NEUROIMAGING

Evaluating the evidence for a neuroimaging subtype of posttraumatic stress disorder

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A recent study used functional neuroimaging and cognitive tasks to identify posttraumatic stress disorder (PTSD) subtypes. Specifically, this study found that a subgroup of patients with verbal memory impairment had a unique neural signature, namely, decreased ventral attention network (VAN) resting-state functional connectivity, and these same individuals responded poorly to psychotherapy. Although this represents one of the first studies to propose a neurocognitive subtype of PTSD and has far-reaching translational potential, the generalizability and specificity of the observed neural network and cognitive domain remain unclear. We attempted to conceptually replicate and extend these findings in a similar cohort of combat-exposed veterans ($n = 229$) tested using a standardized battery of neuropsychological tests and a priori criteria for cognitive impairments. First, we conducted identical and complementary analyses to determine whether subjects with PTSD and neuropsychologically defined verbal memory deficits exhibited the VAN connectivity biomarker. Second, we examined whether cognitive deficits in other domains implicated in PTSD (executive functioning and attention) exhibited the VAN signature. Across multiple measures of verbal memory, we did not find that the subgroup of individuals with PTSD and memory impairments had lower VAN connectivity. However, a subgroup of individuals with PTSD and attentional impairments did have lower VAN connectivity, suggesting that the original subtype could have been related to attention and not memory impairments. Overall, our findings suggest that the previously identified memory-impaired PTSD subtype may not generalize. Further consideration of neuropsychological methods will be important for neurocognitive markers to be implemented clinically.

INTRODUCTION

Posttraumatic stress disorder (PTSD) is a heterogeneous condition in its symptom presentation (*1*), long-term outcome, response to treatment (*2*, *3*), and neurobiology (*4*–*9*). Although there have been important discoveries in our understanding of the neurobiological systems associated with PTSD, this heterogeneity has impeded the identification of consistent biomarkers, which are rarely strong enough to make inferences at the individual level [although see (*10*, *11*)]. One approach to biomarker identification has been the use of functional neuroimaging, often alongside neuropsychological measurements, to identify subtypes of patients with dysfunction in neural networks that may underlie cognitive impairments and clinical symptoms. This approach has the potential to reveal targets for interventions and help predict treatment response (*12*, *13*). Furthermore, this general approach has begun to yield insights in other patient populations [(*13*, *14*), although see (*15*)] and was recently applied to PTSD (*16*). In a recent study, Etkin *et al.* (*16*) identified a PTSD subtype with a specific neurocognitive marker, namely, impaired verbal memory alongside ventral attention network (VAN) dysfunction. Although this work has transformative implications, given its discovery-based nature, focus on a single cognitive measure, and specific analytic approach, the replicability and generalizability of this finding remain unclear. Thus, we sought to replicate and extend the work of Etkin *et al.* (*16*).

To parse the heterogeneity in PTSD, Etkin *et al.* (*16*) used cognitive assessments and resting-state functional magnetic resonance imaging (fMRI) connectomics to discover neurocognitive subtypes of PTSD. The core approach in their study was to consider neuroimaging biomarkers of PTSD in the context of cognitive impairments, which they reasoned were key to the development and maintenance of PTSD. Thus, Etkin *et al.* (*16*) aimed to first identify those individuals with PTSD and a cognitive impairment and then determine whether this subgroup had a unique network-based connectomics signature, relative to those with PTSD but lacking the cognitive impairment as well as those without PTSD. Using a sample with mixed trauma exposures ($n = 87$; 57% sexual and physical abuse; 58% female), Etkin *et al.* found that individuals with PTSD overall performed worse than individuals without PTSD on a verbal recognition memory task. Subsequent exploratory analyses revealed that a subset of individuals with PTSD and relatively impaired verbal memory ($n = 12$) exhibited lower connectivity between regions in the VAN than individuals without PTSD or those with PTSD and relatively intact verbal recognition memory. This finding survived multiple comparisons correction (for analyses conducted in 28 brain network markers). Using a second, independent sample of combat-exposed postdeployed veterans ($n = 240$; 12% female), those with PTSD and a relative impairment in verbal recognition memory ($n = 40$) also exhibited lower VAN connectivity, although other brain networks also exhibited hypoconnectivity. In a subset of participants from the first sample ($n = 36$), those that exhibited both a relative verbal memory impairment and VAN connectivity impairment ($n = 6$) responded less favorably to prolonged exposure therapy for PTSD relative to the other participants.

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Although these findings are an important step in the direction of matching patients with PTSD to specific treatments, the study of Etkin *et al.* (*16*) has limitations. As acknowledged by the authors, this study relied solely upon a single forced choice recognition verbal memory test to define impairment post hoc and did not make use of normative data (*17*–*20*). Including a test of free recall (*17*, *20*), alongside previously established normative data for defining impairment (*21*–*23*), might have provided more evidence for the existence of memory impairments in their sample, as there were potentially ceiling effects in the recognition task (median performance was above 90%) (*17*). In addition, the authors did not assess participants' performance validity or effort testing, although it has been shown to be associated with neuropsychological performance and clinical symptoms (*24*). Etkin *et al.* also did not include comparisons to participants without PTSD but with a relative impairment in verbal memory. Hence, it is unclear whether the VAN marker was specific to PTSD with a memory impairment or to the memory impairment alone. A final limitation of Etkin *et al.* was the primary focus on verbal memory deficits among those with PTSD. Although other cognitive domains were assessed, this focus was driven by an observed main effect of PTSD diagnosis on recognition memory. There is ample evidence of PTSD-related cognitive impairments in other domains, such as attention (*25*–*32*), executive functioning, and inhibitory control (*27*, *32*–*34*), and these could also reveal cognitive-impaired subtypes of PTSD. These cognitive functions are more typically linked to the VAN than verbal memory (*35*).

In this conceptual replication and extension, we address these limitations of Etkin *et al.* using a similar cohort of combat-exposed veterans ($n = 229$), comparable data processing techniques, a more comprehensive and standardized battery of neuropsychological tests with a priori criteria for cognitive impairments, and a variety of matched and complementary analysis strategies. We examined whether individuals with normative-based verbal memory impairments and PTSD exhibited the VAN connectivity biomarker identified by Etkin *et al.* (*16*) using a well-validated neuropsychological measure of verbal memory with both free recall and recognition, the California Verbal Learning Test (CVLT-II) (*36*). Because we had an extensive assessment of executive functioning and attention in our cohort as well as validated composites and impairment cutoffs of each cognitive domain (*29*), we were also able to examine the degree to which other cognitive impairments may be related to alternative PTSD subtypes. Last, we explored whether other brain networks revealed additional subtypes or interactions between cognition and PTSD.

RESULTS

Analysis plan

We applied identical and complementary analytic models on data collected from our sample ($n = 229$) as applied by Etkin *et al.* (*16*) to evaluate the evidence for a neurocognitive subtype of PTSD. Specifically, three generalized linear models (GLMs) were conducted to predict individual differences in within-VAN connectivity. Model 1 was identical to that used by Etkin *et al.*, with a single group factor with three levels ($PTSD^+$/cognitive $impairment^+$, $PTSD^+$/cognitive $impairment^-$, and $PTSD^-$). In model 2, we included PTSD diagnostic status and cognition (impaired and not impaired), as well as the interaction term, as predictors. Given the challenge of defining cutoffs, we conducted model 3 with PTSD status and a continuous cognitive factor (memory performance), as well as an interaction term as predictors of VAN connectivity. To evaluate memory with multiple measures, models 1 to 3 were conducted using three tests of memory (memory composite score, long-delay free recall, and long-delay recognition). To determine whether executive or attentional impairments were associated with VAN connectivity among those with and without PTSD, we evaluated models 1 to 3 using executive and attention composite scores as predictors in place of the different memory scores. All models included the same covariates (age, gender identification, handedness, medication status, and head motion; see Materials and Methods) and effect statistic (Wald statistic) as in the study of Etkin *et al.* (*16*).

Demographics and group characteristics

Age, gender, and head motion did not differ between individuals with and without PTSD ($P > 0.672$). Individuals with PTSD reported completing less education ($P = 0.013$) and were more likely to be diagnosed with mood disorders ($P < 0.001$), anxiety disorders ($P = 0.015$), substance use disorders ($P = 0.017$), and military traumatic brain injury (TBI; $P < 0.001$) than individuals without PTSD. Memory performance scores and the executive function composite score did not differ between the $PTSD^+$ and $PTSD^-$ groups ($P > 0.29$). Individuals with PTSD performed marginally worse on the attention composite score than those without PTSD ($P = 0.076$). Table 1 provides the statistical comparison of the demographics, clinical, and cognitive measures between the $PTSD^+$ and $PTSD^-$ groups.

Neuropsychological performance and impairment cutoffs

Primary verbal memory measure

The criterion of at least two performance scores from the CVLT-II at 1 SD or more below normative expectations was used to define "clinically meaningful" impairment (see Materials and Methods). Accordingly, 30% of individuals with PTSD and 23% of individuals without PTSD were identified as having a verbal memory impairment (Table 2).

Secondary verbal memory measures

We used raw performance scores on the delayed recall and recognition tests and a procedure to equate the rate of memory impairment to those of Etkin *et al.* (*16*) (see Table 2). For the recognition test, a cutoff of <85% accuracy (hit rate − false alarm rate) to denote impairment closely matched to Etkin *et al.* (*16*), with 27% of the $PTSD^+$ group impaired (versus 33%) and 19% of the $PTSD^-$ group impaired (versus 19%). For the free recall test, a cutoff of <56% accuracy to denote impairment closely matched to Etkin *et al.* (*16*), with 29% of the $PTSD^+$ group impaired (versus 33%) and 19% of the $PTSD^-$ group impaired (versus 19%). Using a randomization procedure, we found that the relative match to Etkin *et al.* was not likely to have occurred by chance ($P = 0.023$), thus replicating the rate of impairment across studies.

