Resting-State Functional Connectivity of the Amygdala and Hippocampus in PTSD: Results From the PGC-ENIGMA PTSD Working Group

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Objective: Studies investigating resting-state functional connectivity of the amygdala and hippocampus have produced inconsistent findings. The authors' objective was to conduct the largest systematic comparison of alterations in functional connectivity of the amygdala and hippocampus in individuals with posttraumatic stress disorder (PTSD) using a multicohort mega-analysis with uniform processing steps and parameters across all cohorts.

Methods: Resting-state functional MRI data from 1,017 PTSD patients and 1,702 control participants from 32 international sites were centrally preprocessed with HALFpipe and analyzed using the Image-Based Meta- and Mega-Analysis (IBMMA) package for neuroimaging processing. Group-level seed-based whole-brain analyses were completed for the right and left amygdala and hippocampus. Additional correlation analyses were conducted between PTSD norm-severity scores and resting-state functional connectivity (rs-FC).

Results: Compared to control participants, individuals with PTSD showed stronger rs-FC between the left amygdala seed and right hippocampus and amygdala and the left and right lingual gyri. Greater PTSD total norm-severity scores were significantly associated with rs-FC between the left amygdala and right hippocampus/amygdala and rs-FC between the right amygdala and left hippocampus/amygdala.

Conclusions: Greater connectivity between subcortical threat centers involved in fear processing, memory, and extinction learning characterizes the resting state in PTSD. Future directions include investigating how different interventions, such as brain stimulation, neurofeedback, and psychotherapy, might modulate the aberrant neural networks in PTSD.

Am J Psychiatry 2026; 183:333–342; doi: 10.1176/appi.ajp.20250062

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PTSD is a debilitating disorder that affects about 5.6% of trauma-exposed individuals globally (1). PTSD symptoms include intrusive recollections of the traumatic event, avoidance of reminders of the event, alterations in cognition and mood, and increased arousal and hypervigilance (2). To gain insight into the neural underpinnings of these symptoms, many studies have explored seed-based resting-state functional connectivity (rs-FC) in participants with posttraumatic stress disorder (PTSD). rs-FC provides insights into the intrinsic functional connections in the brain and advances the neurobiological understanding of PTSD to guide development of new treatments. However, many rs-FC studies have used small samples and presented inconsistent findings. The present study leverages a large international, multicohort dataset from the Enhancing NeuroImaging Genetics Through Meta-Analysis (ENIGMA) Psychiatric Genomics Consortium (PGC) to uncover alterations in whole-brain connectivity of the amygdala and hippocampus in participants with PTSD compared to control participants using a mega-analysis of seed-based rs-FC.

Given the importance of altered threat reactivity and extinction in PTSD, studies examining neural alterations in PTSD samples have focused on brain regions involved in threat recognition, response, and extinction. Specifically, altered context processing, generalization of fear reactions, and failure to acquire safety learning have been found in individuals with PTSD (reviewed in 3). Brain regions implicated in these processes have been extensively evaluated for their role in the maintenance and development of PTSD symptoms. Key brain regions include the amygdala, central to fear acquisition and expression (4), and the hippocampus, important in learning and memory (5). The amygdala and hippocampus work in tandem to create contextual associations between threatening stimuli and the environment (6). The ventromedial prefrontal cortex (vmPFC) regulates fear-related responses to cues that no longer signal threat (7). Overall, studies comparing amygdala and hippocampus activation between individuals with PTSD and control participants find that these regions exhibit greater reactivity in response to threatening and trauma-related stimuli. In contrast, lower vmPFC reactivity is typically observed in individuals with PTSD (reviewed in 8).

Over the past decade, methodological advances have been made in exploring functional connections between brain regions inferred from temporally correlated activity rather than examining the activation of individual brain regions elicited by a behavioral task. rs-FC is a powerful approach for investigating the relationship of spontaneous activity of threat response regions, namely, the hippocampus and amygdala, to activity of other threat-relevant brain regions. Numerous studies comparing rs-FC between individuals with PTSD and control participants have employed various analytic techniques, including regional homogeneity, amplitude of low-frequency fluctuations, effect size signed differential mapping (9–11), and seed-based rs-FC (12). Seed-based rs-FC is a standard technique to assess the association between an a priori region of interest (seed) and voxels across the entire brain in the absence of a task. This approach allows researchers to ask unique questions regarding alterations in communication between regions of interest and the whole brain that may contribute to psychopathology. Exploring FC differences between individuals with PTSD and control participants provides an understanding of the relationship between the spontaneous brain activity of different regions, without task influences (13).

