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# Serotonin 1A receptor reductions in postpartum depression: a PET study

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## Abstract

**Objective—**To measure brain serotonin-1A (5HT1A) receptor binding potential (BP) in healthy and depressed postpartum women

**Design—**5HT1A receptor BP was measured with positron emission tomography using [$^{11}$C] WAY100635 a single time. MANOVA was used to determine depression effects on 5HT1A receptor BP in related brain regions.

**Setting—**Academic research environment.

**Patients—**Seven postpartum healthy controls and nine postpartum depressed(PD) subjects with perinatal (antepartum or postpartum) depression onset. Of the 9 PD subjects, 5 had unipolar depression and 4 had bipolar disorder.

**Interventions—**None

**Main Outcome Measures—**5HT1A receptor binding potential.

**Results—**Age, time since delivery, and reproductive hormones did not differ between groups. Postsynaptic 5HT1A receptor binding in PD was reduced 20–28% relative to controls, with most significant reductions in anterior cingulate and mesiotemporal cortices.

**Conclusions—**Postsynaptic 5HT1A receptor binding is reduced in PD by a similar magnitude as has been shown in other depression samples. The postpartum hormonal milieu and the large proportion of bipolar spectrum subjects in the PD group may have accentuated this finding in this small sample. Recognition of this neurobiological deficit in PD may be useful in the development of treatments and prevention strategies for this disabling disorder.

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**Capsule:** Postsynaptic 5HT1A receptor binding is reduced in postpartum depression by a similar magnitude as shown in other depression samples in brain regions critical to mood regulation.

**Key words (6)**

postpartum depression; serotonin; 5HT1A receptor; PET; estradiol

## INTRODUCTION

Postpartum depression is a critical public health problem because it affects at least 580,000 American women annually (1,2), impedes healthy infant and child development (3–6), and disrupts families (7). Existing treatments, although effective for postpartum mood disorders (8–10), are often rejected by puerperal women who prefer no medication (because of lactation) or who minimize/deny mental illness in the context of hormonal fluctuations of childbearing (11). Discovery of altered central neurobiological processes in postpartum mood disorders has the potential to increase treatment acceptability for women with this disorder, raise the importance of postpartum depression treatment among practitioners, and decrease the stigma of postpartum depression.

While there is evidence of heightened mood sensitivity to estrogen and progesterone fluctuations in women with past postpartum depression (12), little is known about specific neurobiological systems that are disrupted by the hormonal changes of childbearing. The serotonin (5HT) system has been proposed as an important mediator of perinatal depression because depression in women (13) and premenstrual dysphoric disorder (14,15) are highly responsive to serotonergic antidepressants. Furthermore, the perinatal hormones estradiol, progesterone (16), and cortisol (17) have been consistently demonstrated to have neuroregulatory effects on the central 5HT system.

The 5HT1A receptor is a well-established molecular target for the action of serotonin. In experimental animals, serotonin-increasing antidepressants inducetonic activation of postsynaptic 5HT1A receptors (18) and the complete absence of 5HT1A receptors (19) is associated with depression-like behavior. 5HT1A receptor reductions (binding potential in imaging studies; mRNA and/or density in postmortem studies) have been demonstrated in a majority of neuroimaging (20–25) and postmortem (17,20,22) studies of major depressive disorder, although several studies have shown increases (26,27).

We evaluated the central 5HT1A receptor system with positron emission tomography (PET) and the selective 5HT1A receptor radioligand [$^{11}$C]WAY100635. We focused on limbic brain regions noted for postsynaptic 5HT1A receptor binding decreases in depression: mesiotemporal cortex (includes amygdala and hippocampus), left lateral orbitofrontal cortex, and subgenual anterior cingulate cortex. We hypothesized that perinatally depressed women (PD is defined as prevalent cases of depression in the 16 weeks following childbirth) would have reduced postsynaptic 5HT1A receptor binding relative to postpartum controls.

