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## RESEARCH ARTICLE

# Neural correlates of emotion processing comparing antidepressants and exogenous oxytocin in postpartum depressed women: An exploratory study

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## Abstract

Despite common use of antidepressants to treat postpartum depression, little is known about the impact of antidepressant use on postpartum brain activity. Additionally, although oxytocin has been investigated as a potential treatment for postpartum depression, the interaction between antidepressants and exogenous oxytocin on brain activity is unknown. We explored postpartum depressed women's neural activation in areas identified as important to emotion and reward processing and potentially, antidepressant response: the amygdala, nucleus accumbens and ventral tegmental area. We conducted a secondary analysis of a functional imaging study of response to sexual, crying infant and smiling infant images in 23 postpartum depressed women with infants under six months (11 women taking antidepressants, 12 unmedicated). Participants were randomized to receive a single dose of oxytocin or placebo nasal spray. There was significantly higher amygdala activation to sexual stimuli than either neutral or infant-related stimuli among women taking antidepressants or receiving oxytocin nasal spray. Among unmedicated women receiving placebo, amygdala activation was similar across stimuli types. There were no significant effects of antidepressants nor oxytocin nasal spray on reward area processing (i.e., in the nucleus accumbens or ventral tegmental area). Among postpartum women who remain depressed, there may be significant interactions between the effects of antidepressant use and exogenous oxytocin on neural activity associated with processing emotional information. Observed effect sizes were moderate to large, strongly suggesting the need for further replication with a larger sample.

## Introduction

Antidepressants are a standard treatment for postpartum depression (PPD) [1]. However, the effect of antidepressants on the postpartum brain are understudied, as most studies of

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antidepressant action have investigated males only [2]. This is a major knowledge gap, given the sex/gender differences noted in antidepressant response [3] as well as in the systems that underlie the putative antidepressant mechanisms such as serotonin transport [4] and functional connectivity [5]. The experience of pregnancy, parturition, and providing maternal care may alter neuroendocrine function in ways that interact with antidepressant actions [6, 7].

Also, there is increasing interest in the impact of antidepressants on neuroendocrine systems relevant to PPD. In particular, oxytocin—a neuropeptide that mediates social behaviors such as maternal [8] and sexual behaviors [9]—may play a role in depression [10], particularly in postpartum [11]. In postpartum women, oxytocin appears to facilitate adaptive reorganization of key neural structures in the hypothalamus, hippocampus, and amygdala [12, 13]. Endogenous oxytocin during the postpartum period may also buffer against the negative effects of cortisol and other aspects of stress reactivity [14–16]—a much needed adaptation to a very stressful time of life. In fact, low endogenous oxytocin has been associated with risk of PPD [11, 17, 18].

As oxytocin may play a role in PPD, exogenous oxytocin administration has been proposed both as a primary treatment [19], or as an adjunctive to antidepressant treatment [20]. While rodent models suggest exogenous oxytocin may improve PPD-like symptoms [21], clinical trials in human mothers have not shown clear benefits [22–25]. These conflicting reports have generally either excluded women taking antidepressants or considered medicated and unmedicated women together, complicating interpretation. Moreover, the effects of oxytocin on antidepressant action in depressed mothers are potentially different from a general depressed population [26, 27], underscoring the need to examine interactions of oxytocin and antidepressant use in the context of PPD specifically.

As a secondary analysis of a previously collected dataset, we explored brain activity in women with PPD who were or were not taking antidepressants, and who received either placebo or an oxytocin nasal spray. While the sample size is small, exploring these data could reveal some clues for further study. Brain response data are scant for postpartum depressed women, and there is even less known about PPD women on antidepressants. Because of the vast amount of information collected during functional neuroimaging, it is particularly important to have as much specificity as possible in pre-defining analyses; this specificity relies on evidence from prior research. Thus, although the exploratory results in the present study are in and of themselves only suggestive, they could be critical to future research. As such, we explored neural activity in areas of most interest to researchers in the areas of emotion processing and antidepressant treatment mechanisms.

Prior meta-analyses of mixed groups of depressed men and women (non-postpartum) have indicated that antidepressant treatment is associated with changes in activation to visual emotional stimuli in the limbic system, including the amygdala, and increased activation in the mesolimbic “reward systems” including the nucleus accumbens (NAc) and ventral tegmental area (VTA) [28]. Antidepressant response in non-postpartum depression has been predicted by changes in activation to these areas [29–33]. The amygdala, VTA and NAc also appear to be sites of significant structural and functional change during the postpartum period [34, 35]. Not surprisingly, these areas become particularly neuroplastic in response to the increased oxytocin signaling during pregnancy and postpartum [36].

Although increased neuroplasticity is beneficial for adapting the brain to the new demands of motherhood, it may also contribute to increased risk of PPD if reorganization is disrupted (e.g., by significant life stressors [37, 38]), leading to persistently maladaptive patterns of activation [39]. This is particularly true for women with histories of early life stressors, as the degree to which oxytocin release leads to increased neuroplasticity may depend on prior stress experiences [40]. That is, women with a history of childhood trauma may be at increased risk

of reproductive mood disorders associated with the increased neuroplasticity induced by oxytocin [41]. There is some evidence that antidepressants can reverse the structural modifications in the amygdala, VTA and NAc that may underlie PPD [37]. In rodent models of PPD, postpartum depressive-like behavior is associated with structural changes to the NAc and amygdala, but citalopram administration reverses these changes [42]. Similarly, while gestational stress appears to disrupt typical neuroplasticity in postpartum rats, these effects are reversed with fluoxetine treatment [37, 43]. Based on these data, we selected the amygdala, VTA, and NAc as our regions of interest (ROI): each has been shown relevant for antidepressant response (including in PPD), each undergoes significant re-organization during the postpartum period, and each has been shown to be responsive to oxytocin.

We hypothesized that, relative to unmedicated PPD women, PPD women taking antidepressants would exhibit lower amygdala activation to sexual stimuli. In a non-postpartum context, antidepressant use is associated with lower sexual interest in women [44], as well as lower amygdala response to sexual images [45]. Healthy (non-depressed) postpartum women have significantly lower amygdala response to sexual images than nulliparous women [46]; insofar as antidepressants result in bringing PPD women's neural responses closer to those of healthy postpartum women, we should expect antidepressants to be associated with lower amygdala response to sexual images. Furthermore, *contrasting* amygdala responses to sexual vs. infant related stimuli may be a marker of initial neuroadaptation to motherhood, as increasing response to infant stimuli and decreasing response to sexual stimuli in the early months postpartum may reflect increased investment in the current offspring vs. potential new offspring [46, 47]. Thus, we additionally hypothesized that, for activation of the amygdala and reward areas (VTA, NAc), the *relative difference* between infant and sexual images would be greater in PPD women taking antidepressants than in unmedicated PPD women, in whom responses would be more muted.

As antidepressants have been shown to amplify reward activation in non-postpartum contexts [32, 48], we hypothesized that PPD women taking antidepressants would have significantly higher VTA and NAc activation to positive emotional images (smiling infants, sexual images) relative to unmedicated women. This means we expected different effects of antidepressants on amygdala vs. reward area processing of sexual images: decreasing activation in the former while increasing the latter. Such effects would parallel report of women's subjective experience of postpartum sexuality: while women's sexual interest decreases in the postpartum period, the degree of pleasure from sexual activity remains stable [49, 50].

Animal models suggest that oxytocin may mediate some of the antidepressant effects of SSRIs [51, 52], and data from clinical studies in humans show resting levels of oxytocin increase following antidepressant administration [53]. These findings hint at possible parallel mechanisms underlying both antidepressant use and oxytocin response. Thus, we hypothesized that the effects of oxytocin on neural activation to emotional stimuli would differ in women who were taking vs. not taking antidepressants. If there are similar systems underlying the response to both antidepressants and oxytocin in postpartum depressed women, we should expect the effects of exogenous oxytocin to be relatively less noticeable among women taking antidepressants. However, given the dearth of prior research, we did not have a priori hypotheses regarding how the combination of exogenous oxytocin and antidepressants would impact contrasts between stimuli types, or differences in activation of amygdala vs. reward processing areas.

