Arch Womens Ment Health (2011) 14:355–359
DOI 10.1007/s00737-011-0226-2

SHORT COMMUNICATION

The neural processing of negative emotion postpartum: a preliminary study of amygdala function in postpartum depression

Michael E. Silverman · Holly Loudon · Xun Liu · Casey Mauro · Gila Leiter · Martin A. Goldstein

Received: 19 August 2010 / Accepted: 16 June 2011 / Published online: 29 June 2011

Abstract While contemporary diagnostic nosology characterizes postpartum depression (PPD) as a specifier of a major depressive disorder (MDD), this classification continues to be questioned. Functional magnetic resonance imaging (fMRI) holds the promise of helping to characterize the neuroanatomical dysfunction associated with dysregulated emotion after childbirth. Twenty postpartum women underwent fMRI in the presence of emotionally valenced stimuli. The observation of relative amygdala non-responsivity in subjects demonstrating greater depression symptomotology stands in contrast to imaging studies of MDD and provides insight into possible phenotypic differences of PPD.

Keywords Postpartum depression · Amygdala · Neuroimaging · fMRI

Introduction

Postpartum depression (PPD) is nosologically classified as a specifier of a major depressive disorder (MDD), however specific differences in the clinical presentation of PPD have been identified (Cooper et al. 2007). As a result, its diagnostic classification continues to be questioned. While neuroimaging research has revealed much about the neurobiologic characteristics associated with mood disorders, to date, no functional imaging study of PPD (Silverman et al. 2007; Moses-Kolko et al. 2010) has directly addressed how these findings might help to classify the disorder. Doing so could significantly enhance the translational knowledge base of this disease, thereby facilitating the development of more refined diagnostic methods and ultimately better-targeted treatment modalities.

The amygdala, a cortical structure consistently showing abnormalities of function in depressed patients and recognized as a critical processing area in both normal and pathological emotional responses, may be a key marker in differentiating disorder subtypes (Almeida et al. 2010; Kaladjian et al. 2009). Given recent findings of amygdala dysregulation in PPD in response to negatively valenced faces (Moses-Kolko et al. 2010), further clarifying amygdala dysregulation associated with PPD symptomatology may lead towards a more accurate characterization of the depression that occurs specifically after childbirth.

The purpose of the study was to use functional magnetic resonance imaging (fMRI) techniques to assess the neuroanatomical responsivity of the amygdala in women 6–8 weeks postpartum with no prior history of treated depression. Given PPD's current classification as a specifier of MDD, we hypothesized that increased amygdalar responsivity to strongly valenced negative stimuli would be observed in those postpartum women expressing greater PPD symptomatology.

Methods

Twenty women, 6–8 weeks postpartum, offered signed consent and underwent both structural and functional

M. E. Silverman (✉) · X. Liu · C. Mauro
Department of Psychiatry, Mount Sinai School of Medicine,
One Gustave L. Levy Place, Box 1230, New York, NY 10029,
USA
e-mail: Michael.silverman@mssm.edu

H. Loudon · G. Leiter
Department of Obstetrics, Gynecology and Reproductive Science,
Mount Sinai School of Medicine,
New York, NY, USA

M. A. Goldstein
Department of Neurology, Mount Sinai School of Medicine,
New York, NY, USA

magnetic resonance imaging in a study approved by the Mount Sinai Medical Center institutional review board. Eight of the 20 subjects participated in our pilot study (Silverman et al. 2007). The data from three subjects were excluded for head movements greater than 3–4 mm leaving 17 subjects (mean age=27 years). All subjects were right handed, native English speakers, with a history free of psychiatric illness (including antepartum depression), neurologic disorders (including head trauma), substance abuse or chemical/alcohol dependence. No subjects were taking birth control or psychoactive medication. A structured psychiatric diagnostic interview (SCID-RV, First et al. 1996) was used to ensure participants were free of any axis I comorbidity. The Hamilton Depression Inventory (HDI-17, Reynolds et al. 1995) was used to identify DSM-IV delineated symptoms of depression. The Edinburgh Postnatal Depression Scale (EPDS, Cox et al. 1987) was administered at week 6 and readministered prior to entering the MRI.

Neuropsychological activation paradigm

Subjects were instructed to perform a right index finger button press immediately upon presentation of a word (e.g., murder) and a right middle finger button press upon presentation of scrambled letters (e.g. xpfamd). There were 400 trials in total. Because subjects were not preinformed of the emotional nature of the words and the emotional qualities were *incidental* relative to the explicit nature of the task, the evocation of potentially confounding cognitive processes was minimized.