## MATERIALS AND METHODS

Enrollment occurred between October 2002 and December 2006 as part of a larger study exploring 5HT1A receptor status in postpartum depression. Subjects provided written informed consent as approved by the University of Pittsburgh Biomedical Institutional Review Board. Subjects were women who delivered a healthy, term infant in the preceding 16 weeks. Multiparous women were included. Breast and bottlefeeders were included. All subjects were interviewed with the Structured Clinical Interview for DSM-IV (28). Depression was defined by DSM IV criteria for unipolar or bipolar major depression and a 25-item Hamilton rating scale for depression score ($HAM_{25}$) $\geq$ 14. Prevalent rather than incident cases of postpartum depression were included because postpartum depression commonly begins antenatally (29)

and to maximize the generalizability of the research. Women with bipolar illness were included, because these women are particularly sensitive to depressive recurrence postpartum (30,31). Postpartum control subjects had no personal history of a major Axis I disorder and had no family history of a mood or psychotic disorder.

Subjects were excluded if they had medical or neurological illnesses likely to affect cerebral physiology or anatomy, gross abnormalities of brain structure evident by magnetic resonance images (MRI), suicidal intent, substance abuse within one year, lifetime history of substance dependence (other than nicotine), eating disorders, use of hormonal contraception, or exposure to psychotropic or other medications likely to alter cerebral physiology or monoamine function within 3 weeks (5 weeks for fluoxetine) in PD subjects.

Nine PD and seven control subjects were enrolled and imaged. Endogenous reproductive hormone exposures were characterized through menstrual cycle charting and through measurement of morning serum concentrations of estradiol, progesterone, follicle stimulating hormone (FSH), luteinizing hormone (LH), and prolactin on the day of the scan. Scan day reproductive hormones blood specimens were drawn between 9:45 am – 12:15 pm, with mean (SD) blood draw time of 10:24 (0:38). Reproductive hormones were analyzed in duplicate. Estradiol and progesterone were measured by radioimmunoassay (RIA) (Coat-A-Count, DPC, Los Angeles, CA), as previously described (32). LH, and FSH were measured using time resolved immunofluorescence (Delfia, Finland), as previously described (32). Intra and inter-assay coefficients of variation (CVs) for each of these assays are less than 10% and less than 5%, respectively. Prolactin was measured using time resolved immunofluorescence (Delfia, Finland), as described previously (32). All specimens from a given participant were analyzed in duplicate and in the same assay run to reduce variability. Between and within assay CVs were less than 10%.

PET scans were acquired on an ECAT HR+ PET scanner (Siemens, Erlangen, Germany) in three-dimensional (3D) mode [63 transaxial planes [2.4-mm thickness; in-plane resolution = 4.1 mm full-width at half-maximum (FWHM) over a 15.2-cm field of view], as previously described (24). Radiosynthesis of [*carbonyl*-$^{11}$C]WAY100635 ([$^{11}$C]WAY) was performed as previously described (33). A transmission scan was obtained to correct the PET data for attenuation effects. A dynamic emission scan (34 frames of increasing length over 90 min) was then initiated following IV bolus administration of 11.7 to 16.2 mCi (mean ± SD = 14.6 ± 1.2) of high specific activity [$^{11}$C]WAY (1.58 ± 0.71 mCi/nmol at time of injection). Arterial blood was sampled during scanning and corrected for radiolabeled metabolites to compute the plasma input function of [$^{11}$C]WAY.

There were 9 breastfeeders (4 PD and 5 controls) in the sample. Approximately 15 minutes after the conclusion of the scan, study participants expressed their milk with a Medela multi-use, electronic, double breast pump (Medela, Inc., McHenry, IL) for 10–30 minutes to reduce discomfort of breast milk engorgement and for analysis of the total radioactivity of total and WAY concentrations in milk (34).