Executive functioning and attention composites

For executive functioning and attention, the criterion of at least two performance scores at 1 SD or more below normative expectations was used to define clinically meaningful impairment in each domain respectively (see Materials and Methods). Individuals with and without PTSD showed significant differences between the percent impaired on the attention ($P = 0.004$) and executive function ($P = 0.037$) composites. The $PTSD^+$ group had a higher percentage with impaired attention, and the $PTSD^-$ group had a higher percentage with impaired executive function (see Table 2).

In sum, those with PTSD in our sample had the most robust cognitive impairment in the attention domain exhibiting higher rates

Table 1. Demographics. Mean ± SD; *P* values are from *t* test and chi-square tests comparing PTSD$^+$ and PTSD$^-$. PTSD$^+$, PTSD participants; PTSD$^-$, trauma-exposed control participants. Head motion was the mean absolute displacement across the six motion parameters: CAPS-IV, Clinician-Administered PTSD Scale for DSM-IV; WHODAS II, World Health Organization Disability Assessment Schedule II; IQ, intelligence quotient; WTAR, Wechsler Test of Adult Reading; HR – FAR, hit rate minus false alarm rate. Long-delay free recall and long-delay recognition are measures from the California Verbal Learning Test II (CVLT-II).

Measure	PTSD$^+$	PTSD$^-$	*P* value
N	140	89	–
Gender (M:F)	125:15	81:8	0.672
Age	31.31 ± 7.71	30.91 ± 8.30	0.717
Handedness (R:L)	125:15	71:18	0.046
Education	13.66 ± 1.69	14.29 ± 1.97	0.013
Head motion	0.26 ± 0.20	0.26 ± 0.19	0.864
PTSD severity (CAPS-IV)	65.96 ± 18.79	21.72 ± 15.01	<0.001
Current mood disorder (%)	36.43%	2.25%	<0.001
Current anxiety disorder (%)	24.29%	11.24%	0.015
Current substance use disorder (%)	17.86%	6.74%	0.017
Antidepressant (%)	29.29%	5.62%	<0.001
Antiepileptic (%)	7.14%	3.37%	0.229
Sedative hypnotic (%)	12.14%	2.25%	0.008
Pain medication (%)	34.29%	21.35%	0.036
Number of military TBIs	1.13 ± 1.87	0.36 ± 0.77	<0.001
Overall daily life functioning (WHODAS II)	22.39 ± 14.87	6.22 ± 6.19	<0.001
Estimated premorbid IQ (WTAR)	101.88 ± 11.23	104.56 ± 11.90	0.094
Long-delay free recall accuracy	0.67 ± 0.21	0.68 ± 0.17	0.572
Long-delay recognition accuracy (HR – FAR)	0.82 ± 0.16	0.84 ± 0.15	0.236
Memory composite	−0.24 ± 1.00	−0.11 ± 0.79	0.290
Attention composite	0.03 ± 0.64	0.17 ± 0.50	0.076
Executive composite	0.09 ± 0.55	0.13 ± 0.58	0.647

of clinically meaningful attention impairments (Table 2). Distributions of the primary and secondary verbal memory, executive, and attention measures are shown in fig. S1.

VAN connectivity and memory impairments in PTSD

Results of models 1 to 3 are presented for each of the memory performance indicators in Table 3 and Fig. 1 (A to C). Using the composite memory measure (Table 3 and Fig. 1A), long-delay free recall accuracy (Table 3 and Fig. 1B), or long-delay recognition accuracy (Table 3 and Fig. 1C), there was no evidence that PTSD, memory impairments, or their co-occurrence were associated with lower VAN connectivity ($P > 0.08$). For the composite measure in model 2, the interaction between PTSD and memory was significant (Wald $\chi^2 = 4.94$, $P = 0.026$). However, this effect was driven by lower VAN connectivity in those without PTSD but with memory impairments (Table 3 and Fig. 1A). Memory results were consistent across other potential alternative cutoffs for the composite, recognition, and recall measures. No correlations (Pearson's *r* and Spearman's ρ) between memory scores and VAN connectivity were significant for the PTSD$^+$ or PTSD$^-$ groups ($P > 0.14$; Fig. 1, D to F). Therefore, in our sample, we did not observe that individuals with PTSD and accompanying verbal memory impairment had reduced within-VAN connectivity.

VAN connectivity and other domains of cognitive impairment in PTSD

Participants with executive functioning impairments and PTSD did not differ in their VAN connectivity (Fig. 2A and Table 3) from those with PTSD and no executive impairment, as well as those without PTSD, across the three statistical models. On the other hand, we did observe a significant difference for the attention composite score, such that individuals with PTSD and impaired attention had lower within-VAN connectivity relative to the other two groups (Fig. 2B and Table 3; Wald $\chi^2 = 8.62$, $P = 0.013$). Because few participants without PTSD had impaired attention ($n = 6$), we did not model this group separately and thus did not conduct model 2 (2 × 2 GLM). In model 3, we did not observe a significant interaction between PTSD diagnosis and continuous performance on the attention composite (Wald $\chi^2 = 0.42$, $P = 0.516$). However, in the PTSD$^+$ group, there was a significant correlation (Pearson's *r* and Spearman's ρ) between VAN connectivity and attention ($r = 0.18$, $\rho = 0.22$, $P < 0.05$) but not executive functioning (Fig. 2, C and D). This indicates that the VAN dysfunction was strongest in those with PTSD and clinically meaningful attentional impairment. Clinical severity and comorbidities were not greater in those with PTSD and attentional impairment compared with those with PTSD but without impairment, although scores were worse in executive functioning ($P = 0.006$; table S1) and estimated premorbid verbal ability ($P = 0.010$; table S1).

Alternative models considering additional confounders

Differences between the PTSD groups with and without attention impairment in estimated premorbid verbal ability suggest that the observed effects could be due to general premorbid cognitive functioning. Therefore, we conducted model 3 with Wechsler Test of Adult Reading (WTAR) scores as the predictor of VAN connectivity (table S2); however, the WTAR did not significantly predict VAN connectivity by itself or in an interaction with PTSD status ($P = 0.603$, $P = 0.179$, respectively). We also considered all previous models with WTAR score as a covariate, and the attention effect remained significant (model 1: Wald $\chi^2 = 9.56$, $P = 0.008$; table S2). In addition, we considered whether modifying the strictness of the exclusion criteria on the basis of effort failures changed the observed results. Specifically, we considered all previous models after excluding 18 additional participants (28 total) who failed any one of the embedded effort measures (see Materials and Methods) and found the same results, as

Table 2. PTSD$^+$ versus PTSD$^-$ impairment proportions. Impairment for each cognitive composite (memory, attention, and executive) was defined by a cutoff of 1 SD below the mean on at least two measures within each cognitive domain (*21*). Long-delay free recall denotes an impairment cutoff of <56% accuracy. Long-delay recognition, calculated as the hit rate minus the false alarm rate, denotes an impairment cutoff of <85% accuracy.

Measure	%PTSD$^+$ impairment	%PTSD$^-$ impairment	χ^2	*P* value
Long-delay free recall accuracy	28.57	19.10	2.61	0.106
Long-delay recognition accuracy	27.14	19.10	1.93	0.165
Memory composite	30.00	22.47	1.56	0.211
Attention composite	20.86	6.74	8.33	0.004
Executive composite	15.83	27.27	4.37	0.037

Table 3. Results from three GLMs predicting VAN connectivity across five cognitive measures. The covariates included in each model were age, gender, education, handedness, medication status, and head motion. Individuals were classified as impaired in memory, executive, and attention by scoring 1 SD below the mean on at least two measures within the specific domain. Individuals were considered impaired if their long-delay recall accuracy was <56%. Individuals were considered impaired if their long-delay recognition accuracy was <85%. Three groups consist of PTSD$^+$ impairment$^+$, PTSD$^+$ impairment$^-$, and PTSD$^-$.

Model significance

	Memory composite		Free recall		Recognition		Executive composite		Attention composite	
Model	Likelihood ratio χ^2	*P* value	Likelihood ratio χ^2	*P* value	Likelihood ratio χ^2	*P* value	Likelihood ratio χ^2	*P* value	Likelihood ratio χ^2	*P* value
1 (3 groups)	5.76	0.889	5.34	0.914	5.47	0.907	4.46	0.954	13.62	0.254
2 (PTSD$^{+/-}$ × impairment$^{+/-}$)	10.89	0.539	5.61	0.935	6.35	0.897	4.50	0.973	–	–
3 (PTSD$^{+/-}$ × cognitive)	8.29	0.762	8.33	0.759	7.52	0.821	5.85	0.924	10.47	0.575

Main effects and interactions

		Memory composite		Free recall		Recognition		Executive composite		Attention composite	
Model	Effect	Wald χ^2	*P* value	Wald χ^2	*P* value	Wald χ^2	*P* value	Wald χ^2	*P* value	Wald χ^2	*P* value
1	PTSD$^+$ impairment$^+$, PTSD$^+$ impairment$^-$, PTSD$^-$	0.58	0.748	0.15	0.926	0.29	0.867	0.08	0.962	8.62	0.013
2	PTSD$^+$/PTSD$^-$	0.50	0.478	0.01	0.928	0.00	0.994	0.03	0.859	–	–
	Impairment$^+$/impairment$^-$	2.10	0.147	0.21	0.651	0.96	0.327	0.07	0.798	–	–
	2 × 2 interaction	4.94	0.026	0.16	0.685	0.30	0.581	0.00	0.966	–	–
3	PTSD$^+$/PTSD$^-$	0.18	0.673	0.43	0.514	0.41	0.523	0.00	0.948	0.14	0.704
	Continuous cognitive score	2.82	0.093	3.01	0.083	1.39	0.238	0.97	0.324	2.81	0.094
	Interaction	0.12	0.726	0.62	0.432	0.33	0.564	0.63	0.426	0.42	0.516

the attention effect remained significant (model 1: Wald χ^2 = 7.31, P = 0.026; table S3). Last, covarying for differential scan length did not alter patterns of the results, as VAN connectivity did not differ between 8 min versus 12 min of resting state fMRI (0.68 versus 0.69, P = 0.69).