The first study to explore seed-based rs-FC in PTSD (14) focused on alterations of the default mode network, using the posterior cingulate cortex (PCC) as a seed. The authors found greater positive FC of the PCC with precuneus, with medial prefrontal cortex, and with bilateral lateral parietal cortex in healthy control participants compared to individuals with PTSD. Since then, additional studies have found differences between individuals with PTSD and control participants (reviewed in 9). When specifically using a seed-based approach, researchers found that individuals with PTSD had enhanced rs-FC between the amygdala seed and insula (15–17), hippocampus and parahippocampus (18), anterior cingulate cortex (ACC) (18), and cortical regions, including the parietal occipital cortex and supplementary motor area (19). However, some studies have shown that PTSD is associated with weaker rs-FC between the right amygdala and hippocampus (20) and the left amygdala and insula (18). When the bilateral hippocampus was used as a seed, results were mixed, with studies showing, in individuals with PTSD versus control participants, both weaker and stronger connectivity patterns to cortical areas to the PCC, pregenual ACC, precuneus (21), and other regions, including the lentiform nucleus, insula, and thalamus (15). These studies are examples of the mixed findings in the literature where the amygdala and hippocampus are used as seed regions.

These foundational seed-based rs-FC studies have been limited in sample size (N<60 per group), likely contributing to the mixed findings and inability to generalize findings across different samples. To date, only one meta-analysis has synthesized the current literature on alterations in seed-based rs-FC in PTSD (9). The authors found that individuals with PTSD showed greater rs-FC between seed regions belonging to the affective network (including the amygdala, hippocampus, nucleus accumbens, orbitofrontal cortex, right frontal lobe, left parahippocampus, and vestibular cortical regions) and the dorsolateral prefrontal cortex and weaker rs-FC between those seed regions and the medial temporal and superior frontal gyri.

Further investigation of rs-FC in PTSD using a much larger, more diverse sample (with greater representation across sex, age, race, ancestry, and index trauma type) is needed to obtain more generalizable results about alterations in amygdala and hippocampal rs-FC and to advance our understanding of the threat neurocircuitry using seed-based rs-FC. Here, we leveraged mega-analysis techniques to investigate pooled data from 32 international study sites that

TABLE 1. Clinical and demographic characteristics of the full sample, the PTSD group, and the control group[a]

	Full sample (N=2,719)		PTSD group (N=1,017)		Control group (N=1,702)			
Variable	N	%	N	%	N	%	χ^2	p
Biological sex							9.89	0.002
Male	1,412	51.9	488	48.0	924	54.3		
Female	1,307	48.1	529	52.0	778	45.7		
	Mean	SD	Mean	SD	Mean	SD	t	p
Age (years)	38.52	16.40	38.61	15.20	38.47	17.09	0.23	0.82
Symptom severity[b]								
PTSD total norm-severity	0.26	0.23	0.48	0.17	0.10	0.11	61.20	<0.001
Cluster B norm-severity	0.27	0.24	0.46	0.20	0.11	0.14	37.92	<0.001
Cluster C norm-severity	0.32	0.31	0.54	0.25	0.11	0.18	33.82	<0.001
Cluster D norm-severity	0.23	0.24	0.40	0.21	0.05	0.10	35.98	<0.001
Cluster E norm-severity	0.30	0.24	0.49	0.18	0.14	0.16	37.74	<0.001
Depression norm-severity	0.24	0.21	0.38	0.19	0.17	0.18	22.66	<0.001
CTQ total	45.78	21.36	59.31	23.70	37.26	14.25	16.11	<0.001

[a] CTQ, Childhood Trauma Questionnaire; PTSD, posttraumatic stress disorder.
[b] Norm-severity refers to norm scores from 0 to 1, where 0 is equivalent to the minimum possible score and 1 is equivalent to the maximum possible score for the symptom assessment instrument in question. All scores between the minimum and maximum possible scores scale linearly to a rational number between 0 and 1.

were centrally preprocessed on a single supercomputing platform and analyzed data from individuals with PTSD and trauma-exposed control participants. Contrary to a meta-analysis, using the mega-analytic approach, statistical models were centralized and fitted to the aggregated data while adjusting for site effects, seed definitions were standardized across sites, and preprocessing was conducted using a single pipeline, reducing sources of variance in the analysis. Following previous findings in smaller samples (9) and given the importance of threat neurocircuitry in PTSD, we hypothesized that individuals with PTSD, compared to trauma-exposed control participants, would exhibit 1) stronger rs-FC between bilateral amygdala seed regions and hippocampus, insula, and dorsal ACC subregion, and 2) stronger rs-FC between bilateral hippocampus seed regions and PCC. We also hypothesized 3) weaker rs-FC between bilateral amygdala seed regions and the vmPFC, specifically rostral and subgenual ACC subregions.

