Altered white matter microstructural organization in posttraumatic stress disorder across 3047 adults

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Published in:
Molecular Psychiatry

DOI:
10.1038/s41380-019-0631-x

Publication date:
2021

Molecular Psychiatry (2021) 26:4315–4330
https://doi.org/10.1038/s41380-019-0631-x

ARTICLE

Altered white matter microstructural organization in posttraumatic stress disorder across 3047 adults: results from the PGC-ENIGMA PTSD consortium

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Received: 20 June 2019 / Revised: 20 November 2019 / Accepted: 2 December 2019 / Published online: 19 December 2019

Abstract

A growing number of studies have examined alterations in white matter organization in people with posttraumatic stress disorder (PTSD) using diffusion MRI (dMRI), but the results have been mixed which may be partially due to relatively small sample sizes among studies. Altered structural connectivity may be both a neurobiological vulnerability for, and a result of, PTSD. In an effort to find reliable effects, we present a multi-cohort analysis of dMRI metrics across 3047 individuals from 28 cohorts currently participating in the PGC-ENIGMA PTSD working group (a joint partnership between the Psychiatric Genomics Consortium and the Enhancing NeuroImaging Genetics through Meta-Analysis consortium). Comparing regional white matter metrics across the full brain in 1426 individuals with PTSD and 1621 controls (2174 males/873 females) between ages 18–83, 92% of whom were trauma-exposed, we report associations between PTSD and disrupted white matter organization measured by lower fractional anisotropy (FA) in the tapetum region of the corpus callosum (Cohen's $d = -0.11$, $p = 0.0055$). The tapetum connects the left and right hippocampus, for which structure and function have been consistently implicated in PTSD. Results were consistent even after accounting for the effects of multiple potentially confounding variables: childhood trauma exposure, comorbid depression, history of traumatic brain injury, current alcohol abuse or dependence, and current use of psychotropic medications. Our results show that PTSD may be associated with alterations in the broader hippocampal network.

Introduction

Posttraumatic stress disorder (PTSD) is a debilitating mental health condition with a lifetime prevalence varying globally between 1 and 9% [1], with higher rates in women. Rates of PTSD are higher in populations exposed to greater levels of trauma, such as combat veterans [2] and civilians in conflict zones [3]. In addition to trauma type, genetics, and other sociological, psychological, and biological factors, individual differences in brain structure and function may explain vulnerability to developing PTSD following exposure to trauma, may result from trauma, or may be exacerbated by PTSD [4]. There is a lack of mechanistic evidence on the effects of stress and trauma on white matter structure. Exposure to trauma could lead to white matter damage, as excessive glucocorticoid levels can be neurotoxic and can impact myelination [5, 6]. Diffusion MRI (dMRI) is able to model white matter tracts and assess microstructural organization [7]. Fractional anisotropy (FA) is the most commonly used metric of microstructural organization, reflecting the degree to which water is diffusing along the axon (axially) as compared with across it (radially). Greater FA can reflect higher myelination, axonal diameter, or fiber density. Mean diffusivity (MD) reflects the average magnitude of diffusion across all directions, axial diffusivity (AD) is diffusion along the primary eigenvector (the dominant fiber direction), and radial diffusivity (RD) estimates diffusion perpendicular to the primary eigenvector. Altered microstructural organization is associated with several

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Supplementary information The online version of this article (https://doi.org/10.1038/s41380-019-0631-x) contains supplementary material, which is available to authorized users.

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different psychiatric disorders and could constitute a risk factor and/or a consequence of the disorders.

Studies of white matter microstructure in PTSD have reported inconsistent results. The majority report that PTSD is associated with lower FA [8–24], but some report higher FA [25–31], higher and lower FA in different regions [32], or null results [33–35]. Alterations in the cingulum bundle are frequently reported [9–13, 16, 18, 21, 23–29, 31, 32, 36], with differences also observed in the uncinate, corpus callosum, and *corona radiata* [14, 16, 18, 19, 24, 26, 29]. Inconsistent findings may be partially due to the use of hypothesis-driven rather than whole brain approaches, choice of analytic pipeline, selection of diffusion metrics, gender-specific studies, homogeneity of single cohort samples such as trauma-exposed vs. unexposed controls, and focus on military vs. civilian samples.

The PGC-ENIGMA PTSD working group is an international collaborative effort of the Psychiatric Genomics Consortium and the Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA) consortium that aims to increase statistical power through meta- and mega-analyses of PTSD neuroimaging biomarkers. This collaborative approach has led to the largest PTSD neuroimaging study to date, reporting smaller hippocampal volume in patients with PTSD compared to controls [37]. Here we applied this approach to investigate the microstructural organization of white matter in PTSD. The ENIGMA Diffusion Tensor Imaging (DTI) workflow [38], which has successfully identified white matter compromise in schizophrenia [39], bipolar disorder [40], major depression [41], 22q11.2 deletion syndrome [42], and obsessive compulsive disorder [43], among others, was used in this study by 28 cohorts to process their dMRI data locally. We hypothesized that the largest effects of compromised microstructure would be evident in the fronto-limbic tracts, such as the cingulum, uncinate, fornix, mid-sagittal corpus callosum and tapetum; these tracts are strongly implicated in behavioral deficits of PTSD such as emotion regulation, working memory, and episodic memory [10, 16, 19, 20, 24, 44].

Materials and methods

Study samples

The PGC-ENIGMA PTSD dMRI analysis included 28 cohorts from seven countries totaling 1621 healthy controls and 1426 individuals with PTSD (either formally diagnosed or with CAPS-4 > 40, see Supplementary Fig. 1). The age range across cohorts was 18–83 years; all but two older Vietnam era cohorts had an average age between 29 and 50. Of the 3047 participants included in these analyses, 2071 (68%) were from military cohorts, which resulted in a disproportionate number of males (71%). The majority of cohorts included trauma-exposed controls (e.g., combat, community violence, intimate partner violence, $N = 1498$), although some included trauma-unexposed controls ($N = 123$), and one included no control group. Table 1 contains demographic and clinical information for each cohort. All participants provided written informed consent approved by local institutional review boards. Quality control was completed by each site, with visual quality checking and outlier detection. Details on ENIGMA-DTI methods [39], inclusion/exclusion criteria, and clinical information may be found in Supplementary Note 1, Supplementary Table 1, and Supplementary Note 2, respectively.

Image acquisition and processing

The acquisition parameters for each cohort are provided in Supplementary Table 2. Preprocessing, including eddy current correction, echo-planar imaging-induced distortion correction and tensor fitting, was carried out at each site. Recommended protocols and quality control procedures are available on the ENIGMA-DTI and NITRC (Neuroimaging Informatics Tools and Resources Clearinghouse) webpages. Harmonization of preprocessing schemes was not enforced across sites to accommodate site- and acquisition-specific pipelines. Once tensors were estimated, they were mapped to the ENIGMA-DTI template and projected onto the ENIGMA-DTI template and were averaged within ROIs (http://enigma.ini.usc.edu/protocols/dti-protocols/). Further details and ROI abbreviations can be seen in Supplementary Note 1. In a subset of sites we extracted motion parameters from the eddy current correction step to determine if motion played a role in our case control findings. We examined rotation and translation averaged across the X, Y, and Z axes and found a marginally significant difference between PTSD and control groups in average rotation ($d = 0.12$ $p = 0.030$). Follow-up analyses including motion parameters as covariates yielded results that were consistent with our main analyses (for details see Supplementary Note 1 and Supplementary Fig. 2).

