Neuropsychopharmacology (2012) 37, 1422–1432

www.neuropsychopharmacology.org

Postpartum and Depression Status are Associated With Lower [^{11}C]raclopride BP_{ND} in Reproductive-Age Women

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The early postpartum period is associated with increased risk for affective and psychotic disorders. Because maternal dopaminergic reward system function is altered with perinatal status, dopaminergic system dysregulation may be an important mechanism of postpartum psychiatric disorders. Subjects included were non-postpartum healthy ($n=13$), postpartum healthy ($n=13$), non-postpartum unipolar depressed ($n=10$), non-postpartum bipolar depressed ($n=7$), postpartum unipolar ($n=13$), and postpartum bipolar depressed ($n=7$) women. Subjects underwent 60 min of [^{11}C]raclopride–positron emission tomography imaging to determine the nondisplaceable striatal $D_{2/3}$ receptor binding potential (BP_{ND}). Postpartum status and unipolar depression were associated with lower striatal $D_{2/3}$ receptor BP_{ND} in the whole striatum ($p=0.05$ and $p=0.02$, respectively) that reached a maximum of 7–8% in anteroventral striatum for postpartum status ($p=0.02$). Unipolar depression showed a nonsignificant trend toward being associated with 5% lower BP_{ND} in dorsal striatum ($p=0.06$). $D_{2/3}$ receptor BP_{ND} did not differ significantly between unipolar depressed and healthy postpartum women or between bipolar and healthy subjects; however, $D_{2/3}$ receptor BP_{ND} was higher in dorsal striatal regions in bipolar relative to unipolar depressives ($p=0.02$). In conclusion, lower striatal $D_{2/3}$ receptor BP_{ND} in postpartum and unipolar depressed women, primarily in ventral striatum, and higher dorsal striatal $D_{2/3}$ receptor BP_{ND} in bipolar relative to unipolar depressives reveal a potential role for the dopamine (DA) system in the physiology of these states. Further studies delineating the mechanisms underlying these differences in $D_{2/3}$ receptor BP_{ND}, including study of DA system responsivity to rewarding stimuli, and increasing power to assess unipolar *vs* bipolar-related differences, are needed to better understand the affective role of the DA system in postpartum and depressed women.
Neuropsychopharmacology (2012) **37,** 1422–1432; doi:10.1038/npp.2011.328; published online 18 January 2012

Keywords: $D_{2/3}$ receptors; postpartum depression; PET; women; major depressive disorder

INTRODUCTION

Postpartum depression (PPD) occurs in 14.5% of women within the first 3 months of postpartum (Gaynes *et al*, 2005; Wisner *et al*, 2006), and is associated with adverse consequences for the mother (England, 1994; Kendler *et al*, 1993), child (Goodman and Gotlib, 1999; Murray, 1992), and family (Goodman, 2004). Despite its high prevalence and pernicious effects on future generations, little is known about the neurobiological mechanisms of PPD and whether they are distinct from non-PPD mechanisms. Greater understanding of PPD neurobiology can improve nosological clarity as well as facilitate development of more effective treatments. In this study, we evaluated dopaminergic mechanisms of PPD based upon alterations in dopamine (DA) system function in postpartum rodents and in major depressive disorder.

Preclinical rodent studies converge upon heightened DA system function during the postpartum period. Increased postpartum dopaminergic activity is essential for maternal–pup caregiving (Hansen *et al*, 1991; Stolzenberg and

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Received 20 June 2011; revised 21 October 2011; accepted 3 December 2011

Numan, 2011), with positive correlations between suckling and maternal striatal DA (Champagne *et al*, 2004). Higher striatal DA concentrations were detected both at 4 days postpartum compared with estrous controls (Glaser *et al*, 1990) and in parous compared with nulliparous rodents (Byrnes *et al*, 2001). Striatal D_2 receptor density was lower in late pregnancy relative to diestrus and early pregnancy (Bakowska and Morrell, 1995), but postpartum, D_2 receptor agonists induced greater stereotypy and disruption of prepulse inhibition in parous compared with nulliparous rodents (Byrnes *et al*, 2001). The perinatal hormones estradiol, progesterone, cortisol, prolactin and oxytocin are all potential modulators of DA and D_2 receptor function (Lammers *et al*, 1999; Tonnaer *et al*, 1989). Evidence of striatal dopaminergic changes in postpartum humans is limited, but has been a subject of speculation given the 24-fold elevated risk for postpartum psychosis in the first postpartum month (Kendell *et al*, 1987a; Munk-Olsen *et al*, 2006). Whether this is related to postpartum DA concentration increases or to increased D_2 receptor density or affinity (Petraglia *et al*, 1987) has not been studied directly. Greater monoamine catabolic enzyme availability reported in early postpartum women (Meyer J, 2008, personal communication) may be a compensatory mechanism for monoamine elevations.

Deficits in striatal dopaminergic function in major depression are well described (Dunlop and Nemeroff, 2007; Nestler and Carlezon, 2006; Willner *et al*, 2005) and highlighted by mood elevation with DA agonists (Cassano *et al*, 2004; Post *et al*, 1978), mood depression with DA antagonists or DA depleting drugs (Willner, 1983; Willner *et al*, 2005), lower CSF and serum concentrations of DA and DA metabolites (Sher *et al*, 2006), lower DA transporter and D_1 receptor binding (Cannon *et al*, 2009; Nutt, 2006), lower pursuit of reward in laboratory simulations, and lower striatal activity to rewards (Forbes and Dahl, 2005; Forbes *et al*, 2009; Pizzagalli *et al*, 2009). $D_{2/3}$ receptors are of particular interest in major depression because of their dense concentration in striatum, their role in antidepressant response (Willner *et al*, 2005; Zarate *et al*, 2004), and their regulatory role within the larger striatal DA system (Grace, 1991).