METHODS

Sample

Table 1 presents clinical and demographic data from the ENIGMA-PGC PTSD working group included in the present study (PTSD group, N=1,017, 53% female; trauma-exposed control group, N=1,702, 46% female). Sample characteristics by site for each seed region are summarized in Table S1 in the online supplement. Individuals were assigned to the PTSD group if they met the full criteria for the disorder based on the diagnostic tools used at the site. Twenty-three participants who did not meet the full criteria for PTSD (i.e., who had subthreshold or partial PTSD) were included in the control group (results of sensitivity analyses with these participants excluded are presented in Table S6 in the online supplement). A complete list of inclusion and exclusion criteria by site is provided in Table S2 in the online supplement. All study procedures were approved by local institutional review boards, and participants provided written informed consent. The Duke University Health System Institutional Review Board granted exempt status to the present study.

Image Acquisition and Processing

Whole-brain T2*-weighted (blood-oxygen-level-dependent) functional MRI (fMRI) images were shared with our consortium working group. All preprocessing and quality control procedures were performed centrally at Duke University using HALFpipe (22), containerized software that enhances reproducibility. Preprocessing steps included spatial smoothing with a 6-mm full width at half maximum (FWHM) Gaussian kernel, grand mean scaling, registration to normalized space (MNI152Nlin2009cAsym template), temporal filtering with a Gaussian filter (128 seconds FWHM), and anatomical component correction (aCompCor) (23). Amygdala and hippocampus seed regions were defined using the most frequently cited coordinates from Neurosynth, using 6-mm spherical regions of interest placed at the following Montreal Neurological Institute (MNI) coordinates: right amygdala, x=26, y=−4, z=−22; left amygdala, x=−22, y=−4, z=−22; right hippocampus, x=32, y=−22, z=−12; left hippocampus, x=−28, y=−18, z=−16. The hippocampus seeds correspond to the anterior hippocampus. Quality control included visual inspection of registration, segmentation, and brain extraction for each participant's MRI scan. Participants were excluded if they had >30% image volumes (time points) with framewise displacement over the threshold, if they had temporal signal-to-noise ratio values below Q1−1.5×interquartile range (thresholds determined per site using box-and-whisker plots), or if more than 85% of independent-component analysis components were

TABLE 2. Significant findings of seed-based resting-state functional connectivity analyses[a]

Seed	Brain region	Peak MNI coordinates			Volume (mm^3)	Cohen's d
		x	y	z		
Right amygdala	n.s.	—	—	—	—	—
Left amygdala	Right hippocampus and amygdala	20	−9	−23	328	0.16
	Right and left lingual gyri	4	−91	−13	168	0.18
Right hippocampus	n.s.	—	—	—	—	—
Left hippocampus	n.s.	—	—	—	—	—

[a] MNI=Montreal Neurological Institute; n.s.=nonsignificant.

classified as noise. Table S3 in the online supplement lists resting-state parameters for each site.

Statistical Analysis

Whole-brain voxel-wise statistical analyses were performed using the Image-Based Meta- and Mega-Analysis (IBMMA) software package. Statistical maps were corrected for multiple comparisons across the entire gray matter mask using probabilistic threshold-free cluster enhancement (24) with family-wise error correction ($p<0.05$, using a two one-tailed test approach) and a minimum cluster extent threshold of 20 contiguous voxels to control for multiple comparisons. For each seed region, the main effect of group was assessed while controlling for an interaction term for group by biological sex, given previous studies that have highlighted sex differences in the prevalence of PTSD (25), age, age-squared, and sex, and site was treated as a random-effect variable in a linear mixed-effects model. Furthermore, whole-brain analyses were included to examine the effect of PTSD total norm-severity scores and each PTSD symptom cluster norm-severity score on rs-FC. Specifically, whole-brain analysis examined the effect of PTSD total norm-severity scores while controlling for an interaction term for PTSD total norm-severity scores by biological sex, age, age-squared, and site as a random effect variable. A separate whole-brain analysis examined all four PTSD norm-severity symptom clusters simultaneously in a single model that controlled for an interaction term for each norm-severity symptom cluster by biological sex, age, age-squared, and site as a random effect variable.

Sensitivity Analyses

Follow-up sensitivity analyses were conducted to determine the strength of the findings while separately controlling for index trauma type (see Table S4 in the online supplement) and motion parameters (see Table S5 in the online supplement) and determining whether the findings hold in an adult-only sample.