Statistical analysis

For each cohort/study, a linear model was fit using the *ppcor* and *matrixStats* packages in R 3.1.3, with the ROI FA as the response variable and PTSD and covariates as predictors. For cohorts/studies including more than one data collection site, site was included as a fixed dummy variable in the site-level analysis. As in prior ENIGMA disease working group meta-analyses [39], a random-

Table 1 Demographic information on adult cohorts included in analyses.

Site	Total *N*	M	F	*N* PTSD	*N* Control	Age range	Average age	PTSD scale	Depression scale	Type of controls	Dataset
ADNI-DoD	134	134	0	70	64	61–83	69.3	CAPS-4	GDS	Exposed	Military
Beijing	67	32	35	32	35	37–61	49.4	PCL-5	na	Exposed	Civilian
Booster	70	36	34	34	36	22–59	39.9	CAPS-4	HADS-D	Exposed	Police
Columbia	33	24	9	16	17	20–58	36.1	CAPS-4	HAM-D	Exposed	Civilian
Duke-1	187	142	45	50	137	21–57	39.4	CAPS-4/5	BDI	Exposed	Military
Duke-2	88	61	27	19	69	23–66	39.9	SCID/DTS	na	Exposed	Military
Duke-3	61	50	11	18	43	23–65	38.8	CAPS-4/5	na	Exposed	Military
Grady trauma project	132	0	132	50	82	18–62	39.6	CAPS-4	BDI	Exposed	Civilian
Groningen	49	0	49	49	0	23–58	40.3	CAPS-4	BDI	No controls	Civilian
INTRuST	214	117	97	77	137	18–56	36	MINI/CAPS-4 /PCL-M/SCID	na	Exposed	Military and civilian
iSCORE	99	86	13	44	55	19–51	35.8	PCL-M	CES-D	Exposed	Military
Lawson	98	52	46	46	52	18–59	34.7	CAPS-4	BDI	Exposed and unexposed	Civilian
McLean	55	0	55	41	14	18–62	37	CAPS-5	BDI	Exposed	Civilian
Münster	25	0	25	14	11	19–51	29	SCID	BDI	Exposed	Civilian
New South Wales	162	62	100	85	77	18–69	40.2	CAPS-4	HAM-D	Exposed	Civilian
South Dakota	90	81	9	55	35	22–45	31.8	PCL-M	na	Exposed	Military
Stellenbosch-1	71	20	51	27	44	21–77	48.0	CAPS-5	na	Both	Civilian
Stellenbosch-2	31	19	12	17	14	21–66	36.6	CAPS-5	na	Both	Civilian
U Sydney	64	34	30	31	33	17–49	36.25	CAPS-4	DASS	Exposed	Civilian
UMC Utrecht	94	94	0	46	48	21–57	35.6	CAPS-4	SCID	Both	Military
UW-Madison	48	44	4	25	23	22–48	31	CAPS-4	BDI	Exposed	Military
VA Boston	493	456	37	305	188	18–65	31.2	CAPS-4	na	Exposed	Military
VA Houston	69	44	25	53	16	21–58	31.4	CAPS-4	BDI	Exposed	Military
VA Minneapolis-1	124	120	4	49	75	23–62	34.2	CAPS-4	SCID	Both	Military
VA Minneapolis-2	130	121	9	67	63	22–59	32.9	CAPS-4	SCID	Both	Military
VA Waco	53	46	7	36	17	25–60	39.6	PCL-5	na	Unexposed	Military
VETSA	239	239	0	33	206	56–66	61.8	PCL-C	CES-D	Exposed	Military
Yale/NCPTSD	67	60	7	37	30	21–60	34.1	CAPS-4	BDI	Exposed	Military
Overall	**3047**	**2174**	**873**	**1426**	**1621**		**39.6**				

effects inverse-variance weighted meta-analysis was conducted at a central coordinating site (the University of Southern California Imaging Genetics Center) in R (metafor package, version 1.99–118 http://www.metafor-project.org/) to combine individual cohort estimated effect sizes. Cohen's *d* for the main effect of group and unstandardized β coefficients (regression parameters) for continuous predictors were computed with 95% confidence intervals. We used the Cohen's d calculation that accounts for covariates in the fixed effects model, using the following equation:

$$d = \mathrm{M1} - \mathrm{M2}/\text{pooled SD, where pooled SD} = \sqrt{((\mathrm{SD}_1^2 + \mathrm{SD}_2^2)/2)}$$

Heterogeneity scores (I^2) for each test were computed, indicating the percent of total variance in effect size explained by heterogeneity across cohorts. Bilaterally averaged FA was the primary imaging measure, with corresponding MD, RD, and AD examined post hoc when FA was significant for an effect of diagnosis. Lateralized ROIs were examined post hoc when a significant association was found with the bilateral average. The corticospinal tract was not analyzed as it has poor reliability [38]. The average correlation in FA between all ROIs was $r = 0.61$. A Bonferroni correction is overly conservative when there are correlations between the multiple dependent measures being tested. Therefore, we calculated the effective number of independent tests based on the observed correlation structure between the alternate responses using two different methods. The equation proposed by Nyholt [45] yielded an estimated 13.3529 effective tests (Meff), giving a significance threshold of $p < 0.05/13.3529 = 0.0037$. The equation of Li and Ji [46] yielded Veff = 9, giving a significance threshold of

$p < 0.05/9 = 0.0057$. Recent empirical work based on simulations concludes that when the number of effective tests were known, the Nyholt calculation is less accurate than the method of Li and Ji because it overestimates the number of effective variables [47]. Given the lack of consensus in the field along with initial evidence that the Li and Ji threshold is more accurate, we adopted this method but also note whether results survived the Nyholt threshold.

Nonlinear age term

We first conducted analyses to examine whether a nonlinear age term should be included in statistical models along with age and sex, as age has a nonlinear effect on FA [48]. As this analysis did reveal a significant effect of nonlinear age above and beyond linear age, age^2 was included in all subsequent analyses. Demographic details are shown in Supplementary Fig. 3.