The positron emission tomography (PET) radioligand [^{11}C]raclopride, a $D_{2/3}$ receptor antagonist that is sensitive to endogenous DA transmission, binds primarily to D_2 receptors (Narendran *et al*, 2006), but also to D_3 receptors, which are concentrated in ventral striatum (Gurevich and Joyce, 1999). Depressed compared to healthy individuals revealed alternatively higher (D'haenen and Bossuyt, 1994; Meyer *et al*, 2006; Shah *et al*, 1997) or equivalent (Ebert *et al*, 1996; Parsey *et al*, 2001, Schneier F, 2012, personal communication, 2012) $D_{2/3}$ receptor binding. Inconsistencies may stem from lack of discrimination between ventral and dorsal striatal $D_{2/3}$ receptor binding, failure to control for concurrent medication use and comorbid psychiatric diagnoses, lack of power to detect gender-specific differences in $D_{2/3}$ receptor binding, and lack of control for menstrual cycle phase (Wong *et al*, 1988). In studies of homogenous subject groups, such as psychomotorically slowed or hospitalized subjects (Ebert *et al*, 1996; Meyer *et al*, 2006; D'haenen and Bossuyt, 1994), depressed individuals had higher $D_{2/3}$ receptor binding relative to controls, and psychomotor slowing was positively correlated with $D_{2/3}$ receptor binding (Meyer *et al*, 2006; Shah *et al*, 1997) measured using techniques sensitive to intrasynaptic DA levels.

Interpretation of [^{11}C]raclopride binding potential (BP_{ND}) presents a challenge to researchers because it can reflect disparate physiological processes. [^{11}C]raclopride BP_{ND} is a measure determined both by density and affinity of $D_{2/3}$ receptors, as well as by the availability of $D_{2/3}$ receptors to bind [^{11}C]raclopride, when not already bound by intrasynaptic DA (Laruelle, 2000). Conditions of high phasic DA release, such as during the rewarding stimulus of monetary receipt, will lead to competitive binding of intrasynaptic DA to $D_{2/3}$ receptors, thus leading to reduced [^{11}C]raclopride BP_{ND} (Zald *et al*, 2004).

Using [^{11}C]raclopride–PET in reproductive-aged women varied for depression and postpartum status, we hypothesized that, relative to non-postpartum healthy women, striatal $D_{2/3}$ receptor binding would be lower in postpartum women due to higher levels of phasic DA release, associated with mother–infant caregiving behaviors, such as nursing, that would compete for [^{11}C]raclopride binding. Given HPA axis alterations through 12 weeks postpartum (Magiakou *et al*, 1996), we further hypothesized that a corticosteroid-related reduction of $D_{2/3}$ receptor expression could contribute to lower [^{11}C]raclopride BP_{ND} in postpartum women. We considered two competing hypotheses for depressed women: (1) Depression would be associated with increased $D_{2/3}$ receptor BP_{ND} on the basis of such findings in the majority of prior PET studies of depression and lower cerebrospinal fluid DA concentrations in depression (Sher *et al*, 2006), conceivably leading to $D_{2/3}$ receptor upregulation (Grace, 1991). (2) Depression would be associated with decreased $D_{2/3}$ receptor BP_{ND} due to the important role of chronic stress in depression in reproductive-aged women and lack of psychomotoric slowing in the selected sample (Dziedzicka-Wasylewska *et al*, 1997). We hypothesized lower $D_{2/3}$ receptor BP_{ND} in PPD relative to healthy controls given the combined contributions of increased phasic DA release of motherhood and decreased expression of $D_{2/3}$ receptors due to hypercortisolemia in postpartum women.

MATERIALS AND METHODS

Subjects

Sixty-three women were enrolled into four groups: non-postpartum healthy ($n=13$), postpartum healthy ($n=13$), non-postpartum depressed ($n=17$ total; 10 unipolar and 7 bipolar), and postpartum depressed ($n=20$ total; 13 unipolar and 7 bipolar) women. The structured clinical interview for DSM-IV (First *et al*, 1998) was used to assess psychiatric status. Healthy subjects had no personal history of an axis I disorder, no family history of a mood or psychotic disorder, and a 17-item Hamilton Rating Scale for Depression score (HAM_{17}) $\leqslant 7$ or Beck Depression Inventory (BDI) score $\leqslant 9$. All depressed subjects met DSM-IV criteria for a current major depressive episode and had a $HAM_{17} \geqslant 14$ or $HAM_{25} \geqslant 18$ in the past month and were scanned during the depressive episode, at which time mean HAM_{25} was 19.8 ± 7.6 and 20.1 ± 7.5 for unipolar and bipolar subjects, respectively. Individuals with bipolar depression also met DSM-IV criteria for past manic or

hypomanic episodes. The psychomotor retardation item of the HAM-D on the scan day was 0 (none) or 1 (slight) for 91% of unipolar and 86% of bipolar subjects. Prevalent rather than incident cases of PPD were included to maximize the generalizability of the research, as PPD commonly begins antenatally (Stowe *et al*, 2005). We assessed maternal–infant attachment in postpartum women with a 19-item self-report scale (Condon and Corkindale, 1998) completed on the scan day in order to characterize the sample and to explore associations with $D_{2/3}$ receptor binding. The psychometric properties of this scale were established by its authors in a sample of 260 perinatal women with a factor analysis that showed clustering of items onto three factors: quality of attachment, pleasure in interaction, and absence of hostility.

Postpartum subjects (both breast and bottle feeders) were included if they delivered a healthy, term infant in the preceding 16 weeks and were not using hormonal contraception. We acquired image data early postpartum or in the early follicular phase (day 3–9 after onset of menses) in order to minimize the potential influence of circulating ovarian hormones on $D_{2/3}$ receptor BP_{ND} (Wong *et al*, 1988). 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 imaging, suicidal intent, substance abuse within the past year, lifetime history of substance dependence (other than nicotine), or exposure to psychotropic or other medications likely to alter cerebral physiology or monoamine function within the 3 weeks (5 weeks for fluoxetine) before scanning.

Subjects provided written informed consent as approved by the University of Pittsburgh Biomedical Institutional Review Board. The sample of healthy control non-postpartum women was supplemented by a concurrently run study of $D_{2/3}$ receptor binding where healthy women served as comparators for women with eating disorders. Inclusion criteria were nearly identical to those of our study, with the exception that BDI rather than HAM_{17} score was used to measure depressive symptoms. Of note, the Radiation Safety Committee of the University of Pittsburgh approved no interruption in lactation after completion of the PET scan on the basis of $<1\,\mu Sv$ radioactivity detected in the breast milk samples of the first five participants (Moses-Kolko *et al*, 2005).

