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Acute Posttrauma Resting-State Functional Connectivity of Periaqueductal Gray Prospectively Predicts Posttraumatic Stress Disorder Symptoms

Elisabeth K. Webb, Ashley A. Huggins, Emily L. Belleau, Lauren E. Taubitz, Jessica L. Hanson, Terri A. deRoon-Cassini, and Christine L. Larson

ABSTRACT

BACKGROUND: Posttraumatic stress disorder (PTSD) is characterized by hyperarousal, avoidance, and intrusive/re-experiencing symptoms. The periaqueductal gray (PAG), which generates behavioral responses to physical and psychological stressors, is also implicated in threat processing. Distinct regions of the PAG elicit opposing responses to threatening or stressful stimuli; the ventrolateral PAG evokes passive coping strategies (e.g., analgesia), whereas the dorsolateral PAG (dlPAG) promotes active responses (e.g., fight or flight). We investigated whether altered PAG resting-state functional connectivity (RSFC) prospectively predicted PTSD symptoms.

METHODS: A total of 48 trauma-exposed individuals underwent an RSFC scan 2 weeks posttraumatic injury. Self-report measures, including the visual analog scale for pain and the Impact of Event Scale, were collected at 2 weeks and 6 months posttrauma. We analyzed whether acute bilateral PAG RSFC was a marker of risk for total 6-month symptom severity and specific symptom clusters. In an exploratory analysis, we investigated whether dlPAG RSFC predicted PTSD symptoms.

RESULTS: After adjusting for physical pain ratings, greater acute posttrauma PAG–frontal pole and PAG–posterior cingulate cortex connectivity was positively associated with 6-month total PTSD symptoms. Weaker dlPAG–superior/inferior parietal lobule connectivity predicted both higher hyperarousal and higher intrusive symptoms, while weaker dlPAG–supramarginal gyrus RSFC was associated with only hyperarousal symptoms.

CONCLUSIONS: Altered connectivity of the PAG 2 weeks posttrauma prospectively predicted PTSD symptoms. These findings suggest that aberrant PAG function may serve as a marker of risk for chronic PTSD symptoms, possibly by driving specific symptom clusters, and more broadly that connectivity of specific brain regions may underlie specific symptom profiles.

Keywords: fMRI, Periaqueductal gray, Posttraumatic stress disorder (PTSD), Resting-state functional connectivity, Trauma

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Up to 90% of American adults will experience a traumatic event (1,2). A minority of trauma-exposed individuals (8%–10%) will develop posttraumatic stress disorder (PTSD) (2,3). PTSD is characterized by a constellation of symptoms, including hyperarousal, avoidance of trauma-related stimuli, negative alterations in mood and cognition, and intrusive thoughts (4). Functional magnetic resonance imaging (fMRI) studies suggest that distinct patterns of brain activity differentiate individuals with PTSD from trauma-exposed control subjects. PTSD is linked with aberrations in neural substrates mediating threat processing and fear learning, including the amygdala (5–7), medial prefrontal cortex (8–10), and hippocampus (11–15).

Establishing early neural markers of PTSD is critical as it would allow for preventive interventions to minimize the risk of PTSD development (16,17). However, identifying sensitive and specific markers of risk is challenging (18,19). Although factors including education, marital status, and gender, as well as peritraumatic psychological processes (e.g., peritraumatic dissociation), confer vulnerability to PTSD, these are estimated to independently predict only 30% of cases (20,21). Thus, research exploring potential early biomarkers may provide more specific process-based markers of risk. Acute post-trauma studies indicate that structural, resting-state, and task-based functional imaging may be useful in identifying biomarkers of PTSD (22–24).

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Consistent with the overarching neurobiological model of PTSD, which suggests that fear-learning circuitry is disrupted (25–28), greater amygdala reactivity is predictive of future PTSD (22,23) and treatment response (29). Amygdala resting-state functional connectivity (RSFC) is disrupted acutely after trauma (30). In general, greater RSFC between regions in the salience network, including the amygdala (30) and insula (24,31), is associated with current, and predictive of future, PTSD symptoms. Importantly, widespread disruption of RSFC in parietal, occipital, and prefrontal regions predicts PTSD symptoms (32). Thus, there is evidence that regions not traditionally defined in neurobiological frameworks of PTSD (e.g., medial prefrontal cortex, amygdala) may be involved.

The periaqueductal gray (PAG), a small structure in the midbrain with a critical role in generating behavioral responses to threat, has emerged in theoretical models of PTSD (33,34). Essential for pain modulation (35), the PAG comprises four columns: dorsolateral (dlPAG), dorsomedial, ventrolateral, and lateral (36,37). Stimulation of the dlPAG evokes active behavioral responses (e.g., fight or flight) (38), whereas activation of the ventrolateral PAG elicits passive behavioral strategies (e.g., analgesia) (39). The human PAG is functionally connected to numerous brain regions, including the thalamus, hypothalamus, prefrontal cortex, amygdala, and insular cortex (40). Previously identified as part of the salience network (41), the PAG appears to have a role in rapidly generating a response to threat (42).