To provide an anatomical framework for analysis of the PET data, magnetic resonance images (MRI) were obtained using a 1.5 T Signa Scanner (GE Healthcare, Milwaukee, WI) and a 3-dimensional spoiled gradient recalled (SPGR) sequence (TE = 5, TR = 25, flip angle = 40°, NEX = 1, section thickness = 1.5 mm with no intersection gap). PET images were aligned with MR images using automated image registration (35). Regions of interest (ROIs) were manually traced on the MR image using a modified version of the IDL-based (Interactive Data Language, Boulder, CO) computer program, ROITOOL, of CTI PET Systems (Knoxville, TN) according to guidelines previously published (23).

We *a priori* hypothesized 5HT1A receptor reductions in the PD relative to control group in the following regions of interest (ROI): mesiotemporal cortex, left lateral orbitofrontal cortex, and subgenual anterior cingulate cortex. These ROI are associated with mood, emotion expression, and emotion regulation (36) and are associated with 5HT1A receptor reductions in major depression (25,37). A reference region for assessing nonspecifically bound and free radioligand was defined in the cerebellum using guidelines that excluded the vermis (38) and minimized the spill-in effects from neighboring cortex (23,24,39–41). ROI analyzed in an exploratory fashion included pregenual anterior cingulate cortex, right lateral orbitofrontal cortex, postcentral gyrus, occipital cortex, and raphe nucleus.

Regional tissue time-activity concentrations were obtained from the dynamic PET image for each ROI. Logan graphical analysis with generalized linear least squares smoothing (41–43) was applied to the arterial input function and regional tissue time-activity concentrations to derive [$^{11}$C]WAY distribution volume (DV). [$^{11}$C]WAY BP (5HT1A receptor binding) was calculated as [(regional DV/cerebellar DV) − 1] (44,45). Because young individuals with major depressive disorder have evidence of regional brain volume reductions (46,47), partial volume correction (48,49) was employed to control for the possible dilutional effect of expanded CSF spaces on brain radioactivity concentrations.

Statistical inference for depression effects on 5HT1A receptor BP was conducted with multivariate analysis of variance (MANOVA) using STATA software, version 8 (Stata Corp, College Station, Tex). MANOVA was the preferred statistical test based on our prediction that 5HT1A receptor binding among distinct ROI is related (23,25,26). The assumption of equal variance in 5HT1A receptor binding between groups was satisfied.

To evaluate the effect of other variables on 5HT1A receptor BP in this small sample, we performed exploratory univariate regressions for all primary ROIs with the independent variables age, BMI, breastfeeding, duration post-birth, and hormone concentrations. Variables that were significantly associated with the dependent measure at $p \geq 0.15$ were then added to the MANCOVA. We set $\alpha = 0.01$ for the individual covariates in the MANCOVA to determine if any of these variables had important effects on 5HT1A receptor BP.

Hormonal values did not satisfy tests for normality and were therefore transformed to natural log (1 + hormone of interest). A MANOVA of lactation status on hormone concentrations was conducted. Statistical tests on group differences in demographic, clinical, and hormone data were performed with Pearson chi-square for categorical and Mann-Whitney U exact tests for continuous variables. Spearman correlations were performed to explore the relationship between 5HT1A receptor BP and estradiol concentrations.

## Results

### Subject Characteristics

Demographic and clinical data for the control and PD subjects are presented in table 1. Subjects were 4 to 13 weeks postpartum at the time of the scan. Six of nine PD subjects experienced depression onset during pregnancy; three subjects had depression onset by 3 weeks postpartum. Two depressed subjects had a history of premenstrual dysphoric disorder, one of whom also had a prior postpartum depressive episode. Four of nine PD subjects had a lifetime diagnosis of bipolar disorder [bipolar I (n=1), bipolar II (n=2), bipolar NOS (n=1)]. Seven of nine PD subjects were psychotropic drug naïve. Mean depression symptom scores ($HAM_{25}$ and EPDS) at enrollment (25.3 ± 8.5) and on the scan day (mean ± SD $HAM_{25}$ = 21.7 ± 7.9) indicated mild to moderate depression in the PD group (Table 1). Clinical evaluation on the scan day confirmed absence of hypomania, mania, and mixed episodes in all subjects. Comorbid disorders in the depressed group included past substance/alcohol use disorders (n=5), panic

disorder (n=1), social phobia (n=2), generalized anxiety (n=1), and obsessive compulsive disorder (n=3).