PET Imaging and Analyses

All subjects underwent single-acquisition PET imaging on an ECAT HR + PET scanner (Siemens, Erlangen, Germany) in three-dimensional (3D) mode (63 transaxial planes (2.4 mm in thickness; in-plane resolution = 4.1 mm full-width at half-maximum over a 15.2-cm field of view; Drevets *et al*, 2001). Radiosynthesis of [11C]raclopride was performed as previously described (Halldin *et al*, 1991). A transmission scan was obtained to correct the PET data for attenuation effects. A dynamic emission scan (22 frames of increasing length over 60 min) was then initiated following IV bolus administration of 7.8 to 11.2 mCi (mean ± SD = 10.1 ± 0.9) of high specific activity [11C]raclopride (1.60 ± 0.43 mCi/nmol at time of injection). Arterial blood was sampled during scanning and corrected for radiolabeled metabolites to compute the plasma input function of [11C]raclopride in a subset of subjects ($n = 26$ of 63; see Table 2 for number of subjects per group).

To provide an anatomical framework for analysis of the PET data, magnetic resonance images were obtained using a 1.5 T Signa Scanner (GE Healthcare, Milwaukee, WI) and a 3D spoiled gradient recalled sequence (TE = 5, TR = 25, flip angle = 40°, NEX = 1, section thickness = 1.5 mm with no intersection gap). PET images were aligned to MR images using Automated Image Registration (Woods *et al*, 1993). The BP_{ND} was examined in anatomically and functionally distinct (Drevets *et al*, 2001) subregions of the striatum. Regions of interest (ROIs) in the anteroventral striatum (AVS), dorsal caudate (DCA), dorsal putamen (DPU), and ventral putamen (VPU) 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 previously published guidelines (Drevets *et al*, 2001). A reference region for assessing the volume of distribution of nondisplaceable (V_{ND}) uptake was defined in the nonvermis cerebellum (CER), which is devoid of $D_{2/3}$ receptors (Hall *et al*, 1994).

Regional tissue time–activity concentrations curves were obtained from the dynamic PET data for each ROI. Regional [11C]raclopride BP_{ND} values were determined using a simplified reference tissue method (SRTM; Gunn *et al*, 1998; Lammertsma *et al*, 1996). In subjects for whom arterial blood was sampled ($n = 26$), Logan graphical analysis (Logan *et al*, 2001) additionally was applied to the arterial input function and regional tissue time–activity concentrations to derive the [11C]raclopride distribution volume (V_T) measure that was used to compute regional BP_{ND} values as $((V_{T-ROI}/V_{ND})-1$; Lammertsma *et al*, 1996; Mintun *et al*, 1984). Regional BP_{ND} values were determined for all subjects using the SRTM as $k_3/k_4 = (B_{avail}/K_d)f_{ND}$, which is equivalent to $(V_{T-ROI}/V_{ND})-1$, where k_3 is the association rate of [11C]raclopride to $D_{2/3}$ receptor, k_4 is the dissociation rate of [11C]raclopride from $D_{2/3}$ receptors, B_{avail} is the available $D_{2/3}$ receptor density, K_d is the equilibrium dissociation constant, and f_{ND} is the free fraction of [11C]raclopride in tissue (Lammertsma *et al*, 1996; Mintun *et al*, 1984).

Hormone Analyses

Reproductive status was assessed through self-reported menstruation charting and scan day reproductive hormone concentrations, measured between 6:00 am and 12:15 pm on the scan day. Specimens were analyzed in duplicate and were assayed as part of a single batch to reduce variability. Estradiol and progesterone concentrations were measured by radioimmunoassay (Coat-A-Count, DPC, Los Angeles, CA). Intra- and inter-assay coefficients of variation for each of these assays are <10% and <5%, respectively. Prolactin concentration was measured using time-resolved immunofluorescence (Delfia, Finland), as described previously (Berga *et al*, 1997). Between- and within-assay CVs were <10%. In the subgroup of non-postpartum controls from a concurrently run study of $D_{2/3}$ receptor binding in eating disorders, estradiol and progesterone concentrations were measured by Chemiluminescent Immunoassay

System (Advia Centaur, Walpole, Massachusetts). Intra- and inter-assay coefficients of variation for this assay were <10% for estradiol and <13 and 6%, respectively, for progesterone. Owing to assay variability for measurement of reproductive hormones, and low power to determine statistical significance of many independent variables, hormone concentrations were not included in the statistical model for $D_{2/3}$ receptor binding.

Statistical Analyses

Statistical analyses were performed with STATA software, version 10 (Stata Corp, College Station, TX) and SPSS software version 17. Subject characteristics were compared with Pearson's χ^2 for categorical, and *t*-tests and ANOVAs for continuous variables. To be complete, we examined differences by postpartum status, depression status, and group (six groups varied for postpartum, unipolar, and bipolar status, and three groups varied for depressive status: no depression, unipolar, and bipolar depression). Pearson correlations were used to measure the agreement between SRTM and Logan-derived $D_{2/3}$ receptor BP_{ND} in the subset of subjects with arterial data.

Mixed-effects regression modeling was used to estimate the fixed effects of age, region, depression, postpartum status, and two-way interactions on $D_{2/3}$ receptor BP_{ND}. We conducted a separate regression each for ventral (AVS and VPU) and dorsal (DPU and DCA) striatal regions based upon their functional differences (Haber *et al*, 2000). On the basis of differences between unipolar and bipolar diagnosis relative to $D_{2/3}$ receptor BP_{ND} in our analyses, we conducted separate models for unipolar and bipolar depression (supplementary data contain regression results for unipolar and bipolar groups combined). ROI was the repeated-measure variable. Exploratory univariate mixed-effect regressions on $D_{2/3}$ BP_{ND} were conducted with the following independent variables: body mass index (BMI), breastfeeding status, race, parity, weeks post birth, smoking, mother–infant attachment, Hamilton anxiety, HAM_{25} scores, and EPDS scores. Variables that were significantly associated with the dependent measure at $p \leqslant 0.15$ were then added to the mixed-effect model. We used $-2\Delta\log$ likelihood to test for the significance of an independent variable or interaction.