Associations With PTSD Total Norm-Severity Scores and Symptom Cluster Norm-Severity Scores

Exploratory analyses were conducted to test additional models beyond the main effect of diagnosis (PTSD, trauma-exposed control) model that used a whole-brain voxel-wise approach. The exploratory linear mixed-effects regression analyses were conducted to test associations of rs-FC between seeds and voxel clusters that were identified from the whole-brain voxel-wise analysis. These voxel clusters were defined as a 6-mm region-of-interest sphere centered at the peak voxel found with the whole-brain analysis. Exploratory linear mixed-effects regression analyses were conducted on PTSD total norm-severity scores, each symptom cluster norm-severity score (to determine the unique contribution of a particular symptom cluster), and extracted rs-FC values from significant voxel clusters obtained from the earlier whole-brain voxel-wise analyses, while controlling for the interaction between that model's respective PTSD norm-severity score by sex, main effects of age, age-squared, and site as a random effect. To preserve information and power while removing outliers, analyses assessed for extreme outliers (z score >3.29); when outliers were present, scores were winsorized to match the score with a z score value <3.29 (26). An additional Bonferroni correction for multiple comparisons across the five PTSD symptom measures, PTSD total norm-severity scores, and clusters B–E norm-severity scores was applied at a corrected $p<0.010$.

RESULTS

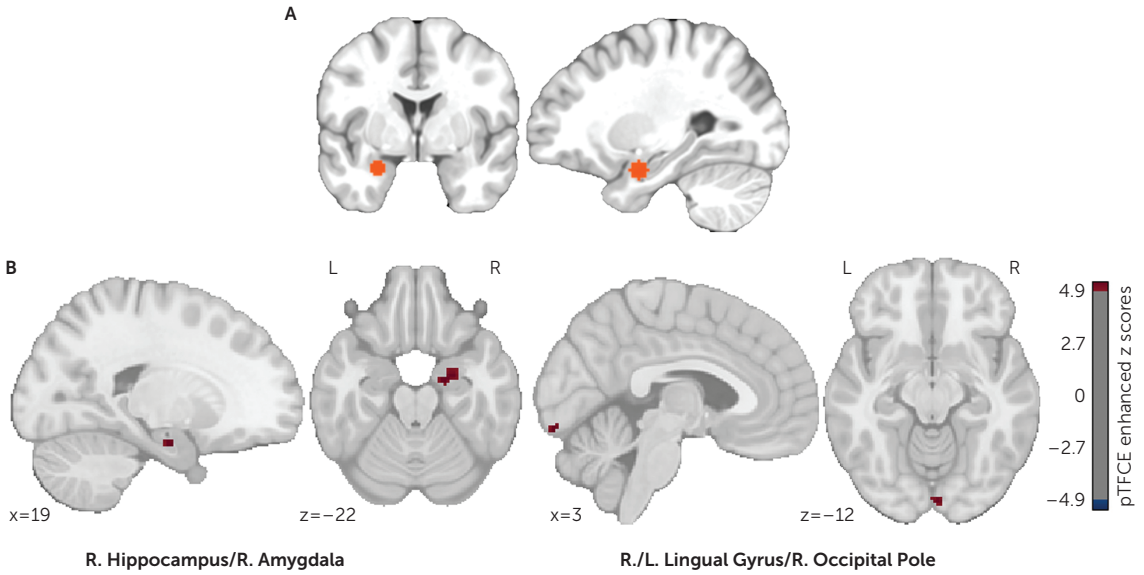
Right Amygdala rs-FC

Whole-brain correlational analyses showed that PTSD total norm-severity scores were associated with greater rs-FC for the right amygdala with the left hippocampus and amygdala, with the right hippocampus, and with the brainstem (see Table S9 in the online supplement). No significant differences were observed between diagnostic groups (Table 2). No significant whole-brain correlations were present for any symptom cluster.

Left Amygdala rs-FC

Individuals with PTSD showed greater rs-FC between the left amygdala and two clusters compared to trauma-exposed control participants (Figure 1). The first cluster included the right hippocampus and amygdala (MNI coordinates: x=20, y=−9, z=−23, Ke=328). The second cluster consisted of the bilateral lingual gyrus and right occipital pole (MNI coordinates: x=4, y=−91, z=−13; Ke=168 (Table 2). After correction, there were no regions in trauma-exposed control participants that showed greater rs-FC with the left amygdala seed compared to individuals with PTSD. Values extracted from voxel clusters were subjected to correlation analyses. The first cluster was significantly positively associated with PTSD

FIGURE 1. Brain regions that exhibit stronger resting-state functional connectivity with the left amygdala seed region in PTSD[a]