Other brain networks

We explored how the other 27 connections between brain networks (28 total network pairs including within-network) differed among those with PTSD and cognitive impairments. Specifically, we restricted these analyses to model 1 (three groups) using the three memory scores, as well as the executive function and attention composites (figs. S2 to S6). The only significant effect was the within-VAN connectivity for the attention composite (described previously; Fig. 2B and Table 3).

DISCUSSION

In this study, we attempted to conceptually replicate and extend recently reported findings (*16*), suggesting that a subset of individuals

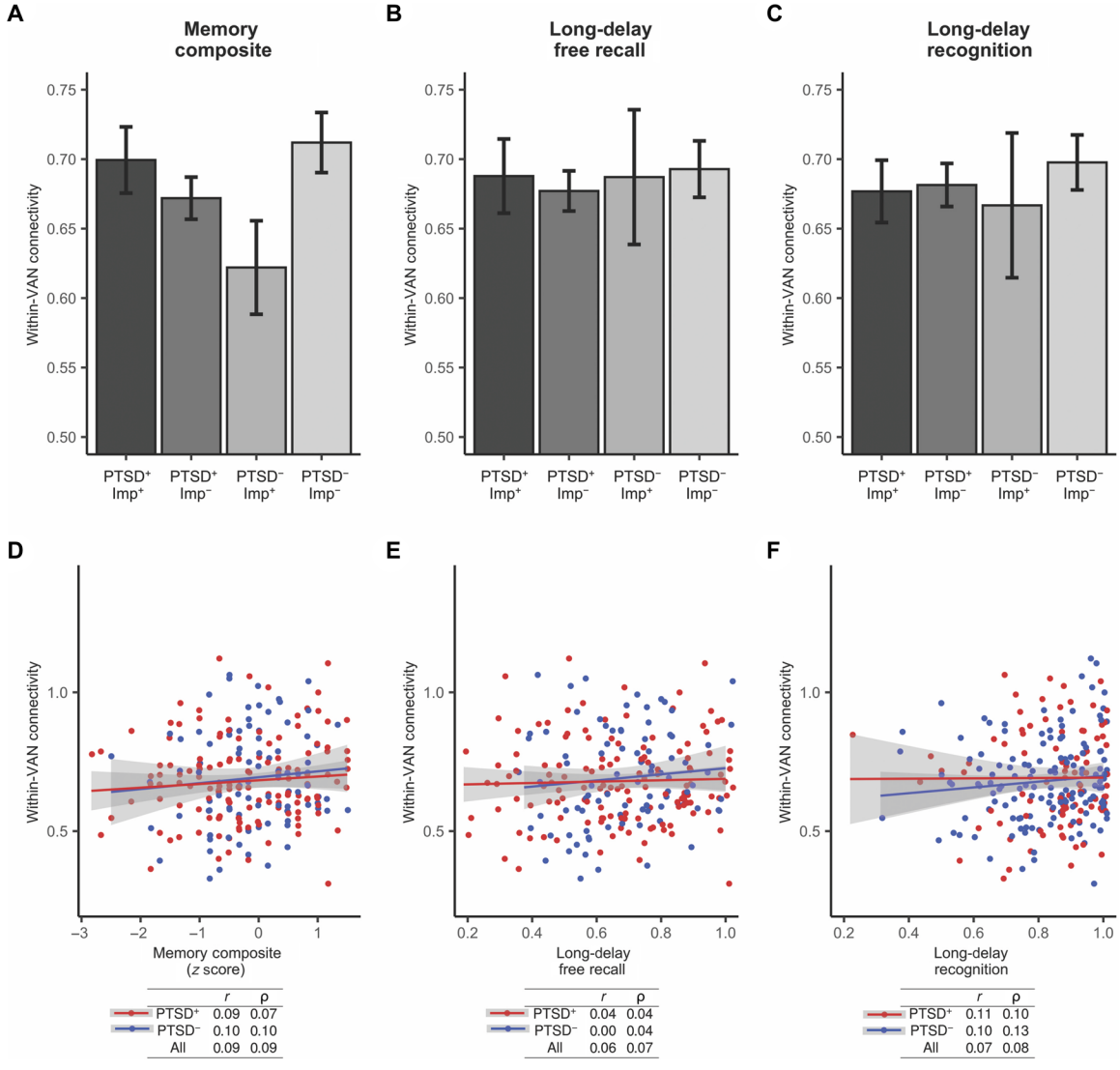

Fig. 1. PTSD with impaired verbal memory is not associated with within-VAN resting-state connectivity. (**A**) Within-VAN connectivity across groups classified by PTSD and the memory composite (*21*). (**B**) Within-VAN connectivity across groups classified by PTSD and CVLT-II long-delay free recall. (**C**) Within-VAN connectivity across groups classified by PTSD and CVLT-II long-delay recognition. (**D**) Within-VAN connectivity and the memory composite score, by $PTSD^{+/-}$. (**E**) Within-VAN connectivity and delayed free recall accuracy, by $PTSD^{+/-}$. (**F**) Within-VAN connectivity and delayed recognition accuracy, by $PTSD^{+/-}$. The tables below each scatter plot report the correlations (Pearson's *r* and Spearman's ρ) between within-VAN connectivity and the corresponding memory measure. $PTSD^{+}$ Imp^{+}, PTSD and impairment; $PTSD^{+}$ Imp^{-}, PTSD and no impairment; $PTSD^{-}$ Imp^{+}, no PTSD and impairment; $PTSD^{-}$ Imp^{-}, no PTSD and no impairment; $PTSD^{+}$, PTSD participants; $PTSD^{-}$, trauma-exposed control participants.

with PTSD and concurrent verbal memory deficits exhibited lower VAN connectivity. Using a similar cohort of combat-exposed veterans with and without PTSD alongside multiple standardized neuropsychological measures of verbal memory and a priori cutoffs for impairment, our results differed from those of Etkin *et al.* (*16*). We found that individuals with PTSD and three different indicators of memory impairment did not have reduced functional connectivity within the VAN compared with those with PTSD and no memory impairments or those without PTSD. This was consistent across multiple statistical models that varied in their treatment of memory score (continuous or dichotomous) and group factors. In sum, we attempted to conceptually replicate and relate VAN connectivity to memory impairments co-occurring with PTSD, yet we did not find a similar pattern as the previous study. We further extended our analysis to examine whether individuals with PTSD and co-occurring executive functioning or attention impairments exhibited this VAN biomarker. First, we found that participants with PTSD had a higher rate of attention dysfunction than those without PTSD. These participants with PTSD and attentional impairment exhibited reduced within-VAN connectivity relative to those with PTSD but without attentional impairments as well as those without PTSD, suggesting that the original findings (*16*) may be related to attention impairments, rather than memory impairments.

There are several potential explanations for our inability to replicate the results of Etkin *et al.* (*16*) with regard to a memory-impaired subtype of PTSD. First, the memory test and criterion for impairment used by Etkin *et al.* (<90% accuracy on the recognition test) may have had differential sensitivity and/or specificity than the CVLT-II

