Inflammation negatively correlates with amygdala-ventromedial prefrontal functional connectivity in association with anxiety in patients with depression: Preliminary results

Neeti D. Mehta, *Emory University*
Ebrahim Haroon, *Emory University*
Xiaodan Xu, *Shenzhen University*
Bobbi J. Woolwine, *Emory University*
Zhihao Li, *Emory University*
Jennifer Felger, *Emory University*

Journal Title: Brain, Behavior, and Immunity
Volume: Volume 73
Publisher: Elsevier: 12 months | 2018-10-01, Pages 725-730
Type of Work: Article | Post-print: After Peer Review
Publisher DOI: 10.1016/j.bbi.2018.07.026
Permanent URL: https://pid.emory.edu/ark:/25593/v0n6n

Final published version: http://dx.doi.org/10.1016/j.bbi.2018.07.026

Copyright information:

HHS Public Access

Author manuscript

Brain Behav Immun. Author manuscript; available in PMC 2019 October 01.

Published in final edited form as:

Brain Behav Immun. 2018 October ; 73: 725–730. doi:10.1016/j.bbi.2018.07.026.

Inflammation negatively correlates with amygdala-ventromedial prefrontal functional connectivity in association with anxiety in patients with depression: preliminary results

Neeti D. Mehta, BA[1,2], **Ebrahim Haroon, MD**[1,3], **Xiaodan Xu, BA**[4,5], **Bobbi J. Woolwine, MS, LCSW**[1], **Zhihao Li, PhD**[1,4,5,*], and **Jennifer C. Felger, PhD, MS**[1,3,*]

[1]Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA 30322

[2]Neuroscience Graduate Program, Graduate Division of Biological and Biomedical Sciences, Emory University, Atlanta, GA 30322

[3]Winship Cancer Institute, Emory University, Atlanta, GA 30322

[4]School of Psychology and Sociology, Shenzhen University, Shenzhen, Guangdong, China 518060

[5]Shenzhen Key Laboratory of Affective and Social Cognitive Science, Shenzhen University, Shenzhen, Guangdong, China 518060

Abstract

Biomarkers of inflammation, including inflammatory cytokines and the acute-phase reactant C-reactive protein (CRP), are reliably increased in a subset of patients with depression, anxiety disorders and post-traumatic stress disorder (PTSD). Administration of innate immune stimuli to laboratory subjects and the associated release of inflammatory cytokines has been shown to affect brain regions involved in fear, anxiety and emotional processing such as the amygdala. However, the role of inflammation in altered circuitry involving amygdala and other brain regions and its subsequent contribution to symptom severity in depression, anxiety disorders and PTSD is only beginning to be explored. Herein, medically-stable, currently unmedicated outpatients with a primary diagnosis of major depressive disorder (MDD; n=48) underwent resting-state functional MRI (rfMRI) to determine whether altered connectivity between the amygdala and whole brain was observed in a subset of patients with high inflammation and symptoms of anxiety. Whole-brain, voxel-wise functional connectivity analysis of the right and left amygdala as a function of inflammation (plasma CRP concentrations) revealed that increased CRP predicted decreased functional connectivity between right amygdala and left ventromedial prefrontal cortex (vmPFC)

[*]**Corresponding Authors**: Jennifer C. Felger, Ph.D., 1365 Clifton Road, Emory University, Clinic B 5103, Atlanta, GA 30322; jfelger@emory.edu. Or, Zhihao Li, Ph.D., Shenzhen University, 536 Science & Technology Building, 3688 Nanhai Ave, Shenzhen, Guangdong, China 518060; zhihao_li@szu.edu.cn.

Financial Disclosure:
All authors declare no conflicts of interest and have nothing to disclose.

(corrected p<0.05). Amygdala-vmPFC connectivity was, in turn, negatively correlated with symptoms of anxiety (r=−0.33, df=46, p=0.022). In exploratory analyses, relationships between low amygdala-vmPFC connectivity and high anxiety were only observed in patients with a secondary diagnosis of an anxiety disorder or PTSD (r=−0.54 to −0.87, p<0.05). More work is needed to understand the role of inflammation and its effects on amygdala-vmPFC circuitry and symptoms of anxiety in MDD patients with comorbid anxiety disorders or PTSD.