In preclinical studies, the PAG was implicated in threat detection (43), estimating threat probability (44,45), and initiating defensive behaviors (46). As threats transition from distal to more imminent, brain activity appears to shift from top-down processing to greater bottom-up control. As threat becomes closer, activity transitions from the ventromedial prefrontal cortex to the PAG (47). Although both the amygdala and PAG appear to be sensitive to threat, the PAG is especially responsive to approaching threatening stimuli (i.e., looming threat) (48). After a threatening encounter, fear learning circuitry, including the hippocampus, amygdala, and subgenual anterior cingulate cortex, is recruited (49). In the context of PTSD neurobiology, the PAG is well positioned to drive symptoms from the bottom up.

Individuals with PTSD demonstrate greater connectivity between the dlPAG and motor regions, potentially driving symptoms by perpetually preparing for a defensive behavioral response (50). Effective connectivity studies have suggested that PTSD is characterized by bottom-up connections between the PAG and ventromedial prefrontal cortex (51). A neural circuit comprising the amygdala, PAG, frontal cortex, and pons may indeed underlie behavior strategies in response to threat and stress (52). The PAG relays information to the amygdala to initiate fear responding (53), whereas activation of prefrontal projecting neurons decreases sensitivity to pain, potentially reducing defensive behavior (54).

As PTSD is a heterogeneous disorder, unique neural correlates may characterize specific features of PTSD (55–58). A small number of studies suggest that while there are common neural correlates of PTSD, distinct neural patterns underlie specific symptom profiles (56,57). The PAG has been particularly insightful in distinguishing PTSD from its dissociative subtype, which is characterized by depersonalization or derealization and conceptualized as an overmodulation of affect (30,33). Beyond dissociation, however, few studies have proposed the PAG as a potential driver of specific symptoms. The PAG is particularly well positioned to underlie both avoidance and hyperarousal (50,51). Hyperarousal can be conceptualized as hypervigilance to potential threats and may facilitate the behavioral responses (e.g., startle response) often present in individuals with PTSD.

Using a prospective longitudinal design, this study examined the role of the PAG in PTSD. We investigated whether PAG RSFC in the early aftermath of a traumatic injury (2 weeks posttrauma) would uniquely predict PTSD symptom severity 6 months posttrauma. Based on previous studies, we hypothesized that greater acute PAG–prefrontal cortex connectivity would predict 6-month posttrauma PTSD symptoms (47). We also expected that increased PAG–cingulate cortex connectivity would be predictive of symptom severity (50). Considering that the PAG is widely recognized as responsible for descending pain modulation and has been extensively implicated in fMRI studies on pain (59–61), we also analyzed whether PAG RSFC was associated with physical pain. PTSD is highly comorbid with chronic pain (62), and patient-perceived injury severity is a significant predictor of PTSD development (63). To our knowledge, no previous studies have considered physical pain when investigating the PAG in the context of PTSD (50,51).

Finally, using a method similar to that of Harricharan *et al.* (50), we conducted an exploratory analysis investigating the relationship between the dlPAG and specific symptom clusters. Based on Harricharan *et al.* (50) and considering the dlPAG's crucial role in coordinating active defensive strategies (38), we hypothesized that altered dlPAG connectivity with the dorsal anterior cingulate cortex would prospectively predict both hyperarousal and avoidance symptoms. Hypervigilance may increase the brain's preparedness for the fight-or-flight response by specifically priming the dlPAG. Broadly, we anticipated increased dlPAG RSFC with brain regions responsible for fight-or-flight responses, including the premotor areas.

METHODS AND MATERIALS

Participants

Participants were recruited from a level 1 trauma center emergency department in southeastern Wisconsin in the U.S. Midwest. Prospective participants were identified via the emergency department's discharge database and were telephonically screened. Eligible participants were between 18 and 65 years of age, right-handed, able to lie flat on their back for 2 hours, and less than 300 pounds and could schedule an appointment within 2 weeks of the traumatic event. Individuals were excluded if they scored below 13 on the Glasgow Coma Scale upon emergency department arrival, experienced head injury with loss of consciousness, or had contraindications to MRI (e.g., pregnancy, irremovable metal in body). Importantly, the recruitment of individuals who were deemed MRI safe may have excluded those with more serious injuries (e.g., gunshot wounds, injuries that required surgical implants). Moderate to severe cognitive impairment, an intentional self-inflicted injury, antipsychotic prescription(s), and a history of seizures were