## Methods

The present study was a secondary analysis from a larger investigation of differences in neural activity between postpartum and nulliparous women; detailed description of study procedures can be found in the primary publications [46, 47, 54].

### Participants

Women who were 3–6 months postpartum, breastfeeding at >75% of feedings, were recruited and screened for depression with the Edinburgh Postnatal Depression Scale (EPDS, [55]). Women with a history of psychosis or manic episodes were excluded. A total of 23 currently depressed postpartum women (scoring  $\geq 12$  on the EPDS) completed a scanning session and provided complete data regarding medication use. Of these, 11 reported current use of an SSRI antidepressant (sertraline,  $N = 8$ , fluoxetine,  $N = 2$ , citalopram,  $N = 1$ ), while 12 reported no antidepressant use. Both groups were similar in demographics (Table 1). Also, on the day of the experimental session, participants completed the Center for Epidemiologic Study–Depression scale (CES-D [56]); the medicated vs. unmedicated groups were similar in level of self-reported depressive symptoms at the time of scanning.

**Table 1. Demographics.** There were no significant differences in demographics across medication group. CESD: Center for Epidemiologic Study–Depression scale.

	Antidepressant group (n = 11)		Unmedicated group (n = 12)	
	Mean	SD	Mean	SD
Age of participant (years)	30.82	4.94	30.17	5.47
CES-D Scale score on day of testing	23.73	9.00	24.91	12.13
Pre-trial urinary oxytocin (pg/mL)	10.01	6.64	9.76	6.74
	<i>n</i>	%	<i>n</i>	%
<b>History of Psychotherapy</b>				
No history	2	18%	7	58%
Past, not current	2	18%	2	17%
Current	7	64%	3	25%
<b>Menstrual period returned?</b>				
Yes	8	72%	7	58%
No	3	27%	5	42%
<b>Race/Ethnicity</b>				
White	10	91%	8	66%
Non-white	1	9%	4	33%
<b>Highest Education</b>				
High school	3	27%	4	33%
College degree	5	45%	7	58%
Postgraduate degree	3	27%	1	8%
<b>Self-reported physical health</b>				
Fair	1	9%	2	17%
Good	9	81%	8	66%
Excellent	1	9%	2	17%
<b>Lifetime number of live births</b>				
1	9	82%	8	66%
2	2	18%	2	17%
3 or more	0	0%	2	17%
<b>Other medications on day of testing</b>				
None	8		10	
Hormonal contraceptives	2		0	
Antihistamines	1		1	
Lansoprazole	0		1	
Ibuprofen	1		0	

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## Experimental procedure

To reduce variability in endogenous oxytocin, participants nursed their infant ~1 hour 15 minutes prior to imaging. All participants were administered nasal spray approximately 30 min prior to imaging; nasal spray condition (oxytocin vs. placebo) was randomized and double-blinded. Oxytocin nasal spray contained an inert carrier solution and 24IU of synthetic oxytocin (Syntocinon, Novartis Pharma, Switzerland), while the placebo spray contained inert carrier only; these sprays have been shown to be indistinguishable to participants [57]. While the elimination half-life of peripheral (plasma) oxytocin is relatively short (~20 minutes [58]), concentrations in cerebrospinal fluid peak approximately 45–75 minutes of nasal spray administration [59].

Participants provided a urine sample before and after nasal spray application, which was tested for oxytocin. These tests confirmed a significant increase in urinary oxytocin in the oxytocin nasal spray group ( $M_{pre} = 7.29$  pg/mL,  $SD = 2.14$ ;  $M_{post} = 44.37$  pg/mL  $SD = 46.27$ ; paired  $t(10) = -2.63$ ,  $p = .025$ ), but not the placebo ( $M_{pre} = 12.34$  pg/mL,  $SD = 8.66$ ;  $M_{post} = 11.34$  pg/mL,  $SD = 11.80$ ; paired  $t(10) = .25$ ,  $p = .809$ ). Baseline urinary oxytocin levels were similar across medication groups (antidepressant  $M = 10.30$  pg/mL,  $SD = 6.86$ ; unmedicated  $M = 9.76$  pg/mL,  $SD = 6.74$ ), and were in the same range reported in prior research on urinary oxytocin in postpartum women [60, 61]. Antidepressant use did not predict changes in urinary oxytocin ( $F(1, 24) = 1.14$ ,  $p = .296$ ).

Following nursing and nasal spray administration, participants viewed emotionally relevant visual stimuli in a functional magnetic resonance imaging (fMRI) paradigm (see below for imaging details). We examined blood oxygenation-level dependent (BOLD) responses to 4 stimuli types: sexually explicit images, smiling and crying infant images, and emotionally neutral images. The neutral images were derived from a set of International Affective Picture Set (IAPS) images validated to evoke low emotional arousal and fall in the middle of the valence range [47, 62]. Infant images were taken from publicly available websites and were validated to evoke moderate but significant emotional arousal; given a Likert scale of 1 (least intense) to 9 (most intense), the average rating for infant images was 4.70 [46]. Sexual images included images of nude heterosexual couples engaging in sexual acts (e.g., oral sex, vaginal intercourse) that were derived from a set of images previously shown to evoke sexual interest in women [46, 63]; these images similarly were rated as moderately but significantly emotionally arousing, with an average intensity rating of 4.35 [46]. During stimuli presentation, participants completed a backwards-matching task to ensure adequate attention. The study was approved by the Institutional Review Board at Indiana University Bloomington, and all participants provided written informed consent.

## Imaging procedures and data processing

The imaging session consisted of a 3 plane-localizing scan to determine slice volumes (10 sec), seven whole brain blood oxygenation-level dependent (BOLD) scans (5 min each), and a whole brain high-resolution anatomical scan (5 min), for a total of approximately 1 hour. Functional (BOLD) scans were started with a 12-sec at-rest baseline, followed by 64 randomized stimuli presented for 2 seconds each (with variable inter-stimuli intervals of 2–6 seconds).

Imaging was conducted in a Siemens Magnetom Trio 3T whole body MRI. All images were collected on a 32-channel phased-array head coil. The field of view of  $220 \times 220$  mm. An in-plane resolution of  $128 \times 128$  pixels, and 35 axial slices of 3.4 mm thickness per volume, produced voxels that were  $1.7 \times 1.7 \times 3.4$  mm. A gradient echo BOLD echo-planar imaging (EPI) sequence was used for capturing functional images, including the following parameters: TE = 24 ms, TR = 2,000 ms, flip angle =  $70^\circ$ . We used parallel imaging with an iPAT factor of

2. For anatomical volumes, we used high-resolution T1-weighted images, acquired with a Turbo-flash 3-D sequence, including the following parameters: TI = 900 ms, TE = 2.67 ms, TR = 1800 ms, flip angle = 9°, with 192 sagittal slices of 1 mm thickness, a field of view of 224 × 256 mm, and an isometric voxel size of 1 mm<sup>3</sup>.

We used BrainVoyager QX 2.2 to prepare imaging data for statistical analysis. Each participants' anatomical volumes were stereotactically transformed using the Talairach atlas with an eight-parameter affine transformation. Using an intensity-based motion correction algorithm, functional volumes were realigned to the volume closest in time to the anatomic volume. We also corrected functional volumes using slice scan-time correction, 3-D spatial Gaussian filtering (FWHM 6 mm), and linear trend removal. These corrected functional volumes were co-registered to the relevant anatomical volume using an intensity-based matching algorithm, and normalized to the common stereotactic space with an eight-parameter affine transformation. Functional data were re-sampled to 3 mm<sup>3</sup> isometric voxels. Beta weights of a random-effects general linear model (based on timing protocol of the blocked stimulus presentation, convolved with a two-gamma hemodynamic response function) were extracted from group ROIs using the VOI/ROI ANCOVA data table tool in BrainVoyager's volume of interest module.