Keywords

Inflammation; amygdala; functional connectivity; fMRI; C-reactive protein; anxiety; depression; post-traumatic stress disorder

Introduction

Inflammation, as measured by inflammatory cytokines and the acute-phase reactant C-reactive protein (CRP), is reliably increased in patients with depression, anxiety disorders and post-traumatic stress disorder (PTSD), and is thought to contribute to symptom severity.[1] Relevant to the effects of inflammation on the brain, numerous laboratories have consistently reported that administration of cytokines or inflammatory stimuli to humans and laboratory animals preferentially affects cortical-basal ganglia reward and motor circuits,[2–4] as well as regions involved in fear, anxiety and emotional processing such as the amygdala.[5–7] For example, administration of endotoxin or typhoid vaccination to healthy persons has been shown to induce symptoms of anxiety, increase amygdala neural activation, and reduce functional connectivity between the amygdala and ventromedial prefrontal cortex (vmPFC), all of which correlated with the release of inflammatory cytokines in peripheral blood.[5–8] Additionally, and in regard to sensitivity of the neural pathways involved in the inflammatory responses to stress, heightened neural activity of the amygdala to a psychosocial laboratory stressor was associated with greater stress-induced release of peripheral blood IL-6.[9] Therefore, not only does the administration of inflammatory stimuli increase amygdala activity and affect its functional connectivity with vmPFC, but exaggerated amygdala responses to stress are also associated with greater production of inflammatory cytokines.[5,7,9]

Patients with depression, anxiety disorders and PTSD exhibit alterations in neural activity and functional connectivity within the circuits that are known to be affected by inflammation. For example, increased amygdala activity and decreased functional connectivity between amygdala and vmPFC has been consistently reported in patients with depression, anxiety disorders and PTSD, and has been shown to correlate with state anxiety.[10–13] Despite similarities between the effects of experimentally administered inflammatory stimuli on brain circuits and alterations observed in patients with psychiatric illnesses like depression, anxiety and PTSD, only a handful of studies have examined relationships between increased inflammation and brain structure and function in these patients.[14–16] We recently reported that higher levels of inflammation, as measured by plasma CRP and inflammatory cytokines, were associated with lower functional connectivity within corticostriatal circuits that regulate motivation and motor activity in patients with major

depressive disorder (MDD).[14] However, whether inflammation also predicts altered functional connectivity in circuits relevant to fear and anxiety in patients with depression is not known. Herein, we assessed whether higher plasma CRP concentrations are associated with altered functional connectivity between the amygdala and whole brain in relation to symptoms of anxiety in medically-stable, currently unmedicated patients with a primary diagnosis of MDD. We also explored whether relationships between inflammation-associated alterations in amygdala connectivity and anxiety symptoms were modified by comorbid diagnosis of an anxiety disorder or PTSD.

Methods

Forty-eight participants (18–65 years) were recruited as previously described[14] based on a primary diagnosis of MDD, or bipolar disorder current episode depressed, as determined by Structured Clinical Interview for Diagnostic and Statistical Manual-IV-TR (SCID-IV). Comorbid diagnosis with an anxiety disorder- generalized anxiety disorder (GAD) or anxiety disorder not otherwise specified (ANOS)- and/or PTSD was also determined by SCID. Subjects were free of psychotropic medications and medications known to affect the immune system and were excluded based on evidence of active infections or uncontrolled medical illnesses (see Supplemental Methods). Procedures were approved *a priori* by the Institutional Review Board of Emory University. All participants provided written informed consent.

