Regional Prefrontal Resting State Functional Connectivity in Posttraumatic Stress Disorder

Supplement

SUPPLEMENTARY METHODS

Participants

Exclusion criteria included history of neurological disorder (including head injury with loss of consciousness over 5 minutes), use of psychotropic medications (aside from a stable dose of an SSRI or SNRI; this occurred in 1 TENC and 2 PTSD participants), alcohol or substance dependence within the past 5 years, past-year alcohol or substance abuse, contraindications to MRI scanning, or positive urine toxicology screen. Additionally, lifetime diagnosis of bipolar disorder, schizophrenia spectrum disorder, psychosis, anorexia nervosa, or obsessive compulsive disorder was exclusionary. Doctoral-level clinical psychologists administered the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I/P) to all participants, and the Clinician Administered PTSD Scale (CAPS-DX) to TENC and PTSD participants. This study entailed a two-day protocol involving interviews, questionnaires, imaging, and a fear conditioning paradigm (not discussed here).

MR image acquisition

Neuroimaging was performed on a 3.0 Tesla Siemens TIM Trio scanner (Siemens, Erlangen, Germany) using a 32-channel head coil. The scanning protocol included structural scans, followed by resting state scans, followed by magnetic resonance spectroscopy (not reported here). Resting state was collected eyes open using standardized instructions ("For this scan, we want you to rest quietly with your eyes open and let your mind wander. Do not move and do not fall asleep. Just let your mind daydream for

the next 6 to 7 minutes as the scanner operates. Do you have any questions?"). The scan was 6 minutes, 4 seconds long.

Image processing and analysis: detailed methods

Preprocessing was conducted in SPM12, using standard preprocessing steps: realignment and unwarping, slice timing correction, coregistration, segmentation, spatial normalization, smoothing (FWHM = 6mm), and reslicing at a resolution of 2 x 2 x 2 mm. For each participant, scan time points with excessive head motion or global signal intensity spikes were flagged using Artifact Detection Tools (ART, www.nitrc.org/projects/artifact_detect). The threshold for head motion was > 1 mm motion from the previous frame; the threshold for signal intensity was > 3 SD from mean intensity. The first scan volume was also flagged for all participants to address possible initial magnetic field inhomogeneity. At the first level, outlier time points were removed via inclusion of a dummy-coded regressor (1 for outlier volumes, 0 for included volumes) to remove outlier volumes from the analysis. Motion parameters also were included, including translation parameters (n = 3), rotation parameters (n = 3), and a parameter reflecting maximum movement between scans (n = 1). All of these motion-related regressors were included for each participant in the denoising step in conn.

FreeSurfer

The Desikan-Killiany atlas (1) was used to derive thickness of the precuneus. We opted to use the Desikan-Killiany atlas for the precuneus because the ROIs are somewhat broader (including both gyri and adjacent sulcal banks), and we had no specific hypotheses about gyri vs sulcal banks. However, we were not able to determine a well-validated method to delineate the DLPFC using the Desikan-Killiany atlas. Therefore, we used the Destrieux atlas (2) to derive the DLPFC, using the method delineated in Yamagishi et al., 2016 (3). Cortical thickness of the DLPFC was derived using the Destrieux atlas (2) by

combining the thickness measurements of the middle frontal gyrus and sulcus, superior frontal gyrus and sulcus, and inferior frontal sulcus (3). A weighted average was computed using each participant's area measurement for that region in order to compute average cortical thickness across the combined DLPFC region.

SUPPLEMENTARY RESULTS

Participant characteristics

Within the PTSD sample, trauma types were diverse and included witnessing a terrorist attack (n = 2), witnessing unexpected death of a loved one (n = 2), witnessing an assault (n = 3), motor vehicle accident (n = 2), sexual assault or abuse (n = 4), physical assault or abuse (n = 4), torture (n = 1), witnessing an accident resulting in severe injuries to a family member (n = 1), and being chased with a weapon (n = 2). All individuals in the PTSD group met full DSM-IV criteria for current PTSD. No individuals in the HC or TENC groups met criteria for lifetime PTSD. Individuals reporting a history of head injury with loss of consciousness greater than 5 minutes were excluded, but the study did not include comprehensive assessment for lifetime history of head injuries without loss of consciousness.