## Results

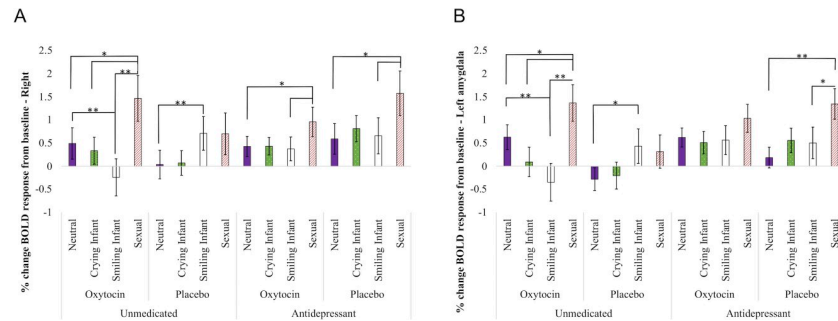
We conducted repeated measures ANCOVAs with stimulus type (neutral, sexual, infant crying, or infant smiling) as the repeated measures variable, medication use and nasal spray group (and their interaction) as fixed effects, and the following covariates: scores on the Center for Epidemiological Studies-Depression (CES-D) scale on the day of the imaging session [56], age, pre-trial urinary oxytocin level, and activation to nonsense images in which the pixels from the other stimuli were scrambled. Controlling for activation to nonsense stimuli accounted for individual differences in general activation to visual stimuli not related to emotion or reward processing. None of the covariates differed significantly between groups, but had considerable variance across the entire sample and were thus used to control for individual differences at baseline. We conducted separate models predicting activation in the left amygdala (Talairach coordinates: -19, -6, -10), right amygdala (Talairach coordinates: 15, -5, -9), left NAc (Talairach coordinates: 11, 12, -8); right NAc (Talairach coordinates: -13, 10, 8), and VTA (Talairach coordinates: 2, -23, -5).

## Amygdala

The main effect of antidepressant use was non-significant (Left:  $F(1, 14) = 3.26, p = .09, \eta^2_{\text{partial}} = 0.19$ ; Right:  $F(1, 14) = 1.052, p = .32, \eta^2_{\text{partial}} = 0.07$ ) as was nasal spray condition (Left:  $F(1, 14) = 0.15, p = .71, \eta^2_{\text{partial}} = 0.01$ ; Right:  $F(1, 14) = 1.052, p = .32, \eta^2_{\text{partial}} = 0.07$ ). In other words, neither antidepressant use nor oxytocin administration were associated with *overall* higher or lower amygdala activation. However, there was a significant interaction between medication, nasal spray condition, and stimuli type (Left:  $F(2, 13) = 6.85, p = .01, \eta^2_{\text{partial}} = 0.51$ ; Right:  $F(2, 12) = 3.67, p = .04, \eta^2_{\text{partial}} = 0.48$ ; see Fig 1); thus, we conducted follow-up contrasts to examine the nature of the interaction (see below).

**Post-hoc specific contrast tests of amygdala activation by stimuli type.** See Table 2 for all specific contrasts; general patterns are summarized below.

The contrast of infant vs. sexual stimuli was of particular interest as a possible marker of neuroadaptation to motherhood. The contrast between smiling infant vs. sexual stimuli was significant in all groups *except* unmedicated women receiving placebo. That is, for women taking antidepressants and/or receiving oxytocin nasal spray, there was significantly greater



**Fig 1. a-b. Activation of amygdala (1a: Left; 1b: Right) to visual emotional stimuli, controlling for age, CES-D score, pre-trial urinary oxytocin, and activation to scrambled images.** Contrast bars represent significant differences between response to different stimuli types within the group (i.e., significant repeated measures effects). \*:  $p < 0.05$ ; \*\*:  $p < 0.01$ .

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amygdala activation to sexual stimuli than smiling infant stimuli; however, for unmedicated women receiving placebo there was no significant difference between stimuli types. The contrast between crying infant and sexual stimuli was significant only among unmedicated women receiving oxytocin nasal spray; in this group amygdala activation to sexual stimuli was significantly greater than to crying infant stimuli.

Contrasts between neutral and smiling infant stimuli were significant in unmedicated women; however, the direction of this contrast differed by nasal spray group. In unmedicated women receiving placebo, amygdala activity to smiling infant stimuli was significantly higher than to neutral stimuli; however, among unmedicated women receiving oxytocin nasal spray, amygdala activation to smiling infant stimuli was significantly *lower* than to neutral stimuli.

Finally, contrasts between neutral and crying infant stimuli, and between crying and smiling infant stimuli, were non-significant across all groups.

### Nucleus accumbens

The interaction between stimuli type, nasal spray condition and medication use on activation of the NAc was non-significant (Left:  $F(2, 14) = 1.91, p = .18, \eta^2_{partial} = 0.32$ ; Right:  $F(2, 14) = 0.36, p = .78, \eta^2_{partial} = 0.08$ ). However, there was a significant interaction between nasal spray condition and antidepressant use in activation of the right NAc ( $F(1, 14) = 5.66, p = .03, \eta^2_{partial} = 0.29$ ), such that unmedicated women receiving placebo nasal spray had significantly higher right NAc activation to all stimuli than women receiving antidepressants and/or oxytocin nasal spray (Fig 2).

### Ventral tegmental area

There were no significant effects by stimuli type, nasal spray condition, or medication use, nor any significant interaction in the VTA.

### Discussion

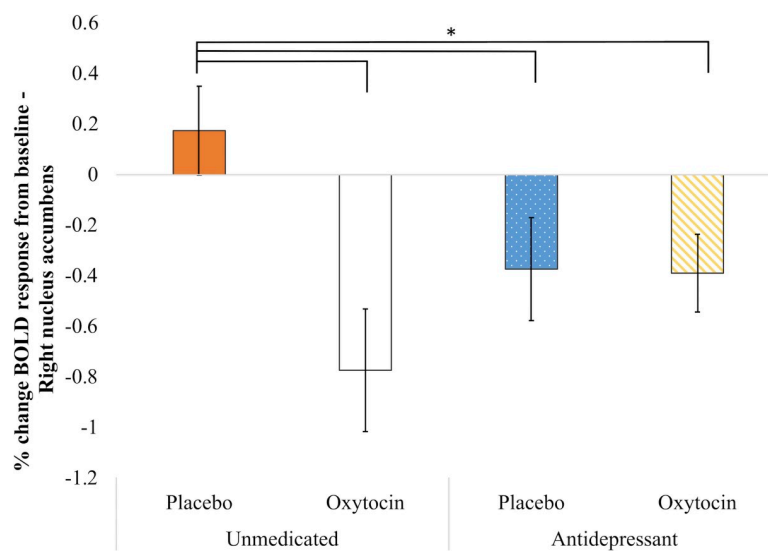
We explored if antidepressant use and exogenous oxytocin administration were associated with neural activation in postpartum depressed women. There were significant interactions between stimuli type, (non-randomized) antidepressant use, and (randomized) exogenous oxytocin administration in amygdala activation. However, antidepressant use and oxytocin administration were not associated with activation in reward processing areas, such the ventral tegmental area and the nucleus accumbens.



**Table 2. Post-hoc simple contrasts between stimuli types by antidepressant use and nasal spray group.** Significant within-group contrasts are highlighted in grey.