Table 1. Sample Characteristics

Characteristic	Value
Age, Years	33.40 (11.99)
Sex, Female	71.83%
Education	
Did not complete high school	4.17%
High school/GED	33.33%
Some postsecondary education/college	35.42%
Completed secondary education or vocational degree	25.00%
No information	2.08%
Race/Ethnicity	
African American/Black	47.92%
White	43.75%
Hispanic/Latino	2.08%
Biracial	4.17%
No information	2.08%
Mechanism of Injury	
Motor vehicle crash	70.83%
Physical assault	18.75%
Other	10.42%
Prescription Medication Use	43.75%
Pain medication (e.g., opioids)	31.25%
Psychotropics (e.g., SSRI)	22.92%
Past Psychiatric Diagnosis	22.92%
Depression	10.42%
Other	12.50%
2-Week Assessment	
VAS pain rating	3.27 (2.39)
IES total	33.09 (19.02)
Avoidance	1.44 (0.95)
Hyperarousal	1.55 (0.87)
Intrusive/re-experiencing	1.53 (1.02)
6-Month Assessment	
VAS pain rating	2.29 (2.68)
IES total	20.53 (21.89)
Avoidance	0.97 (1.05)
Hyperarousal	0.94 (1.20)
Intrusive/re-experiencing	0.81 (1.00)

Values are mean (SD) or %.

IES, Impact of Event Scale–Revised; SSRI, selective serotonin reuptake inhibitor; VAS, visual analog scale for pain.

also exclusionary criteria. Two weeks posttrauma, participants underwent a resting-state fMRI scan and completed self-report measures of PTSD symptom severity and pain. In addition, participants reported current medication use (pain and psychotropic). Six months posttrauma, individuals completed the same self-report measures. Sample characteristics are reported in Table 1.

All participants provided written informed consent to partake in the study and were compensated with cash payment for their participation. This study was approved by the Medical College of Wisconsin Institutional Review Board. Four individuals were removed from analysis owing to poor neuroimaging data quality (i.e., excessive motion), and 11 participants were lost to follow-up. A total of 48 participants were included in the final analyses.

Self-report Measures

At approximately 2 weeks and 6 months posttrauma, participants completed the visual analog scale for pain (VAS) (64) and Impact of Events Scale–Revised (IES) (65) inventories to assess posttraumatic stress symptoms and physical pain severity. The VAS is widely used to evaluate one's subjective experience of pain (64). Participants rated their physical pain using a numbered line with labels ranging from 0 (no pain) to 10 (worst possible pain). The IES consists of 22 questions rated on a scale from 0 (not at all) to 4 (extremely) (65). The items covered three distinct symptom clusters: hyperarousal, avoidance, and intrusive symptoms. Total symptom severity was calculated by taking the sum of all 22 items, while separate scores for each symptom cluster were calculated by averaging the responses to subscale-specific questions. Although the IES is not widely used to diagnosis PTSD, a total score of 24 or higher reflects clinical concern (66).

Imaging Acquisition

Within 2 weeks posttrauma, individuals completed a structural and resting-state fMRI scan. During image acquisition, participants were instructed to keep their eyes open and to view a blue screen. All functional images were acquired using a T2*-weighted gradient-echo, echo-planar pulse sequence. fMRI data were collected using an interleaved slice acquisition order in a sagittal orientation.

A total of 21 participants completed a 6-minute resting-state scan on a 3T long-bore Signa Excite MRI system (General Electric, Waukesha, WI). In total, 38 slices were acquired with the following parameters: repetition time (TR)/echo time (TE) = 2000 ms/25 ms, field of view = 24 mm, matrix = 64 × 64, slice thickness = 3.7 mm, flip angle = 77°, voxel size = 3.45 × 3.75 × 3.7. For registration of functional data, high-resolution T1-weighted anatomical images were also obtained (TR/TE = 8.2 ms/3.2 ms, field of view = 240 mm, matrix = 256 × 224, flip angle = 12°, voxel size = 0.9375 × 0.9375 × 1 mm^3).

The other 27 participants completed a 5-minute resting-state scan on a 3T short-bore Signa Excite MRI system. In total, 41 slices were acquired with the following parameters: TR/TE = 2000 ms/25 ms, field of view = 24 mm, matrix = 64 × 64, slice thickness = 3.5 mm, flip angle = 77°, voxel size = 3.75 × 3.75 × 3.5. High-resolution T1-weighted anatomical images were obtained with the parameters described above.

Data Analysis

Image Preprocessing. Images were preprocessed using the CONN toolbox (http://www.nitrc.org/projects/conn) (67). The first three TRs were discarded to allow for magnetic field stabilization. Preprocessing steps included motion correction using a 6-parameter linear transformation and normalization to Montreal Neurological Institute (MNI152). Images were spatially smoothed using a 3-dimensional Gaussian kernel of 4 mm full width at half maximum (40,50). Regions of interest (ROIs) were created with unsmoothed images. To reduce the signal-to-noise ratio, a temporal bandpass filter was applied (0.01–0.1 Hz).