RESULTS

Subject Characteristics

Sixty-three [11C]raclopride–PET scans were acquired and analyzed according to published methods (Drevets *et al*, 2001). Demographic and clinical data for all subjects are presented in Table 1. Non-postpartum women (31%) were more likely to smoke than postpartum women (6%; $p = 0.02$). There were no smokers in the postpartum healthy group. BMI was not statistically different by group, but trended toward being higher in the postpartum relative to non-postpartum women ($p = 0.06$). When examined by subject group, although not statistically significant, the unipolar depressed group's BMI was remarkably similar between postpartum (27.8 ± 5.0) and non-postpartum women (27.3 ± 7.1), whereas BMI was higher in the postpartum group (26.9 ± 3.8 and 26.9 ± 3.3) for both healthy control women and women, with bipolar depression, relative to the non-postpartum group (23.6 ± 3.7 and 23.9 ± 5.6; Figure 2). All healthy and 61% of depressed women were antidepressant naïve. Women with bipolar disorder were significantly more likely to have prior psychotropic exposure compared with women with unipolar disorder ($p < 0.001$). No subject had prior antipsychotic exposure. All subjects were free of psychotropic drug exposure for a minimum of 3 weeks before scanning. Depressed women were mild-to-moderately depressed on the scan day ($HAM_{25} = 19.9 \pm 7.4$) and had significantly higher depression and anxiety ratings that did healthy women ($p < 0.001$), as expected. There was no difference between HAM_{25} ratings for unipolar (19.8 ± 7.6) and bipolar women (20.1 ± 7.5) on the scan day. Quality of mother–infant attachment and absence of hostility were significantly greater in healthy compared with unipolar depressed postpartum women ($p = 0.02$ and $p = 0.01$).

Variability of within-group hormone concentrations and use of two different laboratories limited the ability to detect between-group differences. As expected, postpartum relative to non-postpartum women had higher prolactin concentrations ($p = 0.002$), although it is noteworthy that prolactin data were missing for eight non-postpartum healthy subjects and one postpartum depressed subject. Low-range estradiol and progesterone concentrations in 54 of 62 subjects suggested that the scan was obtained during the early follicular menstrual cycle phase or during postpartum anovulation, as planned. Eight subjects were scanned in their mid-cycle or luteal phase despite efforts to obtain the scan during low levels of reproductive hormones.

PET Data (Table 2, Figure 1)

Consistent findings across all models were as follows: $D_{2/3}$ receptor binding decreased across all ROI with increasing age, as reported previously, at an approximate rate of 0.2–0.3 BP_{ND} units/decade ($p < 0.001$). ROI was a significant covariate in all models, signifying the expected lower $D_{2/3}$ receptor BP_{ND} in AVS and DCA relative to VPU and DPU ($p < 0.001$). PET data were examined for potential confounds as follows: CER V_T (V_{ND}) was not statistically different between the six groups for those cases in whom an arterial plasma input function was obtained (Table 2). There was no significant group difference in radiotracer mass or R1 (rate of radiotracer delivery to the ROI relative to radiotracer delivery to CER) in any ROI. Logan and SRTM BP_{ND} values were highly correlated (Pearson's *r*) in all regions (AVS 0.89, DCA 0.99, DPU 0.97, VPU 0.91; $p < 0.001$; $n = 26$). The agreement between Logan and SRTM BP_{ND} values supports the use of simpler SRTM BP_{ND} values in the maximal data set for statistical modeling of $D_{2/3}$ receptor binding.

In exploratory univariate models, both BMI and weeks post birth were inversely related with $D_{2/3}$ BP_{ND} ($p < 0.15$). All other independent variables tested were not significantly associated with $D_{2/3}$ BP_{ND} ($p > 0.15$), including injected [11C]raclopride mass, breastfeeding status, race, parity, smoking, mother–infant attachment, Hamilton anxiety, and HAM_{25} and EPDS scores. Weeks post birth proved nonsignificant in the full models.

Table 1 Scan Day Sample Characteristics

	Non-postpartum women						Postpartum women					
	Healthy ($n=13$)		Unipolar dep ($n=10$)		Bipolar dep ($n=7$)		Healthy ($n=13$)		Unipolar dep ($n=13$)		Bipolar dep ($n=7$)	
	N	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%
Caucasian	9	69.2	5	50.0	6	85.7	12	92.3	9	69.2	5	71.4
Smoker[a]	3[A]	23.1	4	40.0	2	28.6	0	0	1	7.7	1	14.3
Antidepressant naive[b]	13	100	8	80.0	1	14.3	13	100	11	91.7	2	28.6
Primiparous (has given birth to only one child)	—	—	—	—	—	—	4	30.8	4	30.8	3	42.9
Breastfeeding	—	—	—	—	—	—	7	53.9	9	69.2	4	57.1
Postpartum amenorrhea	—	—	—	—	—	—	8[A]	61.5	7[E]	0.54	4[F]	0.57
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age	30.7	7.2	29.9	6.0	24.6	5.5	30.8	5.6	29.9	7.5	27.7	8.1
Body mass index[c]	23.6	3.7	27.3	7.1	23.9	5.6	26.9	3.8	27.8	5.0	26.9	3.3
Time since childbirth (weeks)	—	—	—	—	—	—	10.6	2.5	10.3	2.9	8.3	3.4
Estradiol (pg/ml)	82.7	115.5	50.8	18.0	55.2	27.7	60.4	55.5	44.2	15.2	44.3[F]	10.0
Progesterone (pmol/l)	0.6	0.2	1.5	2.8	1.2	0.86	0.7	0.7	1.9	4.1	0.48[F]	0.31
Prolactin (ng/ml)[d]	4.2[B]	2.5	5.1	1.4	8.8	7.6	21.7	25.2	19.5	15.6	26.8[F]	31.5
Hamilton Depression Rating Scale score (25 items)[e]	2.0[B]	1.6	19.7[D]	7.2	16.0	8.3	3.5	3.0	19.9	15.6	24.4	4.0
Hamilton Anxiety Rating Scale score[f]	1.6[B]	2.1	14.4	8.7	14.6	9.7	0.9[A]	1.5	13.4[A]	8.3	16.7	4.3
Beck Depression Scale score	1.6[C]	3.0	—	—	—	—	—	—	—	—	—	—
Edinburgh Postnatal Scale for Depression score[g]	3.0[B]	4.6	13.8	3.7	14.8[B]	6.4	1.9[A]	2.3	14.0[E]	5.2	15.3[G]	8.5
Quality of mother–infant attachment[h]	—	—	—	—	—	—	43.1	1.6	37.7[E]	6.9	38.4[F]	4.1
Absence of maternal–infant hostility[i]	—	—	—	—	—	—	21.2	2.5	17.0[E]	3.6	17.8[F]	4.6
Pleasure in maternal–infant interaction	—	—	—	—	—	—	22.3	2.3	19.2[E]	4.4	20.3[F]	2.9