Contrasts	Antidepressant x placebo nasal spray				Antidepressant x oxytocin nasal spray				Unmedicated x placebo nasal spray				Unmedicated x oxytocin nasal spray			
	<i>M<sub>diff</sub></i>	<i>SE</i>	<i>p</i>	<i>d</i>	<i>M<sub>diff</sub></i>	<i>SE</i>	<i>p</i>	<i>d</i>	<i>M<sub>diff</sub></i>	<i>SE</i>	<i>p</i>	<i>d</i>	<i>M<sub>diff</sub></i>	<i>SE</i>	<i>p</i>	<i>d</i>
<b>Right amygdala</b>																
Neutral vs. crying infant	-0.22	0.37	0.56	0.22	-0.01	0.24	0.98	0.02	-0.03	0.34	0.92	0.03	0.16	0.38	0.68	0.16
Neutral vs. smiling	-0.07	0.20	0.73	0.13	0.05	0.13	0.69	0.15	-0.67	0.18	<0.01	1.41	0.73	0.20	<0.01	1.38
Neutral vs. sexual	-0.99	0.37	0.02	1.01	-0.53	0.24	0.05	0.83	-0.66	0.34	0.07	0.73	-0.98	0.38	0.02	0.97
Crying infant vs. smiling infant	0.15	0.43	0.73	0.13	0.06	0.28	0.84	0.08	-0.64	0.40	0.13	0.60	0.57	0.44	0.21	0.49
Crying infant vs. sexual	-0.77	0.45	0.11	0.65	-0.53	0.30	0.10	0.67	-0.63	0.42	0.16	0.57	-1.13	0.47	0.03	0.91
Smiling infant vs. sexual	-0.92	0.40	0.04	0.87	-0.58	0.26	0.04	0.84	0.01	0.37	0.98	0.01	-1.71	0.41	<0.01	1.58
	<i>M<sub>diff</sub></i>	<i>SE</i>	<i>p</i>	<i>d</i>	<i>M<sub>diff</sub></i>	<i>SE</i>	<i>p</i>	<i>d</i>	<i>M<sub>diff</sub></i>	<i>SE</i>	<i>p</i>	<i>d</i>	<i>M<sub>diff</sub></i>	<i>SE</i>	<i>p</i>	<i>d</i>
<b>Left amygdala</b>																
Neutral vs. crying infant	-0.37	0.27	0.19	0.52	0.11	0.25	0.66	0.17	-0.08	0.29	0.79	0.10	0.54	0.32	0.12	0.64
Neutral vs. smiling	-0.32	0.23	0.20	0.53	0.06	0.22	0.80	0.10	-0.72	0.26	0.01	1.05	0.97	0.28	<0.01	1.31
Neutral vs. sexual	-1.16	0.26	<0.01	1.69	-0.41	0.24	0.11	0.65	-0.6	0.29	0.06	0.78	-0.74	0.32	0.03	0.87
Crying infant vs. smiling infant	0.05	0.33	0.88	0.06	-0.06	0.31	0.86	0.07	-0.64	0.36	0.10	0.67	0.44	0.40	0.29	0.42
Crying infant vs. sexual	-0.79	0.43	0.09	0.69	-0.53	0.39	0.20	0.51	-0.52	0.47	0.29	0.42	-1.28	0.51	0.03	0.95
Smiling infant vs. sexual	-0.85	0.31	0.02	1.04	-0.47	0.29	0.13	0.61	0.12	0.34	0.74	0.13	-1.71	0.38	<0.01	1.70

<https://doi.org/10.1371/journal.pone.0217764.t002>



**Fig 2. Activation of right nucleus accumbens to visual emotional stimuli, controlling for age, CES-D score, pre-trial urinary oxytocin, and activation to scrambled images.** There were no significant contrasts between different stimuli types. \*: *p* < 0.05.

<https://doi.org/10.1371/journal.pone.0217764.g002>

Only three studies have directly compared neural activity in depressed women who were vs. were not taking antidepressants. Briceño et al. [64] found no significant differences in overall neural response to facial emotional stimuli in depressed women who were and were not taking antidepressants. However, as that study did not predesignate ROIs, it was not designed to detect anything but very large whole-brain group differences. Yang et al. [65] examined changes in neural activation to sexual stimuli before and after antidepressant treatment in 7 depressed non-postpartum women. Following antidepressant treatment, participants significantly increased activation in the subcortical reward areas, notably the hypothalamus, septal nuclei and parahippocampal gyrus, but not the amygdala. However, there may be important differences in postpartum vs. non-postpartum women's brain activity, particularly when considering reproductively relevant stimuli (such as the sexual stimuli used here). In non-postpartum women, antidepressants suppress sexual response [44], but as seen in Fig 1, in our sample of depressed *postpartum* women, women taking antidepressants did not have systematically lower amygdala response to sexual stimuli compared to unmedicated women.

Wonch et al. [66] examined amygdala response to infant stimuli in depressed and non-depressed postpartum mothers. Within their PPD group, there were no significant differences in amygdala response among 13 medicated vs. 18 unmedicated women. However, these authors did not include sexual stimuli, which may elicit stronger amygdala response [46]. Also, unlike in Wonch et al [66]'s paradigm, all the participants in our study nursed their infants prior to imaging; it is possible that recent exposure to *endogenous* oxytocin may moderate important differences between medication groups. Finally, the participants in our sample also reported significantly higher EDPS scores ( $M = 13.32$ ,  $SEM = 0.79$ ) than those studied by Wonch et al ( $M = 8.29$ ,  $SEM = 0.84$ ); possibly, the observed effects only emerge during more severe depressive episodes.

Importantly, there were significant interactions between oxytocin administration and antidepressant use in amygdala responsivity to emotional stimuli. Unmedicated women and women taking antidepressants responded differently to exogenous oxytocin administration, suggesting the need for caution as oxytocin is evaluated as an adjunctive to antidepressant treatment in PPD. There is evidence that depression is associated with lower responsivity to positively valenced emotional stimuli [67]. In healthy non-depressed women, administration of escitalopram is associated with lower amygdala activation to negative stimuli and higher activation to positive stimuli [68]. These patterns are thought to indicate that antidepressants attenuate hyper-reactivity to negative or stressful stimuli, while increasing reward salience associated with positive stimuli [69]. Oxytocin, however, appears to inhibit serotonin signaling in the dorsal raphe nucleus via suppression of activity in the amygdala [70]. As such, it is possible that instead of *amplifying* the effects of antidepressants on amygdala response to positive emotional stimuli (as would be beneficial in an adjunctive treatment), oxytocin may *attenuate* antidepressant response. As seen in Fig 1, we found that among PPD women taking antidepressants, oxytocin vs. placebo administration was associated with what appears to be *lower* amygdala activation to sexual stimuli, and no difference in smiling infant stimuli—at a minimum, we did not find evidence for increased amygdala responsiveness to positive emotional stimuli. However, when considering the possible treatment efficacy of adjunctive oxytocin there may be different effects of short-term and long-term exposure to exogenous oxytocin; the data from the present study can only speak to the short-term effects of a single administration. It is possible that longer-term joint oxytocin/antidepressant administration would have down-stream effects that could amplify therapeutic response, such as increasing production of neurotrophic factors [21] or epigenetic changes in the expression of genes for key receptors [71].

Unexpectedly, there were few significant associations of antidepressant use or oxytocin administration with reward area processing. We observed only one such association (namely, that unmedicated women receiving placebo had higher right NAc activity overall than any other group); as this association was not replicated bilaterally, it should be interpreted cautiously. There is evidence that the left NAc has greater involvement in reward-related activation than the right [72], which may lead to different thresholds for detecting depression-related attenuation of reward processing. For example, one study of unmedicated depressed individuals (50% female) found reduced activation in the left but not right NAc [73]. It is possible that the higher sensitivity of the left NAc may have influenced our findings in the left but not right NAc. It is also possible that due to our sample size, we missed some small but potentially relevant effects in the right NAc and VTA. Alternatively, it is possible that antidepressant and oxytocin doses, or the length of exposure, were insufficient to see significant associations in reward areas. Notably, all of the women in this study were depressed at the time of imaging, suggesting incomplete treatment response among the women taking antidepressants: we may have seen greater results if participants were on a higher dose that better managed their depressive symptoms.