Primary group comparison

We compared PTSD cases to all controls (both trauma-exposed and unexposed), PTSD cases to trauma-exposed controls only, and trauma-exposed to trauma unexposed controls. Given the significant impact of trauma exposure on brain structure [49], we compared trauma-exposed with unexposed controls to examine whether potential differences may be attributed to trauma exposure rather than PTSD. We repeated analyses separately in sites acquiring 30 or fewer diffusion directions, sites acquiring more than 30 directions, sites using isotropic voxel dimensions, and sites using anisotropic voxel dimensions. These are discussed in further detail in Supplementary Note 3, Supplementary Table 3, and Supplementary Fig. 4. Secondary subgroups: We examined PTSD associations in males and females separately, and in military and civilian samples separately. These results may be found in Supplementary Note 4. Secondary interactions: We examined potential interactions between PTSD and age or sex. These results can be seen in Supplementary Note 5.

Secondary additional covariates

We tested a model including ancestry, but as this was a meta-analysis and most cohorts were primarily composed of participants of white non-Hispanic descent, this had a very minimal impact, and we did not include this variable as a covariate in our analysis. We examined the impact of five potentially confounding covariates on the associations of PTSD with FA—childhood trauma, depression, alcohol dependence/abuse, traumatic brain injury (TBI, of any severity), and use of psychotropic medications. We compared the white matter microstructure of individuals with PTSD to that of controls with each covariate included individually in the model, and in the subset of sites that collected data on childhood trauma, depression, alcohol use disorders, TBI, or medication without that covariate in the model to determine whether differences in results were due to the inclusion of the covariate or the reduction in sample size. There were not enough participants with all five variables to simultaneously model these potential confounds in a single model. Details of these methods and results are provided in Supplementary Note 6. Briefly, binary variables were created for depression, TBI, and medication use. As depression was assessed using a variety of measures, we used published cut-offs to recode the data as categorical depression (see Supplementary Note 2 for more details). Alcohol use disorders and childhood trauma were coded as three-level ordinal variables based on evidence of dose-dependent effects on brain structure and clinical severity, respectively [50, 51]: Alcohol use disorders: 0 = no alcohol use disorder, 1 = alcohol abuse, 2 = alcohol dependence, as measured by the SCID or AUDIT [52]; childhood trauma (as measured by the Childhood Trauma Questionnaire): 0 = no reported childhood trauma, 1 = one type of childhood trauma exposure, 2 = two or more types of childhood trauma exposure; *PTSD severity*: To examine PTSD severity, we conducted linear regressions on CAPS-4 score in the PTSD group for sites that collected CAPS-4. We examined linear associations with CAPS-4 score covarying for childhood trauma, depression, alcohol use disorders, TBI, and medication use, and we tested associations with CAPS-4 separately in military veterans and civilians as well as males and females (see Supplementary Note 6 for more details).

Results

Group differences

We found significantly lower FA in the PTSD group in the tapetum of the corpus callosum ($d = -0.11$, $p = 0.0055$) when comparing PTSD ($n = 1{,}377$) and all controls ($n = 1{,}620$). This result did not survive the more conservative but potentially less accurate Nyholt threshold. Post hoc analysis revealed a larger effect in the left than in the right tapetum (left $d = -0.13$, $p = 0.00090$; right $d = -0.067$, $p = 0.042$). Post hoc analysis also revealed higher RD in the tapetum in the PTSD group (bilateral $d = 0.09$, $p = 0.027$; left $d = 0.11$, $p = 0.0038$).

In the analysis comparing participants with PTSD ($n = 1{,}319$) to trauma-exposed controls ($n = 1{,}498$), we found

Table 2 Results from the group comparisons.

	PTSD vs all controls[a]				PTSD vs trauma-exposed controls[b]			
ROI	Meta *d*	Meta *p* value uncorrected	95% CI	I^2	Meta *d*	Meta *p* value uncorrected	95% CI	I^2
Average FA	−0.02	0.69	[−0.09, 0.06]	0	−0.03	0.48	[−0.11, 0.05]	0
ACR	−0.01	0.85	[−0.09, 0.07]	7.51	−0.03	0.48	[−0.11, 0.05]	0
ALIC	−0.04	0.26	[−0.12, 0.03]	0	−0.04	0.38	[−0.11, 0.04]	0
BCC	−0.04	0.30	[−0.12, 0.04]	0	−0.05	0.21	[−0.13, 0.03]	0
CC	−0.05	0.24	[−0.12, 0.03]	0	−0.05	0.25	[−0.12, 0.03]	0
CGC	−0.03	0.43	[−0.11, 0.05]	0	−0.03	0.42	[−0.11, 0.05]	0
CGH	0.02	0.67	[−0.06, 0.09]	0	0.01	0.72	[−0.06, 0.09]	0.01
CR	−0.02	0.52	[−0.10, 0.05]	0	−0.04	0.37	[−0.11, 0.04]	0
EC	0.03	0.37	[−0.04, 0.11]	0	0.03	0.52	[−0.05, 0.10]	0
FX	−0.02	0.67	[−0.10, 0.07]	14.33	−0.02	0.61	[−0.12, 0.07]	20.05
FXST	0.00	0.95	[−0.08, 0.07]	0	0.00	0.96	[−0.08, 0.08]	0.01
GCC	−0.01	0.80	[−0.09, 0.07]	0	−0.01	0.74	[−0.09, 0.07]	0
IC	0.00	0.97	[−0.07, 0.08]	0.01	0.01	0.84	[−0.07, 0.09]	0
PCR	−0.04	0.25	[-0.12, 0.03]	0	−0.04	0.37	[−0.11, 0.04]	0
PLIC	0.03	0.51	[−0.06, 0.13]	27.71	0.04	0.39	[−0.05, 0.14]	24.80
PTR	−0.03	0.53	[−0.11, 0.06]	10.68	−0.03	0.48	[−0.12, 0.06]	11.95
RLIC	0.00	1.0	[−0.08, 0.08]	0	0.00	0.97	[−0.08, 0.08]	0
SCC	−0.08	0.096	[−0.18, 0.01]	31.36	−0.06	0.23	[−0.17, 0.04]	33.81
SCR	−0.02	0.60	[−0.10, 0.06]	0	−0.03	0.51	[−0.11, 0.05]	0
SFO	*−0.10*	*0.014*	*[−0.17,−0.02]*	*0*	*−0.11*	*0.0073*	*[−0.19, −0.03]*	*0*
SLF	0.03	0.49	[−0.05, 0.10]	0	0.04	0.35	[−0.04, 0.12]	0
SS	−0.02	0.64	[−0.09, 0.06]	0	−0.03	0.39	[−0.11, 0.04]	0
TAP	**−0.11**	**0.0055**	**[−0.18, −0.03]**	**0**	*−0.10*	*0.011*	*[−0.18, −0.02]*	*0*
UNC	0.02	0.58	[−0.06, 0.10]	0.01	0.01	0.76	[−0.07, 0.09]	0

Cohen's *d* values, uncorrected *p* values, the 95% confidence interval for the *d* statistic, and the I^2 (heterogeneity) are shown for the group comparisons. **Bolded** results are significant when corrected for multiple comparisons, *italicized* results are marginally significant (based on the Li and Ji adjusted Bonferroni correction)

[a]Results comparing PTSD to all controls

[b]Results comparing PTSD to trauma-exposed controls only

lower FA in the left tapetum in PTSD ($d = -0.13$, $p = 0.0014$), although the effect in bilateral tapetum did not survive correction for multiple comparisons but had comparable effect size ($d = -0.10$, $p = 0.011$) (see Table 2 and Fig. 1, see Fig. 2 for site-specific effects, and Fig. 3 for a neuroanatomical figure). PTSD participants from cohorts that only included trauma-unexposed controls were not included.