[a]NP > PP, Pearson's $\chi^2 = 6.6$, $p = 0.02$.
[b]Healthy > all depressed, Pearson's $\chi^2 = 12.6$, $p < 0.0001$. Unipolar > bipolar, Pearson's $\chi^2 = 15.2$, $p < 0.001$.
[c]PP > NP, $t = -1.9$, $p = 0.06$.
[d]PP > NP, $t = -3.2$, $p = 0.002$; six group, $F(5,48) = 2.1$, $p = 0.08$.
[e]All depressed > healthy, $t = -9.27$, $p < 0.001$.
[f]All depressed > healthy, $t = -7.0$, $p < 0.001$.
[g]All depressed > healthy, $t = -8.80$, $p < 0.001$.
[h]Healthy > unipolar depressed, $F(2,27) = 4.6$, $p = 0.02$.
[i]Healthy > unipolar depressed, $F(2,27) = 5.1$, $p = 0.01$.
Sample characteristics for which there were missing data are identified by capital letters placed next to mean values: [A]$n = 12$, [B]$n = 5$, [C]$n = 8$, [D]$n = 9$, [E]$n = 11$, [F]$n = 6$, [G]$n = 3$.

In the unipolar depression model (Table 3, model 1; Figure 1), for the whole striatum and ventral striatum, both unipolar depression ($b = -0.15$, $p = 0.02$; $b = -0.16$, $p = 0.07$) and postpartum status ($b = -0.12$, $p = 0.05$; $b = -0.20$, $p = 0.02$) were associated with 7–8% lower $D_{2/3}$ receptor BP_{ND}. BMI was not significant in any of the unipolar depression models. There was a region × age interaction for $D_{2/3}$ receptor BP_{ND} in the ventral striatum model, such that the slope of the relationship between BP_{ND} and age was steeper for VPU than for AVS. There were no other two- or three-way interactions among age, region, subject group, and BMI. In the dorsal striatum, unipolar depression was associated with a 0.15 reduction in BP_{ND} ($p = 0.06$; 5% lower), similar to the models for whole and ventral striatum, but postpartum status was not a significant predictor variable.

In the bipolar depression model, for both the whole striatum and ventral striatum, postpartum status (model 2a: $b = -0.13$, $p = 0.03$; $b = -0.20$, $p = 0.02$) and BMI (model 2b: $b = -0.02$, $p = 0.03$) were equally good predictors of $D_{2/3}$ receptor BP_{ND} (Table 3, models 2a and 2b). Bipolar depression was not associated with $D_{2/3}$ receptor BP_{ND} in whole or ventral striatum. Neither depression, postpartum status, nor BMI was a significant predictor of dorsal striatal $D_{2/3}$ receptor BP_{ND}. There were no other two- or three-way interactions among age, region, subject group, and BMI. $D_{2/3}$ receptor BP_{ND} was higher in bipolar relative to unipolar depressed women in DCA and DPU (Table 2, $t = -2.3$, $p = 0.03$; $t = -2.6$, $p = 0.01$).

DISCUSSION

This is the first study of $D_{2/3}$ receptor imaging in PPD. Strengths of our study were the inclusion of unmedicated women and the use of control groups for both postpartum

Table 2 Observed $D_{2/3}$ Receptor BP_{ND} by Group (SRTM)

	Non-postpartum women						Postpartum women					
	Healthy ($n=13$)		Unipolar dep ($n=10$)		Bipolar dep ($n=7$)		Healthy ($n=13$)		Unipolar dep ($n=13$)		Bipolar dep ($n=7$)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Ventral striatum												
Anteroventral striatum[a]	2.21	0.34	2.01	0.51	2.09	0.37	1.96	0.25	1.87	0.35	1.95	0.54
Ventral putamen[a]	2.99	0.24	2.78	0.48	2.97	0.40	2.72	0.29	2.66	0.48	2.79	0.40
Dorsal striatum												
Dorsal caudate[b]	2.31	0.25	2.07	0.28	2.37	0.17	2.16	0.25	2.14	0.35	2.32	0.38
Dorsal putamen[b]	2.99	0.42	2.81	0.30	3.14	0.21	2.90	0.33	2.82	0.47	3.11	0.32
CER V_T (V_{ND})	0.44[A]	0.03	0.42[C]	0.06	0.44[E]	—	0.39[B]	0.05	0.42[D]	0.04	0.41[E]	—
Injected mass [^{11}C]raclopride (μg)	2.6	0.7	2.56	1.07	3.57	1.55	2.6	1.2	3.79	3.28	2.35	0.56

[a]In ventral striatum, non-postpartum healthy women had increased $D_{2/3}$ receptor BP_{ND} relative to postpartum healthy women ($b=-0.20$, $p=0.02$) and all women with unipolar depression ($b=-0.16$; $p=0.07$; $\chi^2=750.01$, $p<0.0001$).
[b]$D_{2/3}$ receptor BP_{ND} was higher in bipolar relative to unipolar depressed women ($t=-2.3$, $p=0.03$; $t=-2.6$, $p=0.01$).
Missing data are identified by capital letters placed next to mean values: [A]$n=5$, [B]$n=7$, [C]$n=4$, [D]$n=8$, [E]$n=1$.