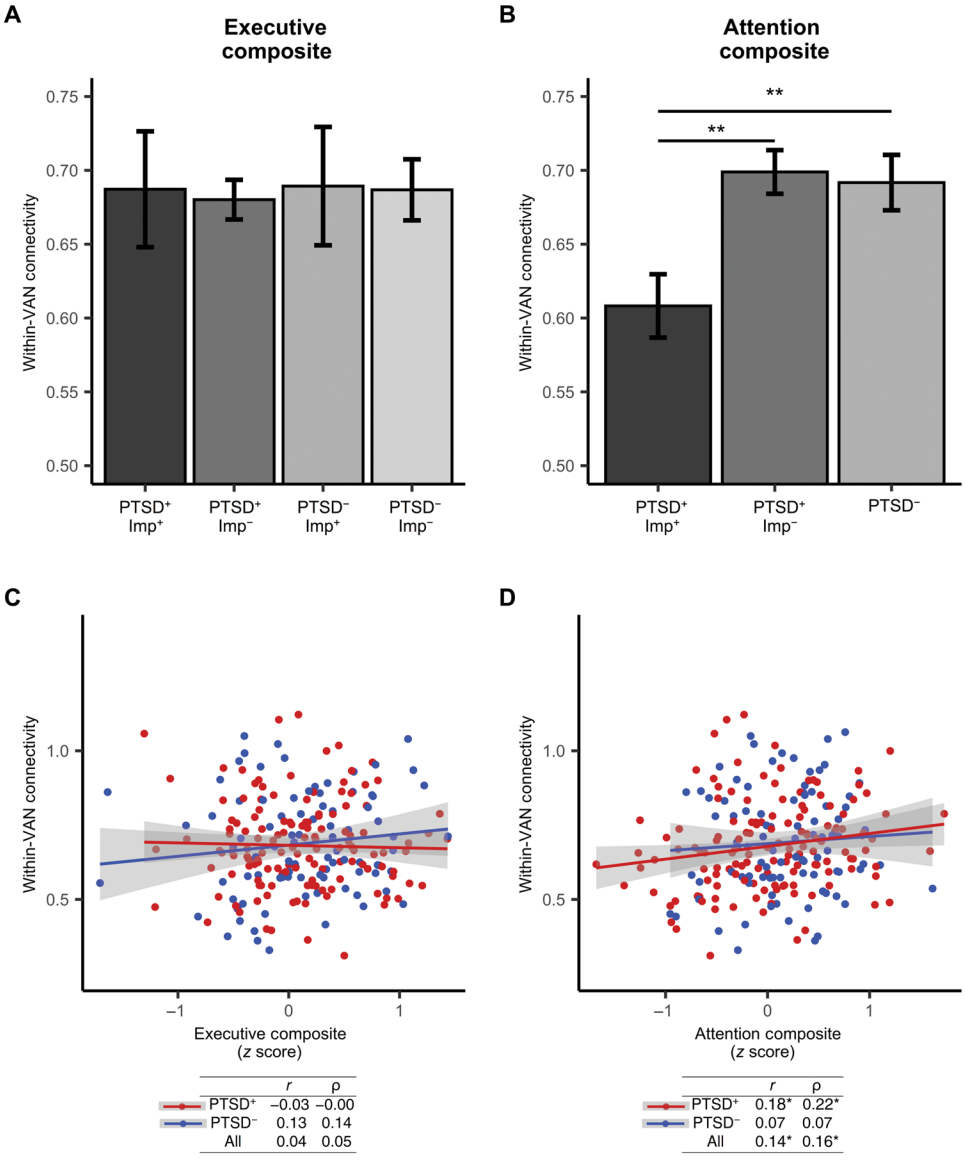

Fig. 2. PTSD with impaired attention, but not executive function, is associated with reduced within-VAN resting-state connectivity. (**A**) Within-VAN connectivity across groups classified by PTSD and the executive function composite (*21*). (**B**) Within-VAN connectivity across groups classified by PTSD and the attention composite. (**C**) Within-VAN connectivity and the executive composite score, by PTSD$^{+/-}$. (**D**) Within-VAN connectivity and attention composite score, by PTSD$^{+/-}$. The tables below each scatter plot report the correlations (Pearson's *r* and Spearman's ρ) between within-VAN connectivity and the corresponding composite measure. For graph (B), the PTSD$^-$ bar is a combination of both impairment$^{+/-}$ groups, as the PTSD$^-$ impairment$^+$ group had a small sample size ($n = 6$). *$P < 0.05$ and **$P < 0.01$.

memory impairments as measured by the CVLT-II (*37*), the meta-analytic effects were weakened when using trauma-exposed controls, as well as when correcting for small study bias; thus, our results are not unexpected. As the CVLT-II is a normed, validated test with acceptable psychometric properties (*36*), we were able to use a standardized neuropsychological measure and an a priori approach to define impairment, namely, when performance fell 1 SD below normative expectations on more than one subtest of memory. Although this analysis revealed similar numbers of participants with memory impairments, normative-based cutoffs also failed to replicate the VAN connectivity marker reported by Etkin *et al.* Whether the differences in the rate of PTSD-related memory impairments between the two samples were due to sample differences or measurement differences remain unclear. Ultimately, if verbal memory impairments are necessary to reveal subtypes of PTSD, the use of standardized tests and normative data across the life span will be critical for its translational utility.

Another potential explanation for our inability to conceptually replicate a biomarker for the memory-impaired subgroup of PTSD is the unreliability of the functional connectivity measure (*38*). Results of a recent meta-analysis indicate that reliability of functional connectivity at the individual connection level is low and can vary on the basis of denoising approaches, networks/spatial location, and scan duration (*38*). For example, one study found that increasing scanning from 6 to 12 min increased test-retest reliability by 20% (*39*). Thus, the use of 8 min in the study of Etkin *et al.* (*16*), and 8 to 12 min in our study, could lack the reliability necessary to detect a PTSD subtype. Optimizing imaging and explicitly testing the reliability of network connectivity measures will be critical for the identification of stable and generalizable biomarkers.

There are a number of limitations in the existing study. These limitations, in addition to the aforementioned methodological factors, may explain the differential results. In experiment 1 of Etkin *et al.* (*16*), a treatment-seeking civilian sample provided the strongest evidence for a VAN-subtype of PTSD, which was further associated with treatment resistance. Thus, a notable limitation of our study is that we could not conceptually replicate with a civilian treatment-seeking sample or evaluate any differential markers of treatment response. Second, it is known that post-9/11 veterans have a more complex polymorbid presentation of PTSD that may differ from civilian

measures used in the current study to detect a PTSD subtype with verbal memory impairments. However, prior versions of the task used by Etkin *et al.* were validated against the CVLT-II (*20*), and using CVLT-II norms to define cutoffs replicated the frequency of memory impairments in those with and without PTSD found by Etkin *et al.* Although overall verbal memory performance did not differ between those with and without PTSD in our sample, this statistic was not reported in the veteran sample of Etkin *et al.* (*16*) and remains unknown (although the number of participants meeting criterion for memory impairment was higher at 33% versus 19%). In addition, although meta-analytic studies of PTSD have found

PTSD in its clinical heterogeneity, medication status, and resistance to treatment (*40*–*42*). Along these lines, our sample had the most robust impairments in attention, whereas the veteran sample of Etkin *et al.* (*16*) had worse memory performance. Thus, sample differences are a possible explanation for our inability to conceptually replicate a memory-impaired neuroimaging subtype of PTSD. In addition, although our memory composite averaged three measures, we acknowledge that our CVLT-II measures are still limited because they are generated from a single word list and may reflect shared CVLT-II variance rather than more robustly reflecting general memory ability. Although the CVLT-II long- and short-delay free recall were highly correlated in our sample ($r = 0.85$), the recognition subscores correlated more moderately with recall ($r = 0.60$ and $r = 0.61$, respectively), indicating that they contributed unique variance to the composite measure. Recognition performance, in particular (as in the study of Etkin *et al.*), can be limited by skewness and ceiling effects. Nonetheless, future studies should include multiple tests of memory with different lists and stimulus modalities (such as visual). Another study limitation is that, although our cutoff methods have been published elsewhere (*21*, *23*) and are based on Diagnostic and Statistical Manual of Mental Disorders [DSM-5; (*43*)] cutoffs for mild neurocognitive disorder, the precise cutoff and tests included are somewhat arbitrary. Last, without premorbid assessments, it remains uncertain whether the cognitive impairments observed in this study are a consequence of PTSD or existed before trauma exposure and subsequent PTSD onset.

Results from our study revealed that individuals with PTSD had greater attention dysfunction relative to those without PTSD, and this impaired PTSD group had weaker VAN connectivity. Although these results and the study of Etkin *et al.* seem to suggest an important discrepancy, it is plausible that the memory impairments among some individuals diagnosed with PTSD observed by Etkin *et al.* were a function of attentional impairments. Etkin *et al.* (*16*) did not examine attentional dysfunction in their participants nor did they formally examine its association with VAN connectivity. In addition, their memory test was a forced choice test that was less difficult than the CVLT-II, as indicated by the high cutoff of 90% accuracy indicating dysfunction (versus our matched CVLT-II cutoff of 85%), and skewed distribution of performance. It has been previously suggested that attentional impairments may affect memory retrieval failures among those with PTSD by increasing distractions or intrusions (*44*). Thus, it is possible that impaired attention contributed to poor performance on the recognition memory test in Etkin *et al.* In addition, poor effort toward the recognition task could have contributed, as no effort testing was reported. Nevertheless, our study was not affected by the inclusion or exclusion of the 10 participants that failed effort testing (or an additional 18 participants who failed embedded effort measures); thus, effort (or lack thereof) alone is unlikely to explain the discrepant results. Much like the memory impairments noted by Etkin *et al.*, attentional impairments would likely reduce response to psychotherapy for PTSD. More specifically, individuals with PTSD who also suffer from attentional impairments would have more difficulty than those without such impairments staying on task and focusing during treatment sessions. Lack of focus would, in turn, prevent the patient from properly cognitively and emotionally processing the traumatic experience needed to resolve symptoms.

Our neuropsychological finding that individuals with PTSD had greater attention dysfunction is not unexpected. In particular, continuous performance sustained attention tasks {such as the Test of Variables of Attention [TOVA; (*45*)] used in this study} are frequently associated with PTSD and trauma-related symptom severity (*25*, *27*, *33*). In addition, several symptoms of PTSD are related to impaired attention, including distraction due to intrusive thoughts, hypervigilance, exaggerated startle, and dissociative symptoms. In particular, dissociative symptoms can interfere with treatment efficacy (*46*). More broadly, attention deficits can have real-world consequences related to safety, school/job performance, and social functioning (*47*–*49*). The VAN, which overlaps with or is synonymous with the salience network (SN; depending on parcellation), has been associated with both PTSD and attentional functioning. With regard to PTSD, regions in the VAN, such as insular, lateral prefrontal, and anterior cingulate cortices, are often overactivated in task-based fMRI studies of PTSD (*4*, *6*, *7*). However, VAN resting-state connectivity studies have been more variable in PTSD, finding both hypoconnectivity versus hyperconnectivity (*5*, *50*, *51*). With regard to the VAN's underlying cognitive functions, neuroimaging has shown activation of VAN/SN in a variety of tasks, but it is most commonly associated with stimulus-driven attention, physiological reactivity, and error monitoring (*35*). More broadly, VAN/SN is thought to integrate motivational, affective, and cognitive factors to appropriately respond to salient endogenous and exogenous information. The right hemisphere VAN/SN, in particular, is associated with arousal and alertness (*52*), and damage to right VAN can cause both spatial and nonspatial attentional deficits (*53*). Together, a linkage between VAN connectivity and attention dysfunction in those with PTSD seems plausible and worthy of future research. However, our finding requires replication using data from other independent samples before making definitive statements about its importance.