Comparing trauma-exposed ($n = 200$) to trauma unexposed controls ($n = 93$) from six sites, we found an effect that did not withstand correction for multiple comparisons but had a comparable effect size of lower FA in exposed controls in the tapetum, splenium of corpus callosum, and fornix/stria-terminalis ($d = -0.41$, $p = 0.014$; $d = -0.48$, $p = 0.0042$; $d = -0.36$, $p = 0.019$, respectively), along with significantly higher MD and RD in the splenium ($d = 0.48$, $p = 0.0017$; $d = 0.56$, $p = 0.00023$, respectively) and an effect that did not survive correction for multiple comparisons but had a comparable effect size of higher RD in the tapetum ($d = 0.32$, $p = 0.036$). Lastly, for a subset of cohorts we had data on lifetime PTSD (444 lifetime PTSD vs. 230 controls across seven cohorts). We did not find any significant results for this comparison.

Subgroups

We examined military vs. civilian cohorts, and male vs. female participants separately. We found significantly lower FA in males in the superior fronto-occipital fasciculus (SFO), along with associations that did not survive correction for multiple comparisons with tapetum FA in the military-only and male-only subgroups separately (see Supplementary Note 4 and Supplementary

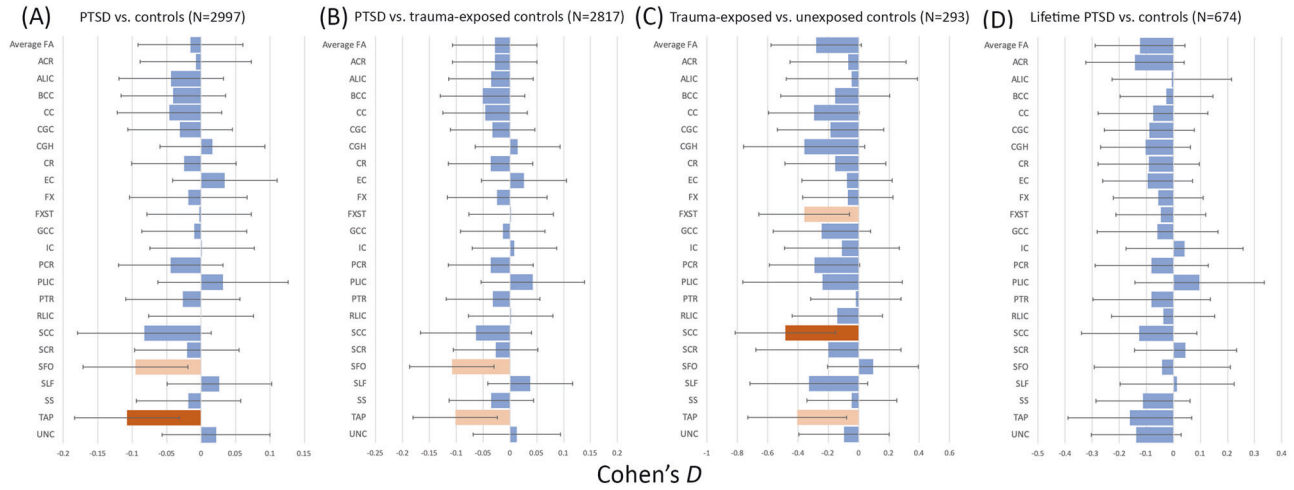

Fig. 1 Results from the group comparisons. a Results comparing PTSD to all controls; **b** results comparing PTSD to trauma-exposed controls only; **c** results comparing trauma-exposed to unexposed participants; **d** lifetime PTSD to controls. Cohen's *d* statistics are shown across all bilateral and midline ROIs and average FA, with bars indicating the 95% confidence interval. The ROI abbreviations are explained in Supplementary Note 1. As PTSD was coded "1" and control "0", negative statistics indicate lower FA in PTSD. Total *N* is listed for each comparison. Dark orange bars indicate significance ($p < 0.0057$) and light orange bars indicate results that did not withstand correction for multiple comparisons ($0.05 > p > 0.0057$). Error bars are 95% CI.

Fig. 5 for more details). Results of group-by-sex and group-by-age interactions were not significant and are shown in Supplementary Note 5 and Supplementary Fig. 6.

Additional covariates

The role of potentially confounding variables on the association between PTSD and the tapetum was tested in several post hoc analyses focused on left, right, and bilateral tapetum FA (see Supplementary Fig. 7). As these analyses were considered post hoc and limited to the tapetum, we used a test-wise significance threshold of $p < 0.05$. Results generally remained significant across all models. *Depression*: Including dichotomous depression as a covariate (699 PTSD vs. 864 controls) resulted in lower bilateral and lower left tapetum FA in the PTSD group (bilateral $d = -0.12$, $p = 0.036$; left $d = -0.16$, $p = 0.0024$). *Alcohol Use Disorders*: Including AUD as a covariate (633 PTSD vs. 524 controls) resulted in lower bilateral and left tapetum FA in the PTSD group (bilateral $d = -0.14$, $p = 0.018$; left $d = -0.16$, $p = 0.0081$) and borderline lower right tapetum FA ($d = -0.11$, $p = 0.077$). *Traumatic Brain Injury*: Including a binary TBI variable (830 PTSD vs. 1035 controls) resulted in lower left tapetum FA ($d = -0.11$, $p = 0.023$). *Medication Use*: Including a dichotomous psychotropic medication covariate (694 PTSD vs. 663 controls) resulted in lower left tapetum FA in the PTSD group (left $d = -0.012$, $p = 0.028$). *Childhood Trauma*: Including childhood trauma as a covariate (367 PTSD vs. 598 controls) did not yield any significant results, but neither did the analysis in the reduced sample without CT in the model, suggesting that the sample reduction impacted these results. To control for covariate- and cohort-dependent changes in sample size, each analysis was repeated in a smaller sample that corresponded to omitting the relevant covariate. The tapetum results remained consistent in nearly all reduced sample analyses—significant effects survived covariate adjustment and effects that disappeared (such as with childhood trauma) were also absent in the reduced sample. Thus, covariates had minimal impact beyond the reduction in sample size (see Supplementary Note 6 and Supplementary Figs. 8–12). A table showing how many participants at each site had information on these potentially confounding variables may be found in Supplementary Table 4.