Inflammatory markers:

Plasma was collected from EDTA whole blood in the morning (10AM±1 hour). The immunoturbidometric method was used to measure high sensitivity CRP with a Beckman AU480 chemistry analyzer and Ultra WR CRP kit (Sekisui Diagnostics). Inflammatory cytokines, interleukin (IL)-6, IL-1beta and tumor necrosis factor (TNF), and their soluble receptors (IL-6sr, IL-1ra, sTNFR2), were assessed in duplicate using multiplex bead-based assays (R& D Systems) as described previously.[14,15] See Supplemental Methods **and** Table S1. CRP was used as a marker of inflammation in primary analyses because of its stability, clinical relevance and previous association with increased inflammatory markers in both the blood and CSF.[17]

Clinical Assessments:

The clinician administered Hamilton Rating Scale for Depression (HAMD) was used to assess depression severity. A subscale for symptoms of anxiety from HAM-D was used as the primary measurement of anxiety symptom severity (see Supplemental Methods for detail and additional assessments).

Functional connectivity:

Wakeful resting-state fMRI images were acquired on a 3T Magnetom Trio scanner (Siemens, USA) with a 20-channel head coil using a Z-saga pulse sequence as described.[14] Analysis of functional connectivity was conducted with AFNI (http://afni.nimh.nih.gov/). After pre-processing, data was spatially normalized into a standard stereotaxic space, Montreal Neurological Institute (MNI) template with $1mm^3$ resolution. Seed-to-whole-brain

connectivity analysis: Amygdala to whole-brain resting-state functional connectivity was examined using left and right amygdala ROIs derived individually from FreeSurfer (https://surfer.nmr.mgh.harvard.edu/) and registered to the preprocessed fMRI data.[18]

Voxel-wise whole-brain correlations were computed as a linear function of plasma CRP (mg/L) to identify brain regions for which functional connectivity with right or left amygdala ROIs was associated with inflammation, with cluster correction ($p<0.001$/voxel plus 354 mm^3 cluster or $p<0.01$/voxel plus 1691 mm^3 cluster, corrected $p<0.05$) using AFNI's "3dClustSim -acf".[19] Subject-level functional connectivity measures (Fisher's Z transformed, $Z(R)=0.5\ln[(1+R)/(1-R)]$) for identified ROIs were used in subsequent regression models. Z-score maps were also generated to visualize patterns of positive functional connectivity with right amygdala separately for patients with "low" versus "high" inflammation (plasma CRP <1 and >3mg/L, respectively). See Supplemental Methods.

Targeted connectivity analysis with vmPFC: To validate our findings and to protect against inflation of regression coefficients that may result from extracting functional connectivity Z-scores from voxels in vmPFC identified by correlation with CRP in whole-brain analysis, we extracted Z-scores for subject-level connectivity analyses of amygdala with a reward-sensitive spherical vmPFC region identified by meta-analysis (MNI coordinates x=0, y=44, z=−8 and volume=1408mm^3).[20] We previously reported decreased connectivity between this vmPFC region and the ventral and dorsal striatum in patients with increased inflammatory markers, high anhedonia and motor slowing.[14]

Statistics:

Patient characteristics were summarized using mean and standard deviation for continuous variables and percent for categorical variables. Subject-level connectivity Z-scores for relationships between amygdala ROIs and brain regions identified by connectivity analyses were entered into linear regression models (as dependent variables) to assess relationships with inflammatory cytokines and their receptors, and (as independent variables) to assess relationships with symptoms of depression related to anxiety. Significant relationships between connectivity Z-scores and inflammatory biomarkers or symptoms were assessed in linear regression models with clinical covariates that may contribute to inflammation and/or influence neural circuitry and symptoms (age, sex, race, smoking status and body mass index [BMI]), and with backward and forward selection using the same criteria where indicated. The Benjamin-Hochberg procedure was used to adjust for multiple comparisons. Non-normal data was natural log transformed for parametric statistics. Significance was two-tailed, $\alpha<0.05$, and statistics were conducted in IBM SPSS Statistics 24.0.