One possible mechanism underlying the association between attention dysfunction, PTSD, and VAN connectivity patterns could be that poor attention represents a vulnerability, such that those with poor attention are more prone to develop PTSD and their VAN may be more prone to dysregulation. This cognitive vulnerability hypothesis is supported by the lower estimated premorbid intelligence quotient (IQ) among those with attentional impairments and is consistent with prior research showing that lower premorbid IQ is a risk factor for PTSD (*29*). The finding of reduced VAN connectivity in those with PTSD and attention impairments is robust to controlling for estimated premorbid IQ (reading ability), and participants with lower premorbid IQ and PTSD did not exhibit lower VAN connectivity per se. Thus, it is possible that attention vulnerabilities present before trauma exposure (before military deployment) make an individual more susceptible to PTSD (*34*, *54*, *55*). In addition, such cognitive vulnerabilities for PTSD may be exacerbated by trauma-related psychological distress (*34*, *56*). The degree to which these neurocognitive markers represent premorbid vulnerabilities has important translational implications, such as whether cognitive interventions should be implemented alongside PTSD treatments or whether PTSD treatments can improve cognitive functioning (*57*). Future research assessing neurocognitive functioning longitudinally, as well as paired with interventions, will be needed to understand this potential subtype of PTSD.

Together, despite the previously highlighted study differences in sample and methods, our results question the generalizability of the finding of a memory-impaired neuroimaging subtype of PTSD by Etkin *et al.* (*16*) and suggest a need for further research to confirm its existence and treatment relevance. Although Etkin *et al.* used a second sample of veterans to confirm the initial findings of a PTSD

subgroup with memory impairments and VAN hypoconnectivity, several additional neural network markers were apparent with stronger effects than the VAN. Hence, there was some lack of correspondence between studies 1 and 2. Thus, we caution readers about the generalizability of both a memory-VAN or our finding of an attention-VAN subtype of PTSD. For the translational utility of work such as Etkin *et al.* (*16*) and the present study to be realized, there are important criteria to consider. The first recommended criterion is whether other researchers can use data collected independently from different samples and identical or similar methods to arrive at the same original conclusion. The second criterion is to determine the generalizability of the findings, with regard to different scanners, preprocessing/processing, statistical approaches, participant characteristics, and measures of cognition and PTSD. Similarly, the reliability of critical measures such as diagnoses, cognition, and fMRI markers are important limiting factors for replicability and generalizability. Along these lines, cognitive tests with known reliability and normative data, as well as continuous measures of cognition and symptom severity, may be preferable to cutoffs and may lead to more generalizable prediction (*15*, *21*, *23*). Last, it is important to consider the biological and theoretical consistency of discovery-based results. For example, the VAN is not primarily associated with or considered essential for verbal memory, and thus, the association between VAN and verbal memory observed by Etkin *et al.* (*16*) may not be a direct link.

Given the observed differences in neurocognitive subtypes observed across the two veteran PTSD samples, there are many future directions that the field should pursue, in addition to the above recommendations regarding replication and generalization. For one, more sensitive and reliable cognitive tasks with better characterized neurobiological substrates may provide us with more specific and replicable results that allow us to identify subtypes of PTSD. For example, we have developed a sustained attention task that is differentially sensitive to PTSD and other trauma-related conditions and is linked to connectivity and activation across many large-scale brain networks (*25*, *32*, *58*, *59*). Similarly, a recent study suggests that context processing may be a key dysfunction in PTSD and presents a task that may be sensitive to the underlying neurobiology (*7*). Different neuroimaging analytics may also improve replicability and sensitivity to PTSD subtypes such as dynamic connectivity (*60*), informational connectivity, and network analyses (*61*, *62*). If this attention subtype of PTSD is shown to be reliable, the included attention tests are relatively short in duration, and thus could be included in interventions to determine whether attention subtypes predict outcomes, or are themselves improved by treatment for PTSD. On the other hand, cognitive neuroscience–based interventions aimed at improving attention could be paired with treatments for PTSD, potentially enhancing treatment efficacy. For example, computer-based attention training has been shown to generalize to other cognitive domains across a range of populations (*63*, *64*), and network-targeted transcranial magnetic stimulation methods have been developed to improve both attention (*60*, *61*) and memory (*62*). For these precision medicine approaches to realize their potential, reliable and accurate neurocognitive predictors, as well as treatment outcomes, will be required to understand their interactions. Last, it is important to consider that transdiagnostic approaches to trauma sequelae, which consider combinations of PTSD alongside TBI, depression, sleep dysfunction, chronic pain, and substance use, may be critical to understand the underlying neurobiological heterogeneity in this polymorbid population.

In summary, we attempted to conceptually replicate the finding that a subtype of PTSD existed with concurrent memory dysfunction and VAN hypoconnectivity, using a standardized battery of neuropsychological tests and a priori criteria for cognitive impairments. We did not replicate these results with closely matched analytic processes and a similar participant cohort. We did find that those with PTSD and clinically meaningful attentional impairment did exhibit hypoconnectivity in the VAN. Although this exploratory result will require validation, it suggests that the original results might have been related to attention deficits or may not be domain-specific with regard to cognition. Our study suggests that caution is warranted when attempting to define subtypes of PTSD with resting fMRI and cognition, before treatment implications can be fully realized.

MATERIALS AND METHODS

Study design

In this conceptual replication and extension of the study of Etkin *et al.* (*16*), we examined fMRI connectivity and neuropsychological performance in a cohort of combat-exposed veterans (n = 229), using comparable data processing techniques and a variety of matched and complementary analysis strategies. Specifically, we examined whether individuals with normative-based verbal memory impairments and PTSD exhibited lower VAN connectivity as observed by Etkin *et al.*, using a well-validated neuropsychological measure of verbal memory with both free recall and recognition, the CVLT-II (*36*). We extended the previous work by using additional assessments of executive functioning and attention, as well as validated composites and DSM-5–based impairment cutoffs of each cognitive domain (*29*), to determine whether individuals with other cognitive impairments and PTSD exhibited this VAN connectivity marker. Last, we explored whether other brain networks revealed additional subtypes or interactions between cognition and PTSD.

Participants

Study participants were part of the Translational Research Center for Traumatic Brain Injury and Stress Disorders [TRACTS; for details regarding recruitment, exclusion criterion, and the characteristics of the TRACTS dataset, see (*41*)]. General exclusion criteria for recruitment into the TRACTS cohort includes prior serious medical and/or neurological illness unrelated to TBI, active suicidal and/or homicidal ideation requiring intervention, or a current diagnosis of bipolar disorder or psychotic disorder (except psychosis not otherwise specified because of trauma-related hallucinations) according to the DSM-IV (fourth edition; American Psychiatric Association, 2000). This sample included post-9/11 veterans that participated in both neuroimaging (resting fMRI) and the primary behavioral assessment (CVLT-II), were combat deployed, and did not have a moderate or severe TBI [mild TBI (mTBI) included; see Table 1]. For our study, data were available for the first consecutive 255 participants. Sixteen were later excluded for failed fMRI quality control (see the "Image processing" section) and 10 for failed performance validity testing (see the "Performance validity" section) for a sample size of 229 participants.

Demographics and clinical measures

We considered the following demographics to describe our sample, to use as covariates, and for replicating the procedures described by

Etkin *et al.* (*16*): age, gender identification, handedness, medication status (antidepressant, antiepileptic, sedative hypnotic, and pain medications considered as separate covariates), and education level attained. To assess PTSD in our study participants, the Clinician-Administered PTSD Scale for the DSM-IV [CAPS-IV; (*65*)] was administered to determine the presence ($PTSD^+$) or absence of PTSD ($PTSD^-$). We assessed the number of military mTBIs using the Boston Assessment of TBI-Lifetime (*66*) and other psychiatric disorders (mood, anxiety, and substance abuse disorder) using the Structured Clinical Interview for the DSM-IV Axis 1 Disorders (*67*). All diagnostic interviews were completed by a doctoral-level clinical psychologist and reviewed by at least three doctoral-level psychologists to achieve diagnostic consensus. See Table 1 for the description of our sample.

Neuropsychological measures

Performance validity

Commonly, practitioners and researchers include a measure of effort to help determine the validity of performance on a neuropsychological test(s), as performance validity has been related to cognitive performance in patients with PTSD and mTBI and is considered a critical part of their neuropsychological assessment (*23*, *68*, *69*). This study used the verbal Medical Symptom Validity Test (MSVT) (*70*) to determine whether effort is sufficient to produce valid scores on neuropsychological tests. MSVT failures included participants that scored an 85% or less on immediate recall, delayed recall, or consistency (*24*). Individuals that failed the MSVT ($n = 10$) were removed from the analysis, as they may have given less effort during the testing session, calling into question the validity of their data (*21*). In addition to the MSVT, three of our metrics included embedded performance validity tests, which were considered in follow-up analyses: four participants had a score >2 on the TOVA Symptom Exaggeration Index, eight participants had a Reliable Digit Span of < 7 on the Wechsler Adult Intelligence Scale–IV (*71*), five participants scored <15/16 on the CVLT-II Forced Choice Recognition, and one participant had poor performance on both the CVLT-II Forced Choice and Reliable Digit Span. Excluding these additional 18 participants did not change the results (table S3).

