Supplementary Materials for Meta-Analysis of 89 Structural MRI Studies in Posttraumatic Stress Disorder and Comparison With Major Depressive Disorder

Methods

MEDLINE (Pubmed) search term

The following MEDLINE search term was used and was completed on July 4th 2016. MEDLINE was used because it has excellent coverage of MRI studies of clinical populations, particularly from 1990s forward.

(("Stress Disorders, Traumatic"[MeSH] OR “PTSD” OR “post traumatic stress” OR "posttraumatic stress") AND MRI)

The search terms in the parenthesis were to catch all studies either tagged by the commonly used MeSH term "Stress Disorders, Traumatic" or the free text terms mentioned. Using the text MRI in pubmed then automatically maps this to the more broader search term:
"magnetic resonance imaging"[MeSH Terms] OR ("magnetic"[All Fields] AND "resonance"[All Fields] AND "imaging"[All Fields]) OR "magnetic resonance imaging"[All Fields] OR "mri"[All Fields]

By hand searching through previous reviews and meta-analyses we identified a number of studies however they were all duplicated from the MEDLINE search except for 5 studies (see Figure S1). Further details of how studies were reviewed can be found at http://www.ptsdmri.uk which includes a list of the 800 studies in the literature search, indicating which studies were included/excluded and the reasons for exclusion.

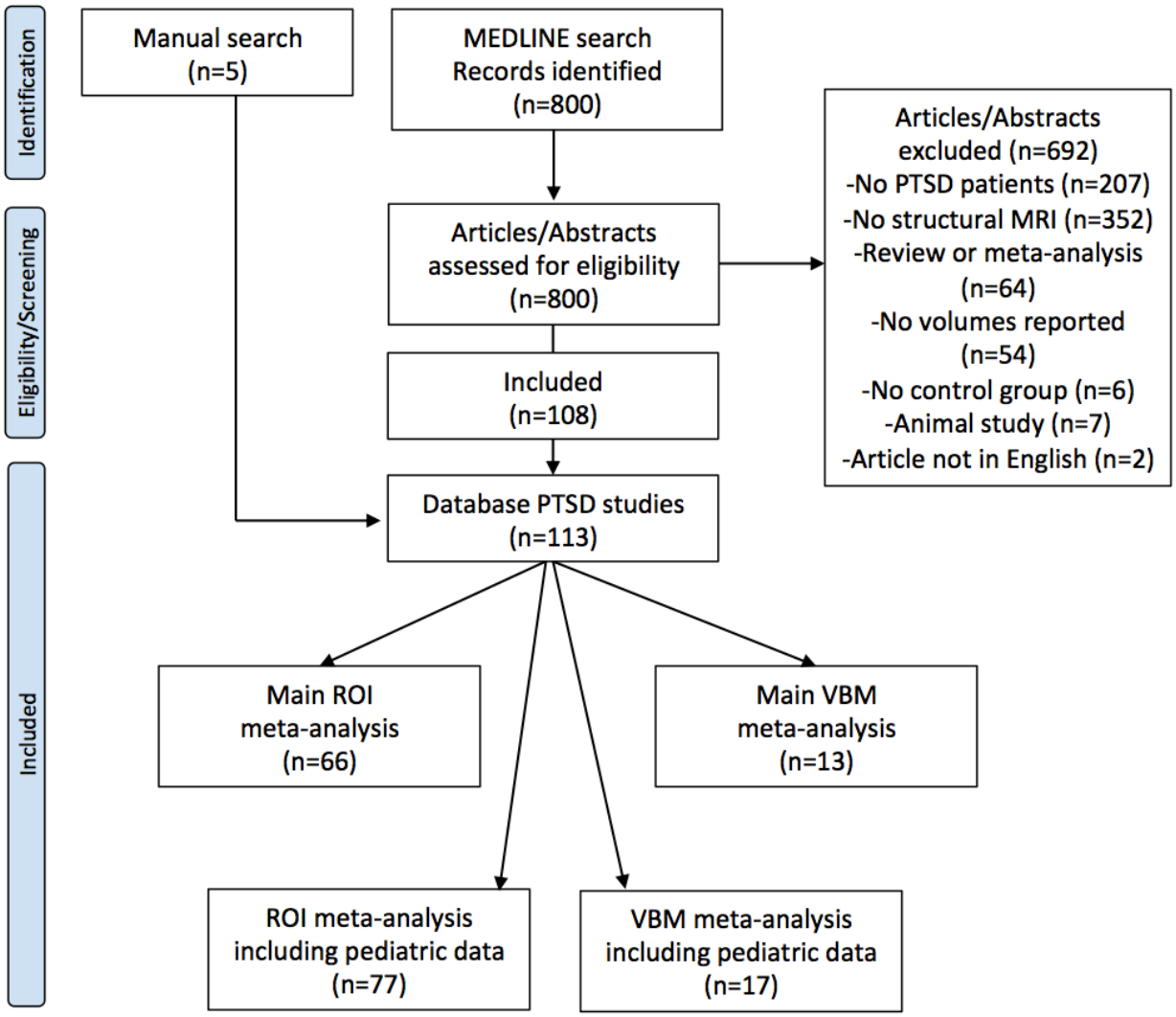


Figure S1: Adapted PRISMA flowchart showing study inclusion. The number of studies included in the meta-analysis including pediatric data is 89 studies (77 region-of-interest studies plus 17 VBM studies, minus 5 overlapping studies)

Database of imaging studies in Post-Traumatic Stress Disorder

Studies were included in the database if patients were diagnosed with PTSD according to standardized diagnostic criteria, and for region-of-interest studies volumetric data was presented in terms of group means and standard deviations, and for VBM studies spatial coordinate data was presented. Control groups differed between studies, the largest proportion used non-traumatised-controls, other studies used a Traumatised-controls and a smaller proportion included two control groups, non-traumatised-

controls and Traumatised-controls. One hundred and thirteen studies satisfied all the criteria and were incorporated in the database (80 region-of-interest studies, 23 VBM studies, and 10 studies presenting both region-of-interest and VBM data).

Data recorded in the database

The following data from each study were included in the database: number of PTSD patients and number of controls, diagnostic classification system used, mean age of patients and controls, number of males and females in the patient and control groups, mean age of illness onset, time since trauma, duration of illness, mean score from Clinician-Administered PTSD Scale (CAPS),[1] and the type of control group used. For medication we recorded the number of patients described as drug free (not necessarily medication naive), using antidepressants, mood stabilizers, or antipsychotics. From the MRI acquisition we recorded slice thickness and magnetic field strength.

Post-traumatic Stress Disorder Region-of-interest Meta-analysis

In order to ensure that the selection of brain structures for the meta-analysis was not biased, we recorded all regions that had been investigated in the 90 studies reporting region-of-interest data included in the database. As observed in previous meta-analyses, exact anatomic definitions of brain structures varied across studies. Where data was unclear or we suspected sample overlap between studies we contacted the authors. Due to the limited information provided by the case-control studies we did not attempt to assess bias in the sample obtainment, although we did analyse publication bias (see below). To ensure that the meta-analysis was sufficiently powered, we included brain regions for which the volume mean and standard deviation in both patient and control groups were reported by three or more studies

Region of interest Sensitivity Analysis

To test how robust the results were to variations in the meta-analysis method, 4 sensitivity analyses were conducted for the region of interest meta-analysis.

(1) For a given region, some authors separately reported left and right measures while others included only the combined total measure. For studies that only reported left and right measurements, we used a previously described method[2] to calculate the mean and standard deviation for the total volume. The method requires an estimate of the correlation coefficient between the left and right volumes. This coefficient was set to 0.8 but was varied in the sensitivity analysis as 0, 0.5 and 1.0.

(2) While most individual studies reported absolute volumes of brain structures a small number of studies reported volumes divided by intracranial volume. In the main analysis we combined studies reporting absolute volumes, and volumes divided by intracranial volume. In the second sensitivity analysis we excluded volumes divided by intracranial volume

(3) While most individual studies reported volumes of brain structures a small number of cortical regions were reported in terms of thickness. For these regions we combined studies reporting thickness and volume, but excluded thickness measures in the third sensitivity analysis.

(4) In the main analysis we excluded studies with paediatric patients to reduce heterogeneity, in the fourth sensitivity analysis we included 11 paediatric studies.

Combining study estimates

The meta-analysis for each brain structure was performed by using meta-analytical equations entered into Excel (see www.ptsdmri.uk). This technique has the advantage of efficient data entry, being publicly available while using identical equations to the METAN command in STATA,[3] which is commonly used in meta-analyses publications. In terms of validation, the method been used in parallel with STATA in three previous meta-analyses[4, 5, 6] and produced the same results.

Combining patient subgroups

A minority of studies reported measures from subgroups of patients and their own matched control group. In this case, we considered subgroups as equivalent to separate studies. Similarly, when studies reported men and women in the patient group separately, we incorporated the results in the meta-analysis as two different studies. This method has been used in a previous meta-analysis.[7] Because the meta-analyses examined a large number of regions and included sub-meta-analyses it is susceptible to type I errors. Therefore, results that survive Bonferroni correction for multiple comparisons are indicated.

Voxel Based Morphometry Meta-analysis using Seed-based d Mapping (SDM)

The following inclusion criteria were applied to the database of 113 studies: 1) gray matter VBM study comparing adult patients with PTSD to either non-traumatised-controls or traumatised-controls; 2) results presented in Talairach or MNI coordinates; 3) studies were only included if a whole brain analysis was performed rather than a small volume correction to ensure no bias in the regions reported. Thirteen

studies met inclusion criteria and are listed in Table S1. We emailed all study authors who used SPM (Statistical Parametric Mapping) to process their data for a 'T-map' image comparing PTSD gray matter volume to the control group. 'T-maps' are three dimensional maps comprising statistical data of volume differences in thousands of voxels in the brain and provide far more detailed information than significant coordinates reported in studies. However, SDM allows both T-maps and coordinates to be combined in a single meta-analysis and the methodology reported in detail by Radua et al.[8] We received 6 T-maps from 6 independent studies and these were included in the meta-analyses. In addition to the main meta-analysis comparing PTSD to all controls, three additional VBM analyses were conducted: 1) comparing the PTSD group with non-traumatised-controls only 2) comparing the PTSD group with traumatised-controls only, 3) comparing PTSD group with all controls and widening the criteria to include paediatric studies. T-maps and coordinates signifying gray matter volume changes from where we were unable to obtain T-maps were extracted from relevant studies and analysed using Seed-based d Mapping[8] (SDM version 5.14, http://www.sdmproject.com). For studies where coordinate data was used, these were convolved with a Gaussian kernel (FWHM=20mm) in order to optimally compensate the sensitivity and specificity of the analysis. As is standard in SDM analyses, the number of randomizations were set to 100 and a threshold was set at $p<0.005$ as well as a cluster-level threshold of 10 voxels in order to increase sensitivity and correctly control false-positive rate.[8] A jackknife sensitivity analysis was performed in order to assess the robustness of the results which was achieved by excluding one study in each of the analyses.

Results

Region of interest sensitivity analysis:

4) Including paediatric data

Eleven pediatric studies were included in the region of interest meta-analysis. In the analysis comparing PTSD patients to all controls there were 11 new significant results: smaller frontal lobe, gray matter, cerebral volume, right and total temporal lobe, right amygdala, cerebellum, vermis, and the anterior midbody, posterior midbody and isthmus of corpus callosum (Table S5, Figure S5a-S5b). The reduction in the volume of the left anterior cingulate was no longer significant. In the PTSD vs non-traumatised-controls comparison, 11 new significant results emerged with the pediatric data: PTSD patients had significant smaller intracranial volume, right and total temporal lobe, total and left amygdala, cerebellum, vermis and anterior midbody, posterior midbody, isthmus and total cross sectional area of the corpus callosum (Table S6, Figure S6). There was no change in significance for the PTSD vs traumatised-controls or traumatised-controls vs non-traumatised-controls comparison.