At 4 months post-scan, 3 PD subjects were remitted in their depression, 1 PD subject experienced depression improvement short of remission, and 5 PD subjects remained depressed. Depression symptom scores in the control group remained unchanged at four months post-scan, which confirmed a stable diagnosis of normal mood in the control sample.

### Hormone and breastfeeding data

In 13 out of 16 subjects, estradiol, progesterone, LH and FSH concentrations on the scan day were consistent with early follicular phase or anovulation, as would be expected in women who are 4–13 weeks postpartum (Table 1). One PD subject had progesterone concentrations of 7.96 ng/ml at intake and 14.38 ng/ml on the scan day which suggested 2 possible menstrual cycles prior to her scan, although she denied menstrual bleeding. Pregnancy was excluded by urine pregnancy test on the scan day. One PD subject was scanned at mid-cycle (on the basis of high estradiol concentration on the day preceding the PET scan). One control subject had unusually high FSH (39.3 IU/L), potentially suggestive of perimenopause or premature ovarian failure. Hormone concentrations were not significantly different between groups. Two control and two PD subjects reported menstrual bleeding prior to the scan day.

There was a significant effect of breastfeeding status on the hypothalamic-pituitary-ovarian axis hormone concentrations estradiol, progesterone, LH, FSH, and prolactin [Wilks' lambda=0.2056; $F(5,10)=7.73$, $p=0.003$]. Post-hoc testing indicated that breastfeeding was significantly associated with lower estradiol [$F(1,14)=8.31$, $p=0.01$], progesterone [$F(1,14)=4.33$, $p=0.06$], and FSH concentrations [$F(1,14)=5.18$, $p=0.04$] and higher prolactin concentrations [$F(1,14)=26.25$, $p=0.0002$], as would be expected (50).

### PET data

Mean [$^{11}$C]WAY BP values (5HT1A receptor binding) for PD and control groups are presented in table 2. MANOVA of [$^{11}$C]WAY BP in the three a priori regions of interest indicated a significant main effect of depression [$F(3,12)=13.67$, Wilks' lambda=0.23, $p=0.0004$] (Figure 1). Post hoc ANOVA tests detected significant depression effects on reducing [$^{11}$C]WAY BP in mesiotemporal cortex [21.6% mean decrease; $F(1,14)=22.5$, $p= 0.0003$], subgenual cingulate cortex [27.6% mean decrease; $F(1,14)=23.4$, $p=0.0002$], and left lateral orbitofrontal cortex [17.9% mean decrease; $F(1,14)=7.13$, $p=0.018$]. Perinatal depression was also associated with reduced [$^{11}$C]WAY BP in secondary ROI [$F(5,10)= 3.24$, Wilks' lambda=.38, $p=0.054$], with the most significant decreases present in right lateral orbitofrontal cortex [23.4% mean decrease; $F(1,14)=8.72$, $p=0.011$) and pregenual anterior cingulate cortex [23.4% mean decrease; $F(1,14)=17.2$, $p=0.001$). [$^{11}$C]WAY BP was not significantly different between subjects with unipolar versus bipolar depression (Figure 2).

In our exploratory analyses, age, BMI, and breastfeeding status reached the critical threshold of $p \leq 0.15$ in univariate regressions. When entered with depression status into the MANCOVA, only depression reached the critical threshold of $p \leq 0.01$.

Injected [$^{11}$C]WAY dose, metabolism of [$^{11}$C]WAY over time, and protein binding of [$^{11}$C]WAY was not different between groups. [$^{11}$C]WAY BP was not correlated with estradiol concentrations in the entire sample or to $HAM_{25}$ score in the depressed subgroup.

