et al*, 2000; Messa *et al*, 2003) and normal (Meyer *et al*, 2001) 5-HT_{2A} receptor binding values. In addition, decreased volume (Hirayasu *et al*, 1999) and reduced cerebral blood flow and metabolism (Drevets *et al*, 1997, 2002; Buchsbaum *et al*, 1997) have been found in the left subgenual cingulate in depressed subjects relative to controls. Thus it is possible that subgenual cingulate findings are not specific for AN–BN, but may be related to the high incidence of lifetime MDD diagnosis in these subjects. It should be noted that AN–BN subjects commonly have comorbid depression and anxiety, so that such traits may be vulnerabilities contributing to this particular ED subtype.

We studied a relatively small number of AN and CW subjects; future replications of our findings in larger samples are clearly needed. A relatively large number of statistical analyses were conducted with a small number of subjects, potentially leading to type I errors. We present the actual significance levels for all analyses, so that the strength of the reported associations can be assessed. We also tried to address some of the limitations of the study design using several different approaches. We often used exact statistical methods, so that the resulting significance levels were on the conservative side. We were not able to use exact methods for the modeling. For many of the models that were fit, we screened the data for potential outliers using standard residual and regression analysis diagnostic techniques and found no unduly influential observations, that is, observations that would change the inferences drawn from the data if they were removed from the analysis. The small sample size also resulted in the ability to detect only large differences between the two groups in order to obtain statistical significance.

When adjusting the significance levels for multiple comparisons, using the method of false discovery rate (Benjamini and Hochberg, 1995), none of our results would be significant at the 0.05 level. However, at an overall significance level of 0.10 group differences in [^{18}F]altanserin BP for the subgenual cingulate, the left subgenual cingulate as well as the left parietal cortex remain significant. Furthermore, correlations between [^{18}F]altanserin BP and age in CW remain significant at the 0.10 level for the left prefrontal, left lateral orbital frontal, right medial orbital frontal, left subgenual cingulate, left lateral temporal, right mesial temporal, and right parietal cortex.

In conclusion, this study supports previous findings of altered 5-HT neuronal transmission after recovery from AN–BN. It is problematic to identify women with AN–BN before they develop the disorder. Studying women after long-term recovery may be the best available approximation to identifying factors that might be involved in the development of AN–BN. Although scarring effects from the illness cannot be excluded, reduced 5-HT_{2A} receptor binding in AN–BN thus could be an indication of a trait-related 5-HT disturbance or, alternatively, a secondary phenomenon in response to increased central 5-HT transmission in this group.

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