Verbal memory

We used the well-validated CVLT-II to assess participants' verbal memory. Specifically, the CVLT-II involves learning 16 words, followed by a short-delay free recall test, a long-delay free recall test, and subsequently, a long-delay recognition test (16 words with 44 foils).

Primary measure. A common set of criteria for determining neurocognitive impairment in a cognitive domain, based on DSM-5 cutoffs for mild neurocognitive disorder, requires performance to be 1 SD below normative expectations on two or more measures within that domain (*21*–*23*). We applied these criteria using three age-adjusted standardized performance scores from the CVLT-II (short-delay recall, long-delay recall, and long-delay recognition), as previously published (*21*). As a complementary continuous measure of memory, the mean *z* scores of the three memory scores were averaged to compute a composite score (*21*).

Secondary measures. To more directly match the work by Etkin *et al.* (*16*), we also evaluated the raw performance scores for the long-delay free recall and recognition tests. To define impairment, since our cohort was similar to the sample from Etkin *et al.* in demographics and trauma type (veterans with combat exposure), we determined cutoff scores that matched as closely as possible the percentage of impaired individuals with and without PTSD (33 and 19%, respectively). To test whether our best matched percentages were closer to that of the work of Etkin *et al.* (*16*) than expected by chance, we used a randomization procedure (100,000 iterations), where clinical labels were randomly assigned, and the best matched percentages of the random data were computed and compared with the actual data.

Other cognitive domains

In addition to the memory composite described previously, we recently published and validated clinical impairment cutoffs and cognitive composite scores for attention and executive function (*21*). The attention composite consisted of the TOVA (*45*) mean reaction time and d' (accuracy), digit span forward (*72*), and Trail Making Test number sequencing subtest A (*73*). The executive composite included the following measures: Trail Making Test number-letter switching subtest B (*73*), Stroop Test (*73*), CANTAB Intra-Extra Dimensional Set Shift (www.cantab.com), verbal fluency (*73*), and Auditory Consonant Trigrams (*74*). The raw performance on all measures was converted to standardized scores. Individuals were considered impaired if they scored 1 SD below the normative expectation on two or more measures that compose each domain. For more details regarding these cognitive composites, refer to the work by Riley *et al.* (*21*). Note that two participants did not have an executive function composite, and one did not have an attention composite; thus, each was excluded from their respective analyses.

Resting-state fMRI acquisition and processing

MRI acquisition

The neuroimaging data were acquired with a 3T Siemens TIM Trio scanner, using a 12-channel head coil. Two T1-weighted anatomical MPRAGE scans [repetition time (TR), 2530 ms; echo time (TE), 3.32 ms; flip angle, 7°, 1-mm isotropic] were acquired for inter-participant registration and normalization. Of the included 229 participants (see the "Participants" section for exclusion criteria), 183 participants completed two 6-min T2* weighted fMRI scans (gradient echo planar imaging: TR, 3000 ms; TE, 30 ms; flip angle, 90°, 3 mm by 3 mm by 3.7 mm slices for 38 slices). Another 44 participants completed two 4-min T2* weighted fMRI scans (gradient echo planar imaging: TR, 2000 ms; TE, 30 ms; flip angle, 90°, 3 mm by 3 mm by 3.7 mm slices for 38 slices), and 2 participants completed one scan of each length (one 6-min and one 4-min scan). fMRI was acquired during resting state while participants were instructed to keep their eyes open and stay awake.

Image processing

Resting-state fMRI images were preprocessed using Analysis of Functional NeuroImages (*75*). This processing pipeline included motion correction, registration to standard space, slice time correction, scan concatenation, censoring of time points with a framewise displacement >0.5 mm, 4-mm full width at half maximum Gaussian smoothing, followed by regression of motion parameters, white matter time series, ventricle time series, and band-pass filtering (0.01 to 0.001 Hz). Control for head motion confounds in resting-state involved removing individuals with greater than 20% of their fMRI scan censored during preprocessing ($n = 15$) or where MRI acquisition did not cover all brain regions in the parcellation ($n = 1$). We also calculated the mean root square motion during the resting scans. None of the remaining participants had greater than 3 mm of motion (although we used this measure as a covariate).

The brain was parcellated using an atlas from the work of Schaefer and colleagues (*76*) that parses the cortex into 100 nodes (regions)

that are embedded within seven large-scale cortical networks identified by Yeo *et al.* (*77*). The networks included the visual (17 regions), sensorimotor (14 regions), dorsal attention (15 regions), ventral attention (12 regions), limbic (5 regions), executive control (13 regions), and default mode (24 regions) networks. The average time series were extracted from each node (averaged across the set of voxels within the node) and correlated (Pearson) across nodes for a total of 4950 pairwise correlations. To calculate both within and between functional connectivity measures at the network-level, the resulting correlation coefficients were Fisher *z*-transformed, grouped, and averaged according to their corresponding large-scale network, resulting in a total of 7 within-network and 21 between-network estimates (total, 28). The primary outcome variable of our analysis was the within-VAN connectivity, which was the marker associated with memory impairments in the work of Etkin *et al.* (*16*) and thus the focus of this replication attempt. The other 27 connections were included in exploratory analyses. Note that the above preprocessing and parcellation were either identical or well-matched (*78*, *79*) to that in the work of Etkin *et al.* (*16*).

Statistical analyses

Three GLMs were conducted in SPSS to predict individual differences in within-VAN connectivity. Model 1 used a single group factor with three levels ($PTSD^+$/cognitive $impairment^+$, $PTSD^+$/cognitive $impairment^-$, and $PTSD^-$). Model 2 included PTSD diagnostic status and cognition (impaired and not impaired), as well as the interaction term, as predictors. Model 3 included PTSD status and the continuous cognitive factor, as well as the interaction term, as predictors of VAN connectivity. Models 1 to 3 were conducted using three tests of memory (memory composite score, long-delay free recall, and long-delay recognition), as well as executive function or attentional composites. All models included the same covariates (age, gender identification, handedness, and medication status) and effect statistic (Wald statistic) as in the study of Etkin *et al.* Significance was determined with α of 0.05.

SUPPLEMENTARY MATERIALS

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Fig. S1. Histograms of cognitive task performance.
Fig. S2. All networks and memory composite.
Fig. S3. All networks and recognition memory.
Fig. S4. All networks and memory recall.
Fig. S5. All networks and attention composite.
Fig. S6. All networks and executive function composite.
Table S1. Attention sample demographics.
Table S2. Results from three GLMs predicting VAN connectivity across six cognitive measures (including WTAR; WTAR included as covariates for all other cognitive models).
Table S3. Results from three GLMs predicting VAN connectivity across six cognitive measures (additional 18 participants excluded based on embedded performance validity measures).

View/request a protocol for this paper from *Bio-protocol*.