The distribution volume (DV) of free and non-specifically bound [$^{11}$C]WAY as estimated by the cerebellum (CER) was $0.73 \pm 0.17$ in the control group and $0.87 \pm 0.31$ in the PD group [p (MWU,2-tailed, exact) = 0.47]. Notably, one subject in the PD group had a CER DV value that was nearly 2 standard deviations greater that the PD CER DV mean. When the analysis

excluded this subject, mean ± SD CER DV of control and PD groups were similar [control = 0.73 ± .17, PD = 0.79 ± .20] and the main findings of reduced [$^{11}$C]WAY BP in the PD group in mesiotemporal, lateral orbitofrontal, and anterior cingulate cortices remained significant.

## Discussion

These preliminary findings demonstrated that postsynaptic 5HT1A receptor BP was reduced in women with PD versus control by a similar magnitude (>20%) as shown previously in non-postpartum samples. Our findings suggest that the previously-described association between depression andreduced 5HT1A receptor binding also extends to the puerperium, a time of multiple physiologic disruptions (metabolic, hormonal, sleep deprivation). Anterior cingulate, mesiotemporal, and lateral orbitofrontal cortices were the brain regions of greatest 5HT1A receptor differences between groups. Because postsynaptic 5HT1A receptors in these brain regions modulate neuronal circuits that regulate emotion, 5HT1A receptor decreases could mediate the heightened anxiety, depressed mood, and suboptimal infant attunement associated with PD. Other roles for postsynaptic 5HT1A receptors through their localization on astrocytes and other glia (51) include release of trophic factors that promote 5HT neuronal outgrowth (52). Reductions of 5HT1A receptors in PD, therefore, could impede the neuroprotection of the broader central nervous system that is needed for optimal mental health.

Because these PD subjects were largely psychotropic drug naïve and could participate in the study unmedicated, the sample may have been less severely depressed or functionally impaired than other PD women. While this is a conservative bias, it is noteworthy that 5HT1A receptor reductions were apparent in a potentially milder sample of PD women. The detection of a significant effect of depression on 5HT1A receptor BP in this small cohort may be attributable to the homogeneous demographic and reproductive characteristics of the sample. The effect does not appear to be a result of the high rate of women with bipolar disorder in the depressed sample, since there didn't appear to be a difference in 5HT1A receptor BP between the unipolar and bipolar subjects. The ability to delineate unipolar versus bipolar neurobiological differences in the puerperium isan important future research direction. Bipolar I disorder is usually a more severe and persistent disorder than unipolar disorder and may be associated with greater neuropathology (36), including 5HT1A receptor deficits (23); however, bipolar spectrum disorder has been less studied.

Because the majority of women in this study experienced depression onset during pregnancy (n=6 out of 9), it is not possible to determine whether timing of childbearing-related depression onset has an effect on 5HT1A receptor binding in postpartum depressed women. In addition, whether the 5HT1A receptor deficit in PD represents a trait abnormality related to depression vulnerability or a state-related change that emerges in women with mood disturbance during the hormonal shifts of childbearing remains an intriguing question that requires additional study. Prior research in a male sample suggested that 5HT1A receptor deficits persist after MDD remission (53). Similar research in postpartum depression would be worthwhile.

Although 5HT1A receptor binding was not related to estradiol concentration, 5HT1A receptor binding may be related to other components of the postpartum endocrine milieu. A possible mechanism for 5HT1A receptor reductions in PD is the known hypercortisolemia of the puerperium, which is less responsive to negative feedback in postpartum depressed relative to postpartum control women (17,54). Whether breastfeeding, associated with attenuated glucocorticoid responses to stress (55,56), modulates 5HT1A receptor binding is another area for further exploration. Breastfeeding was associated with a trend toward increased 5HT1A receptor BP in subgenual cingulate gyrus in exploratory analyses.