The fact that we *did* see significant associations in the amygdala might suggest that the amygdala was relatively more responsive to the effects of antidepressants and/or oxytocin than the NAc or VTA. However, studies in animal models suggest the opposite: antidepressant administration is associated with significant changes in the organization and activation of the NAc but not the basolateral amygdala [42]. It is possible that the stimuli we used may have elicited an emotional, but not necessarily *rewarding*, response. Of the few studies that have found a significant effect of oxytocin administration on reward area processing in postpartum women, most have used stimuli of the participant's own infants [74–76]—a much more salient and arguably more rewarding stimulus than stimuli of other people's infants. It is also possible that when participants nursed shortly prior to imaging, the natural rise in prolactin levels associated with lactation may have temporarily suppressed dopamine production which in turn may have limited activation of these dopaminergic pathways [77] (but see also [78]). Finally, it is possible these findings reflect a true null, in which neither oxytocin nor antidepressants are associated with significant effects in reward processing areas among PPD women. If so, this would require antidepressants to exert their therapeutic effect on depression via some other process—for example, by improving corticolimbic connectivity [79] or decreasing the effect of stress on functional reorganization during the postpartum period [42].

Our sample size was small; however, it is in keeping with similar studies [66], and we observed a number of significant associations with medium to large effect sizes. These effect sizes may serve as a reference point for future researchers in planning studies on neural activation in PPD women. They also signal the need for caution in interpreting null effects. In a few instances (e.g., the main effect of antidepressants on amygdala activation across stimuli), the observed associations were not *statistically* significant but the effect sizes were large enough to suggest a larger sample would achieve significance. Overall, we view the effect sizes observed in this analysis as large enough to suggest that further replication would be fruitful in revealing important group-wise differences. In particular, it will be important to collect samples large enough (and with enough precision) to examine the sub-regions of amygdala that contribute to the observed differences associated with antidepressant use. Such analyses can reveal important clues as to the mechanisms by which antidepressants exert their effects. For example, is a growing literature that suggests that, regardless of treatment modality, antidepressant effects are driven by neuroplastic changes specific to the basolateral amygdala [80–82]; however thus far this literature has not extended to PPD.

This was an observational study, and antidepressant use was not randomized; thus our conclusions must be tempered regarding the effects attributable solely to antidepressants. We cannot conclude antidepressants are causally related to *changes* in neural activity. Lacking randomization with a control group (or other means of controlling for the effect of treatment), it is difficult to conclude what might be driving the differences described here. However, it should be noted that randomizing PPD women to placebo (or no treatment) would raise ethical issues, and would only be warranted if there were sufficient evidence of the need for such a trial—again, highlighting the importance of preliminary findings such as those presented here. It is also possible that there were important differences between the participants who were and were not taking antidepressants. Both groups reported similar CES-D scores, suggesting that the women taking antidepressants may have had a more severe underlying depression that only partially remitted in response to medication. To address these limitations, future research would benefit from a design comparing a larger sample of PPD participants before and after successful antidepressant treatment.

Further research is also needed to examine if antidepressant use during the postpartum transition influences neuroadaptation: it has been proposed that increasing activation to infant-related stimuli and decreasing activation to sexual stimuli may reflect the shift of emotional processing resources from sexual interest to the demands of caring for an infant [47]. Our data suggested differences between women who were medicated vs. unmedicated in contrasts between reproductively relevant stimuli (i.e., sexual vs. infant-related stimuli), which supported the view that PPD represents a maladaptation to the unique challenges of motherhood. These findings, alongside a growing literature in evolutionary medicine [46, 47, 54, 83], underscore the need to consider the reproductive context in which PPD occurs when evaluating potential treatments.

## Conclusions

We compared neural activation in women with PPD who were and were not taking antidepressants. Among PPD women receiving oxytocin nasal spray and/or those taking antidepressants, there was significantly higher amygdala activation to sexual stimuli than to either neutral or smiling infant stimuli. However, among unmedicated PPD women receiving a placebo nasal spray, amygdala activation to sexual stimuli was not significantly different from activation to either neutral or infant-related stimuli. There was no consistent effect of antidepressant use or exogenous oxytocin administration in activation of reward areas (NAC, VTA). These data will help inform and encourage further attention to the growing body of research on the effects of psychoactive medication on neural function during the postpartum reproductive transition.

## Supporting information

**S1 File. BOLD response data.**  
(SAV)

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## References

1. Yonkers KA, Wisner KL, Stewart DE, Oberlander TF, Dell DL, Stotland N, et al. The management of depression during pregnancy: A report from the American Psychiatric Association and the American College of Obstetricians and Gynecologists. *Gen Hosp Psychiatry*. 2009; 31(5):403–13. <https://doi.org/10.1016/j.genhosppsych.2009.04.003> PMID: 19703633
2. Kokras N, Dalla C. Preclinical sex differences in depression and antidepressant response: Implications for clinical research. *J Neurosci Res*. 2017; 95(1–2):731–6. <https://doi.org/10.1002/jnr.23861> PMID: 27870451
3. Keers R, Aitchison KJ. Gender differences in antidepressant drug response. *Int Rev Psychiatry*. 2010; 22(5):485–500. <https://doi.org/10.3109/09540261.2010.496448> PMID: 21047161
4. Cosgrove KP, Mazure CM, Staley JK. Evolving Knowledge of Sex Differences in Brain Structure, Function, and Chemistry. *Biol Psychiatry*. 2007; 62(8):847–55. <https://doi.org/10.1016/j.biopsych.2007.03.001> PMID: 17544382
5. Gong G, He Y, Evans AC. Brain connectivity gender makes a difference. *Neuroscientist*. 2011; 17(5):575–91. <https://doi.org/10.1177/1073858410386492> PMID: 21527724
6. Lévy F. Neuroendocrine control of maternal behavior in non-human and human mammals. *Ann Endocrinol (Paris)*. 2016; 77(2):114–25. <http://dx.doi.org/10.1016/j.ando.2016.04.002>.
7. Brunton PJ, Russell JA. Endocrine induced changes in brain function during pregnancy. *Brain Res*. 2010; 1364:198–215. <https://doi.org/10.1016/j.brainres.2010.09.062> PMID: 20869351
8. Carter CS. Oxytocin pathways and the evolution of human behavior. *Annu Rev Psychol*. 2014; 65:17–39. <https://doi.org/10.1146/annurev-psych-010213-115110> PMID: 24050183
9. Borrow AP, Cameron NM. The role of oxytocin in mating and pregnancy. *Horm Behav*. 2012; 61(3):266–76. <https://doi.org/10.1016/j.yhbeh.2011.11.001> PMID: 22107910
10. McQuaid RJ, McInnis OA, Abizaid A, Anisman H. Making room for oxytocin in understanding depression. *Neurosci Biobehav Rev*. 2014; 45:305–22. <https://doi.org/10.1016/j.neubiorev.2014.07.005> PMID: 25025656
11. Skrundz M, Bolten M, Nast I, Hellhammer DH, Meinlschmidt G. Plasma oxytocin concentration during pregnancy is associated with development of postpartum depression. *Neuropsychopharmacology*. 2011; 36(9):1886–93. <https://doi.org/10.1038/npp.2011.74> PMID: 21562482
12. Kim S, Strathearn L. Oxytocin and maternal brain plasticity. *New Dir Child Adolesc Dev*. 2016; 2016(153):59–72. <https://doi.org/10.1002/cad.20170> PMID: 27589498
13. Haim A, Julian D, Albin-Brooks C, Brothers HM, Lenz KM, Leuner B. A survey of neuroimmune changes in pregnant and postpartum female rats. *Brain, Behav, Immun*. 2017; 59(Supplement C):67–78. <https://doi.org/10.1016/j.bbi.2016.09.026>.
14. Cox E, Stuebe A, Pearson B, Grewen K, Rubinow D, Meltzer-Brody S. Oxytocin and HPA stress axis reactivity in postpartum women. *Psychoneuroendocrinology*. 2015; 55:164–72. <https://doi.org/10.1016/j.psyneuen.2015.02.009> PMID: 25768266
15. Zelkowitz P, Gold I, Feeley N, Hayton B, Carter CS, Tulandi T, et al. Psychosocial stress moderates the relationships between oxytocin, perinatal depression, and maternal behavior. *Horm Behav*. 2014; 66(2):351–60. <https://doi.org/10.1016/j.yhbeh.2014.06.014> PMID: 24956026