REFERENCES AND NOTES

1. L. A. Zoellner, L. D. Pruitt, F. J. Farach, J. J. Jun, Understanding heterogeneity in PTSD: Fear, dysphoria, and distress. *Depress. Anxiety* **31**, 97–106 (2014).
2. M. Hoskins, J. Pearce, A. Bethell, L. Dankova, C. Barbui, W. A. Tol, M. Van Ommeren, J. De Jong, S. Seedat, H. Chen, J. I. Bisson, Pharmacotherapy for post-traumatic stress disorder: Systematic review and meta-analysis. *Br. J. Psychiatry* **206**, 93–100 (2015).
3. K. Cusack, D. E. Jonas, C. A. Forneris, C. Wines, J. Sonis, J. C. Middleton, C. Feltner, K. A. Brownley, K. R. Olmsted, A. Greenblatt, A. Weil, B. N. Gaynes, Psychological treatments for adults with posttraumatic stress disorder: A systematic review and meta-analysis. *Clin. Psychol. Rev.* **43**, 128–141 (2016).
4. T. J. Akiki, C. L. Averill, C. G. Abdallah, A network-based neurobiological model of PTSD: Evidence from structural and functional neuroimaging studies. *Curr. Psychiatry Rep.* **19**, 81 (2017).
5. S. B. J. Koch, M. van Zuiden, L. Nawijn, J. L. Frijling, D. J. Veltman, M. Olff, Aberrant resting-state brain activity in posttraumatic stress disorder: A meta-analysis and systematic review. *Depress. Anxiety* **33**, 592–605 (2016).
6. J. P. Hayes, M. B. Van Elzakker, L. M. Shin, Emotion and cognition interactions in PTSD: A review of neurocognitive and neuroimaging studies. *Front. Integr. Neurosci.* **6**, 89 (2012).
7. I. Liberzon, J. L. Abelson, Context processing and the neurobiology of post-traumatic stress disorder. *Neuron* **92**, 14–30 (2016).
8. A. Etkin, T. D. Wager, Functional neuroimaging of anxiety: A meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. *Am. J. Psychiatry* **164**, 1476–1488 (2007).
9. R. K. Pitman, A. M. Rasmusson, K. C. Koenen, L. M. Shin, S. P. Orr, M. W. Gilbertson, M. R. Milad, I. Liberzon, Biological studies of post-traumatic stress disorder. *Nat. Rev. Neurosci.* **13**, 769–787 (2012).
10. F. Liu, B. Xie, Y. Wang, W. Guo, J. P. Fouche, Z. Long, W. Wang, H. Chen, M. Li, X. Duan, J. Zhang, M. Qiu, H. Chen, Characterization of post-traumatic stress disorder using resting-state fMRI with a multi-level parametric classification approach. *Brain Topogr.* **28**, 221–237 (2014).
11. P. Christova, L. M. James, B. E. Engdahl, S. M. Lewis, A. P. Georgopoulos, Diagnosis of posttraumatic stress disorder (PTSD) based on correlations of prewhitened fMRI data: Outcomes and areas involved. *Exp. Brain Res.* **233**, 2695–2705 (2015).
12. S. J. H. Van Rooij, M. Kennis, M. Vink, E. Geuze, Predicting treatment outcome in PTSD: A longitudinal functional mri study on trauma-unrelated emotional processing. *Neuropsychopharmacology* **41**, 1156–1165 (2016).
13. A. T. Drysdale, L. Grosenick, J. Downar, K. Dunlop, F. Mansouri, Y. Meng, R. N. Fetcho, B. Zebley, D. J. Oathes, A. Etkin, A. F. Schatzberg, K. Sudheimer, J. Keller, H. S. Mayberg, F. M. Gunning, G. S. Alexopoulos, M. D. Fox, A. Pascual-Leone, H. U. Voss, B. J. Casey, M. J. Dubin, C. Liston, Resting-state connectivity biomarkers define neurophysiological subtypes of depression. *Nat. Med.* **23**, 28–38 (2017).
14. K. A. Grisanzio, A. N. Goldstein-Piekarski, M. Y. Wang, A. P. R. Ahmed, Z. Samara, L. M. Williams, Transdiagnostic symptom clusters and associations with brain, behavior, and daily function in mood, anxiety, and trauma disorders. *JAMA Psychiat.* **75**, 201–209 (2018).
15. R. Dinga, L. Schmaal, B. W. J. H. Penninx, M. J. van Tol, D. J. Veltman, L. van Velzen, M. Mennes, N. J. A. van der Wee, A. F. Marquand, Evaluating the evidence for biotypes of depression: Methodological replication and extension of. *NeuroImage Clin.* **22**, 101796 (2019).
16. A. Etkin, A. Maron-Katz, W. Wu, G. A. Fonzo, J. Huemer, P. E. Vértes, B. Patenaude, J. Richiardi, M. S. Goodkind, C. J. Keller, J. Ramos-Cejudo, Y. V. Zaiko, K. K. Peng, E. Shpigel, P. Longwell, R. T. Toll, A. Thompson, S. Zack, B. Gonzalez, R. Edelstein, J. Chen, I. Akingbade, E. Weiss, R. Hart, S. Mann, K. Durkin, S. H. Baete, F. E. Boada, A. Genfi, J. Autea, J. Newman, D. J. Oathes, S. E. Lindley, D. Abu-Amara, B. A. Arnow, N. Crossley, J. Hallmayer, S. Fossati, B. O. Rothbaum, C. R. Marmar, E. T. Bullmore, R. O'Hara, Using fMRI connectivity to define a treatment-resistant form of post-traumatic stress disorder. *Sci. Transl. Med.* **11**, eaal3236 (2019).
17. C. Clark, R. Paul, L. Williams, M. Arns, K. Fallahpour, C. Handmer, E. Gordon, Standardized assessment of cognitive functioning during development and aging using an automated touchscreen battery. *Arch. Clin. Neuropsychol.* **21**, 449–467 (2006).
18. S. M. Silverstein, S. Berten, P. Olson, R. Paul, L. M. Williams, N. Cooper, E. Gordon, Development and validation of a World-Wide-Web-based neurocognitive assessment battery: WebNeuro. *Behav. Res. Methods* **39**, 940–949 (2007).
19. D. Mathersul, D. M. Palmer, R. C. Gur, R. E. Gur, N. Cooper, E. Gordon, L. M. Williams, Explicit identification and implicit recognition of facial emotions: II. Core domains and relationships with general cognition. *J. Clin. Exp. Neuropsychol.* **31**, 278–291 (2009).
20. R. H. Paul, J. Lawrence, L. M. Williams, C. C. Richard, N. Cooper, E. Gordon, Preliminary validity of "integneurotm": A new computerized battery of neurocognitive tests. *Int. J. Neurosci.* **115**, 1549–1567 (2009).
21. E. Riley, A. Mitko, A. Stumps, M. Robinson, W. Milberg, R. McGlinchey, M. Esterman, J. DeGutis, Clinically significant cognitive dysfunction in OEF/OIF/OND veterans: Prevalence and clinical associations. *Neuropsychology* **33**, 534–546 (2019).
22. A. J. Jak, M. W. Bondi, L. Delano-Wood, C. Wierenga, J. Corey-Bloom, D. P. Salmon, D. C. Delis, Quantification of five neuropsychological approaches to defining mild cognitive impairment. *Am. J. Geriatr. Psychiatry* **17**, 368–375 (2009).
23. N. H. Stricker, S. M. Lippa, D. L. Green, S. M. McGlynn, L. J. Grande, W. P. Milberg, R. E. McGlinchey, Elevated rates of memory impairment in military service-members and veterans with posttraumatic stress disorder. *J. Clin. Exp. Neuropsychol.* **39**, 768–785 (2017).
24. A. L. Clark, M. M. Amick, C. Fortier, W. P. Milberg, R. E. McGlinchey, Poor performance validity predicts clinical characteristics and cognitive test performance of OEF/OIF/OND veterans in a research setting. *Clin. Neuropsychol.* **28**, 802–825 (2014).