Group difference analysis controlling for trauma load

As noted in Table 1, the PTSD group endorsed significantly higher lifetime trauma load (LEC score) than the TENC group. Therefore, we ran a univariate model with right DLPFC-precuneus rsFC as the dependent variable and age, sex, LEC, and group as independent variables. After controlling for effects of LEC, group remained significantly associated with rsFC, $F(2,81) = 10.201$, $p < 0.001$. (LEC was not significantly associated with rsFC, $F(1, 81) = 1.527$, $p = 0.220$). This analysis provides reassurance that the group effects reported in this paper are not attributable to trauma load.

Group difference analysis controlling for trauma load

As noted in Table 1, the PTSD group endorsed significantly higher depression severity (BDI score) than the TENC group. Therefore, we ran a univariate model with right DLPFC-precuneus rsFC as the dependent variable and age, sex, BDI, and group as independent variables. After controlling for effects of BDI, group remained significantly associated with rsFC, $F(2,80) = 5.931$, $p = 0.004$. (BDI was not significantly associated with rsFC, $F(1, 80) = 0.684$, $p = 0.411$). This analysis provides reassurance that the group effects reported in this paper are not attributable to depression severity.

Supplementary Table S1. Partial correlations between right DLPFC-precuneus rsFC and symptom scores within the PTSD sample (n = 21), controlling for age and sex