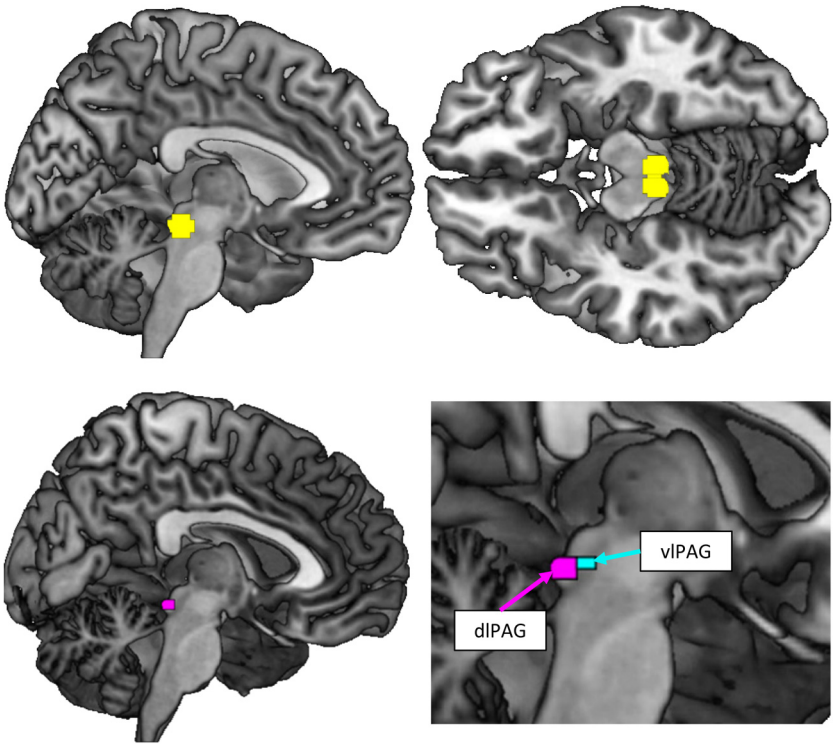

Figure 1. Regions of interest. A bilateral periaqueductal gray (PAG) mask (yellow; left: x = −4, y = 29, z = −12; right: x = 4, y = 29, z = −12) and one subregion mask (dorsolateral PAG [dlPAG]; red; x = 0, y = −32, z = −8.5 plus 6 × 2 × 1.5-mm extensions) (50) were created based on coordinates reported in a meta-analysis (40) and an atlas (50,90), respectively. For reference, the ventrolateral PAG (vlPAG) is also pictured (green) (50,90).

To address any confounding effects of motion, volumes with framewise displacement over 0.3 mm were excluded from analysis (i.e., scrubbed). Nuisance covariates, including head motion parameters (and their first-order derivatives), white matter signal, and cerebrospinal fluid signal, were regressed out during first-level analysis. Participants were excluded from analysis if more than 20% of the volumes were scrubbed.

Statistical Analysis. Seed ROIs were created in MNI space. Based on average coordinates reported in a meta-analysis on neuroimaging of the PAG (40), 2 ROIs were defined as 5-mm radius spheres around the left PAG (x = −4, y = 29, z = −12) and right PAG (x = 4, y = 29, z = −12). For analyses, the primary ROI was created by combining these ROIs (Figure 1). For the exploratory analyses, a box-shaped ROI was created for the dlPAG (x = 0, y = −32, z = −8.5 plus 6 × 2 × 1.5-mm extensions) (50,51).

We investigated whether 2-week posttrauma PAG RSFC predicted 6-month self-reported symptoms of PTSD. In an exploratory analysis, we examined whether acute dlPAG RSFC also predicted 6-month self-reported symptoms of PTSD. Mean blood oxygen level–dependent time series were extracted from each seed region and correlated with the time series of every other voxel in the brain to produce a 3-dimensional correlation (r) map for each subject. For group analyses, correlations were normalized using a Fisher transformation. The statistical threshold for all analyses was set to $p < .05$. The height threshold was set to $p < .001$ uncorrected, and the cluster size threshold was set to an adjusted $p < .05$ false discovery rate (FDR) corrected. To correct for multiple regressions for each seed, we applied the Benjamini–Hochberg procedure (68) using a $p < .05$ threshold. This correction did not alter our results; therefore, only the cluster corrected p value is presented.

Table 2. Pearson Correlation Matrix for Self-report Measures

Measure	VAS (2 Weeks)	VAS (6 Months)	IES Total (6 Months)	Avoidance	Hyperarousal	Intrusive
VAS (2 Weeks)	–					
VAS (6 Months)	.40[b]	–				
IES Total (6 Months)	.14	.54[a]	–			
Avoidance	.15	.49[a]	.88[a]	–		
Hyperarousal	.16	.41[b]	.88[a]	.61[a]	–	
Intrusive	.19	.42[b]	.90[a]	.67[a]	.91[a]	–

IES, Impact of Event Scale–Revised; VAS, visual analog scale for pain.
[a]$p < .001$.
[b]$p < .01$.