PTSD severity

Examining PTSD symptom severity in subjects assessed with CAPS-4 ($N = 1{,}764$ from 17 sites), we found an association, which did not survive correction for multiple comparisons, between higher CAPS-4 score and lower FA in the tapetum and SFO (tapetum: $\beta = -9.0 \times 10^{-5}$, $p = 0.024$; SFO: $\beta = -6.6 \times 10^{-5}$, $p = 0.028$; Fig. 4). PTSD symptom severity in the PTSD group (measured by the CAPS-4, $N = 956$ from 17 sites) was not associated with FA (Fig. 4). Subgroup analyses yielded associations that did not survive correction for multiple comparisons between CAPS-4 score and tapetum FA in the military cohorts and between CAPS-4 score and SFO FA in the

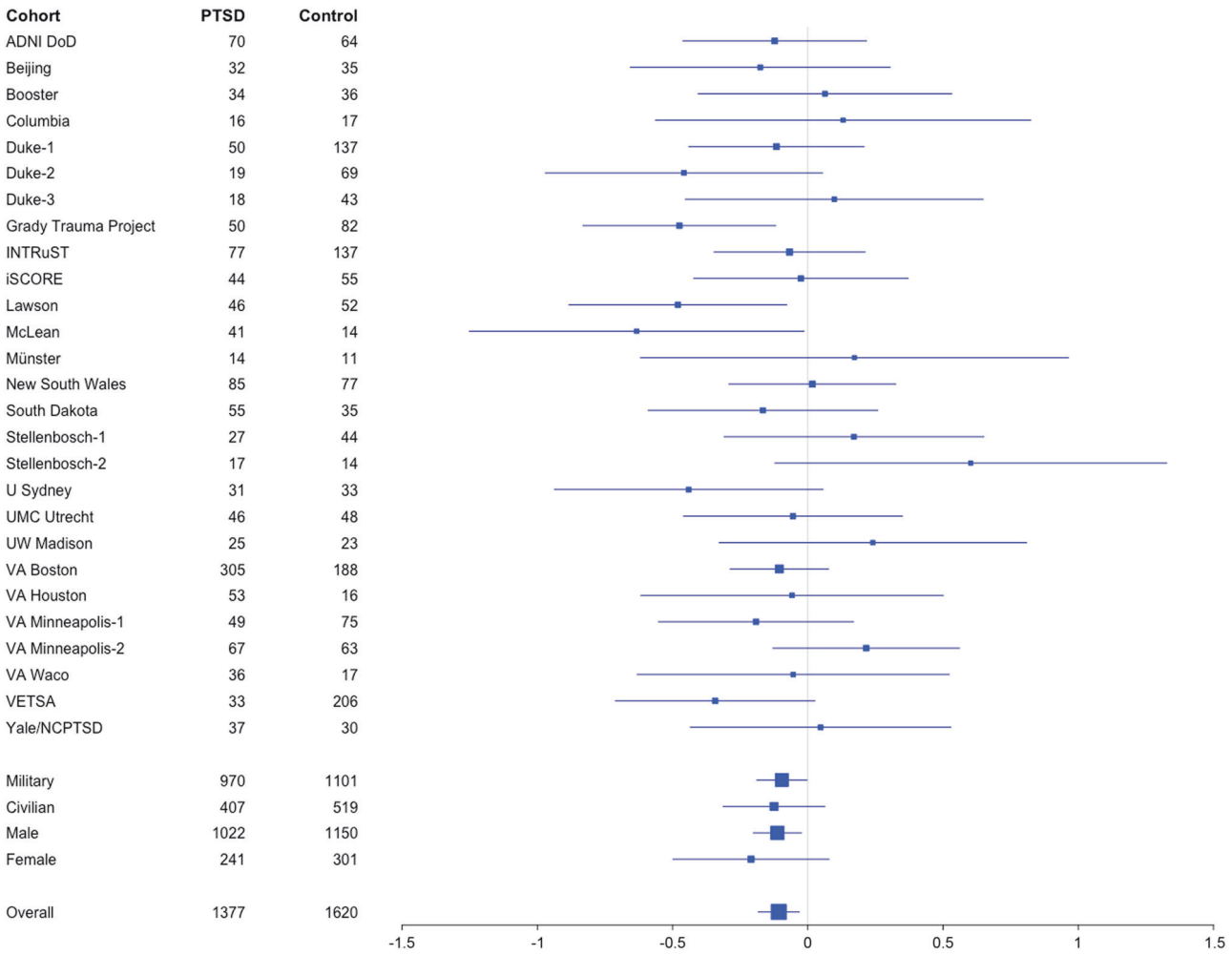

Fig. 2 Site effects for tapetum result. Forest plot shows the effect sizes (Cohen's *d*) for each of the 25 cohorts, scaled by sample size, with bars for 95% CI. The effect size and 95% CI of the meta-analysis is shown at the bottom of the figure, along with effect sizes and 95% CI for the subgroup analyses of the military cohorts, civilian cohorts, male cohorts, and female cohorts.

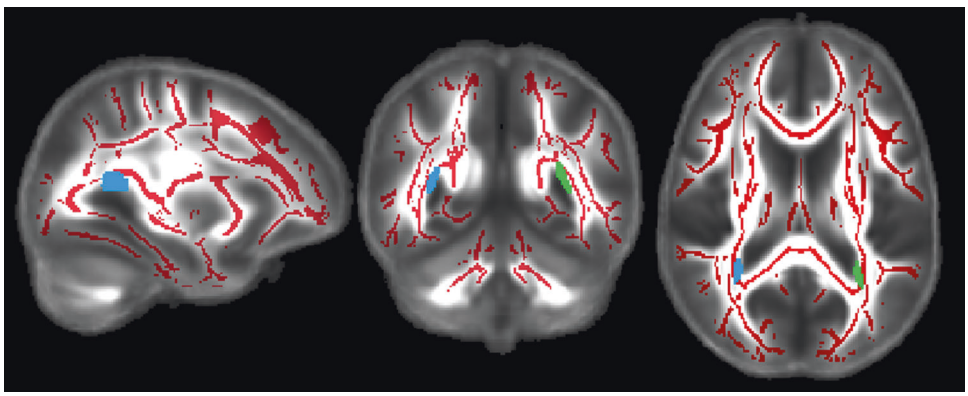

Fig. 3 Tapetum displayed on the ENIGMA template FA. The skeleton is shown in red, the left tapetum (green) and right tapetum (blue) ROIs are displayed. Left in image is right in brain.

male subgroup. Results were similar when potentially confounding variables were included, with no significant associations, although there was an effect in tapetum that did not withstand correction for multiple comparisons when psychotropic medication use was included. Detailed analyses of PTSD severity and covariates within subgroups are in Supplementary Note 6 and Supplementary Figs. 13 and 14.