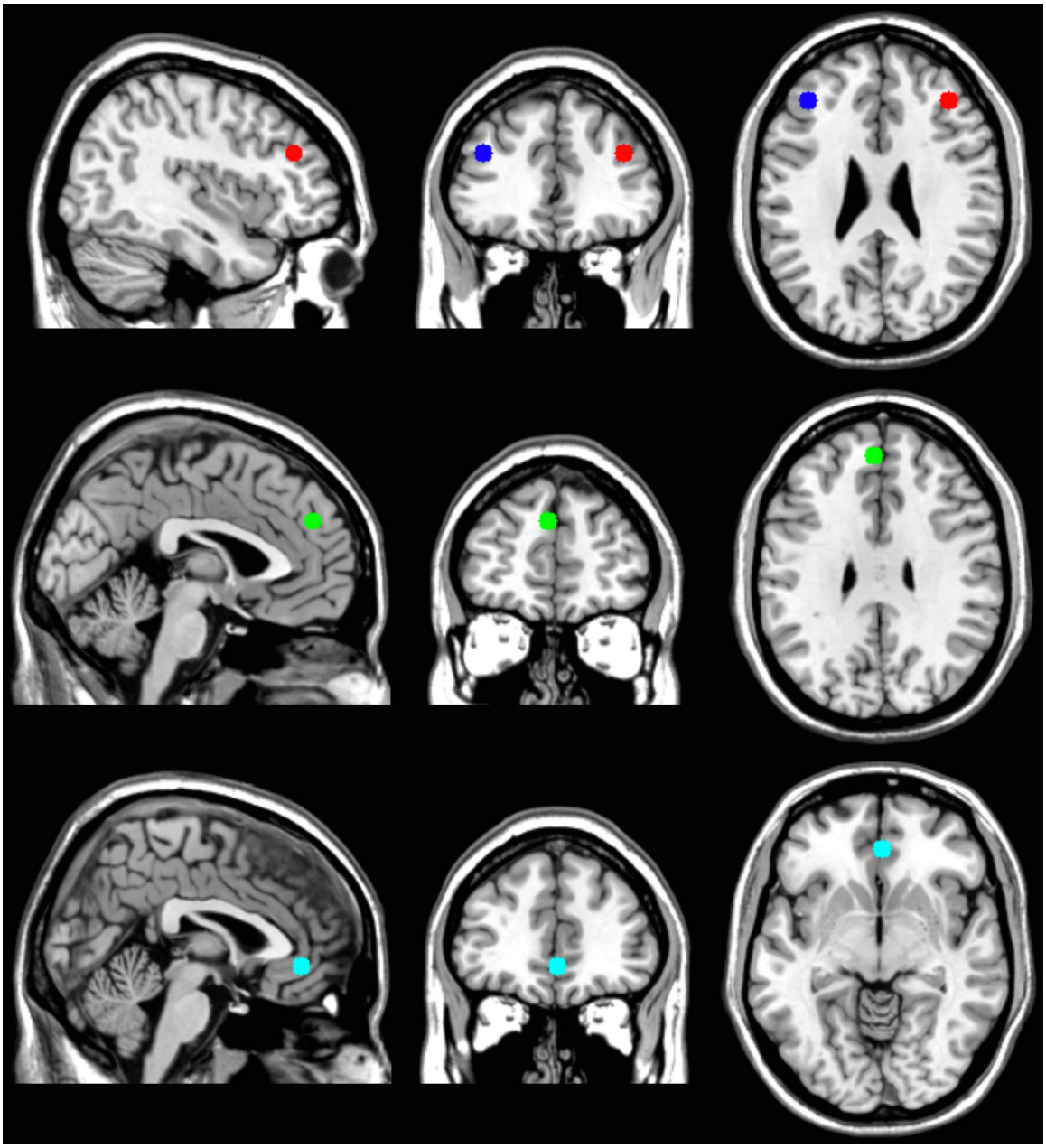
Measure	Partial r, p
Main clinical outcome measure	
CAPS total	-0.463, p = 0.046
CAPS re-exp.	-0.407, p = 0.083
CAPS avoidance	-0.485, p = 0.035
CAPS hyperarousal	-0.130, p = 0.595
Secondary measures	
ACE total	0.021, p = 0.931
CTQ emotional abuse	-0.082, p = 0.739
CTQ physical abuse	-0.128, p = 0.600
CTQ sexual abuse	0.154, p = 0.530
CTQ emotional neglect	-0.325, p = 0.175
CTQ physical neglect	-0.266, p = 0.271
LEC total	0.010, p = 0.968
BDI total[a]	-0.252, p = 0.313

[a] n = 20, one missing data point

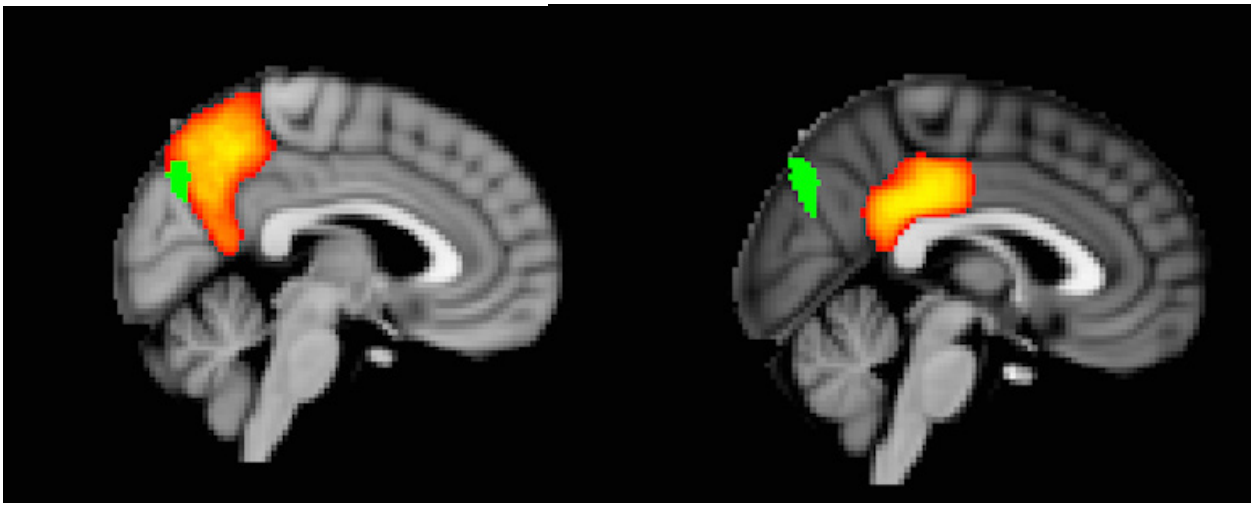
Supplementary Table S2. Precuneus result participation in Yeo 17-network parcellation