It is noteworthy that 5HT1A receptor BP *increases* in MDD have been reported in individuals with enrichment of the G allele distribution of the C(−1019)G 5-HT1A promoter polymorphism (26,57). It would be interesting to examine genetic factors in future studies of 5HT1A receptor BP in unipolar and bipolar PD.

Pregnancy and the puerperium present a unique multidimensional challenge to the homeostasis of women. Biological, psychological, and social states change dramatically over the course of childbearing. This is the first study to measure neuroreceptor changes in the early puerperium which may underlie susceptibility to depression. Recognition of this neurobiological deficit in PD suggests that development of 5HT1A receptor directed treatments (including, perhaps, encouragement of breastfeeding or administration of oxytocin analogues) may be highly beneficial for the treatment and prevention of this disabling disorder.

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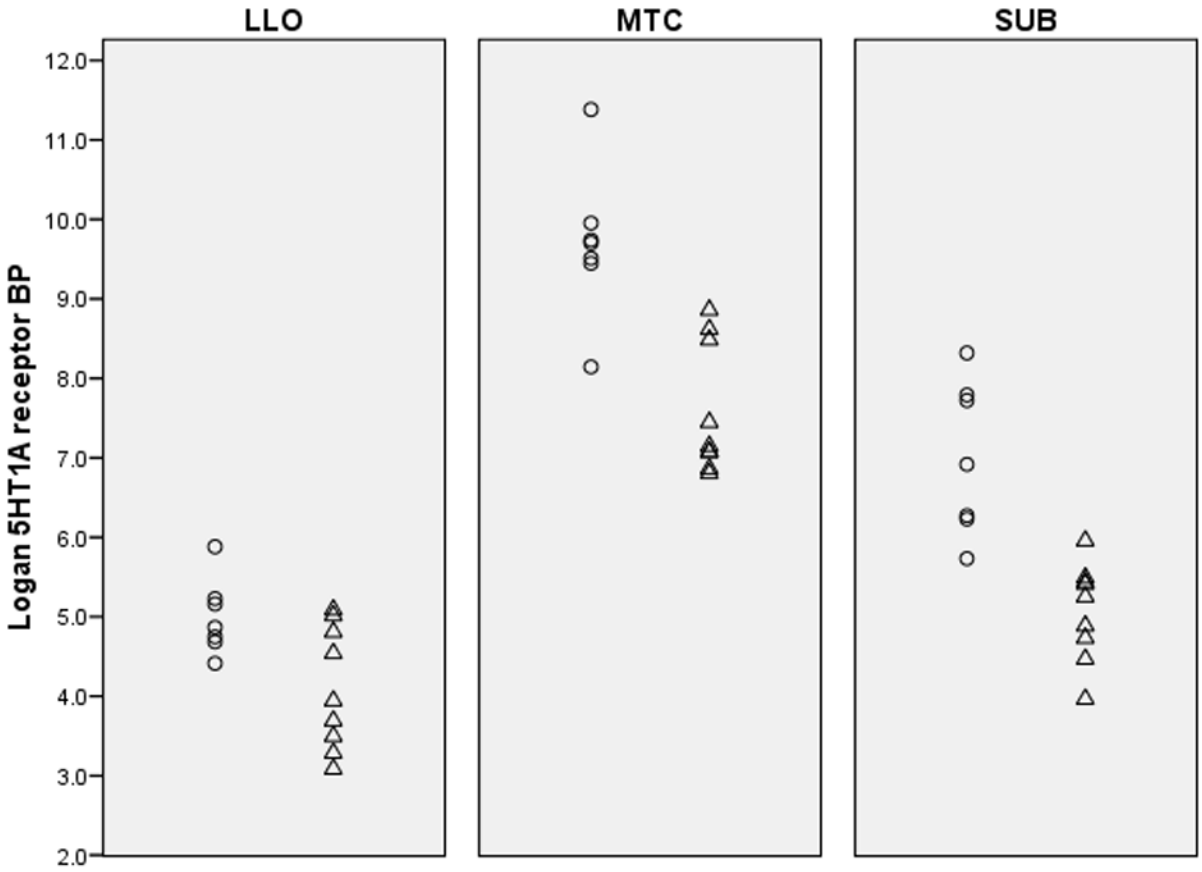


**Figure 1.**
Dot plots indicate that 5HT1A receptor BP is lower in postpartum depressed (△) relative to postpartum control subjects (○) in primary regions of interest. Abbreviations: LLO=left lateral orbitofrontal cortex, MTC=mesiotemporal cortex, SUB=subgenual anterior cingulate.