Table S1. Database of PTSD MRI studies

Study	No. of PTSD Patients	No. Non-Traumatised Controls (NTC)	No. Traumatised Controls (TC)	Diagnostic Criteria	Mean Patient Age, y
Bremner et al (1995)	**26**	**22**	**ns**	**DSM-III-R**	**46**
Gurvits et al (1996)	**7**	**8**	**7**	**DSM-III-R**	**44.4**
Bremner et al (1997)	**17**	**17**	**ns**	**DSM-III-R**	**40.1**
De Bellis et al (1999)	44	61	ns	DSM-III-R	12.2
Bonne et al (2001)	**10**	**ns**	**27**	**DSM-IV**	**33.7**
Carrion et al (2001)	24	24	ns	DSM-IV	11
De Bellis et al (2001)	9	9	ns	DSM-IV	10.6
Schuff et al (2001)	**18**	**19**	**ns**	**DSM-IV**	**51.2**
De Bellis et al (2002)	28	66	ns	DSM-IV	11.47
De Bellis et al (2002)	43	61	ns	DSM-IV	12.2
Fennema-Notestine et al (2002)	**11**	**17**	**11**	**DSM-IV**	**33.35**
Gilbertson et al (2002)	**12**	**23**	**23**	**DSM-IV**	**ns**
Villarreal et al (2002)	**12**	**10**	**ns**	**DSM-IV**	**43**
Bremner et al (2003)	**10**	**11**	**12**	**DSM-IV**	**35**
De Bellis et al (2003)	61	122	ns	DSM-IV	11.74
Hedges et al (2003)	**4**	**4**	**ns**	**DSM-IV**	**54.5**
Rauch et al (2003)	**9**	**ns**	**9**	**DSM-IV**	**52**
Yamasue et al (2003)	*9*	*ns*	*16*	*CAPS*	*44.6*
Lindauer et al (2004)	14	ns	14	DSM-IV	35.4
May et al (2004)	**20**	**24**	**23**	**DSM-IV**	**52.3**
Pederson et al (2004)	**17**	**17**	**17**	**DSM-IV**	**24.8**
Shin et al (2004)	**8**	**ns**	**8**	**DSM-IV**	**50.5**
Villarreal et al (2004)	**12**	**10**	**ns**	**DSM-IV**	**43**
Wignall et al (2004)	**15**	**11**	**ns**	**DSM-IV**	**43**
Winter et al (2004)	**15**	**15**	**15**	**DSM-IV**	**42**
Thomas et al (2004)	61	121	ns	DSM-IV	11.74
Corbo et al (2005)	*14*	*14*	*ns*	*DSM-IV*	*33.36*
Golier et al (2005)	**14**	**20**	**13**	**DSM-IV**	**70.5**
Lindauer et al (2005)	**18**	**ns**	**14**	**DSM-IV**	**39.6**

Table S1. Database of all PTSD MRI studies (1/4, continues over 4 pages) ns = not stated/ not recruited. Rows in BOLD indicate studies included in the PTSD region-of-interest meta-analysis, rows in italics indicate studies included in the VBM meta-analysis, rows in both BOLD and italics indicate studies included in both the region-of-interest and VBM meta-analyses, rows in normal typeface were not included in either meta-analysis.

Table S1. Database of PTSD MRI studies (continued)					
Study	No. of PTSD Patients	No. Non-Traumatised Controls (NTC)	No. Traumatised Controls (TC)	Diagnostic Criteria	Mean Patient Age, y
Chen et al (2006)	*12*	*ns*	*12*	*DSM-IV*	*34.56*
De Bellis et al (2006)	**58**	**98**	**ns**	**DSM-IV**	**12**
Emdad et al (2006)	**23**	**17**	**ns**	**DSM-IV**	**38.7**
Freeman et al (2006)	**10**	**6**	**10**	**DSM-IV**	**79.6**
Jatzko et al (2006)	**15**	**15**	**ns**	**DSM-IV**	**48.2**
Kitayama et al (2006)	**8**	**13**	**ns**	**DSM-IV**	**43**
Lindauer et al (2006)	12	ns	12	DSM-IV	35.1
Richert et al (2006)	23	24	ns	DSM-IV	11
Tupler et al (2006)	61	122	ns	DSM-IV	11.75
Woodward et al (2006)	**51**	**ns**	**48**	**DSM-IV**	**45.25**
Levitt et al (2006)	**18**	**23**	**22**	**DSM-IV**	**52.5**
Li et al (2006)	12	ns	12	DSM-IV	34.56
Kitayama et al (2007)	**9**	**9**	**ns**	**DSM-IV**	**37.8**
Pavic et al (2007)	**15**	**15**	**ns**	**DSM-IV**	**32**
Woodward et al (2007)	**51**	**ns**	**48**	**DSM-IV**	**45.25**
Yehuda et al (2007)	**17**	**ns**	**16**	**DSM-IV**	**60.6**
Hakamata et al (2007)	14	70	100	DSM-IV	45.6
Bonne et al (2008)	**22**	**22**	**ns**	**DSM-IV**	**36**
Bossini et al (2008)	**34**	**34**	**ns**	**DSM-IV**	**38**
Geuze et al (2008)	**25**	**ns**	**25**	**DSM-IV**	**35.08**
Hara et al (2008)	**15**	**15**	**15**	**DSM-IV**	**44.8**
Kasai et al (2008)	*18*	*23*	*23*	*DSM-IV*	*52.8*

Table S1 (Continued). Database of PTSD MRI studies (2/4, continues over 4 pages) ns = not stated ns = not stated/ not recruited. Rows in BOLD indicate studies included in the PTSD region-of-interest meta-analysis, rows in italics indicate studies included in the VBM meta-analysis, rows in both BOLD and italics indicate studies included in both the region-of-interest and VBM meta-analyses, rows in normal typeface were not included in either meta-analysis.

Table S1. Database of PTSD MRI studies (continued)					
Study	No. of PTSD Patients	No. Non-Traumatised Controls (NTC)	No. Traumatised Controls (TC)	Diagnostic Criteria	Mean Patient Age, y
Weniger et al (2008)	**10**	**25**	**ns**	**DSM-IV**	**32**
Schuff et al (2008)	**55**	**49**	**ns**	**DSM-IV**	**48.9**
Bryant et al (2008)	13	13	13	CAPS	ns
Carrion et al (2009)	*24*	*24*	*ns*	*DSM-IV*	*11*
Felmingham et al (2009)	21	ns	17	CIDI	ns
Looi et al (2009)	**19**	**ns**	**17**	**DSM-IV**	**ns**
Rogers et al (2009)	**9**	**ns**	**16**	**CAPS**	**44.56**
Woodward et al (2009)	**50**	**ns**	**47**	**DSM-IV**	**ns**
Chen et al (2009)	12	ns	12	DSM-IV	34.56
Carrion et al (2010)	30	15	ns	CAPS	13.2
Landre et al (2010)	**17**	**17**	**ns**	**DSM-IV**	**24.9**
Nardo et al (2010)	*21*	*ns*	*22*	*DSM-IV*	*41.7*
Wang et al (2010)	***17***	**ns**	**19**	***DSM-IV***	***41***
Thomaes et al (2010)	*33*	30	ns	*DSM-IV*	*35.3*
Sui et al (2010)	*11*	12	8	*DSM-IV*	*25.55*
Sui et al (2010)	*11*	12	ns	*DSM-IV*	*24.46*
Hunter et al (2011)	*7*	11	ns	*DSM-IV*	*57.43*
Baldacara et al (2011)	**42**	**ns**	**42**	**DSM-IV**	**34.91**
Eckart et al (2011)	***20***	**11**	**16**	***DSM-IV***	***36.1***
Eckart et al (2011)	*20*	13	19	*DSM-IV*	*36.2*
Lyoo et al (2011)	*30*	36	ns	*DSM-IV*	*27*
Savitz et al (2011)	**22**	**75**	**ns**	**DSM-IV**	**34.8**
Schulz-Heik et al (2011)	51	ns	48	DSM-IV	49.3
Zhang et al (2011)	**10**	**ns**	**10**	**DSM-IV**	**40.8**
Apfel et al (2011)	41	95	64	DSM-IV	42.1
Ahmed et al (2012)	*21*	*ns*	*32*	*DSM-IV*	*16.17*
Chao et al (2012)	*21*	*ns*	*20*	*DSM-IV*	*35.9*
Chen et al (2012)	***10***	***20***	***10***	***DSM-IV***	***40.8***
Herringa et al (2012)	*13*	*ns*	*15*	*DSM-IV*	*28.9*
Morey et al (2012)	***99***	**ns**	**101**	***DSM-IV***	***38.4***
Rocha-Rego et al (2012)	*16*	*ns*	*16*	*DSM-IV*	*43.3*
Tavanti et al (2012)	***25***	***25***	***ns***	***DSM-IV***	***38.16***

Table S1 (Continued): Database of PTSD MRI studies (3/4, continues over 4 pages) ns = not stated/ not recruited. Rows in BOLD indicate studies included in the PTSD region-of-interest meta-analysis, rows in italics indicate studies included in the VBM meta-analysis, rows in both BOLD and italics indicate studies included in both the region-of-interest and VBM meta-analyses, rows in normal typeface were not included in either meta-analysis.

Table S1. Database of PTSD MRI studies (continued)					
Study	No. of PTSD Patients	No. Non-Traumatised Controls (NTC)	No. Traumatised Controls (TC)	Diagnostic Criteria	Mean Patient Age, y
Kuo et al (2012)	*42*	*ns*	*45*	*DSM-IV*	*49.5*
Chao et al (2013)	***39***	***75***	***43***	***DSM-IV***	***42.7***
Jatzko et al (2013)	***15***	***15***	***ns***	***DSM-IV***	***48.3***
Nardo et al (2013)	*15*	*ns*	*17*	*DSM-IV*	*43.33*
Shu et al (2013)	***11***	***11***	***ns***	***DSM-IV***	***36.3***
Tan et al (2013)	*12*	*ns*	*14*	*DSM-IV*	*37.6*
Weems et al (2013)	*24*	*24*	*ns*	*DSM-IV*	*10.96*
Baldacara et al (2014)	***32***	***ns***	***32***	***DSM-IV***	***34.8***
Starcevic et al (2014)	***49***	***ns***	***30***	***ICD-10***	***46.47***
Zhang et al (2014)	*14*	*25*	*ns*	*DSM-IV*	*33.1*
Levy-Gigi et al (2015)	***26***	***28***	***ns***	***DSM-IV***	***35.46***
Keding et al (2015)	*27*	*28*	*ns*	*DSM-IV*	*14.2*
Chalavi et al (2015)	***16***	***30***	***ns***	***DSM-IV***	***40.75***
Chalavi et al (2015)	***16***	***ns***	***25***	***DSM-IV***	***40.75***
Starcevic et al (2015)	***25***	***59***	***35***	***ICD-10***	***47.08***
Veer et al (2015)	***12***	***24***	***ns***	***DSM-IV***	***28.08***
Cheng et al (2015)	*30*	*27*	*ns*	*DSM-IV*	*26.3*
Mueller et al (2015)	***40***	***ns***	***22***	***CAPS***	***32.7***
Cortese et al (2015)	*20*	*ns*	*45*	*DSM-IV*	*30.5*
Demers et al (2015)	***16***	***ns***	***18***	***DSM-IV***	***34.6***
Nardo et al (2015)	*21*	*25*	*ns*	*DSM-IV*	*42.8*
De Bellis et al (2015)	*38*	*12*	*ns*	*DSM-IV*	*10.3*
Sussman et al (2016)	***23***	***37***	***ns***	***DSM-IV***	***37.3***
Zandieh et al (2016)	*9*	*ns*	*78*	*DSM-IV*	*38.8*
Rubin et al (2016)	***17***	***39***	***11***	***DSM-IV***	***37.5***
Morey et al (2016)	*31*	*57*	*32*	*DSM-IV*	*9.9*
Helpman et al (2016)	***41***	***ns***	***36***	***DSM-IV***	***35.895***
Li et al (2016)	***67***	***ns***	***24***	***DSM-IV***	***41.9***
Luo et al (2016)	***57***	***10***	***ns***	***DSM-IV***	***57.1***

Table S1 (Continued). Database of PTSD MRI studies. (4/4, continues over 4 pages) ns = not stated/ not recruited. Rows in BOLD indicate studies included in the PTSD region-of-interest meta-analysis, rows in italics indicate studies included in the VBM meta-analysis, rows in both BOLD and italics indicate studies included in both the region-of-interest and VBM meta-analyses, rows in normal typeface were not included in either meta-analysis.