[a] Panel A depicts the left amygdala seed. Panel B shows the brain regions that were found to be significantly functionally connected with the left amygdala seed in the PTSD group versus the trauma-exposed control group. Connectivity strengths are depicted at the family-wise error cluster–corrected level. One-tailed statistical maps were thresholded at $z_{pTFCE}>4.9$ (corresponding to pFWE<0.05) with a minimum cluster extent of 20 contiguous voxels to control for multiple comparisons. All visualizations display only voxels exceeding these thresholds. FWE, family-wise error; pTFCE, probabilistic threshold-free cluster enhancement; PTSD, posttraumatic stress disorder.

total norm-severity scores and the following norm-severity symptom clusters: intrusive, negative cognitions in mood, and arousal and reactivity. The second voxel cluster was significantly positively associated with PTSD total norm-severity scores and the following norm-severity symptom clusters: intrusive and avoidance. Whole-brain correlational analyses with PTSD total norm-severity scores showed greater rs-FC of the left amygdala with bilateral amygdala/hippocampus and left parahippocampal gyrus (see Table S9 in the online supplement). No significant whole-brain correlations were present for any symptom cluster.

Hippocampus

No significant group differences or correlations with norm-severity symptom scores were observed in the right or left hippocampus.

DISCUSSION

We conducted the largest mega-analysis to date of resting-state fMRI in individuals with PTSD. Our data were centrally analyzed with uniform hardware, software, quality control procedures, preprocessing pipeline, and postprocessing pipeline for all sites and all participants. Our results demonstrate greater rs-FC between key subcortical regions involved in threat neurocircuitry, as determined by unbiased whole-brain analyses, in participants with PTSD compared to trauma-exposed control participants. Specifically, we showed greater rs-FC of the left amygdala with the right hippocampus and amygdala and the bilateral lingual gyrus in individuals with PTSD as compared to control participants. Our analysis includes data from studies conducted worldwide, covering a fuller range of demographic characteristics and a broader range of types of trauma exposure, promoting the generalizability of the findings.

Our finding of stronger rs-FC between the left amygdala and the right hippocampus and the right amygdala is in line with previous rs-FC studies (18). Specifically, we observed rs-FC with the anterior portion of the right hippocampus, which, together with the amygdala, plays a key role in associative learning and memory (5, 27). These results suggest a potential mechanism underlying alterations in emotional episodic memory processing in individuals with PTSD, whereby there is a heightened binding of emotional response and environmental information related to the traumatic event, potentially contributing to the overgeneralization of trauma memories (28). Further, this exaggerated connectivity might promote heightened communication that hampers the successful withdrawal of attention from a potential environmental threat and a failure to downregulate fear responses after the recognition that there is no immediate danger (29). Ultimately, these findings highlight a functional alteration in individuals with PTSD that may contribute to overly active memory processes and the inability to appropriately disengage from potentially threatening stimuli in one's environment. To better understand the findings discussed above, we conducted exploratory correlation analyses, which revealed significant positive associations between extracted rs-FC values and intrusive symptoms. These findings provide some evidence that greater rs-FC between regions may contribute to

greater memory distortions. These findings were not replicated when we examined the effect of intrusive symptoms using whole-brain analyses, and therefore the correlations using the extracted values should be interpreted with caution.

We also demonstrated stronger rs-FC between the left amygdala and the bilateral lingual gyrus. The lingual gyrus is a part of the occipital lobe, which is important in vision processing. It has recently been highlighted as one of many important regions of the affective visual circuit in PTSD (30). The amygdala projects to the occipital cortex via the parahippocampal segment of the cingulum bundle (31), lending importance to the amygdala in visuosensory-emotional processing. Previous studies have found alterations in the lingual gyrus in PTSD (30). Of note, one small rs-FC exploratory study found lower connectivity between the superficial amygdala and the lingual gyrus (32). While these findings are opposite to those of the present study, they derive from a small sample size (N=10 for each group) in an examination of subregions of the amygdala. We also found significant positive partial correlations between the extracted values from this voxel cluster and PTSD total norm-severity scores. Participants were asked to stay awake and let their mind wander, and our findings illustrate the potential difficulty in doing so for people with PTSD.

Our findings are inconsistent with some other reports. Previous studies highlighted stronger rs-FC between the amygdala seed and other regions of the salience network, including the insula (16, 17), a finding that was not replicated here. Similarly, previous rs-FC PTSD studies have found weaker connectivity between our seed regions and prefrontal cortical areas (reviewed in 9), whereas we found no significant differences between groups. There are several possible reasons for the inconsistency between our findings and prior studies. We had a large sample size and sufficient statistical power to detect an effect, unlike earlier studies (N<60). Furthermore, earlier studies employed less stringent multiple-comparison corrections, which may have increased the likelihood of type I error. Additionally, our sample is more generalizable as it represents a greater diversity of important demographic and clinical characteristics: age (8–86 years), race and ethnicity (18% Black, 8% Asian, 3.3% Hispanic), geographical region (nine countries), biological sex (48% female), and index trauma type (PTSD group breakdown: 23% military trauma, 45% civilian trauma, 22% unknown). Therefore, our study is better powered to find a true effect with a more diverse sample, providing more generalizable findings.