Table 3 Model for $D_{2/3}$ Receptor BP_{ND}

	Whole striatum			Ventral striatum			Dorsal striatum		
			p-value			*p*-value			*p*-value
Model 1 (unipolar only)	χ^2	479.83	<0.001	χ^2	750.01	<0.0001	χ^2	562.39	<0.0001
Postpartum status	b	−0.12	0.05	b	−0.20	0.02	b	—	—
Depression (unipolar)	b	−0.15	0.02	b	−0.16	0.07	b	−0.15	0.06
BMI	b	—	—	b	—	—	b	—	—
ROI	b	A	0.001	b	−0.80	<0.001	b	−0.71	<0.001
Age	b	−0.03	<0.001	b	−0.03	<0.001	b	−0.03	<0.001
Age × ROI	b	—	—	b	9.6×10^{-3}	0.03	b	—	—
Model 2a (bipolar only)	χ^2	460.2	<0.0001	χ^2	680.9	<0.0001	χ^2	485.4	<0.0001
Postpartum status	b	−0.13	0.03	b	−0.20	0.02	b	—	—
Depression (bipolar)	b	—	—	b	—	—	b	—	—
BMI	b	—	—	b	—	—	b	—	—
ROI	b	B	<0.001	b	−0.80	<0.001	b	−0.73	<0.001
Age	b	−0.02	<0.001	b	−0.02	<0.001	b	−0.02	0.001
Model 2b (bipolar only)	χ^2	460.8	<0.0001	χ^2	680.5	<0.0001	χ^2	485.4	<0.0001
Postpartum status	b	—	—	b	—	—	b	—	—
Depression (bipolar)	b	—	—	b	—	—	b	—	—
BMI	b	−0.02	0.03	b	−0.02	0.03	b	—	—
ROI	b	B	<0.001	b	−0.80	<0.001	b	−0.73	<0.001
Age	b	−0.02	<0.001	b	−0.02	<0.001	b	−0.02	0.001

Betas for ROIs relative to DPU

(A) Model 1	ROI	*b*	*p*-value	(B) MODEL 2a, 2b	ROI	*b*	*p*-value
	AVS	−0.88	<0.001		AVS	−0.95	<0.001
	DCA	−0.71	<0.001		DCA	−0.73	<0.001
	VPU	−0.10	0.05		VPU	−0.15	0.01

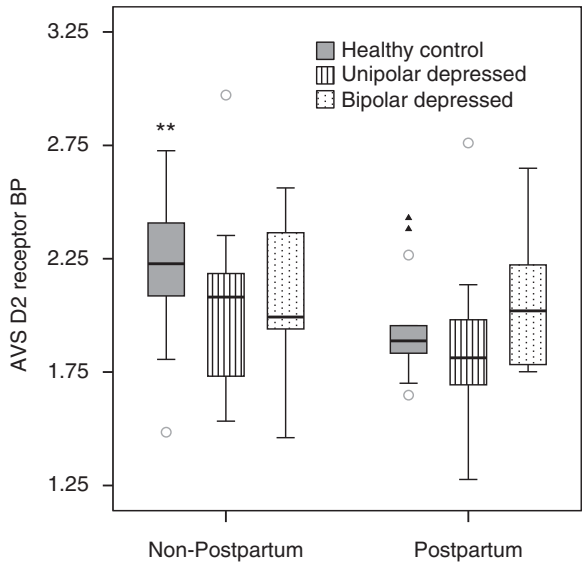

Figure 1 In ventral striatum, healthy, non-postpartum healthy women (**) had increased $D_{2/3}$ receptor BP_{ND} relative to postpartum healthy women ($b=-0.20$, $p=0.02$) and all women with unipolar depression ($b=-0.16$; $p=0.07$; $\chi^2=750.01$, $p<0.0001$). Stippled boxes representing bipolar depressed women are included to show dissimilarity of $D_{2/3}$ receptor BP_{ND} between unipolar and bipolar cohorts. Open circles and triangles denote values >2 SD of the mean. Note: The length of the box is the interquartile range (IQR). AVS = anteroventral striatum.

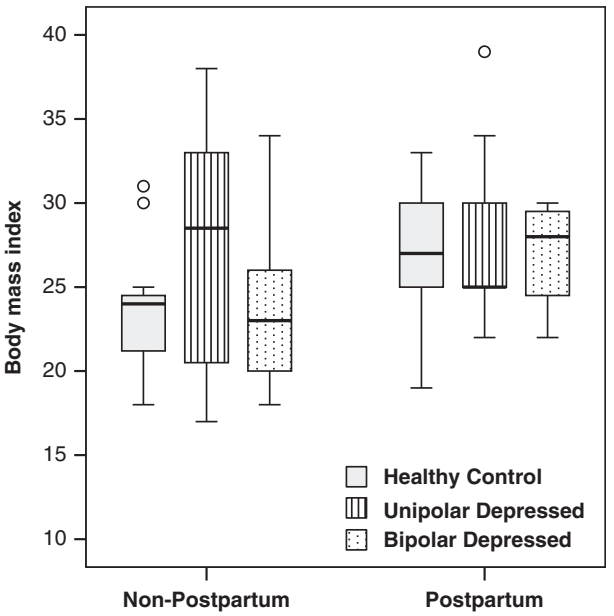

Figure 2 BMI was higher in postpartum relative to non-postpartum women ($p=0.06$) and very similar for healthy and bipolar depressed women. Because the BMI for unipolar, non-postpartum women was higher and more variable compared with healthy controls, this might have limited the ability to discern a relationship between BMI and $D_{2/3}$ receptor BP_{ND} in the regression restricted to unipolar women.