After exiting the scanner subjects were asked to identify words presented during scanning interspersed randomly with distractor words. Subjects were not previously informed of this task as its purpose was to explore differences in *incidental* encoding. Following completion, subjects were asked to rate a subset of stimulus words in order to confirm stimulus valence categorizations. A full description of the task design is described elsewhere (Silverman et al. 2007).

Image acquisition, processing, and analysis

Image data were acquired with a Siemens Allegra Magnetron 3-T head dedicated MRI scanner (maximum gradient strength ~60 mT/m, max gradient slew ~600 T/m/s). T1-weighted spoiled gradient (MP-RAGE) MRI whole brain anatomical scans (208 slices; 8 mm in-plane resolution, 0.8 mm slice thickness, contiguous slices) were acquired followed by T2-weighted turbo spin echo axial whole brain images (3 mm slice thickness) to explore potential pathology. Finally, gradient echo planar imaging–blood oxygen level-dependent (EPI-BOLD) fMRI were acquired (TR=2000 ms, TE=30 ms, 32 slices; 3 mm thickness; 1 mm gap) as an index of neuronal activity during the neuropsychological activation paradigm. Image processing was conducted using FSL (FMRIB's Software Library, v4.1). Prior to analysis, the first two volumes of each run were discarded to allow the MR signal to reach steady state. The remaining images were motion corrected, spatially smoothed, and temporally filtered using a high-pass filter. Specifics of anatomical and gradient EPI-BOLD fMRI acquisition and image analysis have been previously published (Silverman et al. 2007).

A mask of the amygdala (Automated Anatomical Labeling) was created in MNI space and an initial t map threshold of $p=0.05$, $k>90$ uncorrected was used to identify activation specific to the hypothesis. Within the amygdala, a priori regions of interest were specified using a surrounding sphere (radius 4 mm). A correlation analysis was then performed using the Statistical Package for Social Sciences (Windows v16.0.1) to determine the association between amygdala activation, the presentation of stimuli, and PPD symptomatology. To confirm the specificity of amygdala responsivity, pairwise comparisons between the differential BOLD signals for *threat vs. neutral* and *negative vs. neutral* contrasts were conducted.

Results

Of the 17 subjects, 6 had an average EPDS score >12 indicating probable depression (Cox et al. 1987). The remaining had scores <8 (mean=7.5; range=0–23; SD=7.6). EPDS scores between the two administrations never varied more than two points. Administration of the HDI-17 indicated that seven women obtained scores at or above the mild level >12 (mean=11.7, range=1–28, SD=10.2) and were likely experiencing a DSM-IV-defined *postpartum* depression. Correlational analyses between the EPDS and HDI-17 revealed a significant relationship ($r=0.842$, two-tailed $p_{corr}<0.001$).

Affective valence ratings A repeated-measures ANOVA of the post-scan ratings of all stimulus words confirmed our assignment of stimuli to positive, negative, threat, and neutral categories ($F(3, 60)=323.22$, $p<0.001$), respectively. Post hoc analysis exploring the behavioral rating differences of negative (depressive content) stimuli and negative (threat) stimuli demonstrated a significant difference in valence ($t=3.06$, $p\leq0.012$; two tailed) in that threat words were perceived as significantly more negative in valance than the negative stimuli with depressive content (Table 1).

Reaction times Analysis of reaction times demonstrated no effect or association of depression symptoms on

Table 1 Table of behavioral and imaging results to neuropsychological activation paradigm

Subject mean reaction time (ms)			
Valence	Neutral	Negative	Negative with threat content
All subjects	707.44	734.18	739.79
EPDS <8	702.84	728.69	740.67
EPDS >12	717.57	746.24	737.84
Incidental recognition accuracy (%)			
Valence	Neutral	Negative	Negative with threat content
All subjects	69	72	75
EPDS <8	71	74	79
EPDS >12	67	71	70
Subject valence ratings [scale: very positive (0) to very negative (5)]			
Valence	Neutral	Negative	Negative with threat content
All subjects	3.05	4.01	4.14
EPDS <8	3.13	3.99	4.16
EPDS >12	2.99	4.03	4.13
Amygdala [threat words vs. neutral words] × [EPDS >12 vs. EPDS <8]			
Right amygdala	20, 4, −16	$Z \geq -2.58$	$k=29$
Amygdala (correlation to EPDS)			
Right, $r=-0.536$		$p_{corr} \leq 0.027$ (two tailed)	$k=33$
Left, $r=-0.403$		p_{corr} = n.s.	
Right amygdala (contrasts)			
Threat words vs. neutral words		$r=-0.474$	$p<0.027$
Negative words vs. neutral words		$r=-0.043$	n.s.

responsivity during the activation paradigm ($r=0.186$, two-tailed p_{corr} = n.s.; Table 1).