While the size of the sample is a major strength, diversity can lower power if it is not adequately captured in statistical models. We explicitly modeled sources of heterogeneity in a large sample from multiple sites by including site as a random effect. A study with a large sample size is able to reliably detect smaller effect sizes than a study with a small sample size (33). As the sample size increases, the sample mean more closely approximates the true population mean, so that the sample variance is lower and the effect size is more stable (34). A large sample size guards against spurious overestimates of the effect size, which may occur with small samples (35). Furthermore, findings may be specific for subgroups, explaining the discrepancy between this study and other studies. For example, when including index trauma type in the model, we see an interaction such that some group differences are greater in the military trauma subgroup. This underscores the importance of modeling sources of heterogeneity (e.g., index trauma type, sex) to explain the associated variance and increase statistical power. However, inadequate modeling of variance in heterogeneous samples results in greater noise and lower statistical power.

The absence of group differences in rs-FC of amygdala and hippocampal seed regions with prefrontal, particularly ventromedial prefrontal, cortical areas was unexpected. Neurocircuitry models of PTSD typically suggest that greater amygdala, lesser hippocampal, and lesser vmPFC activation contribute to symptomatology (reviewed in 8), and weaker connectivity was previously found between these regions in PTSD (9). Given our large sample size, the absence of this group difference is meaningful. Most studies of threat neurocircuitry in PTSD presented threatening or fearful stimuli, which was the context when impaired FC was shown. Our findings suggest that during rest, a distinct pattern occurs, with no aberrant functional connections between the subcortical seed regions and the prefrontal cortex. Instead, our findings suggest that the amygdala and hippocampus are hyperconnected and might contribute to an inability to downregulate fear responses even in the absence of threatening or fearful stimuli. When individuals are presented with a threat, prefrontal regulation may be hindered by the greater FC between the amygdala and hippocampus, which might result in the inability of the vmPFC to regulate amygdala threat reactivity successfully. Indeed, studies do support alterations in dynamic FC during threat in individuals with PTSD compared to control participants that might contribute to an inability of brain networks to disengage effectively (8). Further investigation is warranted to explore FC in individuals with PTSD during change from a fear-related task to rest.

Although not a primary goal, an additional strength of this study is the analysis of hemispheric lateralization effects in rs-FC in PTSD. A review of lesion and neuroimaging studies suggested that the right amygdala may specifically play a role in sensory-mediated fear expression (36). The right amygdala has been implicated in PTSD more consistently than the left amygdala, which may have a more significant role in cognitive-mediated fear acquisition and extinction learning (36). The findings from the present study show greater functional connections between the left and right amygdala in PTSD and stronger functional connections with the right hippocampus. More work is needed to understand the significance of the laterality of the hippocampus in PTSD.

This is the largest mega-analysis of rs-FC in PTSD to date, and it was implemented in a large multicohort consortium dataset. While this is a major strength, some limitations and considerations should be acknowledged. First, many sites did not provide item-level data for relevant covariates, so we

were unable to investigate the effects of relevant covariates such as medication status, more than two index trauma types, and traumatic brain injury exposure. However, we included the most pertinent covariates—age, biological sex, and study site. Second, rs-FC scans are inherently prone to scanner artifacts, motion-induced effects, and effects from physiological sources such as cardiac and respiratory cycles (37). To address this, we ensured that our data were centrally analyzed and underwent strict quality assessment before we conducted analyses. Third, this study is cross-sectional; future longitudinal research will be imperative to better understand whether altered rs-FC confers risk for PTSD or changes as a function of the disorder (as expressed in 38). Fourth, a recent narrative review explored altered FC of amygdala subnuclei in PTSD (39), and rs-FC of the anterior and posterior hippocampus has been previously explored in PTSD (40). In the present study, we focused not on subnuclei but rather on a 6-mm sphere of the most frequently cited coordinates from Neurosynth, which is a limitation and a direction for future study. Relatedly, we took a hypothesis-driven approach when selecting these seed regions and conducted a whole-brain analysis of each seed for an unbiased analytic approach. Still, data-driven approaches are relevant and informative for discoveries that are beyond known systems and circuits. Fifth, the present study did not assess neural networks; however, it is important to highlight that the seed regions in this investigation are a part of larger neural networks. Thus, the interpretations of our results highlight the potential role that the connectivity of our seed regions plays within these networks. Of course, it is important to use caution with these interpretations, given that we did not directly assess networks in this study. Lastly, we did not collect qualitative data on participants' thoughts, such as intrusive memory recall, during the resting-state scan.