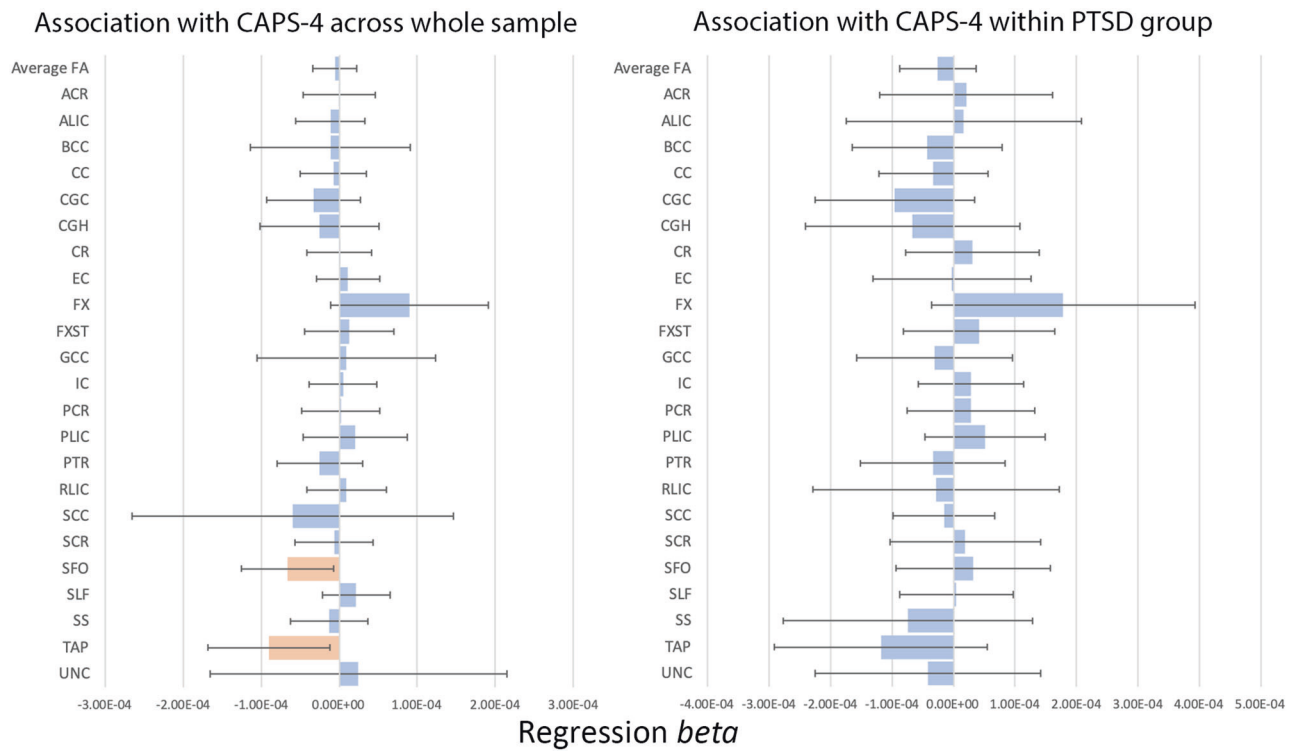

Fig. 4 Linear association with CAPS-4 across the whole sample (left) and within the PTSD cases only (right). Meta-regression unstandardized β statistics are shown across all bilateral and midline ROIs and average FA, with bars indicating the 95% confidence interval. The ROI abbreviations are explained in Supplementary Note 1. Light orange bars indicate results that did not withstand correction for multiple comparisons ($0.05 > p > 0.0057$). Error bars are 95% CI.

Discussion

We present dMRI results from a multicohort study conducted by the PGC-ENIGMA PTSD consortium. In a meta-analysis of 3047 participants from 28 sites, we found lower FA and higher RD in the tapetum among adults with PTSD (neuroanatomical figure—Fig. 3), which remained after accounting for several potentially confounding factors. The tapetum is a major tract within the corpus callosum that serves as a conduit between right and left hippocampus. Prior studies of white matter disruption in PTSD have found alterations in other hippocampal tracts, but were generally hindered by small sample sizes leading to inconsistent findings across studies. Our results add to the existing literature in identifying structural disruptions that compromise putative hippocampal functions, which are known to play a central role in PTSD symptomatology [53, 54].

The tapetum is a small segment of the corpus callosum that connects the temporal lobes, in particular the left and right hippocampus [55]. It is one of the last corpus callosum segments to develop and experiences rapid growth around age 14, which may make it vulnerable to the effects of trauma for a longer period of time [56]. Structural and functional alterations in the hippocampus are frequently reported in PTSD, with smaller volumes [37], decreased activation, and disrupted functional connectivity with the medial and lateral prefrontal cortices [57, 58]. Disrupted functional connectivity between the left and right hippocampus has also been previously reported in PTSD [59]. Here we report microstructural evidence that *structural* connectivity between the left and right hippocampus may also be disrupted in PTSD.

We did not find PTSD-related effects in the cingulum, uncinate, fornix, and corpus callosum, as some prior studies of smaller, more homogeneous populations have shown [9–14, 16, 18–21, 23–29, 31, 32, 36, 60]. This may reflect a limitation in the meta-analysis of heterogeneous study samples, but this is an unlikely explanation given our low estimates of heterogeneity (I^2) in these tracts (<10%). However, these effects were not entirely absent in our subgroup analyses, suggesting that they may be more specific to population, trauma type, etc. While many studies have reported that PTSD is associated with alterations in the cingulum bundle [9–13, 16, 18, 21, 23–29, 31, 32, 36], which has a hippocampal component, the tapetum has not yet emerged for several possible reasons. Many prior studies took an ROI approach, which limited analyses to predetermined regions that frequently omitted the tapetum, a small region often grouped with other tracts such as the splenium or posterior thalamic radiation. Critically, in 2013, an error was uncovered in the JHU atlas used as part of the

TBSS pipeline, with the uncinate incorrectly identified as the inferior fronto-occipital fasciculus, and the tapetum incorrectly identified as the uncinate [61]. Thus, the tapetum was simply not examined in prior studies, with one very recent exception showing that tapetum abnormalities are associated with lower major depressive disorder remission [62]. There are further data suggesting that the absence of tapetum findings may partly relate to methodological limitations of prior studies; in a recent dMRI meta-analysis of attention deficit hyperactivity disorder (ADHD), lower tapetum FA was found to characterize ADHD, despite the fact that this specific region of the CC has not frequently emerged in ADHD studies [63]. Finally, the precise role of the tapetum in connecting the left and right hippocampus was only recently elucidated by mapping the subcortical connectome with exquisitely high-resolution mapping capable of discerning the intermingling of tapetum and other corpus callosum fibers [55].