16. Julian MM, Rosenblum KL, Doom JR, Leung CY, Lumeng JC, Cruz MG, et al. Oxytocin and parenting behavior among impoverished mothers with low vs. high early life stress. *Arch Womens Ment Health*. 2017;1–8.
17. Feldman R, Weller A, Zagoory-Sharon O, Levine A. Evidence for a neuroendocrinological foundation of human affiliation: plasma oxytocin levels across pregnancy and the postpartum period predict mother-infant bonding. *Psychol Sci*. 2007; 18(11):965–70. <https://doi.org/10.1111/j.1467-9280.2007.02010.x> PMID: [17958710](https://pubmed.ncbi.nlm.nih.gov/17958710/)
18. Massey SH, Backes KA, Schuette SA. Plasma oxytocin concentration and depressive symptoms: a review of current evidence and directions for future research. *Depress Anxiety*. 2016; 33(4):316–22. <https://doi.org/10.1002/da.22467> PMID: [26756305](https://pubmed.ncbi.nlm.nih.gov/26756305/)
19. Kim S, Soeken TA, Cromer SJ, Martinez SR, Hardy LR, Strathearn L. Oxytocin and postpartum depression: Delivering on what's known and what's not. *Brain Res*. 2014; 1580:219–32. <https://doi.org/10.1016/j.brainres.2013.11.009> PMID: [24239932](https://pubmed.ncbi.nlm.nih.gov/24239932/)
20. Scantamburlo G, Hansenne M, Geenen V, Legros J-J, Ansseau M. Additional intranasal oxytocin to escitalopram improves depressive symptoms in resistant depression: An open trial. *Eur Psychiatry*. 2015; 30(1):65–8. <https://doi.org/10.1016/j.eurpsy.2014.08.007> PMID: [25282363](https://pubmed.ncbi.nlm.nih.gov/25282363/)
21. Wang T, Shi C, Li X, Zhang P, Liu B, Wang H, et al. Injection of oxytocin into paraventricular nucleus reverses depressive-like behaviors in the postpartum depression rat model. *Behav Brain Res*. 2018; 336:236–43. <https://doi.org/10.1016/j.bbr.2017.09.012> PMID: [28889022](https://pubmed.ncbi.nlm.nih.gov/28889022/)
22. Gu V, Feeley N, Gold I, Hayton B, Robins S, Mackinnon A, et al. Intrapartum Synthetic Oxytocin and Its Effects on Maternal Well-Being at 2 Months Postpartum. *Birth*. 2015.
23. Mah BL, Van Ijzendoorn MH, Smith R, Bakermans-Kranenburg MJ. Oxytocin in postnatally depressed mothers: Its influence on mood and expressed emotion. *Prog Neuropsychopharmacol Biol Psychiatry*. 2013; 40:267–72. <https://doi.org/10.1016/j.pnpbp.2012.10.005> PMID: [23085508](https://pubmed.ncbi.nlm.nih.gov/23085508/)
24. Clarici A, Pellizzoni S, Guaschino S, Alberico S, Bembich S, Giuliani R, et al. Intranasal administration of oxytocin in postnatal depression: implications for psychodynamic psychotherapy from a randomized double-blind pilot study. *Front Psychol*. 2015; 6(426). <https://doi.org/10.3389/fpsyg.2015.00426> PMID: [25941501](https://pubmed.ncbi.nlm.nih.gov/25941501/)
25. Kroll-Desrosiers AR, Nephew BC, Babb JA, Guilarte-Walker Y, Moore Simas TA, Deligiannidis KM. Association of peripartum synthetic oxytocin administration and depressive and anxiety disorders within the first postpartum year. *Depress Anxiety*. 2017; 34(2):137–46. <https://doi.org/10.1002/da.22599> PMID: [28133901](https://pubmed.ncbi.nlm.nih.gov/28133901/)
26. Mah BL. Oxytocin, postnatal depression, and parenting: a systematic review. *Harv Rev Psychiatry*. 2016; 24(1):1–13. <https://doi.org/10.1097/HRP.000000000000093> PMID: [26735320](https://pubmed.ncbi.nlm.nih.gov/26735320/)
27. Mah BL, Van Ijzendoorn MH, Out D, Smith R, Bakermans-Kranenburg MJ. The Effects of Intranasal Oxytocin Administration on Sensitive Caregiving in Mothers with Postnatal Depression. *Child Psychiatry Hum Dev*. 2016; 1–8. <https://doi.org/10.1007/s10578-016-0642-7> PMID: [27100724](https://pubmed.ncbi.nlm.nih.gov/27100724/)
28. Delaveau P, Jabourian M, Lemogne C, Guionnet S, Bergouignan L, Fossati P. Brain effects of antidepressants in major depression: A meta-analysis of emotional processing studies. *J Affect Disord*. 2011; 130(1):66–74. <http://dx.doi.org/10.1016/j.jad.2010.09.032>.
29. Sheline YI, Barch DM, Donnelly JM, Ollinger JM, Snyder AZ, Mintun MA. Increased amygdala response to masked emotional faces in depressed subjects resolves with antidepressant treatment: an fMRI study. *Biol Psychiatry*. 2001; 50(9):651–8. PMID: [11704071](https://pubmed.ncbi.nlm.nih.gov/11704071/)
30. Williams LM, Korgaonkar MS, Song YC, Paton R, Eagles S, Goldstein-Piekarski A, et al. Amygdala reactivity to emotional faces in the prediction of general and medication-specific responses to antidepressant treatment in the randomized iSPOT-D trial. *Neuropsychopharmacology*. 2015; 40(10):2398–408. <https://doi.org/10.1038/npp.2015.89> PMID: [25824424](https://pubmed.ncbi.nlm.nih.gov/25824424/)
31. Klimes-Dougan B, Schreiner MW, Thai M, Gunlicks-Stoessel M, Reigstad K, Cullen KR. Neural and neuroendocrine predictors of pharmacological treatment response in adolescents with depression: a preliminary study. *Prog Neuropsychopharmacol Biol Psychiatry*. 2018; 81:194–202. <https://doi.org/10.1016/j.pnpbp.2017.10.015> PMID: [29100972](https://pubmed.ncbi.nlm.nih.gov/29100972/)
32. Godlewska B, Browning M, Norbury R, Igoumenou A, Cowen P, Harmer C. 136-Neural Response to Implicit Emotions as Biomarkers of Clinical Response to SSRI Treatment in Depression. *Biol Psychiatry*. 2017; 81(10):S57.
33. Godlewska B, Browning M, Norbury R, Cowen PJ, Harmer CJ. Early changes in emotional processing as a marker of clinical response to SSRI treatment in depression. *Translational psychiatry*. 2016; 6(11):e957. <https://doi.org/10.1038/tp.2016.130> PMID: [27874847](https://pubmed.ncbi.nlm.nih.gov/27874847/)
34. Kim P, Leckman JF, Mayes LC, Feldman R, Wang X, Swain JE. The plasticity of human maternal brain: longitudinal changes in brain anatomy during the early postpartum period. *Behav Neurosci*. 2010; 124(5):695. <https://doi.org/10.1037/a0020884> PMID: [20939669](https://pubmed.ncbi.nlm.nih.gov/20939669/)