Results

Plasma CRP predicted decreased amygdala to ventromedial prefrontal (vmPFC) functional connectivity in association with symptoms of anxiety

Characteristics of the patient sample and their relationship with plasma CRP are summarized in Supplemental Table 2. Increasing plasma CRP (mg/L) was associated with reduced connectivity between the right amygdala and a cluster in vmPFC ($r=-0.55$, $df=46$, $p<0.001$; cluster centroid: BA32, x=−12, y=36, z=−6, volume=353mm^3; Figures 1a,b), which was part

of a larger vmPFC cluster identified at the voxel-level threshold of $p<0.01$ (Supplemental Figure 1). Consistent with this negative relationship between CRP and amygdala-vmPFC functional connectivity, Z-score maps demonstrated that patients with low inflammation (CRP<1mg/L) had positive amygdala-vmPFC functional connectivity, whereas subjects with high inflammation (CRP>3mg/L) exhibited no significant connectivity between these brain regions (Figure 1c). Negative correlations were also observed between CRP and functional connectivity of right amygdala to a cluster in the left precentral gyrus ($r=-0.37$, $df=46$, $p<0.01$; cluster centroid: BA6, x=−61, y=8, z=28, cluster=648mm^3). Plasma CRP continued to predict right amygdala to vmPFC and precentral gyrus connectivity when controlling for clinical covariates ($p<0.05$, Supplemental Table 3). CRP was not significantly associated with connectivity between left amygdala and any brain region.

Amygdala-vmPFC connectivity, which was negatively associated with plasma CRP concentrations, also predicted increased anxiety as measured by a subscale from the HAM-D ($r=-0.33$, $df=46$, $p=0.022$) (Supplemental Figure 2). Amygdala-vmPFC connectivity was the strongest predictor of anxiety as measured by HAM-D in backward and forward linear regression models containing clinical covariates and CRP ($p<0.05$), and also mediated an association between plasma CRP and the HAM-D anxiety subscale (see Supplemental Figure 3). To further validate these findings, for correlation with other inflammatory markers, and for further exploration of relationships between amygdala-vmPFC connectivity and comorbid diagnoses described below, functional connectivity between the right amygdala ROI and a previously identified vmPFC cluster was assessed.[14,20] Consistent with findings from whole-brain analysis, targeted connectivity between the right amygdala ROI and this *a priori* defined vmPFC cluster was negatively correlated with plasma CRP ($r=-0.37$, $df=46$, $p=0.01$). Of the other inflammatory markers, IL-6 ($r=-0.30$, $df=46$, $p=0.041$) and IL-1ra ($r=-0.35$, $df=46$, $p=0.016$) were most significantly negatively associated with amygdala-vmPFC connectivity in backward and forward linear regression models with clinical covariates using the same selection criteria. Targeted amygdala-vmPFC connectivity also predicted symptoms of anxiety ($r=-0.33$, $df=46$, $p=0.023$) (Table 1).

Amygdala-vmPFC functional connectivity, symptoms of anxiety and role of comorbid diagnoses: exploratory analyses

Whether relationships between amygdala-vmPFC connectivity and anxiety were affected by diagnosis with a comorbid anxiety disorder or PTSD was addressed in exploratory analyses. Both patients with an anxiety disorder (GAD or ANOS) (n=7) and patients with PTSD (n=19) showed a significant negative relationship between amygdala-vmPFC and anxiety symptoms ($r=-0.87$, $df=5$, $p=0.024$ and $r=-0.54$, $df=17$, $p=0.018$, respectively) (Table 1). Of note, these relationships were significant using both parametric and non-parametric statistics ($p<0.05$), and remained significant after correction for multiple comparisons. Patients without comorbid diagnoses of an anxiety disorder or PTSD (n=23) exhibited no significant correlation between functional connectivity and anxiety ($p=0.551$). Primarily women had PTSD (n=17/19, Supplemental Table 4), yet women without comorbid anxiety disorders or PTSD (n=13) did not show a relationship between amygdala-vmPFC connectivity and anxiety ($p=0.765$). See Supplemental Results for further detail.