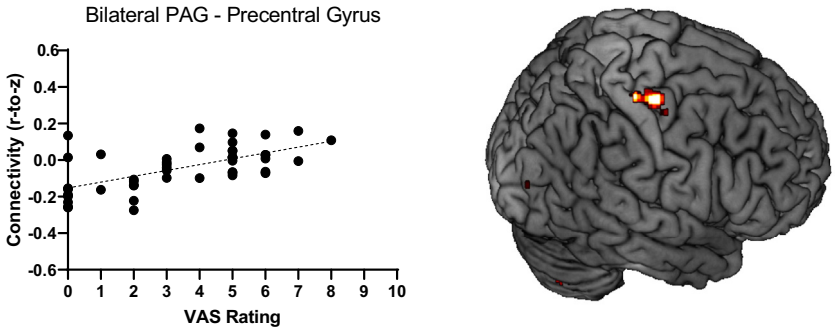

Figure 2. Higher physical pain ratings were associated with greater periaqueductal gray (PAG) resting-state functional connectivity (Fisher's *z*) with the precentral gyrus (x = 42, y = −18, z = 65; t_{45} = 5.07, false discovery rate-corrected p = .031). VAS, visual analog scale.

First, a multiple regression analysis examined whether PAG RSFC was associated with 2-week or 6-month posttrauma. VAS scores. We then conducted a multiple regression analysis investigating whether PAG RSFC predicted IES total scores after adjusting for 2-week physical pain. Additional analyses (reported in the Supplement) examined whether PAG RSFC predicted hyperarousal, avoidance, and intrusion symptoms. Finally, we explored whether dlPAG RSFC predicted specific PTSD symptoms. Because data were collected using 2 MR scanners, scanner was included as a covariate in all analyses.

RESULTS

Self-report Measures

Correlations were computed among VAS pain ratings, IES total scores, and IES symptom subscales (Table 2). There was a significant positive correlation between 6-month posttrauma physical pain ratings and total 6-month PTSD symptoms, r_{46} = .54, $p < .001$; however, 2-week VAS scores were not predictive of 6-month PTSD symptoms, r_{46} = .14, p = .353. Although none of the 6-month IES subscales were associated with 2-week VAS scores (hyperarousal: r_{46} = .16, p = .237; avoidance: r_{46} = .15, p = .323; intrusive: r_{46} = .19, p = .200), they all were positively associated with 6-month pain ratings (hyperarousal: r_{46} = .41, p = .003; avoidance: r_{46} = .49, $p < .001$; intrusive: r_{46} = .42, p = .003).

As expected, symptom clusters were highly intercorrelated. At 6 months, avoidance symptoms were significantly associated with intrusive symptoms (r_{46} = .67, $p < .001$) and hyperarousal symptoms (r_{46} = .61, $p < .001$), and intrusive symptoms were significantly correlated with hyperarousal symptoms (r_{46} = .91, $p < .001$). Furthermore, the 6-month subscales were highly correlated with 6-month total IES scores (hyperarousal: r_{46} = .88, $p < .001$; avoidance: r_{46} = .88, $p < .001$; intrusive: r_{46} = .90, $p < .001$).

Resting-State Functional Connectivity

RSFC analyses can be sensitive to confounding factors, particularly head motion (69,70). We confirmed that average head motion was not correlated with 2-week pain symptoms (r_{46} = .16, p = .265) or 6-month PTSD symptom severity (r_{46} = .13, p = .398). Medication use had no effect on RSFC.

Altered PAG Connectivity Was Associated With Physical Pain Ratings. There was a significant association between PAG RSFC and 2-week physical pain ratings. PAG RSFC with the precentral gyrus (x = 42, y = −18, z = 65; cluster size k = 100; t_{45} = 5.07, pFDR = .031) was associated with increased pain ratings (Figure 2). PAG RSFC did not predict 6-month physical pain. Results of multiple regression analyses examining PAG and dlPAG RSFC are reported in Tables 3 and 4, respectively.

Altered PAG Connectivity Predicted 6-Month Total PTSD Symptoms. After adjusting for 2-week pain ratings, greater PAG RSFC with the frontal pole (x = 0, y = 68, z = 0; cluster size k = 117; t_{45} = 5.57, pFDR = .004) (Figure 3A) and the posterior cingulate cortex (PCC) (x = −8, y = −58, z = 36; cluster size k = 243; t_{45} = 4.81, pFDR < .001) (Figure 3B) prospectively predicted 6-month PTSD symptoms. Altered PAG connectivity was also predictive of specific symptom clusters (results reported in Supplement).

Table 3. Altered PAG Functional Connectivity Associated With Pain Ratings and Posttraumatic Symptoms

						Peak Coordinates (MNI)		
Contrast	Symptom(s)	Brain Region	Number of Voxels	t_{45}	FDR-Corrected p	x	y	z
Positive	Pain	Precentral gyrus	100	5.07	.031	42	−18	65
	Total PTSD	PCC	243	4.81	<.001	−8	−58	36
		Frontal Pole	117	5.57	.004	0	68	0

FDR, false discovery rate; MNI, Montreal Neurological Institute; PAG, periaqueductal gray; PCC, posterior cingulate cortex; PTSD, posttraumatic stress disorder.