25. S. J. Dutra, B. P. Marx, R. McGlinchey, J. DeGutis, M. Esterman, Reward ameliorates posttraumatic stress disorder-related impairment in sustained attention. *Chronic Stress* **2**, 2470547018812400 (2018).
26. S. L. Pineles, S. M. Mostoufi, C. B. Ready, A. E. Street, M. G. Griffin, P. A. Resick, Trauma reactivity, avoidant coping, and PTSD symptoms: A moderating relationship? *J. Abnorm. Psychol.* **120**, 240–246 (2011).
27. J. DeGutis, M. Esterman, B. McCulloch, A. Rosenblatt, W. Milberg, R. McGlinchey, Posttraumatic psychological symptoms are associated with reduced inhibitory control, not general executive dysfunction. *J. Int. Neuropsychol. Soc.* **21**, 342–352 (2015).
28. M. Esterman, J. DeGutis, R. Mercado, A. Rosenblatt, J. J. Vasterling, W. Milberg, R. McGlinchey, Stress-related psychological symptoms are associated with increased attentional capture by visually salient distractors. *J. Int. Neuropsychol. Soc.* **19**, 835–840 (2013).
29. J. J. Vasterling, L. M. Duke, K. Brailey, J. I. Constans, A. N. Allain, P. B. Sutker, Attention, learning, and memory performances and intellectual resources in Vietnam veterans: PTSD and no disorder comparisons. *Neuropsychology* **16**, 5–14 (2002).
30. D. Swick, N. Honzel, J. Larsen, V. Ashley, Increased response variability as a marker of executive dysfunction in veterans with post-traumatic stress disorder. *Neuropsychologia* **51**, 3033–3040 (2013).
31. F. C. Fortenbaugh, J. DeGutis, M. Esterman, Recent theoretical, neural, and clinical advances in sustained attention research. *Ann. N. Y. Acad. Sci.* **1396**, 70–91 (2017).
32. M. Esterman, F. C. Fortenbaugh, M. E. Pierce, J. R. Fonda, J. DeGutis, W. Milberg, R. McGlinchey, Trauma-related psychiatric and behavioral conditions are uniquely associated with sustained attention dysfunction. *Neuropsychology* **33**, 711–724 (2019).
33. D. Swick, N. Honzel, J. Larsen, V. Ashley, T. Justus, Impaired response inhibition in veterans with post-traumatic stress disorder and mild traumatic brain injury. *J. Int. Neuropsychol. Soc.* **18**, 917–926 (2012).
34. R. L. Aupperle, A. J. Melrose, M. B. Stein, M. P. Paulus, Executive function and PTSD: Disengaging from trauma. *Neuropharmacology* **62**, 686–694 (2012).
35. V. Menon, *Brain Mapping: An Encyclopedic Reference* (Academic Press, 2015).
36. S. P. Woods, D. C. Delis, J. C. Scott, J. H. Kramer, J. A. Holdnack, The California Verbal Learning Test–second edition: Test-retest reliability, practice effects, and reliable change indices for the standard and alternate forms. *Arch. Clin. Neuropsychol.* **21**, 413–420 (2006).
37. J. C. Scott, G. E. Matt, K. M. Wrocklage, C. Crnich, J. Jordan, S. M. Southwick, J. H. Krystal, B. C. Schweinsburg, A quantitative meta-analysis of neurocognitive functioning in posttraumatic stress disorder. *Psychol. Bull.* **141**, 105–140 (2015).
38. S. Noble, D. Scheinost, R. T. Constable, A decade of test-retest reliability of functional connectivity: A systematic review and meta-analysis. *Neuroimage* **203**, 116157 (2019).
39. R. M. Birn, E. K. Molloy, R. Patriat, T. Parker, T. B. Meier, G. R. Kirk, V. A. Nair, M. E. Meyerand, V. Prabhakaran, The effect of scan length on the reliability of resting-state fMRI connectivity estimates. *Neuroimage* **83**, 550–558 (2013).
40. S. M. Lippa, J. R. Fonda, C. B. Fortier, M. A. Amick, A. Kenna, W. P. Milberg, R. E. McGlinchey, Deployment-related psychiatric and behavioral conditions and their association with functional disability in OEF/OIF/OND veterans. *J. Trauma. Stress* **28**, 25–33 (2015).
41. R. E. McGlinchey, W. P. Milberg, J. R. Fonda, C. B. Fortier, A methodology for assessing deployment trauma and its consequences in OEF/OIF/OND veterans: The TRACTS longitudinal prospective cohort study. *Int. J. Methods Psychiatr. Res.* **26**, e1556 (2017).
42. M. M. Steenkamp, B. T. Litz, C. W. Hoge, C. R. Marmar, Psychotherapy for military-related PTSD: A review of randomized clinical trials. *JAMA* **314**, 489–500 (2015).
43. American Psychiatric Association, Diagnostic and statistical manual of mental disorders—Fifth Edition (DSM-5) (Washington, DC, 2013).
44. J. J. Vasterling, K. Brailey, J. I. Constans, P. B. Sutker, Attention and memory dysfunction in posttraumatic stress disorder. *Neuropsychology* **12**, 125–133 (1998).
45. G. K. Henry, Probable malingering and performance on the test of variables of attention. *Clin. Neuropsychol.* **19**, 121–129 (2005).
46. P. A. Resick, M. K. Suvak, B. D. Johnides, K. S. Mitchell, K. M. Iverson, The impact of dissociation on PTSD treatment with cognitive processing therapy. *Depress. Anxiety* **29**, 718–730 (2012).
47. L. M. Bennett Murphy, C. Laurie-Rose, T. M. Brinkman, K. A. Mcnamara, Sustained attention and social competence in typically developing preschool-aged children. *Early Child Dev. Care* **177**, 133–149 (2007).
48. M. R. Yanko, T. M. Spalek, Driving with the wandering mind: The effect that mind-wandering has on driving performance. *Hum. Factors* **56**, 260–269 (2014).
49. R. Steinmayr, M. Ziegler, B. Träuble, Do intelligence and sustained attention interact in predicting academic achievement? *Learn. Individ. Differ.* **20**, 14–18 (2010).
50. Y. Zhang, F. Liu, H. Chen, M. Li, X. Duan, B. Xie, H. Chen, Intranetwork and internetwork functional connectivity alterations in post-traumatic stress disorder. *J. Affect. Disord.* **187**, 114–121 (2015).
51. A. MacNamara, J. DiGangi, K. L. Phan, Aberrant spontaneous and task-dependent functional connections in the anxious brain. *Biol. Psychiatry Cogn. Neurosci. neuroimaging* **1**, 278–287 (2016).
52. W. Sturm, A. De Simone, B. J. Krause, K. Specht, V. Hesselmann, I. Radermacher, H. Herzog, L. Tellmann, H. W. Müller-Gärtner, K. Willmes, Functional anatomy of intrinsic alertness: Evidence for a fronto-parietal-thalamic-brainstem network in the right hemisphere. *Neuropsychologia* **37**, 797–805 (1999).
53. I. H. Robertson, Do we need the "lateral" in unilateral neglect? Spatially nonselective attention deficits in unilateral neglect and their implications for rehabilitation. *Neuroimage* **14**, S85–S90 (2001).
54. D. Brandes, G. Ben-Schachar, A. Gilboa, O. Bonne, S. Freedman, A. Y. Shalev, PTSD symptoms and cognitive performance in recent trauma survivors. *Psychiatry Res.* **110**, 231–238 (2002).
55. K. W. Samuelson, J. Newman, D. Abu Amara, M. Qian, M. Li, K. Schultebraucks, E. Purchia, A. Genfi, E. Laska, C. Siegel, R. Hammamieh, A. Gautam, M. Jett, C. R. Marmar, Predeployment neurocognitive functioning predicts postdeployment posttraumatic stress in Army personnel. *Neuropsychology* **34**, 276–287 (2019).
56. B. P. Marx, S. Doron-Lamarca, S. P. Proctor, J. J. Vasterling, *Journal of the International Neuropsychological Society* (Cambridge Univ. Press, 2009), vol. 15, pp. 840–852.
57. A. J. Jak, L. D. Crocker, R. L. Aupperle, A. Clausen, J. Bomyea, *Current Topics in Behavioral Neurosciences* (Springer, 2018), vol. 38, pp. 93–116.
58. M. Esterman, S. K. Noonan, M. Rosenberg, J. Degutis, In the zone or zoning out? Tracking behavioral and neural fluctuations during sustained attention. *Cereb. Cortex* **23**, 2712–2723 (2013).
59. M. Esterman, D. Rothlein, Models of sustained attention. *Curr. Opin. Psychol.* **29**, 174–180 (2019).
60. M. Esterman, M. Thai, H. Okabe, J. DeGutis, E. Saad, S. E. Laganiere, M. A. Halko, Network-targeted cerebellar transcranial magnetic stimulation improves attentional control. *Neuroimage* **156**, 190–198 (2017).
61. M. A. Halko, F. Farzan, M. C. Eldaief, J. D. Schmahmann, A. Pascual-Leone, Intermittent theta-burst stimulation of the lateral cerebellum increases functional connectivity of the default network. *J. Neurosci.* **34**, 12049–12056 (2014).
62. J. X. Wang, L. M. Rogers, E. Z. Gross, A. J. Ryals, M. E. Dokucu, K. L. Brandstatt, M. S. Hermiller, J. L. Voss, Targeted enhancement of cortical-hippocampal brain networks and associative memory. *Science* **345**, 1054–1057 (2014).
63. J. DeGutis, M. Grosso, T. VanVleet, M. Esterman, L. Pistorino, A. Cronin-Golomb, Sustained attention training reduces spatial bias in Parkinson's disease: A pilot case series. *Neurocase* **22**, 179–186 (2016).
64. J. M. Degutis, T. M. Van Vleet, Tonic and phasic alertness training: A novel behavioral therapy to improve spatial and non-spatial attention in patients with hemispatial neglect. *Front. Hum. Neurosci.* **4**, 60 (2010).
65. D. D. Blake, D. G. Kaloupek, F. W. Weathers, F. D. Gusman, L. M. Nagy, D. S. Charney, T. M. Keane, The development of a clinician-administered PTSD scale. *J. Trauma. Stress* **8**, 75–90 (2005).
66. C. B. Fortier, M. M. Amick, L. Grande, S. McGlynn, A. Kenna, L. Morra, A. Clark, W. P. Milberg, R. E. McGlinchey, The Boston assessment of traumatic brain injury-lifetime (bat-l) semistructured interview: Evidence of research utility and validity. *J. Head Trauma Rehabil.* **29**, 89–98 (2014).
67. M. First, R. Spitzer, M. Gibbon, J. Williams, User's guide for the structured clinical interview for DSM-IV axis I disorders SCID-I: Clinician version. (1997).
68. R. L. Heilbronner, J. J. Sweet, J. E. Morgan, G. J. Larrabee, S. R. Millis, American academy of clinical neuropsychology consensus conference statement on the neuropsychological assessment of effort, response bias, and malingering. *Clin. Neuropsychol.* **23**, 1093–1129 (2009).
69. G. L. Iverson, Outcome from mild traumatic brain injury. *Curr. Opin. Psychiatry* **18**, 301–317 (2005).
70. P. Green, Medical Symptom Validity Test (MSVT) for Microsoft Windows: User's manual (2004).
71. D. Wechsler, Wechsler Adult Intelligence Scale—Fourth Edition (WAIS–IV) (Pearson, San Antonio, TX, 2008).
72. D. W.-S. Antonio, T. N. Pearson, undefined 2008, Wechsler adult intelligence scale–Fourth Edition (WAIS–IV); https://pdfs.semanticscholar.org/2858/f906a462c4424192f80361f689bdec24c16d.pdf.
73. G. L. Delis, D. Kaplan, E. Kramer, *D-KEFS Examiner's and Technical Manual* (Pearson Education, 2001).
74. D. T. Stuss, P. Ely, H. Hugenholtz, M. T. Richard, S. LaRochelle, C. A. Poirier, I. Bell, Subtle neuropsychological deficits in patients with good recovery after closed head injury. *Neurosurgery* **17**, 41–47 (1985).
75. R. W. Cox, AFNI: Software for analysis and visualization of functional magnetic resonance neuroimages. *Comput. Biomed. Res.* **29**, 162–173 (1996).
76. A. Schaefer, R. Kong, E. M. Gordon, T. O. Laumann, X.-N. Zuo, A. J. Holmes, S. B. Eickhoff, B. T. T. Yeo, Local-global parcellation of the human cerebral cortex from intrinsic functional connectivity MRI. *Cereb. Cortex* **28**, 3095–3114 (2018).
77. B. T. Yeo, F. Krienen, J. S.-J. The organization of the human cerebral cortex estimated by intrinsic functional connectivity (2011); www.physiology.org/doi/abs/10.1152/jn.00338.2011.

78. T. R. Oakes, T. Johnstone, K. S. Ores Walsh, L. L. Greischar, A. L. Alexander, A. S. Fox, R. J. Davidson, Comparison of fMRI motion correction software tools. *Neuroimage* **28**, 529–543 (2005).
79. R. Pauli, A. Bowring, R. Reynolds, G. Chen, T. E. Nichols, C. Maumet, Exploring fMRI results space: 31 variants of an fMRI analysis in AFNI, FSL, and SPM. *Front. Neuroinform.* **10**, 24 (2016).

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Evaluating the evidence for a neuroimaging subtype of posttraumatic stress disorder

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The intricate nature of PTSD

Posttraumatic stress disorder (PTSD) is a psychiatric condition with heterogeneous symptoms and response to treatment. Patient stratification using noninvasive biomarkers could potentially result in more effective treatments and better outcome. A recent study used functional magnetic resonance imaging (fMRI) and identified a common signature associated with memory impairments in a subgroup of patients. Now, Esterman *et al.* used a similar approach in a cohort of patients and failed to replicate the results. However, the authors identified a cohort of patients with similar fMRI impairments but different cognitive features. The results suggest that patient stratification using fMRI and neuropsychological methods might require further consideration.