Recognition memory Signal detection (d') analysis for the incidental encoding and recognition of the stimulus words revealed a weak, yet meaningful, relationship between PPD symptoms and recognition ($r=-0.246$, two-tailed p_{corr} = n.s.; Table 1).

fMRI data

We first explored whether a main effect of stimulus condition (threat words vs. neutral words) by emotional status (EPDS <8 vs. EPDS >12) was observed using a repeated-measures ANOVA. Neural responses significant at $p<0.05$ corrected for multiple comparisons revealed significantly greater BOLD response to threat stimuli in the right

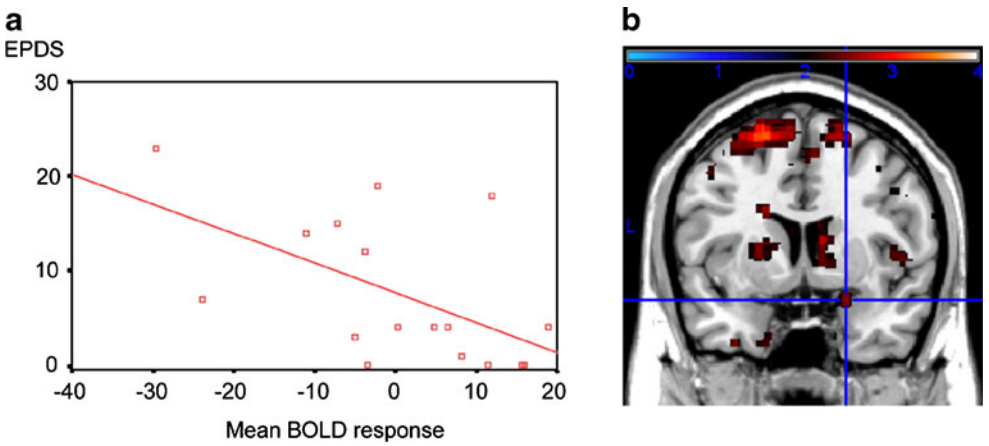

Fig. 1 **a** Scatter plot of the Edinburgh Postnatal Depression Scale (*EPDS*) total score over mean BOLD response at the maxima of the right amygdale (x, y, z; 19, 6, −15) in the threat condition showing a negative correlation ($r=-0.536$; $p_{corr} \leq 0.027$, two tailed) between the lack of postpartum depressive symptoms and increased amygdala activation. **b** Statistical map for the contrast of threat vs. neutral stimuli demonstrating differences in BOLD response in the right amygdala associated with PPD symptomology as measured by the overall EPDS score ($p<0.05$, uncorrected for visualization)

amygdala ($F(1, 15)=5.35$; $p\leq0.035$). Secondary correlational analyses associated with the a priori hypothesis demonstrated a BOLD response for threat words in the right amygdala that was correlated (negative) with PPD symptomatology. That is, subjects reporting fewer PPD symptoms as measured by the EPDS demonstrated greater responsivity to negatively valenced threat content (Table 1, Fig. 1a).

In order to confirm the specificity of amygdala responsivity to threat stimuli associated with PPD symptoms, ROI analyses of *threat stimuli vs. neutral stimuli* and *negative stimuli vs. neutral stimuli* in relation to EPDS scores were conducted. Correlation coefficients of the pairwise comparisons between the differential BOLD signal revealed significant differences in the *threat vs. neutral* contrast, but not the *negative vs. neutral* contrast (Table 1).

Discussion and conclusion

The temporal relation between reproductive events and affect dysregulation has been observed for centuries. Yet the relationship between PPD and phenotypes of depression that occurs at other times remains poorly understood. Indeed, while contemporary diagnostic nosology currently considers PPD to be a specifier of a unipolar-type depressive disorder (MDD), the criteria associated with PPD as defined by the DSM-IV can equally characterize episodes of depression in patients with other disorders (see Sharma et al. 2009). Clinically, the characterization of PPD seems inadequate.