Table 4. Altered dlPAG Functional Connectivity Associated With Posttraumatic Symptoms

Contrast	Symptom(s)	Brain Region	Number of Voxels	t_{45}	FDR-Corrected *p*	Peak Coordinates (MNI)		
						x	y	z
Negative	Hyperarousal	SPL/IPL	131	5.39	.003	−24	−36	54
	Intrusive	SMG	118	4.22	.003	−50	−36	34
		SPL/IPL	147	4.68	.002	−24	−36	54

dlPAG, dorsolateral periaqueductal gray; FDR, false discovery rate; IPL, inferior parietal lobule; MNI, Montreal Neurological Institute; SMG, supramarginal gyrus; SPL, superior parietal lobule.

Altered Connectivity of the dlPAG Predicted Symptom Clusters. Results of the exploratory analysis revealed weaker dlPAG RSFC with the superior/inferior parietal lobule (x = −24, y = −36, z = 54; cluster size *k* = 131; t_{45} = 5.39, *p*FDR = .003) and the supramarginal gyrus (x = −50, y = −36, z = 34; cluster size *k* = 118; t_{45} = 4.22, *p*FDR = .003) predicted hyperarousal symptoms (Figure 4A). Weaker dlPAG RSFC with the superior/inferior parietal lobule also predicted intrusive symptoms (x = −24, y = −36, z = 54; cluster size *k* = 147; t_{45} = 4.68, *p*FDR = .002) (Figure 4B). dlPAG RSFC did not predict total PTSD symptoms or avoidance symptoms.

DISCUSSION

We examined whether PAG RSFC acutely posttrauma predicted PTSD symptoms 6 months later. Greater PAG–frontal pole connectivity predicted total PTSD symptoms, adding to the growing body of literature indicating that PAG and frontal lobe are sensitive to threats (47,49). For individuals with PTSD, threat-related attentional bias may result in the person's perceiving the stimuli as being increasingly threatening and imminent even when the stimuli are distal or nonthreatening (71). Increased PAG–frontal pole connectivity acutely posttrauma is likely capturing the transition from top-down to bottom-up control. Greater connectivity between the PAG and the PCC, a region that directs attention to information and drives states of arousal (72), also predicted symptoms. The PCC is responsible for getting caught up in one's own experiences and feelings (73). Increased PAG–PCC connectivity may reflect increased arousal to both internal negative affect and external trauma-related cues.

Regarding the exploratory dlPAG analysis, weaker dlPAG connectivity with the parietal lobules (superior and inferior) and supramarginal gyrus (also an area of the parietal lobe) predicted hyperarousal symptoms, whereas intrusive symptoms were predicted only by weaker dlPAG–parietal lobules. These regions are involved with cognitive and attentional control (74,75) and may be disrupted in PTSD (76–78). Individuals with PTSD demonstrate decreased recruitment of the parietal cortex (76,79). The frontal–parietal network assists with controlling emotional influence on working memory and attention (79,80). Although the PAG–parietal relationship has been understudied, PAG–parietal connections have been reported (81,82).

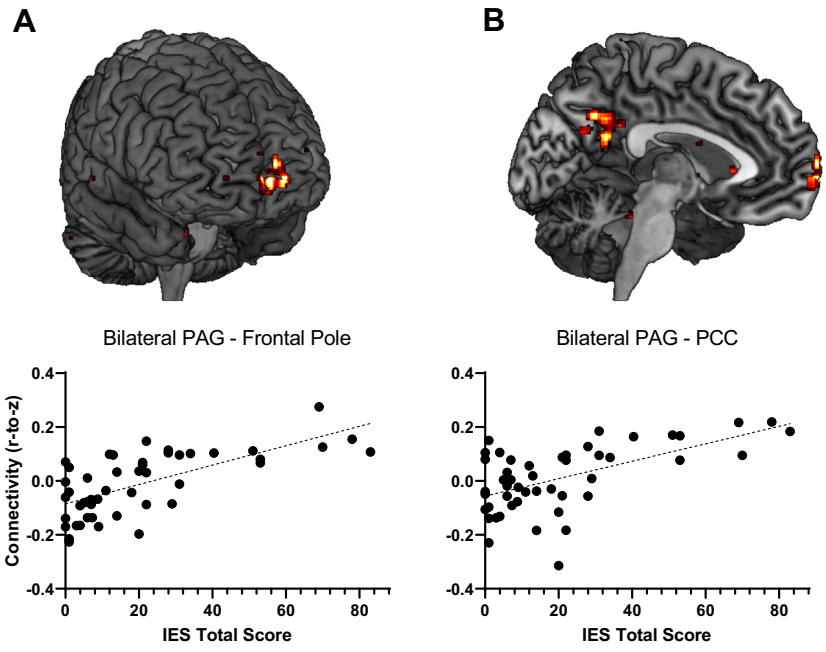

Figure 3. Increased functional connectivity of the periaqueductal gray (PAG) with the frontal pole (x = 0, y = 68, z = 0; t_{45} = 5.57, false discovery rate-corrected *p* = .004) **(A)** and the posterior cingulate cortex (PCC) (x = −8, y = −58, z = 36; t_{45} = 4.81, false discovery rate-corrected $p < .001$) **(B)** predicted total posttraumatic stress symptom severity at 6 months posttrauma. IES, Impact of Events Scale–Revised.