Discussion

Increased inflammation was associated with decreased functional connectivity between the right amygdala and vmPFC in patients with depression, which in turn predicted increased symptoms of anxiety. Interestingly, the relationship between amygdala-vmPFC connectivity and increased anxiety was observed only in MDD patients who also had a comorbid diagnosis of an anxiety disorder or PTSD. Together these findings suggest that inflammation may affect amygdala-vmPFC circuitry to drive symptoms of anxiety in depressed patients who are susceptible to anxiety disorders and PTSD.

Decreased amygdala-vmPFC functional connectivity has been reported previously in persons administered inflammatory stimuli and in patients with psychiatric disorders compared to controls.[10–13] Indeed, this pattern of decreased right amygdala to vmPFC functional connectivity has been observed in association with cytokine production following typhoid vaccination and in patients with MDD.[6,13] Additionally, lateralized findings specific to right amygdala are also consistent with evidence of greater involvement of the right amygdala in fear conditioning.[21] During viewing of fearful stimuli, patients with PTSD had higher amygdala reactivity and as well as decreased right amygdala to left vmPFC functional connectivity in association with symptoms of hyperarousal.[12] With regard to sources of inflammation and its effects on the brain in these patients, previous work has shown that individuals with high levels of inflammatory markers prior to or immediately following trauma exposure are more susceptible to PTSD,[22,23] and chronic low-grade inflammation induced by early life stress increases susceptibility to depression.[24] Both plasma CRP and a risk haplotype for the IL-18 gene have also been shown to predict increased amygdala reactivity and symptoms of anxiety and depression in college students.[25,26] While a growing body of literature has found that administration of inflammatory stimuli causes changes in amygdala activity and connectivity, stress-induced production of inflammatory cytokines has also been found to correlate with heightened amygdala reactivity.[5,7,9] It then follows that inflammation may play a role in the behavioral symptoms of persons who are more reactive to stress or trauma, whereby exaggerated and prolonged release of cytokines may feedback on and weaken circuits that drive symptoms of depression, anxiety or PTSD. Therefore, inflammation may provide a pathophysiological mechanism whereby amygdala-vmPFC circuitry is weakened in depressed patients with comorbid anxiety and/or PTSD.

It is worthy to mention that decreased amygdala-vmPFC connectivity did correlate with overall HAM-D scores ($r=-0.373$, $df=46$, $p=0.009$), but did not significantly correlate ($p=0.06–0.98$) with the symptoms of anhedonia that were associated with decreased ventral striatalvmPFC connectivity in our previous work.[14] Additionally, ventral striatum to amygdala functional connectivity was not associated with plasma CRP at the statistical thresholds employed in this study. These findings indicate that high CRP is related to decreased connectivity in two distinct circuits involving inflammation-sensitive subcortical structures[1–3,5] and the vmPFC, which may then drive specific behavioral symptoms that are relevant to the primary function of the subcortical structure. Future imaging studies combining fMRI and diffusion tensor imaging (DTI) are required to understand whether

inflammation-related decreases in amygdala-vmPFC functional connectivity are driven by heightened amygdala reactivity, and whether it is influenced by white matter integrity.

This preliminary study enrolled participants with a primary diagnosis of MDD and anxiety-related comorbidities diagnosed by SCID. A substantial limitation is that dedicated anxiety and PTSD symptom severity scales were not used, and that primary analyses focused on only two anxiety symptoms from HAM-D. Future work using anxiety- and PTSD-specific scales will examine whether amygdala-vmPFC connectivity that is associated with inflammation is also related to overall severity of anxiety symptoms, as well as those related to threat sensitivity or hyperarousal.[12,27] Trait (but not state) anxiety was assessed with a dedicated scale. Therefore, analyses involving functional connectivity were focused on current symptoms of anxiety, yet we also examined the role of diagnosis of anxiety related disorders or trait anxiety. Another limitation of this study was the lack of healthy controls or a trauma-exposed non-MDD/PTSD comparison group. fMRI data was also not motion censored per current standards for functional connectivity analysis.[28] Despite these methodological concerns, a strength of examining relationships between inflammation-related changes in amygdala connectivity and anxiety in patients enrolled based on a primary diagnosis of MDD is that not every patient had a comorbid anxiety disorder or PTSD; thus, this enrollment strategy provided a sample with a full range of anxiety symptom severity and a reference group with no comorbid diagnosis. However, a primary limitation was the small sample size, particularly with respect to subgroup analysis based on diagnosis. Patients with low inflammation (CRP<1mg/L) also exhibited significant positive amygdala-vmPFC connectivity similar to that reported in non-psychiatric controls, which served as a reference group for connectivity in patients with high inflammation. As a cross-sectional study, causation cannot be established, yet formal mediation analysis demonstrated that decreased amygdala-vmPFC connectivity mediated the relationship between plasma CRP and symptoms of anxiety. Longitudinal studies using administration of anti-inflammatory pharmacological agents are required to determine causal links between inflammation and alterations in amygdala-vmPFC connectivity in patients with depression and/or PTSD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding sources:

This work was supported by funds from the National Institute of Mental Health to JCF (R01MH109637, R21MH106904) and EH (K23MH091254), the Brain and Behavioral Research Foundation and Dana Foundation to JCF (BBRF22296, CADF49143), and from the Natural Science Foundation of China/Shenzhen to ZL (31671169, 31530031/000099). In addition, the study was supported in part by PHS Grants UL1TR000454 and KL2TR000455 from the Clinical and Translational Science Award program, and by the NIH/NCI under award number P30CA138292.

References

1. Felger JC. Imaging the role of inflammation in mood and anxiety-related disorders. Curr Neuropharmacol. 2017.
2. Capuron L, Pagnoni G, Drake D, et al. Dopaminergic mechanisms of reduced basal ganglia responses to hedonic reward during interferon alfa administration. Arch Gen Psychiatry. 2012;69(10):1044–1053. [PubMed: 23026954]
3. Eisenberger NI, Berkman ET, Inagaki TK, Rameson LT, Mashal NM, Irwin MR. Inflammation-induced anhedonia: endotoxin reduces ventral striatum responses to reward. Biological psychiatry. 2010;68(8):748–754. [PubMed: 20719303]
4. Harrison NA, Voon V, Cercignani M, Cooper EA, Pessiglione M, Critchley HD. A Neurocomputational Account of How Inflammation Enhances Sensitivity to Punishments Versus Rewards. Biol Psychiatry. 2015.
5. Inagaki TK, Muscatell KA, Irwin MR, Cole SW, Eisenberger NI. Inflammation selectively enhances amygdala activity to socially threatening images. NeuroImage. 2012;59(4):3222–3226. [PubMed: 22079507]
6. Harrison NA, Brydon L, Walker C, Gray MA, Steptoe A, Critchley HD. Inflammation causes mood changes through alterations in subgenual cingulate activity and mesolimbic connectivity. Biol Psychiatry. 2009;66(5):407–414. [PubMed: 19423079]
7. Harrison NA, Brydon L, Walker C, et al. Neural origins of human sickness in interoceptive responses to inflammation. Biol Psychiatry. 2009;66(5):415–422. [PubMed: 19409533]
8. Lasselin J, Elsenbruch S, Lekander M, et al. Mood disturbance during experimental endotoxemia: Predictors of state anxiety as a psychological component of sickness behavior. Brain, behavior, and immunity. 2016;57:30–37.
9. Muscatell KA, Dedovic K, Slavich GM, et al. Greater amygdala activity and dorsomedial prefrontal-amygdala coupling are associated with enhanced inflammatory responses to stress. Brain, behavior, and immunity. 2015;43:46–53.
10. Makovac E, Watson DR, Meeten F, et al. Amygdala functional connectivity as a longitudinal biomarker of symptom changes in generalized anxiety. Soc Cogn Affect Neurosci. 2016;11(11): 1719–1728. [PubMed: 27369066]
11. Hahn A, Stein P, Windischberger C, et al. Reduced resting-state functional connectivity between amygdala and orbitofrontal cortex in social anxiety disorder. NeuroImage.2011;56(3):881–889. [PubMed: 21356318]
12. Stevens JS, Jovanovic T, Fani N, et al. Disrupted amygdala-prefrontal functional connectivity in civilian women with posttraumatic stress disorder. J Psychiatr Res.2013;47(10):1469–1478. [PubMed: 23827769]
13. Tang Y, Kong L, Wu F, et al. Decreased functional connectivity between the amygdala and the left ventral prefrontal cortex in treatment-naive patients with major depressive disorder: a resting-state functional magnetic resonance imaging study. Psychol Med.2013;43(9):1921–1927. [PubMed: 23194671]
14. Felger JC, Li Z, Haroon E, et al. Inflammation is associated with decreased functional connectivity within corticostriatal reward circuitry in depression. Mol Psychiatry.2016;21(10):1358–1365. [PubMed: 26552591]
15. Haroon E, Fleischer CC, Felger JC, et al. Conceptual convergence: increased inflammation is associated with increased basal ganglia glutamate in patients with major depression. Mol Psychiatry. 2016;21(10):1351–1357. [PubMed: 26754953]
16. Savitz J, Frank MB, Victor T, et al. Inflammation and neurological disease-related genes are differentially expressed in depressed patients with mood disorders and correlate with morphometric and functional imaging abnormalities. Brain, behavior, and immunity.2013;31:161–171.
17. Felger JC, Haroon E, Patel TA, et al. What does plasma CRP tell us about peripheral and central inflammation in depression? Mol Psychiatry. 2018.