Neuroimaging offers the possibility of clarifying the pathophysiologic processes underlying various psychiatric disorders. While the literature assessing amygdala activity in depression is sometimes conflicting, the majority of functional imaging reports examining the response of *unipolar* depressed patients to emotional stimuli, specifically those negatively valenced in nature, suggest that amygdala responsivity is heightened in comparison to healthy controls (Drevets et al. 2008; Sheline et al. 2001). Our key finding was that unmedicated postpartum depressive symptoms were associated with the failure to activate right amygdala regions in response to threat-related linguistic stimuli—a pattern distinct from cerebral responsivity associated with unipolar depression (Abler et al. 2007) but consistent with a recent report using negatively valenced faces in PPD (Moses-Kolko et al. 2010).

Without doubt, one could easily see how an increased sensitivity to threat content in the postpartum period would be evolutionarily advantageous toward protection of the newborn. In such light, the postpartum literature has numerous examples of how women experiencing PPD are prone to disadvantageous decision making (Cooper et al. 2007) that puts their infant(s) at increased risk throughout early development. The possibility that depression in the postpartum period is associated with a blunted threat response is interesting given the more regularly observed increased threat response in non-postpartum depressed subjects (Drevets et al. 2008) and is something that should be further explored.

While the observation of relative amygdala non-responsivity in subjects demonstrating greater PPD symptomotology was unexpected given the current classification of postpartum depression as a specifier of a unipolar depressive disorder, it leads to the suspicion of PPD's possible relation to other affective disorders. These findings therefore suggest the potential to identify an empirically based neural characterization of PPD that may help clarify the characterization of mood change in the postpartum period, but will also provide a necessary cornerstone for developing more targeted, biologically based diagnostic and therapeutic strategies specific to mood changes as a consequence of reproduction.

In conclusion, this study was an initial attempt to assess amygdala function in PPD. Accordingly, observed amygdala activation patterns associated with PPD appear somewhat different than those of non-postpartum-related unipolar depression. This finding provides potential insight into neurophysiologic mechanisms responsible for the mood dysregulation frequently observed in the postpartum period. Elucidating the neurobiological and behavioral features of PPD is critical for developing adequate methods for early diagnosis and intervention. Doing so will also increase our understanding of the neurobiological spectrum of affective disorders in women across the lifecycle and provide a foundation for explorations into the mechanisms responsible for PPD.

References

Abler B, Erk S, Herwig U, Walter H (2007) Anticipation of aversive stimuli activates extended amygdala in unipolar depression. J Psychiatr Res 41(6):511–522

Almeida JR, Versace A, Hassel S, Kupfer DJ, Phillips ML (2010) Elevated amygdala activity to sad facial expressions: a state marker of bipolar but not unipolar depression. Biol Psychiatry 67:414–421

Cooper C, Jones L, Dunn E, Forty L, Haque S, Oyebode F et al (2007) Clinical presentation of postnatal and non-postnatal depressive episodes. Psychol Med 37:1273–1280

Cox JL, Holden JM, Sagovsky R (1987) Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. Br J Psychiatry 150:782–786

Drevets WC, Price JL, Furey ML (2008) Brain structural and functional abnormalities in mood disorders: implications for neurocircuitry models of depression. Brain Struct Funct 213:93–118

First MB, Spitzer RL, Gibbon M, Williams J (1996) Structured clinical interview for DSM-IV, research version (SCID-RV). American Psychiatric Press, Washington

Kaladjian A, Jeanningros R, Azorin JM, Nazarian B, Roth B, Anton JL et al (2009) Remission from mania is associated with a decrease in amygdala activation during motor response inhibition. Bipolar Disord 11:530–538

Moses-Kolko EL, Perlman SB, Wisner KL, James J, Saul AT, Phillips ML (2010) Abnormally reduced dorsomedial prefrontal cortical activity and effective connectivity with amygdala in response to negative emotional faces in postpartum depression. Am J Psychiatry 167(11):1373–1380

Reynolds WM, Kobak KA (1995) Hamilton Depression Inventory: a self-report version of the Hamilton Depression Rating Scale. Professional Manual. Odessa, Psychological Assessment Resources

Sharma V, Burt VK, Ritchie HL (2009) Bipolar II postpartum depression: detection, diagnosis, and treatment. Am J Psychiatry 166:1217–1221

Sheline Y, Barch D, Donnelly J, Ollinger J, Snyder A, Mintun M (2001) Increased amygdala response to masked emotional faces in depressed subjects resolves with antidepressant treatment: an fMRI study. Biol Psychiatry 50:651–658

Silverman ME, Loudon H, Safier M, Protopopescu X, Leiter G, Goldstein M (2007) Neural dysfunction in postpartum depression: an fMRI pilot study. CNS Spectr 12:853–862