	Network Label (Baker et al., 2014)(4, 5)	Cerebral cortical regions (Yeo et al., 2011; Baker et al., 2014)(4–6)	# nonzero voxels
1	Visual peripheral	Striate, extrastriate	0
2	Visual central	Striate, extrastriate	128
3	Somatomotor A	Central sulcus, secondary somatosensory	0
4	Somatomotor B	Central sulcus, secondary somatosensory, insula, auditory	0
5	Dorsal attention A	Posterior temporal occipital, superior parietal, inferior parietal occipital	0
6	Dorsal attention B	Posterior temporal, postcentral gyrus, frontal eye fields, precentral ventral frontal	0
7	Ventral attention	Parietal operculum, medial parietal, medial frontal, precentral ventral frontal, insula, temporal, precentral frontal, posterior temporal	0
8	Salience	Medial posterior prefrontal, ventral prefrontal, cingulate sulcus, inferior parietal, lateral prefrontal	0
9-10	Limbic	Temporal pole, orbitofrontal	0
11	Control C	Precuneus, posterior cingulate	516
12	Control A	Intraparietal sulcus, lateral prefrontal, posterior temporal, dorsal prefrontal, cingulate, orbitofrontal, medial posterior prefrontal, lateral posterior prefrontal	0
13	Control B	Lateral posterior prefrontal, lateral anterior prefrontal, inferior parietal, temporal, medial posterior prefrontal	0
14	Default D (Auditory)	Temporal cortex	0
15	Default C	Retrosplenial, parahippocampal complex, ventral inferior parietal	0
16	Default A	Medial prefrontal, posterior inferior parietal, posterior cingulate, dorsal prefrontal, orbitofrontal, temporal	66
17	Default B	Dorsal prefrontal, temporal, anterior inferior parietal	0
Voxels outside Yeo parc.			1282
Total voxels			1992

Table S2 method: The precuneus result was transformed to 1mm isotropic space and then multiplied by each of the Yeo et al. (2011) 17 resting state functional networks; the number of non-zero voxels was used to assess network membership.



Supplementary Figure S1. Seeds used for rsFC analysis. Red: right DLPFC (39, 37, 26); glue: left DLPFC (-39, 37, 26); green: DMPFC (-3, 48, 30); cyan: VMPFC (2, 41, -6). Spheres of 5mm radius were inflated around the peak coordinates and binarized to create ROIs.



Supplementary Figure S2. Location of the present finding in relation to precuneus cortex (left) and posterior cingulate cortex (right). Regions drawn from the Harvard-Oxford Cortical Structural Atlas, thresholded at 40% probability.

Supplemental References

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3. Yamagishi T, Takagishi H, Fermin A de SR, Kanai R, Li Y, Matsumoto Y (2016): Cortical thickness of the dorsolateral prefrontal cortex predicts strategic choices in economic games. *Proc Natl Acad Sci*. 113: 5582–5587.

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6. Yeo BTT, Krienen FM, Sepulcre J, Sabuncu MR, Lashkari D, Hollinshead M, *et al.* (2011): The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *J Neurophysiol*. 106: 1125–65.