Table S2. Meta-analysis Comparing Patients with PTSD vs Non-traumatised-controls (NTC)											
		Comparison of PTSD patients and NTC						Heterogeneity		S.S. Bias	Leave-one-out
Region	No. of studies	Effect size	95% CI			Effect size p-value	Size vs Control, %	I2 (%)	p-value	p-value	% effect sizes, p<0.05
CSF (total)	5	-0.19	-1.12	to	0.74	0.69	99.0	87	<0.01	0.93	-
Brain (total)	**16**	**-0.23**	**-0.39**	**to**	**-0.07**	**<0.01**	**98.2**	**0**	**0.57**	**0.07**	**100**
White Matter (total)	7	0.03	-0.35	to	0.40	0.89	100.0	52	0.05	0.00	-
Gray Matter (total)	**7**	**-0.47**	**-0.83**	**to**	**-0.11**	**0.01**	**96.2**	**46**	**0.08**	**0.86**	**86**
Intracranial Volume (total)	6	-0.14	-0.44	to	0.16	0.36	98.4	0	0.47	0.48	-
Insula (total)	**4**	**-0.84**	**-1.11**	**to**	**-0.56**	**<0.01***	**93.7**	**0**	**0.63**	**0.08**	**100**
Insula (right)	**3**	**-0.53**	**-0.89**	**to**	**-0.16**	**<0.01**	**95.1**	**0**	**0.73**	**-**	**67**
Insula (left)	**3**	**-0.78**	**-1.29**	**to**	**-0.28**	**<0.01**	**93.0**	**43**	**0.18**	**-**	**67**
Anterior Cingulate (total)	4	-0.10	-0.50	to	0.29	0.61	97.8	18	0.30	-	-
Anterior Cingulate (right)	4	-0.04	-0.52	to	0.45	0.88	98.5	44	0.15	-	-
Anterior Cingulate (left)	4	-0.18	-0.54	to	0.17	0.31	97.3	0	0.54	-	-
Rostral Anterior Cingulate (total)	3	-0.23	-0.72	to	0.27	0.37	97.0	68	0.05	-	-
Caudate (total)	3	-0.06	-0.42	to	0.30	0.75	99.5	0	0.43	-	-
Caudate (right)	3	-0.07	-0.43	to	0.29	0.69	99.2	0	0.52	-	-
Caudate (left)	3	-0.05	-0.41	to	0.31	0.78	99.5	0	0.41	-	-
Temporal Lobe (total)	5	-0.21	-0.61	to	0.20	0.31	98.0	47	0.11	0.33	-
Temporal Lobe (right)	4	-0.25	-0.60	to	0.11	0.17	97.2	23	0.27	-	-
Temporal Lobe (left)	4	-0.06	-0.67	to	0.54	0.84	100.1	73	0.01	-	-
Parahippocampal Gyrus (total)	**3**	**-0.37**	**-0.68**	**to**	**-0.06**	**0.02**	**96.0**	**0**	**0.44**	**-**	**33**
Hippocampus (total)	**30**	**-0.60**	**-0.79**	**to**	**-0.41**	**<0.01***	**92.4**	**53**	**<0.01**	**0.39**	**100**
Hippocampus (right)	**28**	**-0.52**	**-0.71**	**to**	**-0.32**	**<0.01**	**92.7**	**51**	**<0.01**	**0.05**	**100**
Hippocampus (left)	**28**	**-0.49**	**-0.69**	**to**	**-0.29**	**<0.01**	**92.7**	**52**	**<0.01**	**0.14**	**100**
Amygdala (total)	13	-0.26	-0.57	to	0.05	0.11	96.1	66	<0.01	0.76	-
Amygdala (right)	12	-0.22	-0.57	to	0.14	0.23	95.8	68	<0.01	0.43	-
Amygdala (left)	12	-0.25	-0.61	to	0.10	0.16	95.6	68	<0.01	0.62	-
Corpus Callosum (total)	4	-0.36	-0.99	to	0.27	0.26	95.2	70	0.02	-	-

Table S2. Meta-analysis of regional brain volumes comparing patients with post-traumatic stress disorder to non-trauma exposed controls. Bold indicates significant differences. S.S Bias = Small Study Bias, CI = confidence interval, Non-traumatised-controls = healthy non-trauma-exposed controls. *Result remained significant after Bonferroni correction for multiple comparisons of 26 brain structures. Leave-one-out analysis examines if the pooled effect size becomes non-significant when removing one effect size at a time; a value of 100% which is the most robust result indicates that the pooled effect size remains significant when 100% of effect sizes are removed in turn.

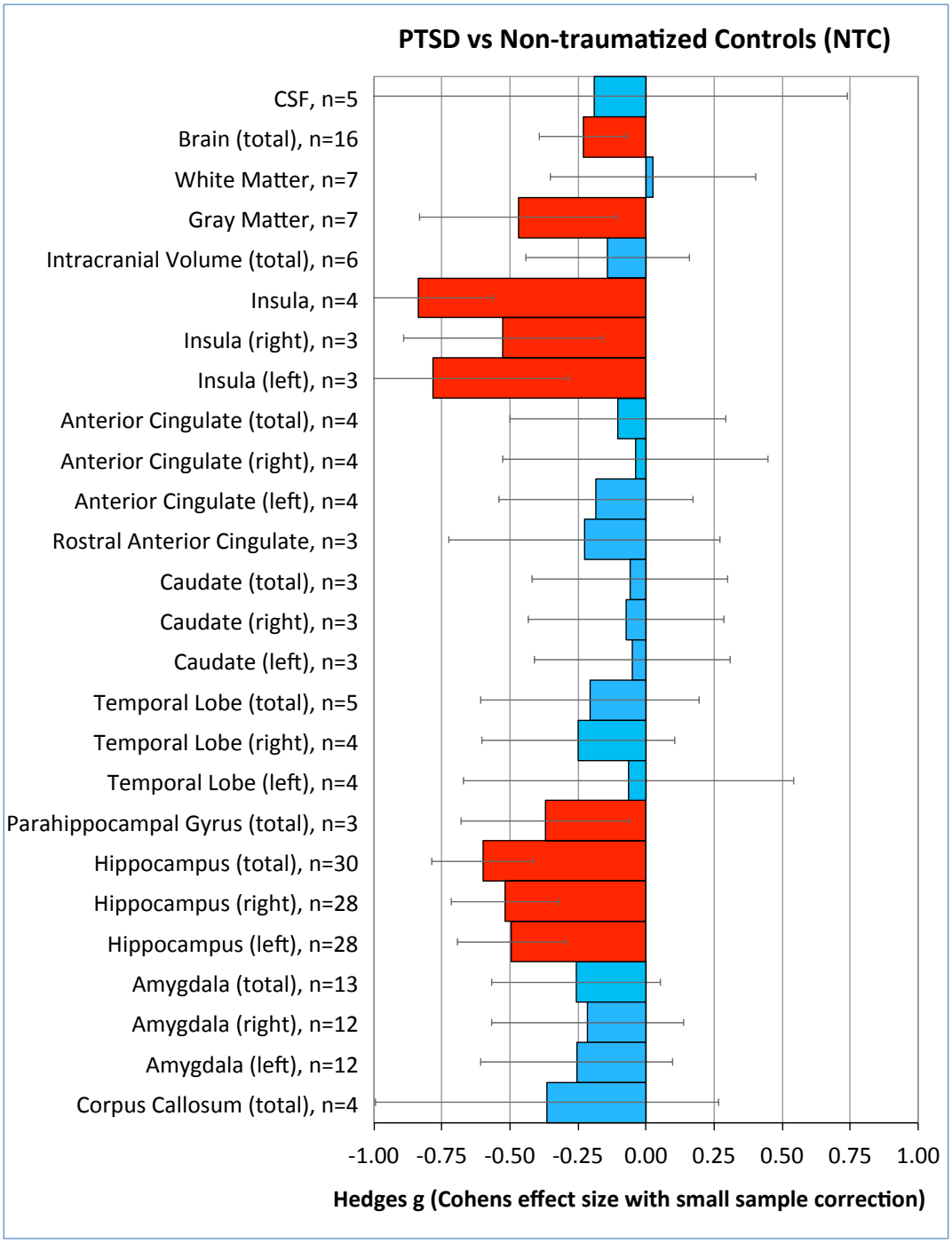


Figure S2. Meta-analysis of regional brain volumes comparing patients with post-traumatic stress disorder to non-traumatised control group. Hedges *g* (Cohen effect size with small sample correction) is shown for each structure, with 95% confidence intervals. The effect size is positive when the structure is larger in patients with PTSD compared with controls and negative when the structure is smaller in PTSD patients. Red indicates significant differences. The number of studies included in each meta-analysis is indicated with each structure. Non-traumatised-controls = healthy non-trauma exposed controls.

Table S3. Meta-analysis of Comparing Patients with PTSD vs Traumatised-controls (TC)											
		Comparison of PTSD patients and TC						Heterogeneity		S.S. Bias	Leave-one-out
Region	No. of studies	Effect size	95% CI			Effect size p-value	Size vs Control, %	I2 (%)	p-value	p-value	% effect sizes, p<0.05
CSF (total)	3	0.01	-0.43	to	0.45	0.96	100.0	0	0.70	-	-
Brain (total)	**12**	**-0.24**	**-0.44**	**to**	**-0.03**	**0.02**	**97.9**	**13**	**0.31**	**0.89**	**83**
White Matter (total)	4	-0.23	-0.58	to	0.11	0.19	97.8	0	0.92	-	-
Superior Frontal Gyrus (total)	**3**	**-0.52**	**-0.81**	**to**	**-0.24**	**<0.01***	**94.7**	**14**	**0.31**	**-**	**100**
Gray Matter (total)	5	-0.04	-0.54	to	0.46	0.86	99.5	55	0.07	0.18	-
Intracranial Volume (total)	**10**	**-0.24**	**-0.46**	**to**	**-0.02**	**0.030**	**97.4**	**15**	**0.29**	**0.18**	**60**
Entorhinal Cortex (total)	3	-0.04	-0.31	to	0.22	0.742	98.9	0	0.37	-	-
Insula (total)	**3**	**-0.46**	**-0.73**	**to**	**-0.19**	**<0.01***	**97.5**	**0**	**0.71**	**-**	**-**
Pars Orbitalis IFG (total)	3	-0.19	-0.42	to	0.05	0.118	98.7	0	0.74	-	-
Anterior Cingulate (total)	**5**	**-0.49**	**-0.78**	**to**	**-0.20**	**<0.01***	**92.4**	**40**	**0.14**	**0.96**	**100**
Rostral Anterior Cingulate (total)	3	-0.11	-0.42	to	0.19	0.46	98.0	18	0.30	-	-
Isthmus Anterior Cingulate (total)	3	-0.09	-0.53	to	0.36	0.70	99.2	67	0.05	-	-
Orbitofrontal Cortex, lateral (total)	**3**	**-0.35**	**-0.59**	**to**	**-0.12**	**<0.01**	**98.0**	**0**	**0.97**	**-**	**100**
Parahippocampal Gyrus (total)	6	0.06	-0.42	to	0.55	0.80	101.1	81	<0.01	0.17	-
Parahippocampal Gyrus (right)	**3**	**0.43**	**0.02**	**to**	**0.83**	**0.04**	**108.2**	**12**	**0.32**	**-**	**33**
Parahippocampal Gyrus (left)	**3**	**0.43**	**0.06**	**to**	**0.80**	**0.02**	**108.1**	**0**	**0.64**	**-**	**67**
Hippocampus (total)	**25**	**-0.24**	**-0.42**	**to**	**-0.06**	**<0.01**	**97.2**	**55**	**<0.01**	**0.16**	**100**
Hippocampus (right)	**23**	**-0.22**	**-0.40**	**to**	**-0.03**	**0.020**	97.4	**49**	**<0.01**	**0.09**	**100**
Hippocampus (left)	23	-0.17	-0.37	to	0.03	0.094	97.2	56	<0.01	0.05	-
Amygdala (total)	15	-0.11	-0.39	to	0.16	0.42	98.5	75	<0.01	0.59	-
Amygdala (right)	13	-0.13	-0.44	to	0.18	0.41	98.3	76	<0.01	0.37	-
Amygdala (left)	13	-0.14	-0.46	to	0.18	0.39	98.0	77	<0.01	0.86	

Table S3. Meta-analysis of regional brain volumes comparing patients with post-traumatic stress disorder to trauma-exposed without PTSD. Bold indicates significant differences. S.S Bias = Small Study Bias, CI = confidence interval, Non-traumatised-controls = healthy non-trauma exposed controls. *Result remained significant after Bonferroni correction for multiple comparisons of 22 brain structures. Leave-one-out analysis examines if the pooled effect size becomes non-significant when removing one effect size at a time; a value of 100% which is the most robust result indicates that the pooled effect size remains significant when 100% of effect sizes are removed in turn.