18. Cullen KR, Westlund MK, Klimes-Dougan B, et al. Abnormal amygdala resting-state functional connectivity in adolescent depression. JAMA psychiatry. 2014;71(10):1138–1147. [PubMed: 25133665]
19. Cox RW, Chen G, Glen DR, Reynolds RC, Taylor PA. FMRI Clustering in AFNI: False-Positive Rates Redux. Brain Connect. 2017;7(3):152–171. [PubMed: 28398812]
20. Diekhof EK, Kaps L, Falkai P, Gruber O. The role of the human ventral striatum and the medial orbitofrontal cortex in the representation of reward magnitude - an activation likelihood estimation meta-analysis of neuroimaging studies of passive reward expectancy and outcome processing. Neuropsychologia. 2012;50(7):1252–1266. [PubMed: 22366111]
21. Baker KB, Kim JJ. Amygdalar lateralization in fear conditioning: evidence for greater involvement of the right amygdala. Behav Neurosci. 2004;118(1):15–23. [PubMed: 14979779]
22. Pervanidou P, Kolaitis G, Charitaki S, et al. Elevated morning serum interleukin (IL)-6 or evening salivary cortisol concentrations predict posttraumatic stress disorder in children and adolescents six months after a motor vehicle accident. Psychoneuroendocrinology.2007;32(8–10):991–999. [PubMed: 17825995]
23. Eraly SA, Nievergelt CM, Maihofer AX, et al. Assessment of plasma C-reactive protein as a biomarker of posttraumatic stress disorder risk. JAMA psychiatry. 2014;71(4):423–431. [PubMed: 24576974]
24. Danese A, Moffitt TE, Pariante CM, Ambler A, Poulton R, Caspi A. Elevated inflammation levels in depressed adults with a history of childhood maltreatment. Arch Gen Psychiatry. 2008;65(4): 409–415. [PubMed: 18391129]
25. Swartz JR, Prather AA, Di Iorio CR, Bogdan R, Hariri AR. A Functional Interleukin-18 Haplotype Predicts Depression and Anxiety through Increased Threat-Related Amygdala Reactivity in Women but Not Men. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 2017;42(2):419–426. [PubMed: 27430614]
26. Swartz JR, Prather AA, Hariri AR. Threat-related amygdala activity is associated with peripheral CRP concentrations in men but not women. Psychoneuroendocrinology.2017;78:93–96. [PubMed: 28183031]
27. O'Donovan A, Ahmadian AJ, Neylan TC, Pacult MA, Edmondson D, Cohen BE. Current posttraumatic stress disorder and exaggerated threat sensitivity associated with elevated inflammation in the Mind Your Heart Study. Brain, behavior, and immunity.2017;60:198–205.
28. Satterthwaite TD, Elliott MA, Gerraty RT, et al. An improved framework for confound regression and filtering for control of motion artifact in the preprocessing of resting-state functional connectivity data. NeuroImage. 2013;64:240–256. [PubMed: 22926292]