Childhood trauma is the greatest single risk factor for future vulnerability to PTSD [64]; numerous studies show significant alterations in brain structure and function in individuals who experience significant early life stress [51, 65]. Some of these alterations likely contribute to a higher risk for psychopathology, but childhood trauma exposure alone did not explain the association between tapetum white matter disruption and PTSD that we report here. While it is likely that childhood trauma exposure plays some role in tapetum organization, these analyses indicate that our PTSD results are not solely due to confounding effects between PTSD and exposure to childhood trauma. Depression is frequently comorbid with PTSD [66] and is associated with disrupted white matter organization, although the affected tracts are broadly distributed [67]. Accounting for depression in group comparisons did not significantly alter our results, suggesting that tapetum white matter disruption is not confounded by depression. The UK Biobank sample revealed FA reductions associated with depression in commissural and association fibers, thalamic radiations, left superior longitudinal fasciculus (SLF), superior and forceps major [68]. The ENIGMA MDD Working Group reports alterations in the corpus callosum and hippocampal cingulum but not in the tapetum (labeled in that paper as the uncinate, $p = 0.172$) [69]. Particularly in military populations, which formed the majority of our sample, PTSD is often comorbid with traumatic brain injury (TBI) [70]. White matter is particularly vulnerable to TBI, which produces stretching and shearing of axons and altered neurometabolism [71]. Accounting for TBI also had some effect on our results but the left tapetum remained significant in post hoc analyses, indicating that TBI is not specifically associated with white matter damage in the tapetum despite numerous reports mild TBI is associated with white matter damage generally. Preliminary results from the ENIGMA Military Brain Injury group have not shown significant differences in the tapetum [72]. Psychotropic medications are another potential confound, given their neurotrophic and neuroprotective effects [73]. The result in the tapetum persisted after covarying for psychotropic medication, indicating that our findings are unlikely to be explained by medication. Lastly, PTSD can be comorbid with alcohol use disorders, which have a poorer clinical prognosis [74, 75]. Alcohol use disorders have been associated with significant changes in white matter organization [76, 77] but did not influence the present results. Although none of these potentially confounding variables fully explained our reported results, it is possible that altered tapetum microstructure could represent a more general response to trauma or stress. As shown in Fig. 1, altered tapetum FA is present in trauma-exposed controls compared to unexposed controls, although the sample size for this comparison was around 10% of the total sample size. The post hoc analysis of the tapetum was still significant comparing PTSD to trauma-exposed controls, suggesting a dose response, with some alterations related to trauma that does not lead to psychopathology but more in PTSD. Trauma is one form of severe stress, but we do not know how more minor stress may affect tapetum organization. Smaller hippocampal volume has been reported across disorders, suggesting that it may be a nonspecific marker of disease [78].

We found an association that did not withstand correction for multiple comparisons of PTSD with FA in the tapetum in male and military subgroups separately. Although results were nonsignificant in female or civilian subgroups, the effect size was slightly larger and in the same direction. The female and civilian subgroups were smaller and therefore the analyses had lower power than in male and military subgroups. Most prior dMRI studies in civilians report lower FA in PTSD [9, 10, 12–14, 16, 17, 21–25, 30–32, 60]. Studies of military cohorts have been mixed, reporting higher FA [26–29, 36], lower FA [8, 15, 18–20], and null results [33–35]. This discrepancy may be due to differences in age, chronicity, and type of trauma exposure, although military personnel may also experience civilian trauma. Combat-related PTSD is often comorbid with TBI, which is also associated with white matter disruption, constituting a potentially confounding factor for studies [72].

In the absence of longitudinal data, our analysis cannot make causal inferences nor make conclusions about the direction of the relationship between PTSD and tapetum white matter organization. Disrupted white matter of the tapetum may represent a vulnerability that predates the onset of PTSD, or a pathological response to trauma. In twins discordant for exposure to combat stress, the unexposed twins of combat veterans with PTSD have smaller

hippocampal volume than the unexposed twins of combat veterans without PTSD [79]. Individuals with two risk alleles of the *FKBP5* gene have demonstrated lower cingulum FA above and beyond the association of cingulum FA with PTSD [11, 60]. These studies suggest that heritable differences in brain structure may influence risk of developing PTSD. Evidence that alterations are caused by PTSD was observed in Israeli Defense Force recruits with reduced structural connectivity between the hippocampus and ventromedial prefrontal cortex, but only after exposure to military stress [80]. With the varying developmental trajectories of brain structure, function, and connectivity, along with the varying distribution of stress hormone receptors in the brain, the complex question of vulnerability vs. consequence will require prospective longitudinal neuroimaging studies.

Some evidence indicates that high FA is a marker of resilience to the effects of stress [81, 82]. A putative marker of resilience is the ability to attenuate stress-induced increases in corticotropin-releasing hormone and glucocorticoids through an elaborate negative feedback system, and to modulate the expression of brain-derived neurotrophic factor (BDNF) [83, 84]. BDNF has myriad functions including supporting neuronal differentiation, maturation, and survival [85, 86]. In particular, hippocampal BDNF is implicated in the development of neural circuits that promote stress adaptations [83]. These stress adaptation circuits involve white matter in the fornix and other fronto-limbic connections [87].

Limitations

Our study has several limitations. One limitation of TBSS studies is the inability to fully attribute results to particular fiber bundles, especially given that the tapetum is a relatively small structure. Future studies may benefit by using tractography to more reliably identify the affected bundles, but this is difficult across sites. Second, not all participants classified as PTSD received clinician-administered interview (such as the CAPS) to confirm diagnoses. Third, we could not reliably measure chronicity across different cohorts. Other variables that we could not examine given the heterogeneity across sites include treatment effects, symptom clusters, and trauma types, as opposed to current PTSD diagnosis. Given that effects have not been previously reported in the tapetum, it would be helpful to know if altered tapetum organization is linked to particular symptoms or trauma type and we encourage researchers to examine this possibility in their datasets. Although we analyzed data from over 3000 participants, we may have been underpowered to examine group-by-sex interactions, as 55% of our sample came from cohorts including only males or only females or samples that were >90% male. Diffusion metrics are not scanner invariant, and can vary even in scanners of the same model. For this reason, we were limited to a meta-analytic approach which may have lower power than mega-analysis. However, studies including both meta- and mega-analyses of brain volume in other ENIGMA groups have found minimal differences [88, 89]. Lastly, our cross-sectional design did not allow us to investigate to what degree WM differences predate the onset of PTSD.

Future studies should further investigate the tapetum using high spatial and angular resolution tractography to replicate our findings. Future and existing studies with more in-depth phenotyping than was possible here could examine how alterations in the tapetum vary with trauma type, chronicity, treatment, and whether they are associated with specific symptom clusters. The current study excluded pediatric cases, so additional research on white matter disruption in pediatric trauma and PTSD is warranted. Lastly, while we considered comorbidities as potential confounding variables, we did not examine their association with dMRI metrics. Future collaborations with the ENIGMA Brain Injury, MDD, and Addiction working groups will provide opportunities to separate general neuroimaging biomarkers of psychopathology and disorder-specific effects.

Conclusions

Here we presented results from the PGC-ENIGMA PTSD working group, reporting poorer white matter organization in the tapetum in individuals currently suffering from PTSD. We present the largest dMRI study in PTSD to date and the first to use harmonized image processing across sites, increasing our power to detect subtle effects. While future studies need to confirm the involvement of the tapetum specifically, our results add to the existing literature implicating the hippocampus and associated white matter connections as neural markers of structural disruptions in PTSD.