CONCLUSIONS

Greater functional connectivity between subcortical threat centers was discovered in PTSD patients compared to control participants, perhaps contributing to enhanced threat responses in the absence of stimuli. Examining large-scale brain networks, in contrast to single regions of interest related to PTSD, provides a more holistic view of alterations that contribute to pathology. Following interesting developments in neuromodulation (41), our study offers cortical targets for neuromodulation and indirect stimulation of the hippocampus and amygdala. Future studies could leverage rs-FC to inform treatments and investigate how different interventions, such as brain stimulation, neurofeedback, and psychotherapy, might modulate the aberrant neural networks in PTSD.

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Dr. Stein died December 2025.

Dr. Hinojosa received support from NIAAA grants K99AA031333 and R00AA031333. Dr. Sun, Ms. Russell, Mr. Hussain, Dr. Jahanshad, Dr. Thompson, and Dr. Morey received support from NIMH grants R01MH111671 and R01MH129832. Dr. Sun and Dr. Morey were also supported by the VISN 6 Mental Illness Research, Education, and Clinical Center. Dr. Jahanshad was also supported by National Institute on Aging (NIA) grant R01AG059874 and Michael J. Fox Foundation grant 14848. Dr. Salminen receives joint funding support from the NIA and the National Institute of Environmental Health Sciences (R01ES033961). Dr. Thompson was also supported by Department of Defense award W81XWH-12-2-0012, and ENIGMA was also supported in part by the NIH Big Data to Knowledge (BD2K) program under consortium grant U54 EB020403 and by grant U54 EB020403 from the BD2K program, NIA grant R56AG058854, NIMH grant R01MH116147, and National Institute of Biomedical Imaging and Bioengineering grant P41 EB015922. Dr. Olff received support from ZonMw (the Netherlands Organization for Health Research and Development) (40-00812-98-10041) and the Academic Medical Center Research Council (110614). Dr. Li Wang, Dr. Ye Zhu, and Dr. Gen Li received support from National Natural Science Foundation of China (U21A20364 and 31971020), the Key Project of the National Social Science Foundation of China (20ZDA079), the Key Project of Research Base of Humanities and Social Sciences of Ministry of Education (16JJD190006), and the Scientific Foundation of Institute of Psychology, Chinese Academy of Sciences (E2CX4115CX). Dr. Stein received support from the South African Medical Research Council Unit on Risk and Resilience in Mental Disorders. Dr. Neria received support from NIMH grant R01MH105355-01A. Dr. Zhu received support from NARSAD award 27040. Dr. Suarez-Jimenez received support from NIMH grant K01 MH118428-01. Dr. Ressler, Dr. Jovanovic, and Dr. Stevens received support from NIMH grants MH098212 and MH071537, NIH National Centers for Research Resources grant M01RR00039, National Center for Advancing Translational Sciences grant UL1TR000454, and National Institute of Child Health and Human Development grants HD071982 and HD085850. Dr. Fani received support from NIMH grant MH101380. Dr. Mueller received support from grant 01J05415 from the Special Research Fund (BOF) at Ghent University. Dr. Daniels received support from German Research Foundation grants DA 1222/4-1 and WA 1539/8-2). Dr. Říha was supported by grant AZV NV18-7 04-00559 from the Ministry of Health of the Czech Republic. Dr. Kaufman received support from NIMH grants R21MH112956 and R01MH119227, the McLean Hospital Trauma Scholars Fund, and the Julia Kasparian Fund for Neuroscience Research. Dr. Lebois received support from NIMH grant K01MH118467 and the Julia Kasparian Fund for Neuroscience Research. Dr. Liberzon received support from NIMH grant R01MH113574. Dr. Davenport received support from VA Rehabilitation Research and Development Program grant 1IK2RX000709. Dr. Disner received support from VA Rehabilitation Research and Development Program grants 1K1RX002325 and 1K2RX002922. Dr. Sponheim received support from VA Rehabilitation Research and Development Program grant I01RX000622 and Congressionally Directed Medical Research Program grant W81XWH-08-2-0038. Dr. Straube and Dr. Hofmann received support from the German Research Society (Deutsche Forschungsgemeinschaft; SFB/TRR 58: C06, C07). Dr. Qi received support from the Natural Science Foundation of Jiangsu Province (BK20221554) and the Foundation for the Social Development Project of Jiangsu (BE2022705). Dr. Xin Wang received support from NIMH grants 1R01MH110483 and 1R21MH098198. Dr. El-Hage received support from the Programme Hospitalier de Recherche Clinique, the Fondation Pierre Deniker, and SFR FED4226. Dr. Grupe, Dr. Nitschke, and Dr. Davidson received support from a core grant to the Waisman Center from NICHD (P30-HD003352). Dr. Grupe was also supported by a National Science Foundation Graduate Research Fellowship. Dr. Nitschke was also supported by the Dana Foundation. Dr. Davidson was also supported by NIMH grants R01-MH043454 and T32-MH018931. Dr. Larson and Dr. deRoon-Cassini received support from NIMH grant R01MH106574. Dr. Urbano-Blackford and Dr. Olatunji received support from NIMH grant R21MH106998. Dr. May, Dr. Nelson, and Dr. Gordon received support from Congressionally Directed Medical Research Program grant 1IK2CX001680 and VISN17 Center of Excellence Pilot funding. Dr. Abdallah received support from the VA National Center for PTSD and the Beth K. and Stuart Yudofsky Chair in the Neuropsychiatry of Military Post Traumatic Stress Syndrome. Dr. Lanius received support from the Canadian Institutes of Health Research and the Canadian Institute for Military and Veteran Health Research. Dr. Baugh, Dr. R.M. Simons, Dr. J.S. Simons, Dr. Magnotta, and Dr. Fercho received support from Department of Defense grant W81XWH-10-1-0925, a Center for Brain and Behavior Research Pilot Grant, and a South Dakota Governor's Research Center Grant. Dr. Kremen received support from NIA grants R01AG050595 and R01AG022381. Dr. van Rooij received support from a NARSAD Young Investigator Award and from NIMH grant K01MH121653.