and depression status. Because unipolar *vs* bipolar depression diagnoses diverged in their relationship to $D_{2/3}$ receptor BP_{ND}, separate models enabled us to make inferences about each diagnostic category. Our main study finding when we restricted the sample to women with unipolar depression was lower striatal $D_{2/3}$ receptor BP_{ND} in association with both depression and postpartum status in ventral striatum (7–8%) and depression alone in dorsal striatum (5%). Because both ventral and dorsal striatal percent differences in $D_{2/3}$ receptor BP_{ND} observed are similar to test–retest reliability rates of 8.6 and 4.4%, respectively (Mawlawi *et al*, 2001), the magnitude of change related to depression and postpartum status is considered small, but similar to the magnitude of group differences in other PET studies. Combined depressed and postpartum status did not produce additive lowering of $D_{2/3}$ receptor binding; therefore, there were no differences in $D_{2/3}$ receptor BP_{ND} between depressed and healthy postpartum women. In the model for bipolar depression, depression was not associated with $D_{2/3}$ receptor BP_{ND}. Instead, postpartum status and BMI were equally good predictors of $D_{2/3}$ receptor BP_{ND}. Aside from the association of $D_{2/3}$ receptor BP_{ND} decreases with increasing age (Volkow *et al*, 1996; Wong *et al*, 1984) and increasing BMI (Wang *et al*, 2001b), no other demographic or clinical characteristics were significantly associated with $D_{2/3}$ receptor BP_{ND} in our final models.

It was unexpected that depression was not associated with any change in $D_{2/3}$ receptor BP_{ND} in bipolar depressed relative to healthy control subjects. We may have been underpowered to detect a significant association for bipolar depression, but it is more likely the case that the DA system is functionally different in unipolar relative to bipolar depressed, reproductive-aged women. Indeed, $D_{2/3}$ receptor BP_{ND} was higher in bipolar relative to unipolar depressed women (Table 2, $t=-2.3$, $p=0.03$; $t=-2.6$, $p=0.01$). That significantly more bipolar than unipolar depressed women had prior psychotropic exposure might also relate to neurobiological differences between the groups related to prior drug exposure or severity of illness. It is also noteworthy that in the bipolar depression regression, postpartum status and BMI were interchangeable variables in prediction of ventral striatal $D_{2/3}$ receptor BP_{ND}. We note (Figure 2) the similarity of BMI for healthy and bipolar women, and higher BMI in the postpartum compared with the non-postpartum group; therefore, we can speculate that BMI might be a mediator of the postpartum association with lower $D_{2/3}$ receptor BP_{ND} in this model (applicable to healthy women and women with bipolar depression). Indeed, a study of morbidly obese individuals (BMI > 40) revealed lower $D_{2/3}$ receptor BP_{ND} in obese relative to nonobese subjects, which was attributed to low number of $D_{2/3}$ receptors common among addictive behaviors including overeating (Wang *et al*, 2001a). Because the BMI for unipolar, non-postpartum women was higher and more variable (Figure 2) compared with healthy controls, this might have limited the ability to discern a relationship between BMI and $D_{2/3}$ receptor BP_{ND} in the regression restricted to unipolar women. Because we had limited power to detect significant interactions, it remains conceivable that high BMI might have contributed to the observed reduction in $D_{2/3}$ receptor BP_{ND} observed in depressives in the unipolar regression.

The association of unipolar depression with lower $D_{2/3}$ receptor BP_{ND} concurs with Klimke *et al* (Klimke *et al*, 1999), in which lower pretreatment $D_{2/3}$ receptor BP_{ND} was

reported for depressed individuals who later proved to be SSRI treatment responders. Our findings of lower $D_{2/3}$ receptor BP_{ND} in depression contrast, however, with reports of higher (D'haenen and Bossuyt, 1994; Meyer *et al*, 2006; Shah *et al*, 1997) or equivalent (Ebert *et al*, 1996; Parsey *et al*, 2001) striatal $D_{2/3}$ receptor BP_{ND} in the whole striatum of depressed subjects relative to controls. It remains unclear how these data compare with ours; however, these studies did not discriminate the AVS from the remainder of the striatum, and the differences we identified were maximal in the ventral striatum. Moreover, these studies lacked sufficient power to conduct gender-based analyses, and did not control for menstrual cycle phase, so it remains possible that the differences we report herein may not generalize to males. In addition, the results of some of these previous studies were confounded by recent exposure to psychotropic drugs. Finally, several prior studies were in hospitalized or psychomotorically retarded depressives (Ebert *et al*, 1996; Meyer *et al*, 2006; D'haenen and Bossuyt, 1994), and several reported positive correlations between $D_{2/3}$ receptor BP_{ND} and ratings of psychomotor slowing (Meyer *et al*, 2006; Shah *et al*, 1997). Such patients may have had lower dopaminergic tone or lower intrasynaptic DA concentrations in the dorsal striatal regions that subserve motor processing, which putatively may result in compensatory increases in $D_{2/3}$ receptor expression or affinity, or in reduced competition for binding to [^{11}C]raclopride or [^{123}I]- iodobenzamide, which are sensitive to endogenous DA levels (Laruelle, 2000). The depressed sample we studied, in contrast, did not include subjects who overtly manifested psychomotor slowing. Therefore, it is conceivable that homogeneous subgroups of depressed subjects (ie, psychomotorically slowed, treatment responders, women in early follicular phase) have distinct patterns of dopaminergic system function, suggesting that a single, specific underlying dopaminergic deficit is not universal in all individuals with depressive disorders.