Code availability

All analyses were conducted using generalizable scripts available on the ENIGMA-GitHub https://github.com/ENIGMA-git/ENIGMA/tree/master/WorkingGroups/EffectSize_and_GLM. Individual ROI level data were shared with the central site and processed using a set of R scripts with regressions customized for the current PGC-ENIGMA-PTSD dMRI analysis, publicly available on a set of Google Spreadsheet configuration files.

Acknowledgements K99NS096116 to ELD; CIHR, CIMVHR; Dana Foundation (to JBN); the University of Wisconsin Institute for Clinical and Translational Research (to Dr Emma Seppala); a National Science

Foundation Graduate Research Fellowship (to DWG); R01MH043454 and T32MH018931 (to RJD); and a core grant to the Waisman Center from the National Institute of Child Health and Human Development (P30HD003352); Defense and Veterans Brain Injury Centers, the U.S. Army Medical Research and Materiel Command (USAMRMC; W81XWH-13-2-0025) and the Chronic Effects of Neurotrauma Consortium (CENC; PT108802-SC104835); Department of Defense award number W81XWH-12-2-0012; ENIGMA was also supported in part by NIH U54EB020403 from the Big Data to Knowledge (BD2K) program, R56AG058854, R01MH116147, R01MH111671, and P41EB015922; Department of Veterans Affairs via support for the National Center for PTSD, NIAAA via its support for (P50) Center for the Translational Neuroscience if Alcohol, and NCATS via its support of (CTSA) Yale Center for Clinical Investigation; DoD W81XWH-10-1-0925; Center for Brain and Behavior Research Pilot Grant; South Dakota Governor's Research Center Grant; F32MH109274; Funding from the Bill & Melinda Gates Foundation; Funding from the SAMRC Unit on Risk & Resilience in Mental Disorders; German Research Foundation grant to JKD (numbers DA 1222/4-1 and WA 1539/8-2).; German Research Society (Deutsche Forschungsgemeinschaft, DFG; SFB/TRR 58: C06, C07); I01-CX000715 & I01-CX001542; K01MH118428; K23MH090366; K2CX001772, Clinical Science Research and Development Service, VA Office of Research and Development; MH098212; MH071537; M01RR00039; UL1TR000454; HD071982; HD085850; MH101380; NARSAD 27040; NARSAD Young Investigator, K01MH109836, Young Investigator Grant, Korean Scientists and Engineers Association; NHMRC Program Grant # 1073041; R01AG050595, R01AG022381; R01AG058822; R01EB015611; R01MH105355; R01MH105355, R01DA035484; R01MH111671, R01MH117601, R01AG059874, MJFF 14848; R01MH111671; VISN6 MIRECC; R21MH112956, Anonymous Women's Health Fund, Kasparian Fund, Trauma Scholars Fund, Barlow Family Fund; South African Medical Research Council for the "Shared Roots" Flagship Project, Grant no. MRC-RFA-IFSP-01-2013/SHARED ROOTS" through funding received from the South African National Treasury under its Economic Competitiveness and Support Package. The work by LLvdH reported herein was made possible through funding by the South African Medical Research Council through its Division of Research Capacity Development under the SAMRC CLINICIAN RESEARCHER (M.D PHD) SCHOLARSHIP PROGRAMME from funding received from the South African National Treasury.; South African Research Chairs Initiative in Posttraumatic Stress Disorder through the Department of Science and Technology and the National Research Foundation.; the National Natural Science Foundation of China (No. 31271099, 31471004), the Key Research Program of the Chinese Academy of Sciences (No. ZDRW-XH-2019-4); The study was supported by ZonMw, the Netherlands organization for Health Research and Development (40-00812-98-10041), and by a grant from the Academic Medical Center Research Council (110614) both awarded to MO.; Translational Research Center for TBI and Stress Disorders (TRACTS), a VA Rehabilitation Research and Development (RR&D) Traumatic Brain Injury Center of Excellence (B9254-C) at VA Boston Healthcare System.; VA CSR&D 1IK2CX001680; VISN17 Center of Excellence Pilot funding; VA CSR&D 822-MR-18176 and Senior Career Scientist Award; VA National Center for PTSD; VA RR&D 1IK2RX000709; VA RR&D 1K1RX002325; 1K2RX002922; VA RR&D I01RX000622; CDMRP W81XWH-08–2–0038; W81XWH08-2-0159 (PI: MBS) from the US Department of Defense. The views reflected here are strictly those of the authors and do not constitute endorsement by any of the funding sources listed here.

Author contributions ELD, SGD, NF, LES, ML, EKC, NJ, and RAM wrote the initial draft, all authors reviewed and edited the manuscript. All authors contributed data to the analyses.

Compliance with ethical standards

Conflict of interest CGA has served as a consultant, speaker and/or on advisory boards for FSV7, Lundbeck, Genentech and Janssen, and editor of Chronic Stress for Sage Publications, Inc.; he has filed a patent for using mTOR inhibitors to augment the effects of antidepressants (filed on August 20, 2018). RJD is the founder and president of, and serves on the board of directors for, the nonprofit organization Healthy Minds Innovations, Inc. JK is a consultant for AbbVie, Inc., Amgen, Astellas Pharma Global Development, Inc., AstraZeneca Pharmaceuticals, Biomedisyn Corporation, Bristol-Myers Squibb, Eli Lilly and Company, Euthymics Bioscience, Inc., Neurovance, Inc., FORUM Pharmaceuticals, Janssen Research & Development, Lundbeck Research USA, Novartis Pharma AG, Otsuka America Pharmaceutical, Inc., Sage Therapeutics, Inc., Sunovion Pharmaceuticals, Inc., and Takeda Industries; is on the Scientific Advisory Board for Lohocla Research Corporation, Mnemosyne Pharmaceuticals, Inc., Naurex, Inc., and Pfizer; is a stockholder in Biohaven Pharmaceuticals; holds stock options in Mnemosyne Pharmaceuticals, Inc.; holds patents for Dopamine and Noradrenergic Reuptake Inhibitors in Treatment of Schizophrenia, US Patent No. 5,447,948 (issued September 5, 1995), and Glutamate Modulating Agents in the Treatment of Mental Disorders, U.S. Patent No. 8,778,979 (issued July 15, 2014); and filed a patent for Intranasal Administration of Ketamine to Treat Depression. U.S. Application No. 14/197,767 (filed on March 5, 2014); US application or Patent Cooperation Treaty international application No. 14/306,382 (filed on June 17, 2014). Filed a patent for using mTOR inhibitors to augment the effects of antidepressants (filed on August 20, 2018). NJ received partial research support from Biogen, Inc. (Boston, USA) for research unrelated to the content of this paper. PMT received partial research support from Biogen, Inc. (Boston, USA) for research unrelated to the topic of this paper.

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