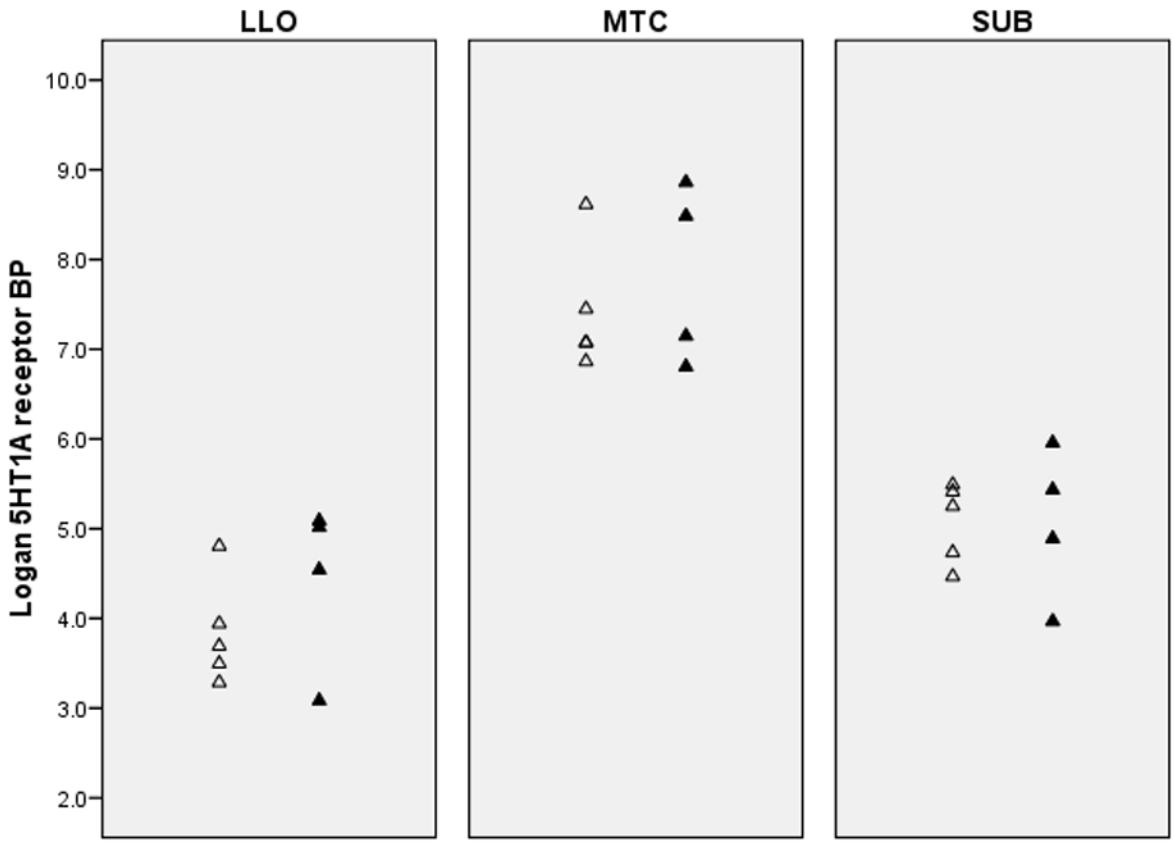


**Figure 2.**
Dot plots indicate that 5HT1A receptor BP is not different between unipolar (△) and bipolar (▲) depressed subjects in all primary regions of interest. Abbreviations as per Figure 1.