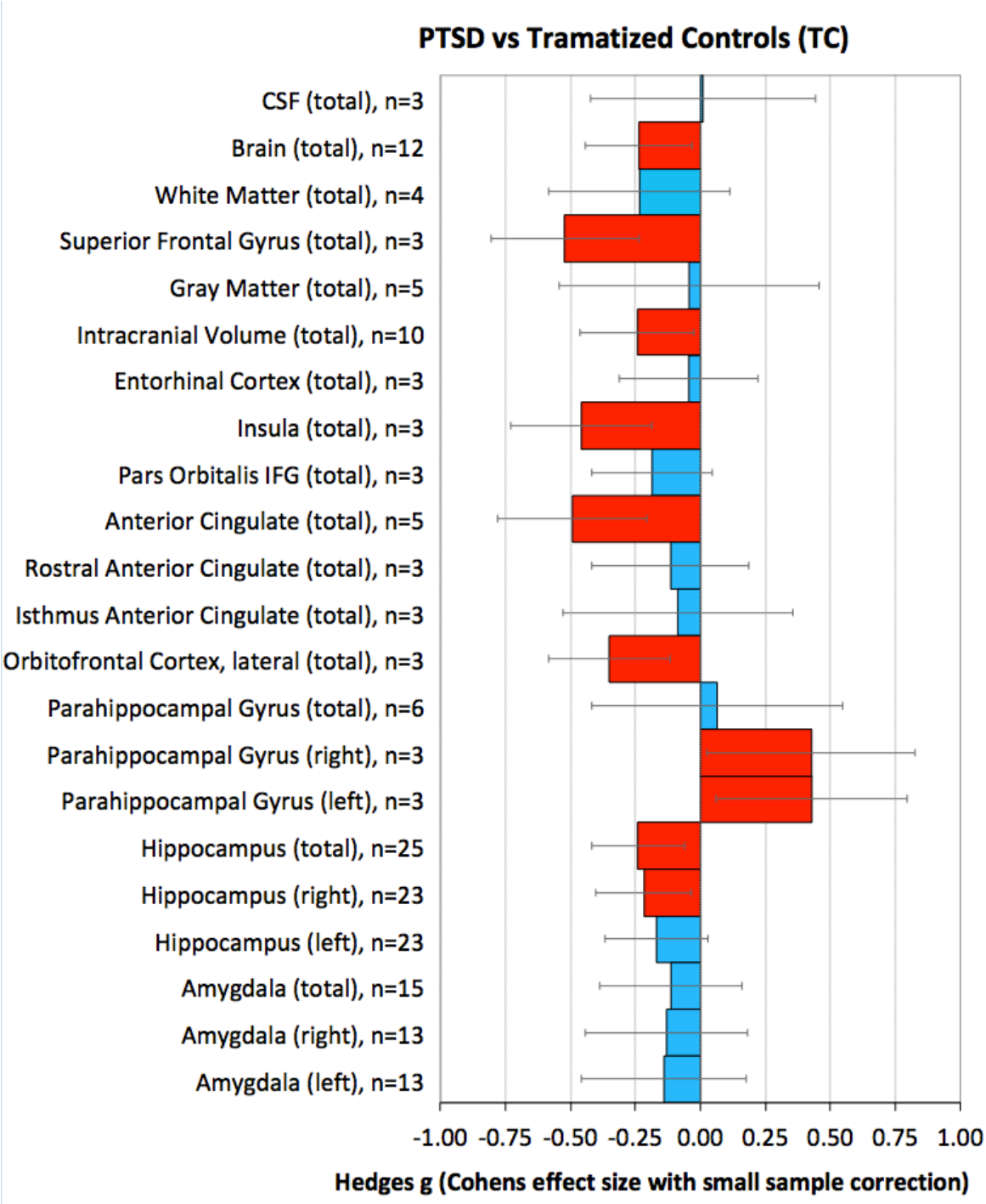


Figure S3. Meta-analysis of regional brain volumes comparing patients with post-traumatic stress disorder to trauma-exposed without PTSD. Hedges *g* (Cohen effect size with small sample correction) is shown for each structure, with 95% confidence intervals. The effect size is positive when the structure is larger in patients with PTSD compared with controls and negative when the structure is smaller in PTSD patients. Red indicates significant differences. The number of studies included in each meta-analysis is indicated with each structure. Traumatised-controls = exposed to trauma but without PTSD.

Table S4. Meta-analysis Comparing Traumatised-controls (TC) vs Non-traumatised-controls (NTC)											
		Comparison of TC and NTC						Heterogeneity		S.S. Bias	Leave-one-out
Region	No. of studies	Effect size	95% CI			Effect size p-value	Size vs Control,%	I2 (%)	p-value	p-value	% effect sizes, p<0.05
Brain (total)	7	0.03	-0.23	to	0.29	0.84	100.1	0	0.88	0.17	-
Intracranial Volume (total)	3	-0.21	-1.14	to	0.71	0.65	98.6	72	0.03	-	-
Hippocampus (total)	**13**	**-0.37**	**-0.55**	**to**	**-0.19**	**<0.01***	**96.1**	**5**	**0.40**	**0.97**	**100**
Hippocampus (right)	**12**	**-0.35**	**-0.60**	**to**	**-0.10**	**<0.01**	**95.4**	**35**	**0.11**	**0.40**	**100**
Hippocampus (left)	**12**	**-0.35**	**-0.54**	**to**	**-0.15**	**<0.01***	**95.6**	**0**	**0.52**	**0.16**	**100**
Amygdala (total)	6	-0.15	-0.48	to	0.18	0.366	98.9	48	0.09	0.86	-
Amygdala (right)	5	0.07	-0.35	to	0.49	0.74	101.6	50	0.09	0.57	-
Amygdala (left)	5	-0.10	-0.40	to	0.20	0.51	99.4	12	0.34	0.59	-

Table S4. Meta-analysis of regional brain volumes comparing trauma-exposed without PTSD to healthy controls. Bold indicates significant differences. S.S Bias = Small Study Bias, CI = confidence interval, Traumatised-controls = exposed to trauma but without PTSD; Non-traumatised-controls = healthy non-trauma exposed controls. *Result remained significant after Bonferroni correction for multiple comparisons of 8 brain structures. Leave-one-out analysis examines if the pooled effect size becomes non-significant when removing one effect size at a time; a value of 100% which is the most robust result indicates that the pooled effect size remains significant when 100% of effect sizes are removed in turn.

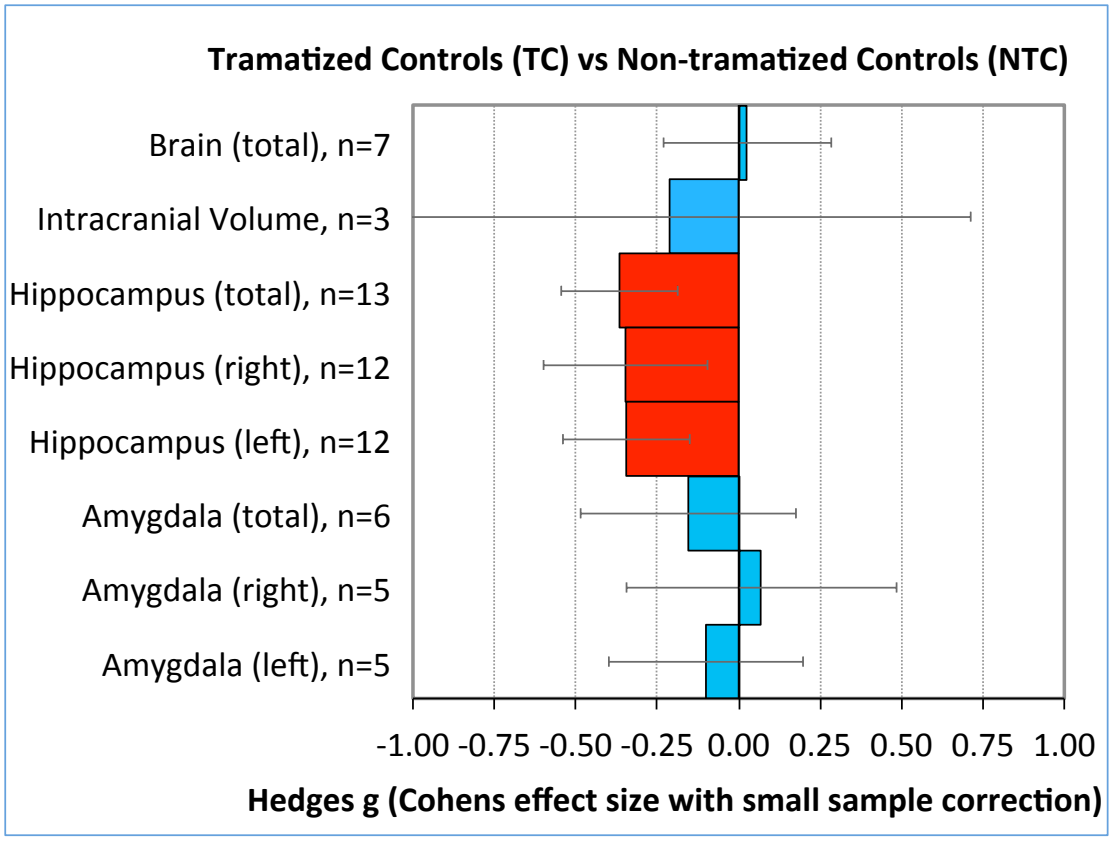


Figure S4. Meta-analysis of regional brain volumes comparing trauma-exposed without PTSD to healthy controls. Hedges *g* (Cohen effect size with small sample correction) is shown for each structure, with 95% confidence intervals. The effect size is positive when the structure is larger in patients with PTSD compared with controls and negative when the structure is smaller in PTSD patients. Red indicates significant differences. The number of studies included in each meta-analysis is indicated with each structure. Traumatised-controls = exposed to trauma but without PTSD; Non-traumatised-controls = healthy non-trauma exposed controls.