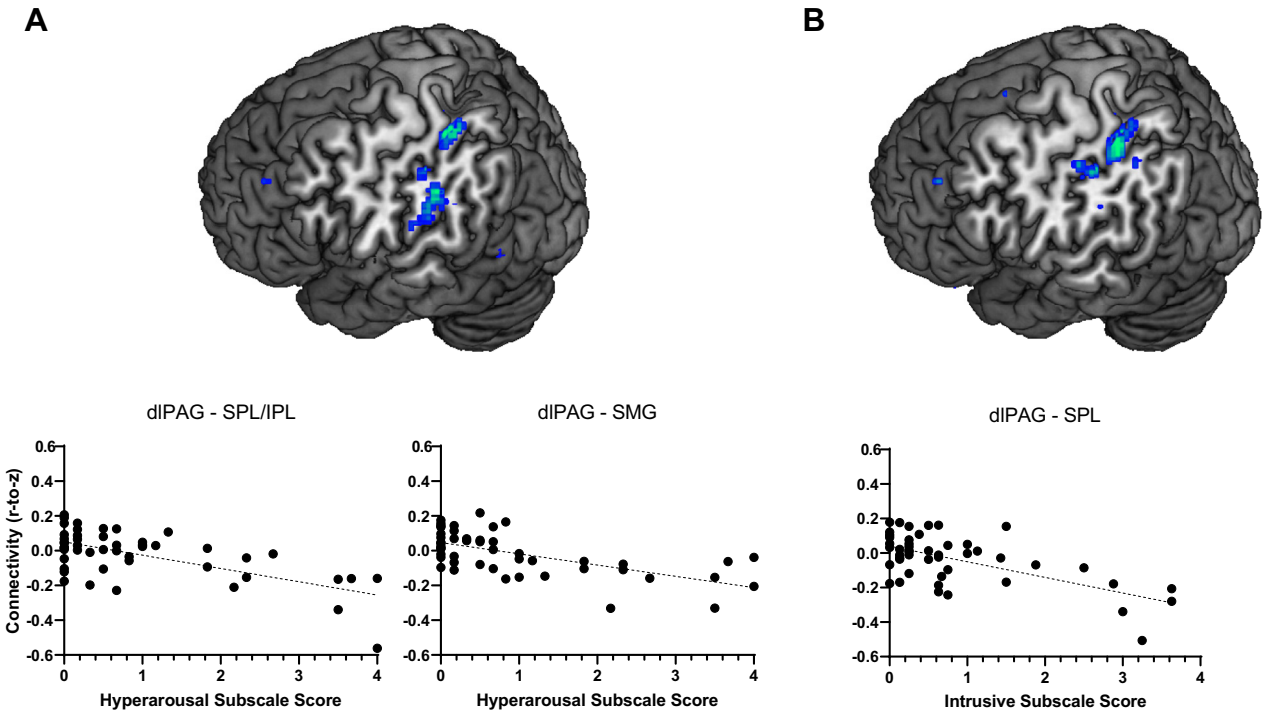

Figure 4. Weaker functional connectivity of the dorsolateral periaqueductal gray (dlPAG) with the superior parietal lobule (SPL)/inferior parietal lobule (IPL) (x = −24, y = −36, z = 54; t_{45} = 5.39, false discovery rate-corrected p = .003) and supramarginal gyrus (SMG) (x = −50, y = −36, z = 34; t_{45} = 4.22, false discovery rate-corrected p = .003) predicted hyperarousal scores **(A)**, whereas weaker dlPAG resting-state functional connectivity with the SPL (x = −24, y = −36, z = 54; t_{45} = 4.68, false discovery rate-corrected p = .002) predicted intrusive symptoms **(B)**.

Initiating active avoidance is a key function of the PAG (83); however, dlPAG RSFC did not predict avoidance symptoms. This may have been a limitation of the self-report measure selected. While the IES avoidance subscale includes some assessment of behavioral avoidance (e.g., "I stayed away from reminders about it"), it more thoroughly assesses cognitive avoidance (e.g., "I tried not to think about it," "I tried to remove it from my memory") (65). Therefore, this cognitive avoidance may be weighed more heavily on the IES and may less sufficiently capture behavioral avoidance such as changing a driving route to avoid a crash site. Future work would benefit from using the Clinician-Administered PTSD Scale for DSM-5 (84), which includes more comprehensive assessment of behavioral avoidance, and from assessing the role of the PAG during behavioral tasks of avoidance in both trauma-unexposed and trauma-exposed individuals.