We posit that stress or hypercortisolemia may be a common mechanism that explains the reduction of $D_{2/3}$ receptor BP_{ND} in postpartum and unipolar depressed women in this sample. Although the current study cannot clarify whether lower $D_{2/3}$ receptor binding is a mechanism or consequence of postpartum status or depression, it is noteworthy that animal models of depression and chronic stress similarly revealed lower $D_{2/3}$ receptor mRNA in ventral striatum in rodents (Dziedzicka-Wasylewska *et al*, 1997) and lower [^{11}C]raclopride–PET measurements in nonhuman primates (Morgan *et al*, 2002; Shively *et al*, 1997). In rodents, chronic (Moore *et al*, 2001) and acute (Valenti *et al*, 2011) stressors were associated with increased subpopulations or total DA neuron burst firing. On this basis, in depressed and postpartum subjects in this cohort, the combination of chronic (depression or childcare stress) and acute stress (arterial cannulation/PET scanning procedure; Drevets *et al*, 2002) could also conceivably increase phasic DA release that could compete with [^{11}C]raclopride binding. It is thus conceivable that lower striatal $D_{2/3}$ receptor BP_{ND} in postpartum (regardless of depressive status) and unipolar depressed women (regardless of postpartum status) may be a result of stress-related effects on reducing $D_{2/3}$ receptor expression and increasing intrasynaptic DA concentrations. Likewise, the healthy women may have experienced the PET scan as less stressful, thus having less phasic DA release to compete with [^{11}C]raclopride binding and higher measured $D_{2/3}$ receptor BP_{ND}. If the postulated stress mechanism for lower $D_{2/3}$ receptor BP_{ND} is indeed similar for postpartum and unipolar depressed women, $D_{2/3}$ receptor BP_{ND} does not appear to be a specific biomarker for depression among reproductive-aged women. Because the anatomical extent of striatal $D_{2/3}$ receptor reductions differed between depressed and postpartum women (Table 3), there remains the possibly of mechanistic differences. Furthermore, because of the hormonal excursions and maternal behavioral adaptations unique to perinatal women and due to challenges in the interpretation of $D_{2/3}$ receptor BP_{ND}, we suspect that other experimental designs could more precisely distinguish between DA system functional alterations that accompany depression *vs* those of the postpartum period.

It is of interest whether the postpartum-related differences in prolactin concentration could inform the lower $D_{2/3}$ receptor BP_{ND} in postpartum women. It is conceivable that higher prolactin concentrations might result from lower brain DA concentration overall, as DA inhibits prolactin secretion. Prior studies in rodents also describe that prolactin not only modulated tuberoinfundibular DA, but also was associated with increased striatal DA release (Perkins and Westfall, 1978) and striatal D_2 receptor density (Di Paolo *et al*, 1982). As human peripheral prolactin concentration is highly variable and easily altered by behaviors, such as motor activity and food intake, it is unlikely our measure was precise enough to use as a guide for interpretation of $D_{2/3}$ receptor BP_{ND}.

In conclusion, this study provides evidence for a dopaminergic mechanism for unipolar depression in reproductive-aged women, which may provide greater rationale for DA-modifying treatments in this population. This study also reveals postpartum modifications of the striatal DA system, which may contribute to the high relative risk of depression, psychosis, and mania in this reproductive period (Kendell *et al*, 1987b; Munk-Olsen *et al*, 2006). Studies of presynaptic DA, use of $D_{2/3}$ agonist radioligands, use of DA challenge paradigms, and examination of the broader reward circuitry in this population are needed to shed further light on these observations.

ACKNOWLEDGEMENTS

We thank members of the PET Facility Staff who carried out the acquisition of PET data and care of all subjects during PET procedures; Tova Saul, Andrea Confer, Michael Lightfoot, Carl Becker, Danielle Mullen, Julie Giombetti, and Alicia Corominal who assisted with study recruitment, data entry, image analysis, and endocrine analyses; NIMH, NARSAD for supporting this research; Magee-Women's Clinical Research Center and Womens Behavioral HealthCARE for providing infrastructure to run this project; and Medela for donating a breast pump for use during scanning procedures. The study was financially supported by National Alliance for Research in Schizophrenia and Depression; MH64561 to ELMK; M01-RR000056 to University of Pittsburgh; CCM's time was supported by K24 MH64625; and KLW's time was supported by MH 57102 and

MH 53735. Data for non-postpartum control subjects were obtained with R01 MH042984.

DISCLOSURE

Eydie L Moses-Kolko: Small honorarium given as guest speaker for La Leche League Regional Conference Summer, 2009.

Julie Price: No financial interests to disclose.

Katherine L Wisner: Katherine L. Wisner received transdermal estradiol patches and matching placebo patches for an NIMH-funded randomized controlled trial, and participated in an advisory board for Eli Lilly Company.

Carolyn C Meltzer: No financial interests to disclose.

Sarah Berga: Board of Directors: Member, University of Virginia Medical Alumni Association Board of Directors, 2007 to present (Gratis). **CONSULTANTSHIP**: Agile Therapeutics Medical Advisory Board, March 2011; AHC Media; LLC, Consultant, Annual business meeting, April 2008, April 2009, June 2010; Noven Pharmaceutical Medical Advisory Board, Feb 2010; Promedica Communications, Bayer Pharmaceutical Medical Advisory Board Meeting, June 2009, August 2009; Watson Pharmaceutical Women's Health Strategic Advisory Board, April 2010. **LEGAL CONSULTING:** Kirkland and Ellis, LLC; Leydig, Voit and Mayer, LLC; Reed Smith, LLC. **Editorial Boards and Positions:** ACOG, Editorial Committee, *Guidelines for Women's Health Care*, 2009–2011(Gratis); *American Journal of Obstetrics and Gynecology*, 2003 to present (Gratis); Advisory Board for Subspecialty Neuroendocrinology and Reproductive Neurobiology; The Endocrine Society: Member, Endocrine Self-Assessment Program Committee (June 2007–June 2011); Clinical Practice Guideline Task Force on Hypothalamic Amenorrhea, January 2011 to present (Gratis);Editorial Board for *Endocrinology*, January 2010 to present (Gratis); *Menopause*, Editorial Board, 1999 to present (Gratis). **NIH Study Section reviewer:** Society for Women's Health Research, ISIS CVD Network Member, 2009 to present. UpToDate Peer Review Board for 2005 to present.

Anthony A Grace: Consultant for Johnson & Johnson; research grants from Lundbeck, GSK, EMD Serono, pharmaceutical company talks (Abbott, Roche, Lilly); advisory boards (as non-member invited speaker, including Merck).

Barbara H Hanusa: No financial interests to disclose.

Teresa Lanza di Scalea: No financial interests to disclose.

Walter H Kaye: No financial interests to disclose.

Carl Becker: No financial interests to disclose.

Wayne C Drevets: Has served as a consultant to Pfizer, Johnson and Johnson, Eisai, and Rules Based Medicine.

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