Dr. Sendi has served as a consultant for Niji Corp and is the co-founder of Vitalytic AI. Dr. Jahanshad has received research support from Biogen. Dr. Stein has received consultancy honoraria from Discovery Vitality, Johnson & Johnson, Kanna, L'Oreal, Lundbeck, Orion, Sanofi, Servier, Takeda, and Vistagen. Dr. Walter has received honoraria and loyalties from Becker Joest Volk Verlag, Hilden, Thieme Verlag Stuttgart, and Springer Verlag Heidelberg, and lecture and related travel fees from Academy of Neuroscience, Köln, Rovi-GmbH, Holzkirchen, and Psi-Fit GmbH, Wolfsburg. Dr. Lebois has served as an unpaid member of the Scientific Committee for the International Society for the Study of Trauma and Dissociation, and she reports spousal IP payments from Vanderbilt University for technology licensed to Acadia Pharmaceuticals and spousal private equity in Violet Therapeutics. Dr. Baker has received consulting fees from and has an equity stake in Tetricus Labs. Dr. El-Hage has received payments from Air Liquide, Chugai, Eisai, Jazz Pharmaceuticals, Janssen, Lundbeck, Otsuka, and UCB. Dr. Herringa

has served as a consultant for Jazz Pharmaceuticals. Dr. Abdallah has served as a consultant, speaker, and/or on advisory boards for Douglas Pharmaceuticals, Freedom Biosciences, FSV7, Lundbeck, Psilocybin Labs, Genentech, and Janssen; and he has filed a patent for using mTOR inhibitors to augment the effects of antidepressants. Dr. Magnotta has received research support from GE Healthcare and SpinTech. Dr. Thompson received partial research support from Biogen. The other authors report no financial relationships with commercial interests.

Received January 15, 2025; revisions received October 9 and November 13, 2025; accepted November 25, 2025; published online April 2, 2026.

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Examination Questions for "Resting-State Functional Connectivity of the Amygdala and Hippocampus in PTSD: Results From the PGC-ENIGMA PTSD Working Group"

1. **Which of the following is an advantage of using a mega-analytic approach compared to a meta-analytic approach?**
   A. Data are centrally analyzed and fitted to the aggregated data while adjusting for covariates.
   B. Increased sample size
   C. Increased generalizability
   D. Identification of sample heterogeneity
2. **In comparison to trauma-exposed control participants, individuals with PTSD exhibited:**
   A. Greater right amygdala resting-state functional connectivity to the insula.
   B. Greater left amygdala resting-state functional connectivity to the right hippocampus/amygdala.
   C. Lesser right amygdala resting-state functional connectivity to the left hippocampus.
   D. Lesser left amygdala resting-state functional connectivity to the left hippocampus.
3. **PTSD total norm-severity scores were associated with greater resting-state connectivity between the right amygdala and what other brain region?**
   A. Insula
   B. Putamen
   C. Rostral anterior cingulate
   D. Hippocampus