Table S5. Meta-analysis Comparing Patients with PTSD vs All Controls (includes pediatric samples)												
			Comparison of PTSD patients and all controls						Heterogeneity			S.S. Bias
Region	No. of studies	No. of PTSD/Ctrls	Effect size	95% CI			Effect size p-value	Size vs Controls, %	Q	I2 (%)	p-value	p-value
Lateral Ventricles (total)	3	79/135	0.20	-0.09	to	0.48	0.17	109.0	1.3	0	0.52	-
Brain (total)	**22**	**422/500**	**-0.30**	**-0.46**	**to**	**-0.15**	**<0.01***	**97.4**	**25.5**	**18**	**0.23**	**0.27**
Cerebellum (total)	**3**	**138/199**	**-0.57**	**-0.80**	**to**	**-0.35**	**<0.01***	**94.4**	**1.5**	**0**	**0.47**	**-**
Intracranial Volume (total)	**15**	**282/348**	**-0.33**	**-0.51**	**to**	**-0.15**	**<0.01***	**96.6**	**22.5**	**25**	**0.16**	**1.00**
Frontal Lobe (total)	**3**	**110/171**	**-0.48**	**-0.72**	**to**	**-0.23**	**<0.01***	**94.1**	**1.8**	**0**	**0.41**	**-**
Prefrontal Cortex (total)	3	121/157	-0.32	-0.74	to	0.09	0.13	95.0	5.5	64	0.06	-
Gray Matter (total)	**13**	**297/374**	**-0.42**	**-0.68**	**to**	**-0.16**	**<0.01**	**96.2**	**27.5**	**56**	**<0.01**	**0.92**
Insula (total)	**6**	**161/216**	**-0.58**	**-0.89**	**to**	**-0.28**	**<0.01***	**96.1**	**9.6**	**48**	**0.09**	**0.69**
Insula (right)	**4**	**82/96**	**-0.35**	**-0.69**	**to**	**-0.02**	**0.04**	**97.0**	**3.6**	**17**	**0.31**	**-**
Insula (left)	**4**	**82/96**	**-0.61**	**-1.09**	**to**	**-0.13**	**0.01**	**95.1**	**7.0**	**57**	**0.07**	**-**
Cerebellar Gray Matter (total)	3	73/100	-0.38	-0.80	to	0.04	0.08	95.7	3.4	40	0.19	-
Cerebral Volume (total)	**4**	**168/244**	**-0.48**	**-0.70**	**to**	**-0.26**	**<0.01***	**95.7**	**6.6**	**10**	**0.36**	**-**
Superior Temporal Gyrus (total)	6	162/192	-0.15	-0.48	to	0.19	0.39	98.6	11.5	57	0.04	0.89
Superior Temporal Gyrus (right)	5	122/147	-0.07	-0.47	to	0.34	0.75	99.4	10.4	61	0.03	0.63
Superior Temporal Gyrus (left)	5	122/147	-0.21	-0.64	to	0.23	0.35	97.7	11.5	65	0.02	0.92
Anterior Cingulate (total)	**11**	**279/367**	**-0.30**	**-0.58**	**to**	**-0.01**	**0.041**	**95.7**	**31.5**	**65**	**<0.01**	**0.52**
Anterior Cingulate (right)	8	191/238	-0.09	-0.31	to	0.13	0.43	98.4	10.0	20	0.27	0.49
Anterior Cingulate (left)	8	191/238	-0.26	-0.55	to	0.04	0.09	94.6	16.7	52	0.03	0.79
Putamen (total)	5	172/250	0.10	-0.10	to	0.29	0.33	100.7	3.9	0	0.42	0.13
Putamen (right)	5	172/250	0.14	-0.06	to	0.34	0.17	101.3	4.0	0	0.41	0.02
Putamen (left)	5	172/250	0.05	-0.15	to	0.25	0.62	100.0	3.9	0	0.42	0.34
Caudate (total)	7	217/287	-0.02	-0.21	to	0.18	0.88	**99.9**	6.9	13	0.33	0.48
Caudate (right)	7	217/287	0.00	-0.20	to	0.20	0.99	100.2	7.0	14	0.32	0.58
Caudate (left)	7	217/287	-0.04	-0.22	to	0.14	0.66	99.4	6.0	1	0.42	0.42
Temporal Lobe (total)	**8**	**187/245**	**-0.42**	**-0.69**	**to**	**-0.15**	**<0.01**	**95.5**	**12.1**	**42**	**0.10**	**0.46**
Temporal Lobe (right)	**7**	**178/236**	**-0.44**	**-0.66**	**to**	**-0.21**	**<0.01***	**95.1**	**7.4**	**19**	**0.29**	**0.32**
Temporal Lobe (left)	7	178/236	-0.29	-0.64	to	0.05	0.09	96.8	16.5	64	0.01	0.08
Hippocampus (total)	**47**	**1066/1240**	**-0.43**	**-0.57**	**to**	**-0.29**	**<0.01***	**94.9**	**109.8**	**58**	**<0.01**	**<0.01**
Hippocampus (right)	**43**	**932/1067**	**-0.38**	**-0.52**	**to**	**-0.24**	**<0.01***	**95.1**	**91.0**	**54**	**<0.01**	**<0.01**
Hippocampus (left)	**43**	**932/1067**	**-0.34**	**-0.48**	**to**	**-0.20**	**<0.01***	**95.3**	**91.2**	**54**	**<0.01**	**0.02**
Amygdala (total)	**28**	**759/925**	**-0.25**	**-0.43**	**to**	**-0.06**	**<0.01**	**96.4**	**84.6**	**68**	**<0.01**	**0.58**
Amygdala (right)	**25**	**656/781**	**-0.22**	**-0.43**	**to**	**-0.01**	**0.04**	**96.3**	**78.6**	**69**	**<0.01**	**0.83**
Amygdala (left)	**25**	**656/781**	**-0.26**	**-0.47**	**to**	**-0.05**	**0.02**	**95.8**	**83.5**	**71**	**<0.01**	**0.41**
Vermis (total)	**5**	**180/245**	**-0.63**	**-1.12**	**to**	**-0.14**	**0.01**	**91.5**	**21.6**	**82**	**<0.01**	**0.42**
Corpus Callosum (total)	7	183/289	-0.34	-0.72	to	0.03	0.07	95.1	19.2	69	<0.01	0.30
Corpus Callosum, rostrum	3	82/141	-0.16	-0.44	to	0.11	0.25	95.3	1.8	0	0.41	-
Corpus Callosum, genu	3	82/141	-0.41	-0.84	to	0.02	0.06	91.6	2.8	29	0.24	-
Corpus Callosum, rostral body	3	82/141	-0.18	-0.46	to	0.09	0.19	**95.9**	1.6	0	0.44	-
Corpus Callosum, anterior midbody	**3**	**82/141**	**-0.50**	**-0.78**	**to**	**-0.22**	**<0.01***	**90.7**	**0.4**	**0**	**0.82**	**-**
Corpus Callosum, posterior midbody	**3**	**82/141**	**-0.61**	**-0.96**	**to**	**-0.26**	**<0.01**	**87.0**	**2.3**	**12**	**0.32**	**-**
Corpus Callosum, isthmus	**3**	**82/141**	**-0.56**	**-1.07**	**to**	**-0.04**	**0.03**	**88.5**	**3.5**	**43**	**0.17**	**-**
Corpus Callosum, splenium	3	82/141	-0.33	-0.92	to	0.25	0.26	94.4	4.5	56	0.11	-

Table S5. Meta-analysis of regional brain volumes (including paediatric samples) comparing patients with post-traumatic stress disorder to controls. Brain regions are shown where pediatric data changes the effect size given in table 2. **Bold** indicates significant differences. S.S Bias = Small Study Bias. *Result remained significant after Bonferroni correction for multiple comparisons for 42 brain structures.

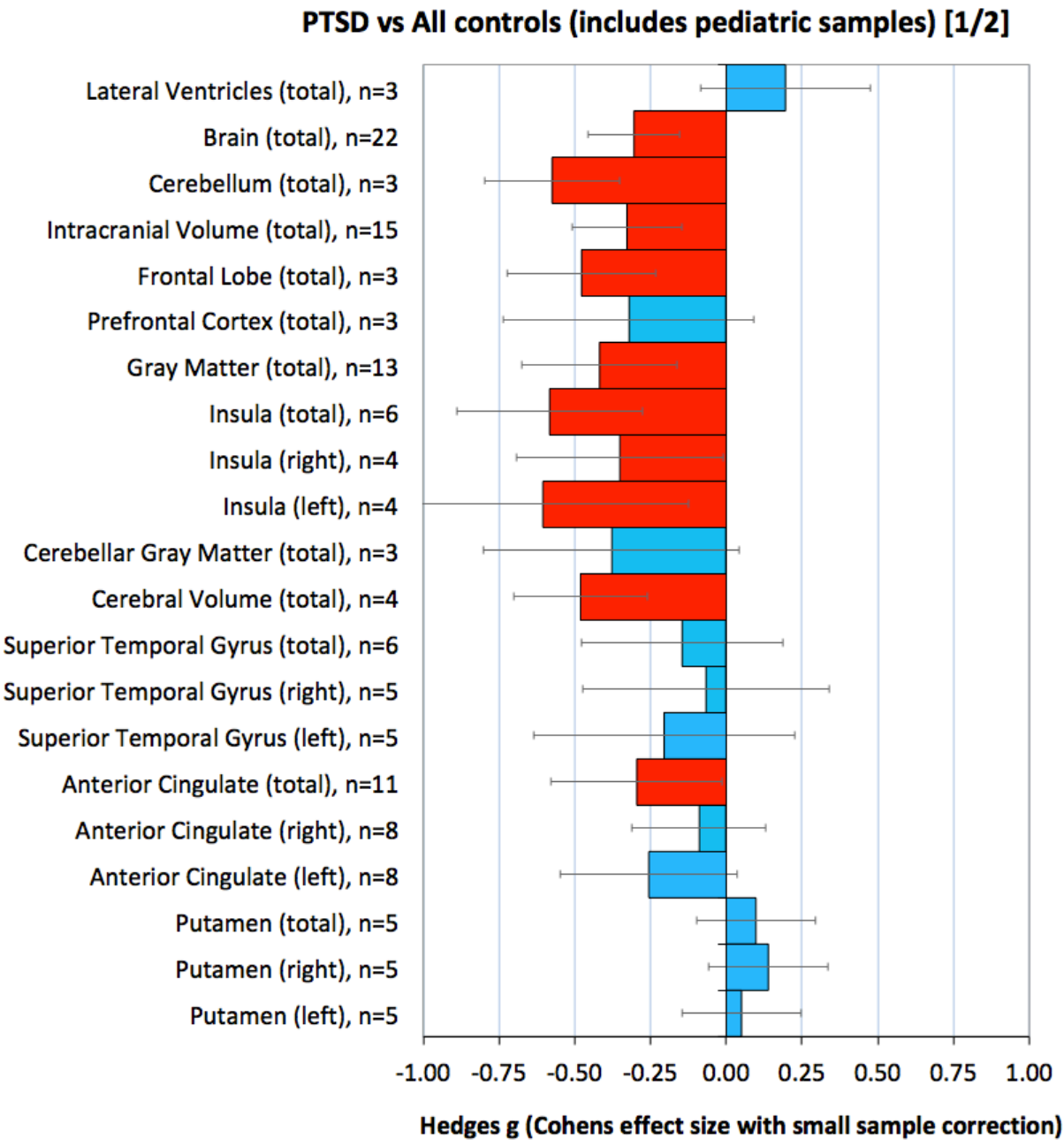


Figure S5a. Meta-analysis of regional brain volumes (including paediatric samples) comparing patients with post-traumatic stress disorder to controls. Hedges *g* (Cohen effect size with small sample correction) is shown for each structure, with 95% confidence intervals. The effect size is positive when the structure is larger in patients with PTSD compared with controls and negative when the structure is smaller in PTSD patients. Red indicates significant differences. The number of studies included in each meta-analysis is indicated for each structure.