35. Kim P, Strathearn L, Swain JE. The maternal brain and its plasticity in humans. *Horm Behav.* 2016; 77 (Supplement C):113–23. <https://doi.org/10.1016/j.yhbeh.2015.08.001>.
36. Sabihi S, Dong SM, Durosko NE, Leuner B. Oxytocin in the medial prefrontal cortex regulates maternal care, maternal aggression and anxiety during the postpartum period. *Front Behav Neurosci.* 2014; 8.
37. Gemmel M, Rayen I, van Donkelaar E, Loftus T, Steinbusch HW, Kokras N, et al. Gestational stress and fluoxetine treatment differentially affect plasticity, methylation and serotonin levels in the PFC and hippocampus of rat dams. *Neuroscience.* 2016; 327:32–43. <https://doi.org/10.1016/j.neuroscience.2016.03.068> PMID: 27060483
38. Hillerer KM, Reber SO, Neumann ID, Slattery DA. Exposure to chronic pregnancy stress reverses peripartum-associated adaptations: implications for postpartum anxiety and mood disorders. *Endocrinology.* 2011; 152(10):3930–40. <https://doi.org/10.1210/en.2011-1091> PMID: 21846798
39. Pawluski JL, Lonstein JS, Fleming AS. The Neurobiology of Postpartum Anxiety and Depression. *Trends Neurosci.* 2017; 40(2):106–20. <https://doi.org/10.1016/j.tins.2016.11.009> PMID: 28129895
40. Pawluski JL, Lambert KG, Kinsley CH. Neuroplasticity in the maternal hippocampus: Relation to cognition and effects of repeated stress. *Horm Behav.* 2016; 77:86–97. <https://doi.org/10.1016/j.yhbeh.2015.06.004> PMID: 26122302
41. Walsh EC, Eisenlohr-Moul TA, Pedersen CA, Rubinow DR, Girdler SS, Dichter GS. Early Life Abuse Moderates the Effects of Intranasal Oxytocin on Symptoms of Premenstrual Dysphoric Disorder: Preliminary Evidence From a Placebo-Controlled Trial. *Frontiers in psychiatry.* 2018; 9:547–. <https://doi.org/10.3389/fpsy.2018.00547> PMID: 30555357.
42. Haim A, Albin-Brooks C, Sherer M, Mills E, Leuner B. The effects of gestational stress and Selective Serotonin reuptake inhibitor antidepressant treatment on structural plasticity in the postpartum brain—A translational model for postpartum depression. *Horm Behav.* 2016; 77(Supplement C):124–31. <https://doi.org/10.1016/j.yhbeh.2015.05.005>.
43. Leuner B, Fredericks PJ, Nealer C, Albin-Brooks C. Chronic gestational stress leads to depressive-like behavior and compromises medial prefrontal cortex structure and function during the postpartum period. *PLoS One.* 2014; 9(3):e89912. <https://doi.org/10.1371/journal.pone.0089912> PMID: 24594708
44. Serretti A, Chiesa A. Treatment-Emergent Sexual Dysfunction Related to Antidepressants: A Meta-Analysis. *J Clin Psychopharmacol.* 2009; 29(3):259–66. <https://doi.org/10.1097/JCP.0b013e3181a5233f> 00004714-200906000-00011. PMID: 19440080
45. Graf H, Walter M, Metzger CD, Abler B. Antidepressant-related sexual dysfunction—Perspectives from neuroimaging. *Pharmacol Biochem Behav.* 2014; 121(Supplement C):138–45. <https://doi.org/10.1016/j.pbb.2013.12.003>.
46. Rupp HA, James TW, Ketterson ED, Sengelaub DR, Ditzen B, Heiman JR. Lower sexual interest in postpartum women: Relationship to amygdala activation and intranasal oxytocin. *Horm Behav.* 2013; 63(1):114–21. <https://doi.org/10.1016/j.yhbeh.2012.10.007> PMID: 23085496
47. Rupp HA, James TW, Ketterson ED, Sengelaub DR, Ditzen B, Heiman JR. Amygdala response to negative images in postpartum vs nulliparous women and intranasal oxytocin. *Soc Cogn Affect Neurosci.* 2014; 9(1):48–54. <https://doi.org/10.1093/scan/nss100> PMID: 22956670
48. Macoveanu J. Serotonergic modulation of reward and punishment: Evidence from pharmacological fMRI studies. *Brain Res.* 2014; 1556(Supplement C):19–27. <https://doi.org/10.1016/j.brainres.2014.02.003>.
49. McDonald E, Woolhouse H, Brown SJ. Sexual pleasure and emotional satisfaction in the first 18 months after childbirth. *Midwifery.* 2017; 55:60–6. <https://doi.org/10.1016/j.midw.2017.09.002> PMID: 28942215
50. Kim K, Hong JP, Cho MJ, Fava M, Mischoulon D, Lee D-W, et al. Loss of sexual interest and premenstrual mood change in women with postpartum versus non-postpartum depression: A nationwide community sample of Korean adults. *J Affect Disord.* 2016; 191(Supplement C):222–9. <https://doi.org/10.1016/j.jad.2015.11.050>.
51. Uvnäs-Moberg K, Björkstrand E, Hillegaart V, Ahlenius S. Oxytocin as a possible mediator of SSRI-induced antidepressant effects. *Psychopharmacology (Berl).* 1999; 142(1):95–101.
52. Emiliano AB, Cruz T, Pannoni V, Fudge JL. The interface of oxytocin-labeled cells and serotonin transporter-containing fibers in the primate hypothalamus: a substrate for SSRIs therapeutic effects? *Neuropsychopharmacology.* 2007; 32(5):977–88. <https://doi.org/10.1038/sj.npp.1301206> PMID: 17035935
53. Ozsoy S, Esel E, Kula M. Serum oxytocin levels in patients with depression and the effects of gender and antidepressant treatment. *Psychiatry Res.* 2009; 169(3):249–52. <https://doi.org/10.1016/j.psychres.2008.06.034> PMID: 19732960
54. Gregory R, Cheng H, Rupp HA, Sengelaub D, Heiman JR. Oxytocin increases VTA activation to infant and sexual stimuli in nulliparous and postpartum women. *Horm Behav.* 2015; 69:82–8. <https://doi.org/10.1016/j.yhbeh.2014.12.009> PMID: 25562711

55. Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. *The British Journal of Psychiatry*. 1987; 150(6):782–6.
56. Radloff LS. The CES-D scale A self-report depression scale for research in the general population. *Appl Psychol Meas*. 1977; 1(3):385–401.
57. Meyer-Lindenberg A, Domes G, Kirsch P, Heinrichs M. Oxytocin and vasopressin in the human brain: social neuropeptides for translational medicine. *Nat Rev Neurosci*. 2011; 12(9):524–38. <https://doi.org/10.1038/nrn3044> PMID: 21852800
58. Leng G, Ludwig M. Intranasal oxytocin: myths and delusions. *Biol Psychiatry*. 2016; 79(3):243–50. <https://doi.org/10.1016/j.biopsych.2015.05.003> PMID: 26049207
59. Striepens N, Kendrick KM, Hanking V, Landgraf R, Wüllner U, Maier W, et al. Elevated cerebrospinal fluid and blood concentrations of oxytocin following its intranasal administration in humans. *Sci Rep*. 2013; 3:3440–. <https://doi.org/10.1038/srep03440> PMID: 24310737.
60. Feldman R, Gordon I, Zagoory-Sharon O. Maternal and paternal plasma, salivary, and urinary oxytocin and parent–infant synchrony: considering stress and affiliation components of human bonding. *Developmental Science*. 2011; 14(4):752–61. <https://doi.org/10.1111/j.1467-7687.2010.01021.x> PMID: 21676095
61. Pratt M, Apter-Levi Y, Vakart A, Feldman M, Fishman R, Feldman T, et al. Maternal depression and child oxytocin response; moderation by maternal oxytocin and relational behavior. *Depress Anxiety*. 2015; 32(9):635–46. <https://doi.org/10.1002/da.22392> PMID: 26130435
62. Lang PJ, Bradley MM, Cuthbert BN. International affective picture system (IAPS): Affective ratings of pictures and instruction manual. NIMH, Center for the Study of Emotion & Attention, 2005 A-8.
63. Rupp HA, Wallen K. Sex-specific content preferences for visual sexual stimuli. *Arch Sex Behav*. 2009; 38(3):417–26. <https://doi.org/10.1007/s10508-008-9402-5> PMID: 18719987
64. Briceño E, Weisenbach S, Rapport L, Hazlett K, Bieliauskas L, Haase B, et al. Shifted inferior frontal laterality in women with major depressive disorder is related to emotion-processing deficits. *Psychol Med*. 2013; 43(07):1433–45.
65. Yang J-C, Park J-I, Kim G-W, Eun S-J, Lee M-S, Han K-L, et al. Effects of antidepressant treatment on sexual arousal in depressed women: A preliminary fMRI study. *Psychiatry Investig*. 2012; 9(4):379–83. <https://doi.org/10.4306/pi.2012.9.4.379> PMID: 23251203
66. Wonch KE, de Medeiros CB, Barrett JA, Dudin A, Cunningham WA, Hall GB, et al. Postpartum depression and brain response to infants: Differential amygdala response and connectivity. *Soc Neurosci*. 2016; 11(6):600–17. <https://doi.org/10.1080/17470919.2015.1131193> PMID: 26680151
67. Yang J-C, Park K, Eun S-J, Lee M-S, Yoon J-S, Shin I-S, et al. Assessment of cerebrocortical areas associated with sexual arousal in depressive women using functional MR imaging. *The journal of sexual medicine*. 2008; 5(3):602–9. <https://doi.org/10.1111/j.1743-6109.2007.00737.x> PMID: 18194182
68. Outhred T, Das P, Felmingham KL, Bryant RA, Nathan PJ, Malhi GS, et al. Impact of acute administration of escitalopram on the processing of emotional and neutral images: a randomized crossover fMRI study of healthy women. *J Psychiatry Neurosci*. 2014; 39(4):267–75. <https://doi.org/10.1503/jpn.130118> PMID: 24690370.
69. Godlewska B, Norbury R, Selvaraj S, Cowen P, Harmer C. Short-term SSRI treatment normalises amygdala hyperactivity in depressed patients. *Psychol Med*. 2012; 42(12):2609–17. <https://doi.org/10.1017/S0033291712000591> PMID: 22716999
70. Mottolese R, Redouté J, Costes N, Le Bars D, Sirigu A. Switching brain serotonin with oxytocin. *Proceedings of the National Academy of Sciences*. 2014; 111(23):8637–42. <https://doi.org/10.1073/pnas.1319810111> PMID: 24912179
71. Galbally M, Ryan J, van IJzendoorn M, Watson SJ, Spigset O, Lappas M, et al. Maternal depression, antidepressant use and placental oxytocin receptor DNA methylation: Findings from the MPEWS study. *Psychoneuroendocrinology*. 2018; 90:1–8. <https://doi.org/10.1016/j.psyneuen.2018.01.004> PMID: 29407512
72. Liu X, Hairston J, Schrier M, Fan J. Common and distinct networks underlying reward valence and processing stages: A meta-analysis of functional neuroimaging studies. *Neurosci Biobehav Rev*. 2011; 35(5):1219–36. <https://doi.org/10.1016/j.neubiorev.2010.12.012> PMID: 21185861
73. Pizzagalli DA, Holmes AJ, Dillon DG, Goetz EL, Birk JL, Bogdan R, et al. Reduced caudate and nucleus accumbens response to rewards in unmedicated individuals with major depressive disorder. *Am J Psychiatry*. 2009; 166(6):702–10. <https://doi.org/10.1176/appi.ajp.2008.08081201> PMID: 19411368
74. Atzil S, Hendler T, Feldman R. Specifying the neurobiological basis of human attachment: brain, hormones, and behavior in synchronous and intrusive mothers. *Neuropsychopharmacology*. 2011; 36(13):2603–15. <https://doi.org/10.1038/npp.2011.172> PMID: 21881566



75. Strathearn L, Fonagy P, Amico J, Montague PR. Adult attachment predicts maternal brain and oxytocin response to infant cues. *Neuropsychopharmacology*. 2009; 34(13):2655–66. <https://doi.org/10.1038/npp.2009.103> PMID: 19710635
76. Kim P, Feldman R, Mayes LC, Eicher V, Thompson N, Leckman JF, et al. Breastfeeding, brain activation to own infant cry, and maternal sensitivity. *Journal of child psychology and psychiatry*. 2011; 52(8):907–15. <https://doi.org/10.1111/j.1469-7610.2011.02406.x> PMID: 21501165
77. Brown R, Herbison A, Grattan D. Effects of prolactin and lactation on A15 dopamine neurones in the rostral preoptic area of female mice. *J Neuroendocrinol*. 2015; 27(9):708–17. <https://doi.org/10.1111/jne.12297> PMID: 26132331
78. Yip SH, Romanò N, Gustafson P, Hodson DJ, Williams EJ, Kokay IC, et al. Elevated Prolactin during Pregnancy Drives a Phenotypic Switch in Mouse Hypothalamic Dopaminergic Neurons. *Cell Reports*. 2019; 26(7):1787–99.e5. <https://doi.org/10.1016/j.celrep.2019.01.067> PMID: 30759390
79. Chase HW, Moses-Kolko EL, Zevallos C, Wisner KL, Phillips ML. Disrupted posterior cingulate–amygdala connectivity in postpartum depressed women as measured with resting BOLD fMRI. *Soc Cogn Affect Neurosci*. 2013; 9(8):1069–75. <https://doi.org/10.1093/scan/nst083> PMID: 23709351
80. Carceller H, Perez-Rando M, Castren E, Nacher J, Guirado R. Effects of the antidepressant fluoxetine on the somatostatin interneurons in the basolateral amygdala. *Neuroscience*. 2018; 386:205–13. <https://doi.org/10.1016/j.neuroscience.2018.06.041> PMID: 30018016
81. Joshi SH, Espinoza RT, Pirnia T, Shi J, Wang Y, Ayers B, et al. Structural plasticity of the hippocampus and amygdala induced by electroconvulsive therapy in major depression. *Biol Psychiatry*. 2016; 79(4):282–92. <https://doi.org/10.1016/j.biopsych.2015.02.029> PMID: 25842202
82. Langevin J-P, Koek RJ, Schwartz HN, Chen JW, Sultzer DL, Mandelkern MA, et al. Deep brain stimulation of the basolateral amygdala for treatment-refractory posttraumatic stress disorder. *Biol Psychiatry*. 2016; 79(10):e82–e4. <https://doi.org/10.1016/j.biopsych.2015.09.003> PMID: 26475671
83. Rantala MJ, Luoto S, Krams I, Karlsson HJB, behavior, immunity. Depression subtyping based on evolutionary psychiatry: Proximate mechanisms and ultimate functions. 2017.