Our results vary from previous research demonstrating extensive altered PAG connectivity in individuals with PTSD compared with healthy control subjects (50,51). Harricharan *et al.* (50) found that widespread PAG connectivity with prefrontal and cingulate regions was associated with PTSD. In the current study, PAG RSFC with only the frontal pole and PCC significantly predicted PTSD symptoms. This likely reflects the temporality of the study design; participants completed scanning acutely posttrauma. We demonstrated that altered PAG RSFC not only is present in individuals diagnosed with PTSD (50) but also is predictive of symptom development. Although studies have demonstrated a PAG–hippocampus–amygdala circuit, which is theorized to underlie the re-experiencing of traumatic memories (85,86), we did not observe altered PAG–amygdala or PAG–hippocampus connectivity. Despite strong theoretical evidence and support from preclinical models, altered activation of the amygdala is surprisingly inconsistent in human studies on PTSD (87). We postulate that investigations into the relationship between midbrain and cortical structures may offer an explanation for these inconsistencies.

Despite pain modulation and PAG activity being nearly synonymous (83,88) and high comorbidity between chronic pain and PTSD (89), most of the research on the PAG's role in PTSD does not consider physical pain. We discovered a relationship between PTSD symptoms and pain ratings. Importantly, there was also a significant association between PAG–precentral gyrus connectivity and 2-week pain. In healthy humans, the lateral PAG and ventrolateral PAG are functionally connected to the precentral gyrus, which is responsible for voluntary movements (90). In certain populations pain may be less relevant to PTSD development; however, pain has been demonstrated to be a significant predictor of PTSD in motor vehicle crash survivors (70% of our sample) (91). Our findings demonstrate that pain is an important consideration when examining the PAG in the context of PTSD.

Several limitations to the current study are noteworthy. First, the scan length of both acquisitions was relatively short. In general, reliability of resting-state scans can be improved by increasing scan duration (92); however, the ideal scan length is disputed, with recommendations ranging from 5 minutes (93) to more than an hour (94). Notwithstanding this fact, if a proposed neural biomarker is unreliable and/or unstable across time, then it cannot be classified as a predictive risk indicator. In addition, after one scanner was phased out for research, data were collected on two scanners. We cannot entirely rule out any effects of scanner on the current findings; however, consistent with previous work (95,96), scanner was controlled for in all analyses. Moreover, other multisite studies with pooled neuroimaging data suggest minimal effects of scanner differences in RSFC (97). Our sample was relatively homogeneous, with 70% of participants being female and involved in a motor vehicle crash. In general, individuals in this sample had lower/subthreshold symptoms, with 14 individuals having a total score greater than 24 on the IES and scores ranging overall from 0 to 83. This reduces the generalizability of our findings, and future work should replicate this study with a larger, more heterogeneous sample. Participants were excluded for antipsychotic medication use but not for prescription pain medication use. Even after controlling for medication use, PAG RSFC predicted PTSD symptoms, suggesting that our results do not reflect medication exposure. Still, future research should assess the effect of medication on PAG connectivity in PTSD. Finally, our analysis of dlPAG was exploratory. We did not have the optimal spatial resolution to explore the PAG subregions; therefore, these specific results should be interpreted with caution. Nevertheless, even with these considerations in mind, our findings highlight the importance of examining regions outside the traditional neurobiological framework of PTSD.

Our results align with previous work demonstrating that PAG RSFC is disrupted in PTSD. Importantly, we demonstrated that this connectivity prospectively predicts PTSD symptoms, suggesting that it may be a useful biomarker of PTSD risk. Future work should continue disentangling the heterogeneity of PTSD because knowledge of the distinct neural patterns underlying specific symptom profiles may aid in the development of more precise theoretical models and targeted therapeutic interventions.

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ARTICLE INFORMATION

From the Department of Psychology (EKW, AAH, CLL), University of Wisconsin–Milwaukee; Department of Psychology (JLH), Marquette University; and Division of Trauma/Critical Care (TAd-C), Department of Surgery, Medical College of Wisconsin, Milwaukee, Wisconsin; Center for Depression, Anxiety and Stress Research (ELB), McLean Hospital, Belmont, and Department of Psychiatry (ELB), Harvard Medical School, Boston, Massachusetts; and Rogers Behavioral Health (LET), Minneapolis, Minnesota.

EKW and AAH contributed equally to this work.

TAd-C and CLL share senior authorship.

Address correspondence to Elisabeth K. Webb, B.A., Garland 334, 2441 E. Hartford Ave., Milwaukee, WI 53211; E-mail: ekwebb@uwm.edu.

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