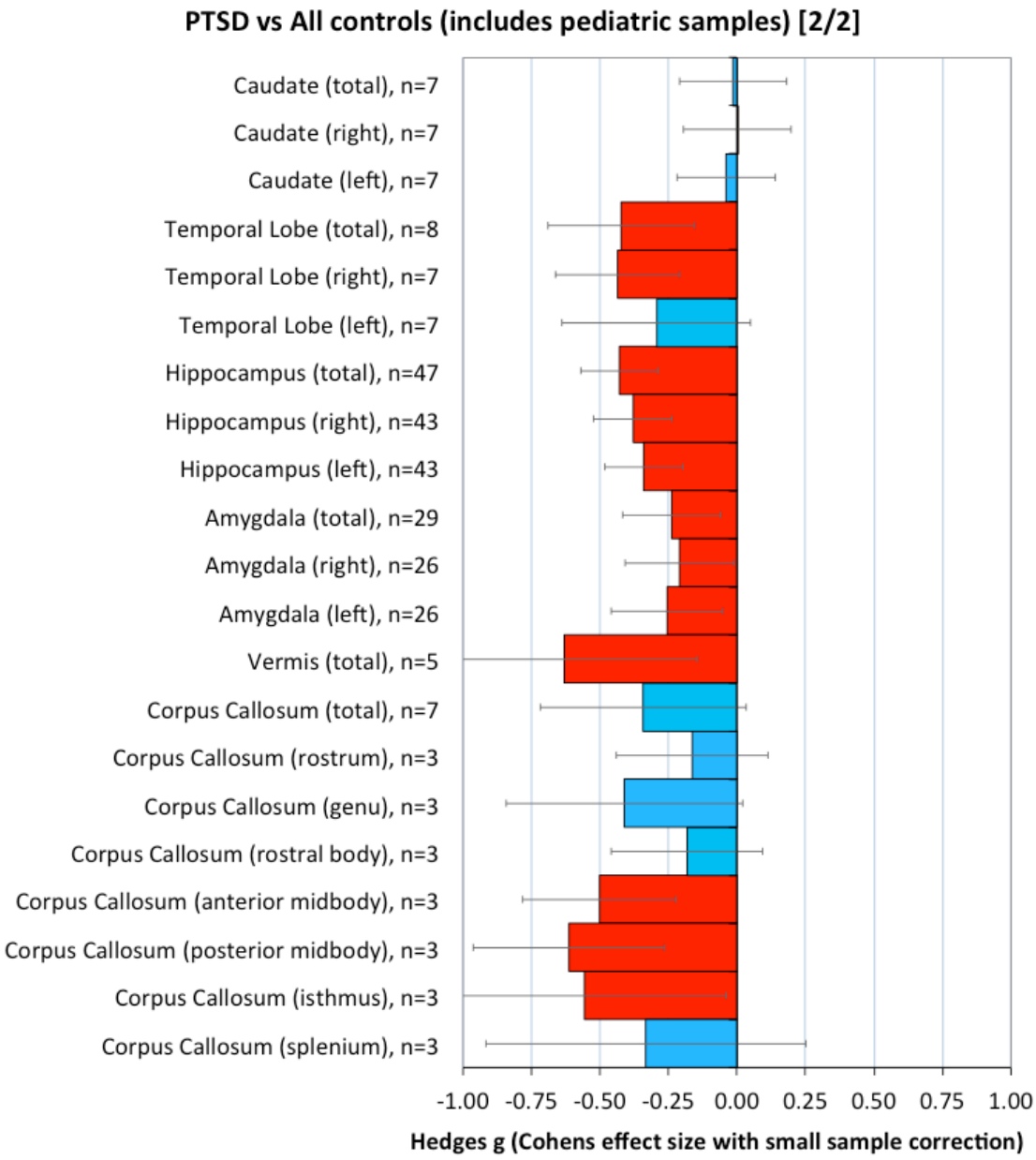


Figure S5b. Meta-analysis of regional brain volumes (including paediatric samples) comparing patients with post-traumatic stress disorder to controls. Hedges *g* (Cohen effect size with small sample correction) is shown for each structure, with 95% confidence intervals. The effect size is positive when the structure is larger in patients with PTSD compared with controls and negative when the structure is smaller in PTSD patients. Red indicates significant differences. The number of studies included in each meta-analysis is indicated for each structure.

Table S6. Meta-analysis Comparing Patients with PTSD vs non-traumatised-controls (NTC), (includes pediatric samples)											
		Comparison of PTSD patients and NTC						Heterogeneity			S.S. Bias
Region	No. of studies	Effect size	95% CI			Effect size p-value	Size vs Control %	Q	I2 (%)	p-value	p-value
Lateral Ventricles (total)	3	0.20	-0.09	to	0.48	0.17	109.0	1	0	0.52	-
Brain (total)	**17**	**-0.28**	**-0.45**	**to**	**-0.12**	**<0.01***	**97.5**	**18**	**12**	**0.31**	**0.14**
Gray Matter (total)	**10**	**-0.52**	**-0.75**	**to**	**-0.29**	**<0.01***	**95.4**	**14**	**35**	**0.13**	**0.20**
Cerebellar Gray Matter (total)	3	-0.38	-0.80	to	0.04	0.08	95.7	3	40	0.19	-
Intracranial Volume (total)	**7**	**-0.31**	**-0.62**	**to**	**-0.01**	**0.05**	**96.8**	**10**	**0**	**0.47**	**0.48**
Caudate (total)	5	-0.13	-0.36	to	0.10	0.26	98.1	3	0	0.64	0.32
Caudate (right)	5	-0.13	-0.36	to	0.10	0.26	98.2	2	0	0.79	0.34
Caudate (left)	5	-0.13	-0.36	to	0.10	0.27	98.0	3	0	0.52	0.33
Temporal Lobe (total)	**8**	**-0.42**	**-0.69**	**to**	**-0.15**	**<0.01***	**95.5**	**12**	**42**	**0.10**	**0.46**
Temporal Lobe (right)	**7**	**-0.44**	**-0.66**	**to**	**-0.21**	**<0.01**	**95.1**	**7**	**19**	**0.29**	**0.32**
Temporal Lobe (left)	7	-0.29	-0.64	to	0.05	0.09	96.8	17	64	0.01	0.08
Hippocampus (total)	**35**	**-0.53**	**-0.70**	**to**	**-0.37**	**<0.01***	**93.2**	**71**	**52**	**<0.01**	**0.16**
Hippocampus (right)	**32**	**-0.46**	**-0.63**	**to**	**-0.29**	**<0.01***	**93.6**	**61**	**49**	**<0.01**	**0.02**
Hippocampus (left)	**32**	**-0.43**	**-0.61**	**to**	**-0.26**	**<0.01***	**93.6**	**63**	**51**	**<0.01**	**0.07**
Amygdala (total)	**19**	**-0.25**	**-0.45**	**to**	**-0.05**	**0.02**	**96.2**	**38**	**52**	**<0.01**	**0.71**
Amygdala (right)	17	-0.19	-0.42	to	0.04	0.10	96.1	37	57	<0.01	0.50
Amygdala (left)	**17**	**-0.25**	**-0.48**	**to**	**-0.01**	**0.04**	**95.6**	**38**	**58**	**<0.01**	**0.64**
Prefrontal Cortex (total)	3	-0.34	-0.74	to	0.07	0.11	94.9	5	58	0.10	-
Vermis (total)	**4**	**-0.40**	**-0.73**	**to**	**-0.07**	**0.02**	**94.4**	**6**	**49**	**0.12**	**0.40**
Corpus Callosum (total)	**6**	**-0.49**	**-0.82**	**to**	**-0.17**	**<0.01**	**93.1**	**10**	**51**	**0.07**	**0.33**
Corpus Callosum, rostrum	3	-0.16	-0.44	to	0.11	0.25	95.3	2	0	0.41	-
Corpus Callosum, genu	3	-0.41	-0.84	to	0.02	0.06	91.6	3	29	0.24	-
Corpus Callosum, rostral body	3	-0.18	-0.46	to	0.09	0.19	95.9	2	0	0.44	-
Corpus Callosum, anterior midbody	**3**	**-0.50**	**-0.78**	**to**	**-0.22**	**<0.01***	**90.7**	**0**	**0**	**0.82**	**-**
Corpus Callosum, posterior midbody	**3**	**-0.61**	**-0.96**	**to**	**-0.26**	**<0.01***	**87.0**	**2**	**12**	**0.32**	**-**
Corpus Callosum, isthmus	**3**	**-0.56**	**-1.07**	**to**	**-0.04**	**0.03**	**88.5**	**4**	**43**	**0.17**	**-**
Corpus Callosum, splenium	3	-0.33	-0.92	to	0.25	0.26	94.4	4	56	0.11	-

Table S6. Meta-analysis of regional brain volumes (including paediatric samples) comparing patients with post-traumatic stress disorder to non-traumatised controls. Brain regions are shown where pediatric data changes the effect size given in table S2. Bold indicates significant differences. S.S Bias = Small Study Bias, CI = confidence interval, Non-traumatised-controls = healthy non-trauma-exposed controls. * Result remained significant after Bonferroni correction for multiple comparisons for 27 brain structures

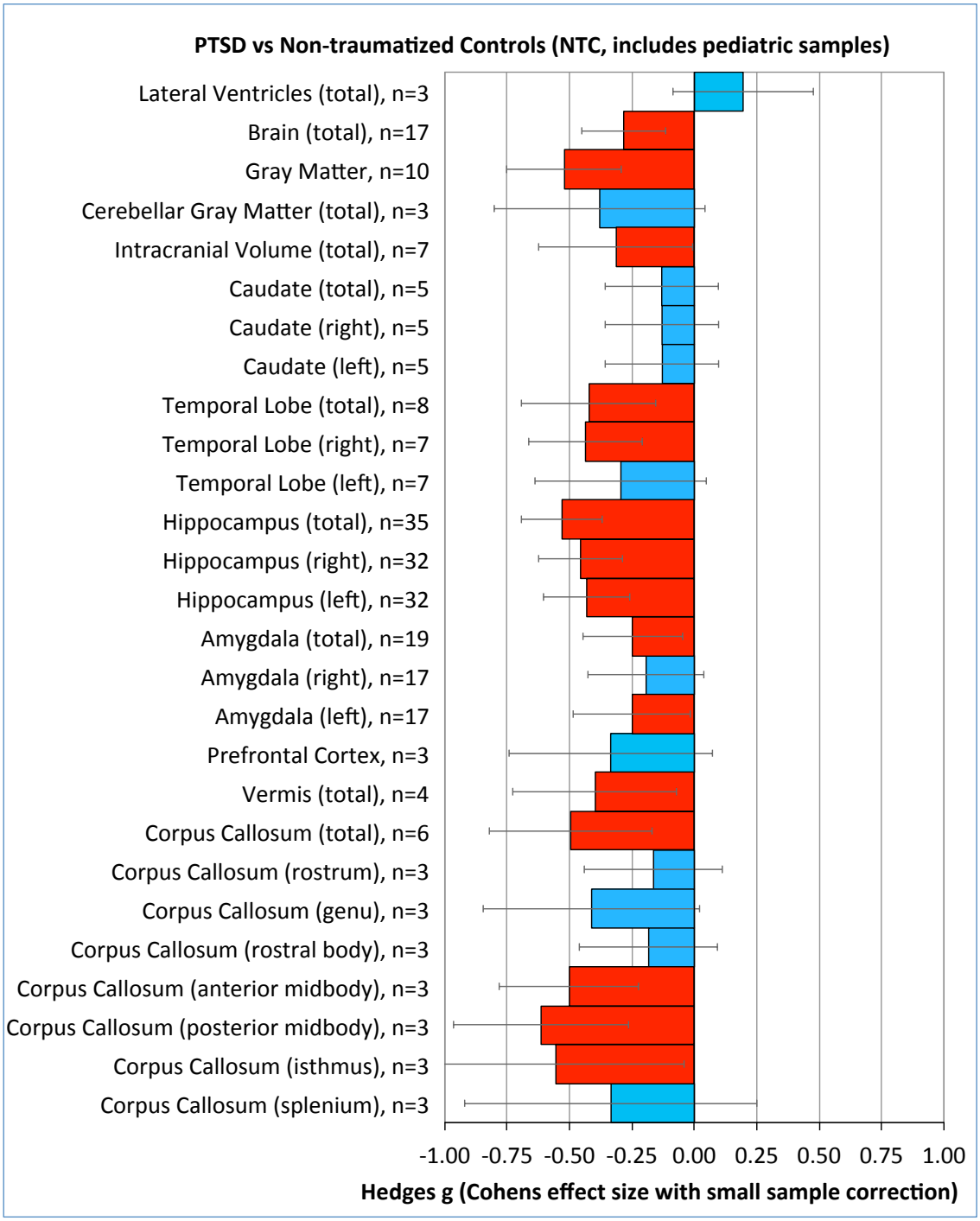


Figure S6. Meta-analysis of regional brain volumes (including paediatric samples) comparing patients with post-traumatic stress disorder to non-traumatized control group. Hedges *g* (Cohen effect size with small sample correction) is shown for each structure, with 95% confidence intervals. The effect size is positive when the structure is larger in patients with PTSD compared with controls and negative when the structure is smaller in PTSD patients. Red indicates significant differences. The number of studies included in each meta-analysis is indicated with each structure. Traumatised-controls = exposed to trauma but without PTSD.