- Inflammatory stimuli affect brain regions involved in depression, anxiety and PTSD
- In depression, high CRP predicted decreased amygdala-vmPFC functional connectivity
- Low amygdala-vmPFC connectivity was associated with increased symptoms of anxiety
- This relationship was only seen in patients with comorbid anxiety disorders or PTSD

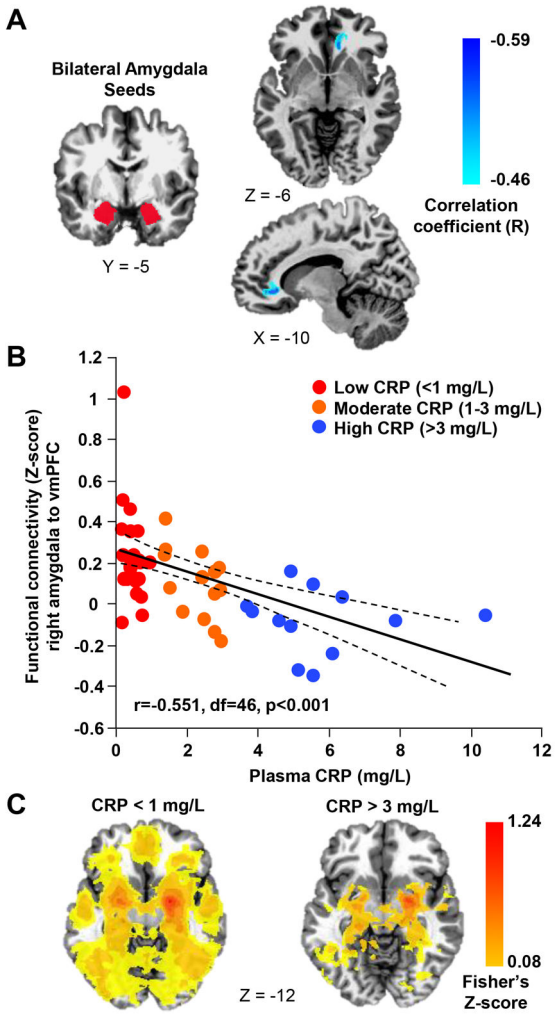

Figure 1.

Plasma C-reactive protein (CRP) was negatively associated with functional connectivity between the right amygdala and left ventromedial prefrontal cortex (vmPFC; BA32, x=−12, y=36, z=−6), with increasing CRP predicting decreasing connectivity (cyan-blue intensity, r=−0.46 to −0.59) in patients with depression (**a** and **b**). Z-score maps demonstrated that whereas patients with high inflammation (CRP>3mg/L) exhibited no significant connectivity between right amygdala and vmPFC, subjects with low inflammation (CRP<1mg/L) exhibited positive connectivity (yellow-red intensity) between these brain regions (**c**). Clusters are overlaid onto "MNI_N27" structural brain images in the axial (z=−6 and −12: **a, c**) and sagittal (x=−10: **a**) planes, corrected p<0.05.

Table 1.

Correlation between anxiety symptoms and right amygdala to vmPFC connectivity by diagnosis.

	All	Anxiety (GAD/ANOS)	PTSD	No Anxiety or PTSD
n	48	7[+]	19[+]	23
r (p-value)	**−0.33 (0.022)**	**−0.87 (0.024)**	**−0.54 (0.018)**	−0.13(0.551)

Data is represented as a Pearson correlation r (p-value). Significant relationships ($p<0.05$) are bolded.

[+]One patient had both GAD/NOS and PTSD. ANOS-anxiety disorder not otherwise specified; GAD-generalized anxiety disorder; HAM-D-Hamilton depression rating scale; PTSD-post-traumatic stress disorder