## Table 1

Subject characteristics [mean (SD)]

| | CONTROL | PD | Statistics |
|---|---|---|---|
| **n** | 7 | 9 | |
| **INTAKE DATA** | | | |
| **Age** | 33.0 (3.9) | 26.9 (7.9) | $MWU_{exact}$ = 13.0; p=0.06 |
| **Bipolar number (%)** | 0 (0%) | 4 (44%) | n/a |
| **Antidepressant naïve (%)** | 7 (100%) | 7 (77.8%) | n/a |
| **Breastfeeder number (%)** | 5 (71%) | 4 (44%) | Pearson chi2 = 1.2; p = 0.28 |
| **$HAM_{25}$*** | 3.1 (2.3) | 21.7 (7.9) | $MWU_{exact}$ = 4.5; p=0.003 |
| **EPDS*** | 1.4 (1.4) | 13.3 (3.1) | $MWU_{exact}$ = 0.0; p=0.000 |
| **Weeks post-birth** | 11.1 (2.2) | 9.6 (2.9) | $MWU_{exact}$ = 19.0; p=0.21 |
| **BMI** | 26.1 (3.7) | 27.6 (3.8) | $MWU_{exact}$ = 25.5; p=0.55 |
| **LH (IU/L)** | 5.0 (6.7) | 2.9 (2.4) | $MWU_{exact}$ = 25.0; p=0.54 |
| **FSH† (IU/L)** | 10.4 (12.8) | 6.4 (1.9) | $MWU_{exact}$ = 31.0; p=1.00 |
| **Estradiol (pg/ml)** | 36.1 (20.5) | 45.5 (18.6) | $MWU_{exact}$ = 21.0; p=0.30 |
| **Progesterone (ng/ml)** | 0.4 (0.3) | 2.2 (4.6) | $MWU_{exact}$ = 20.0; p=0.24 |
| **Prolactin (ng/ml)** | 23.9 (22.3) | 19.6 (26.0) | $MWU_{exact}$ = 26.0; p=0.61 |

* p(MWU,2-tailed) < 0.02.

† Wide variability in FSH is attributed to a postpartum control subject who might be experiencing ovarian failure or early perimenopause with FSH = 39.3 IU/L. Abbreviations: EPDS = Edinburgh Postnatal Scale for Depression (58); $HAM_{25}$ = 25-item Hamilton Scale for Depression (59).

## Table 2

5HT1A receptor BP [mean (SD)] measured with [$^{11}$C]WAY100635 derived with 90 minutes of Logan graphical analysis, corrected for partial volume effects.

| | PP-C | PP-D | % DIFF |
|---|---|---|---|
| **A priori regions of interest** * **[F(3,12)=13.67, Wilks' lambda=0.23, p=0.0004]** | | | |
| Mesiotemporal cortex | 9.69 (0.95) | 7.60 (0.82) | 21.66 |
| L. lateral orbitofrontal cortex | 5.00 (0.48) | 4.11 (0.77) | 17.85 |
| Subgenual anterior cingulate | 7.00 (0.97) | 5.07 (0.61) | 27.60 |
| **Post hoc regions of interest** * **[F(5,10)= 3.24, Wilks' lambda=.38, p=0.054]** | | | |
| Pregenual anterior cingulate | 5.80 (0.68) | 4.44 (0.62) | 23.38 |
| R. lateral orbitofrontal cortex | 5.24 (0.64) | 4.01 (0.94) | 23.41 |
| Postcentral gyrus | 4.06 (0.67) | 3.29 (0.56) | 19.13 |
| Occipital cortex | 2.20 (0.26) | 1.78 (0.32) | 19.04 |
| Raphe nucleus (Presynaptic region) | 4.09 (0.45) | 3.66 (0.62) | 10.58 |

* Multivariate analysis of variance (MANOVA) test of the main effect of depression on 5HT1A receptor BP.