Table S7. Meta-analysis Comparing Patients with PTSD vs Traumatised-controls (TC), (includes pediatric samples)											
		Comparison of PTSD patients and TC						Heterogeneity			S.S. Bias
Region	No. of studies	Effect size	95% CI			Effect size p-value	Size vs Control,%	Q	I2 (%)	p-value	p-value
Insula (total)	**4**	**-0.51**	**-0.96**	**to**	**-0.07**	**0.02**	**96.9**	**9**	**67**	**0.03**	**-**
Gray Matter (total)	5	-0.04	-0.54	to	0.46	0.86	99.5	9	55	0.07	0.18
Anterior Cingulate (total)	**7**	**-0.34**	**-0.64**	**to**	**-0.04**	**0.03**	**97.6**	**17**	**59**	**0.02**	**0.84**
Anterior Cingulate (right)	4	-0,13	-0.38	to	0.12	0.31	93.5	4	6	0.37	0.55
Anterior Cingulate (left)	4	-0.30	-0.76	to	0.16	0.21	97.2	14	72	<0.01	0.93
Hippocampus (total)	**27**	**-0.25**	**-0.42**	**to**	**-0.08**	**<0.01***	**97.2**	**56**	**53**	**<0.01**	**0.15**
Hippocampus (right)	**25**	**-0.23**	**-0.40**	**to**	**-0.06**	**<0.01**	**97.3**	**46**	**48**	**<0.01**	**0.09**
Hippocampus (left)	25	-0.18	-0.36	to	0.00	0.055	97.2	52	54	<0.01	0.13
Amygdala (total)	17	-0.13	-0.38	to	0.11	0.28	98.3	57	72	<0.01	0.57
Amygdala (right)	15	-0.14	-0.40	to	0.13	0.32	98.2	51	72	<0.01	0.32
Amygdala (left)	15	-0.17	-0.45	to	0.11	0.24	97.6	55	75	<0.01	0.86

Table S7. Meta-analysis of regional brain volumes (including paediatric samples) volumes comparing patients with post-traumatic stress disorder to trauma-exposed controls without PTSD. Brain regions are shown where pediatric data changes the effect size given in table S3. Bold indicates significant differences. S.S Bias = Small Study Bias, CI = confidence interval, Non-traumatised-controls = healthy non-trauma exposed controls. *Result remained significant after Bonferroni correction for multiple comparisons for 11 brain structures

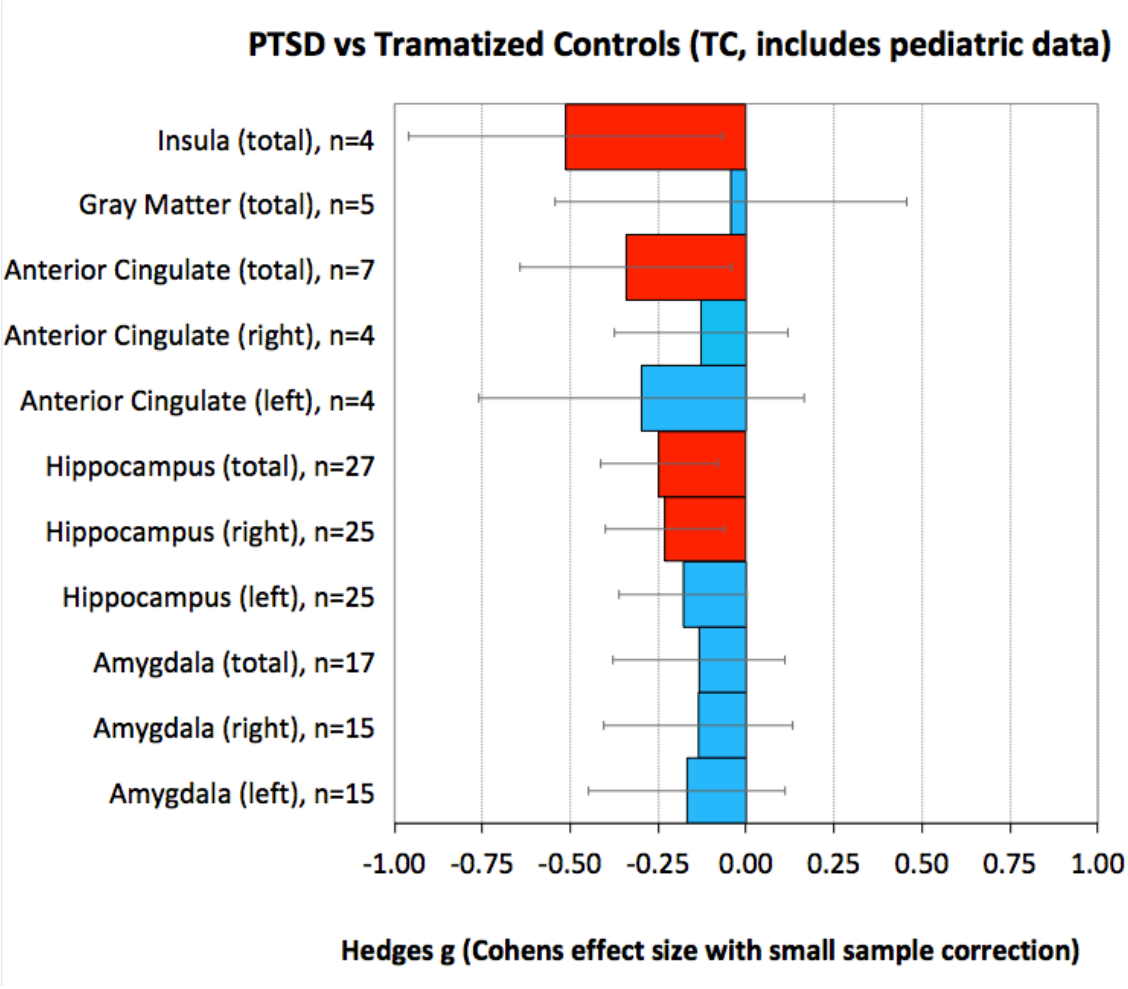


Figure S7. Meta-analysis of regional brain volumes (including paediatric samples) comparing patients with post-traumatic stress disorder to trauma-exposed without PTSD. Hedges *g* (Cohen effect size with small sample correction) is shown for each structure, with 95% confidence intervals. The effect size is positive when the structure is larger in patients with PTSD compared with controls and negative when the structure is smaller in PTSD patients. Red indicates significant differences. The number of studies included in each meta-analysis is indicated with each structure. Traumatised-controls = exposed to trauma but without PTSD.

Table S8. Statistical Comparison of the PTSD vs NTC and MDD vs controls								
	PTSD vs Control Meta-analysis			MDD vs Control Meta-analysis			PTSD vs MDD	
Region	No. of studies	Effect size	P Value	No. of studies	Effect Size	P Value	Effect Size	P Value
CSF	5	-0.19	0.69	7	0.53	0.001	-0.72	0.15
Brain	16	-0.23	0.005	25	-0.05	0.27	-0.17	0.07
Intracranial volume	6	-0.14	0.36	20	-0.12	0.056	-0.03	0.88
Gray matter	7	-0.47	0.0011	7	-0.13	0.19	-0.34	0.10
Anterior Cingulate	4	-0.10	0.61	6	-0.21	0.22	0.10	0.70
Caudate	3	-0.06	0.75	12	-0.20	0.017	0.14	0.48
Hippocampus	30	-0.60	<0.001	32	-0.48	<0.001	-0.11	0.36
Amygdala	13	-0.26	0.11	17	-0.02	0.89	-0.24	0.24

Table S8. Statistical Comparison of the present PTSD Meta-analysis With a previous Meta-analysis of Major-depressive-disorder[4]. The comparison is PTSD vs Non-traumatised-controls compared to Major-depressive-disorder vs controls. For the PTSD vs Major-depressive-disorder comparison, negative effect sizes indicate that the region is smaller in PTSD patients; positive effect sizes indicate that the region is smaller in Major-depressive-disorder patients.

Table S9 Regions of Significant Changes in GMV Between Patients with PTSD and NTC or TC group – SDM Analysis					
Regions	MNI coordinates X, Y, Z	SDM z-value	P-value	Number of voxels	Number of studies Jacknife Sensitivity analysis
Right anterior cingulate	6, 32, 28	4.507	<0.0001	2348	13
Left superior frontal gyrus, dorsoratelal	-26, 52, 20	3.425	<0.0001	763	13
Right fusiform gyrus	28, -38, -18	3.144	0.0005	86	12
Left amygdala	-28, -10, -18	2.806	0.002	58	8
Right amygdala	26, -2, -14	2.880	0.002	54	10
Left precentral gyrus	-48, 2, 42	3.078	0.0006	48	11
Right inferior temporal gyrus	56, -52, -8	2.980	0.001	28	9
Left median cingulate	-6, 16, 34	2.759	0.003	21	6
Left postcentral gyrus	-56, -6, 24	2.954	0.001	15	8
Left inferior occipital gyrus	-44, -82, -10	2.994	0.001	13	10
Left inferior frontal gyrus, triangular part	-46, 40, 6	2.781	0.003	13	7
Right inferior frontal gyrus, orbital part	28, 30, -20	2.844	0.002	12	9
Left inferior frontal gyrus, orbital part	-30, 34, -18	2.791	0.003	10	9

Table S9. Seed-based d Mapping (SDM) analysis showing decreased gray matter volumes in PTSD group compared to control group. Jackknife Sensitivity analysis demonstrates the robustness of the results, the larger the value the more consistent the result.

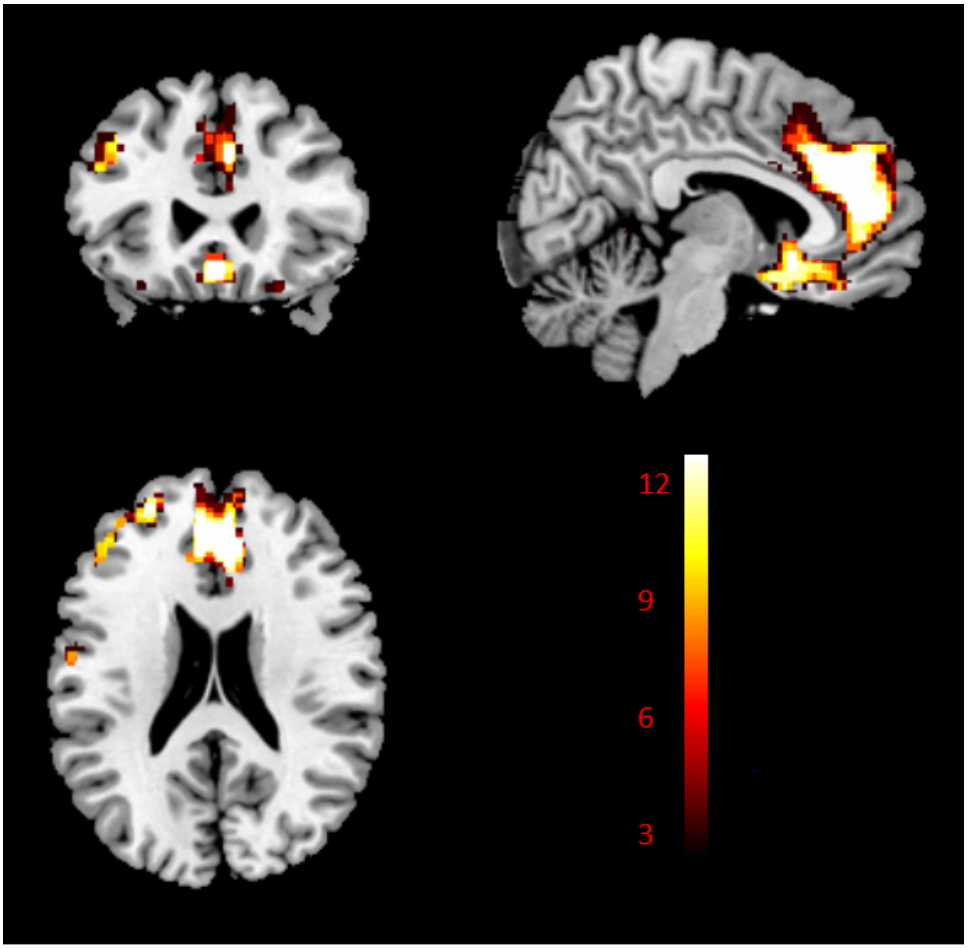


Figure S8. Binarised map of Jackknife Analyses (Main VBM Analyses). The overlaid colored regions indicate the number of sensitivity analyses reporting volume reductions in the same region. Thus the higher the value the more consistent the results.

Table S10 Regions of Significant Changes in GMV Between Patients with PTSD and NTC group – SDM Analysis					
Regions	MNI coordinates X, Y, Z	SDM z-value	P-value	Number of voxels	Number of studies in Jacknife Sensitivity analysis
Right anterior cingulate	4, 38, 22	-4.111	<0.0001	1612	5
Left precentral gyrus	-54, 2, 40	-3.420	<0.0001	391	3
Left middle frontal gyrus	-40, 32, 30	-3.397	0.0001	319	3

Table S10. Seed-based d Mapping (SDM) Analysis of 5 VBM studies showing decreased gray matter volumes in PTSD group compared to non-traumatised-control group. Jackknife Sensitivity analysis demonstrates the robustness of the results, the larger the value the more consistent the result.

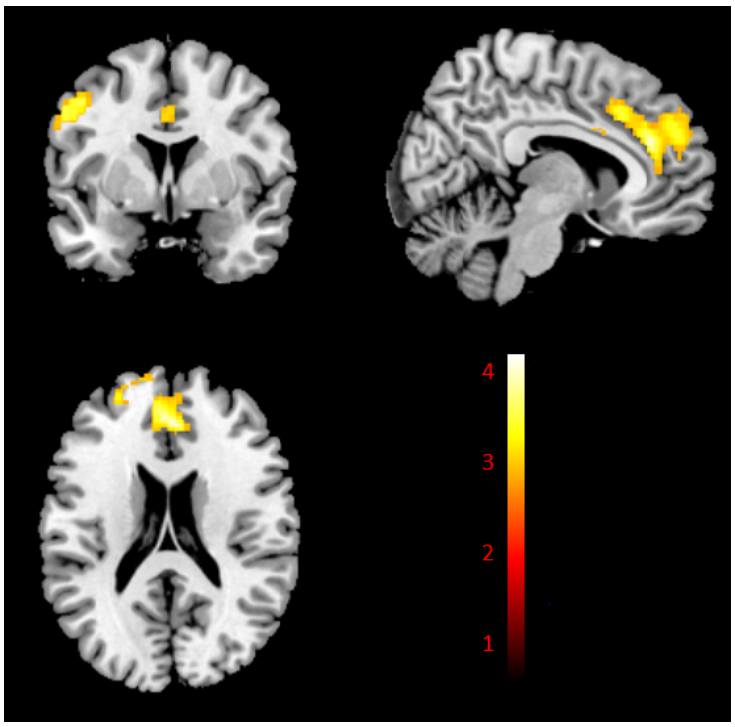


Figure S9. SDM meta-analysis of 5 VBM studies showing significant decreased gray matter volumes in PTSD group compared to non-traumatised-controls. Color bar indicates z scores. The 3D statistical map of this data is available to download.

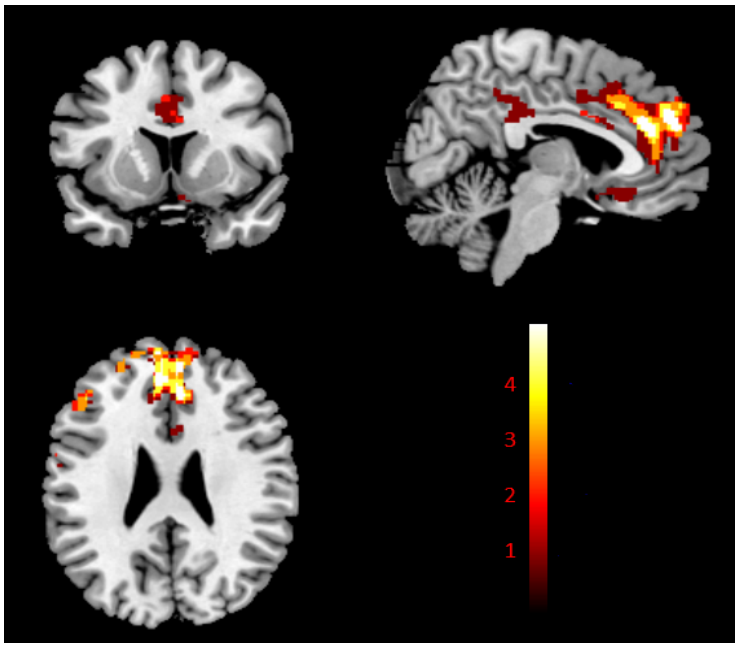


Figure S10. Binarised map of Jackknife Analyses (PTSD- Non-traumatised-controls). The overlaid coloured regions indicate the number of sensitivity analyses reporting volume reductions in the same region. Thus the higher the value the more consistent the results.

Table S11 Regions of Significant Changes in GMV Between Patients with PTSD and TC group – SDM Analysis					
Regions	MNI coordinates X, Y, Z	SDM z-value	P-value	Number of voxels	Number of studies Jacknife Sensitivity analysis
Left insula	-34, 0, -16	-2.499	0.0004	380	8
Right superior frontal gyrus	0, 22, -12	-2.454	0.0005	214	8
Right anterior cingulate	6, 32, 28	-2.594	0.0003	137	9
Left inferior frontal gyrus	-44, 38, 8	-2.373	0.008	94	7
Left middle frontal gyrus	-32, 50, 28	-2.396	0.0007	75	7
Left middle frontal gyrus, orbital part	-38, 54, -6	-2.159	0.003	56	6
Left inferior temporal gyrus	-56, -56, -10	-2.356	0.0009	43	6
Right inferior network, inferior longitudinal fasciculus	38, -34, -14	-2.164	0.003	14	5
Right fusiform gyrus	28, -38, -18	-2.163	0.003	10	5
Left anterior cingulate	-8, 52, 2	-2.133	0.003	10	4

Table S11. Seed-based d Mapping (SDM) Analysis of 9 VBM studies showing decreased gray matter volumes in PTSD group compared to traumatised-control group. Jackknife Sensitivity analysis demonstrates the robustness of the results, the larger the value the more consistent the result.

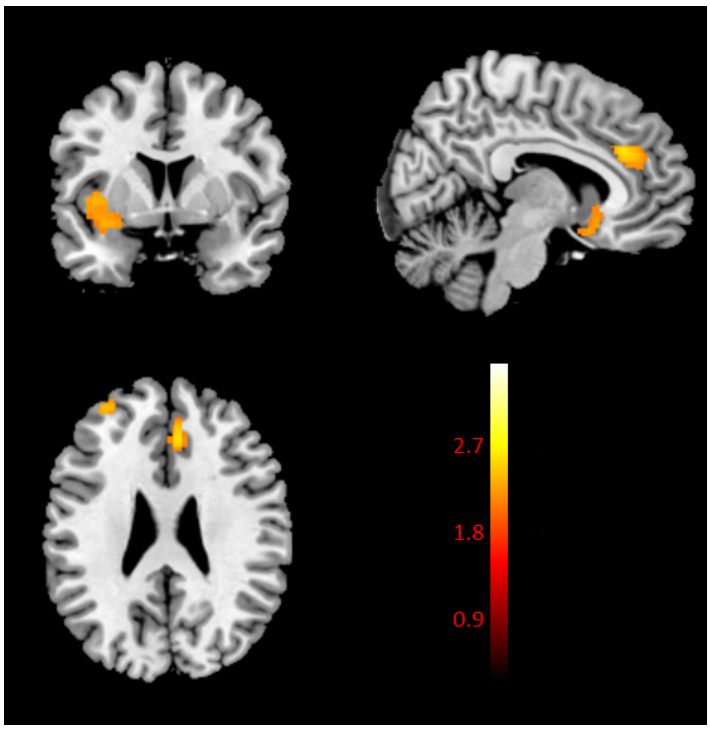


Figure S11. SDM meta-analysis of 9 VBM studies showing significant decreased gray matter volumes in PTSD group compared to Traumatised-controls. Color bar indicates z scores. The 3D statistical map of this data is available to download.

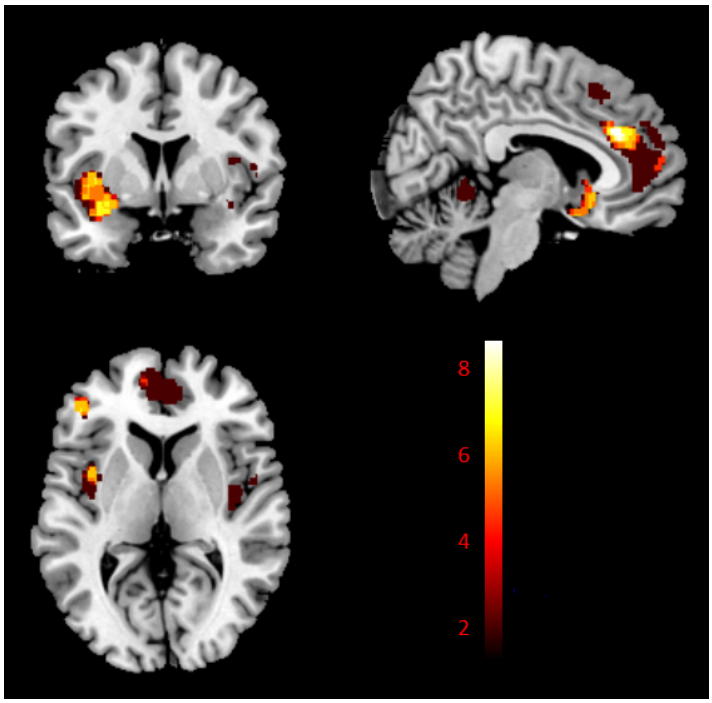


Figure S12. Binarised map of Jackknife Analyses (PTSD- Non-traumatised-controls). The overlaid colored regions indicate the number of sensitivity analyses reporting volume reductions in the same region. Thus, the higher the value the more consistent the results.

Regions	MNI coordinates X, Y, Z	SDM z-value	Number of voxels	Number of studies Jacknife Sensitivity analysis
Right anterior cingulate	6, 36, 26	-4.267	1453	17
Left superior frontal gyrus, dorsolateral	-26, 52, 20	-3.358	761	17
Right striatum	8, 14, -16	-2.732	49	13
Right median cingulate	6, -38, 40	-2.658	22	13
Right superior frontal gyrus, medial orbital	10, 66, -14	-2.733	21	14
Left precentral gyrus	-48, 0, 42	-2.757	17	13
Right inferior frontal gyrus, orbital part	28, 30, -20	-2.683	14	12
Left hippocampus	-28, -12, -20	-2.640	14	12
Right inferior temporal gyrus	54, -54, -10	-2.672	13	11
Left inferior frontal gyrus, orbital part	-34, 34, -18	-2.606	11	11

Table S12. Seed-based d Mapping (SDM) Analysis showing decreased gray matter volumes in PTSD group compared to control group. Jackknife Sensitivity analysis demonstrates the robustness of the results, the larger the value the more consistent the result.

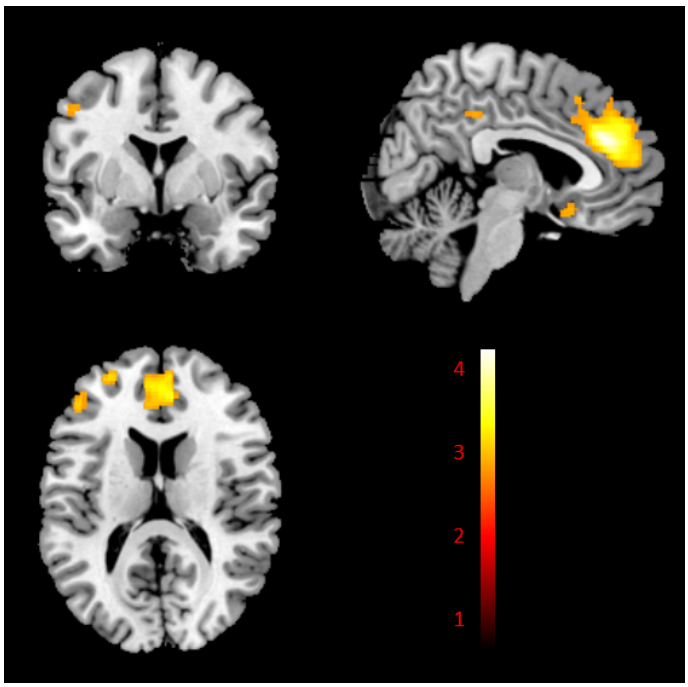


Figure S13. SDM meta-analysis of 17 VBM studies showing significant decreased gray matter volumes in PTSD group compared to all controls (including pediatric data). Color bar indicates z scores. The 3D statistical map of this data is available to download.

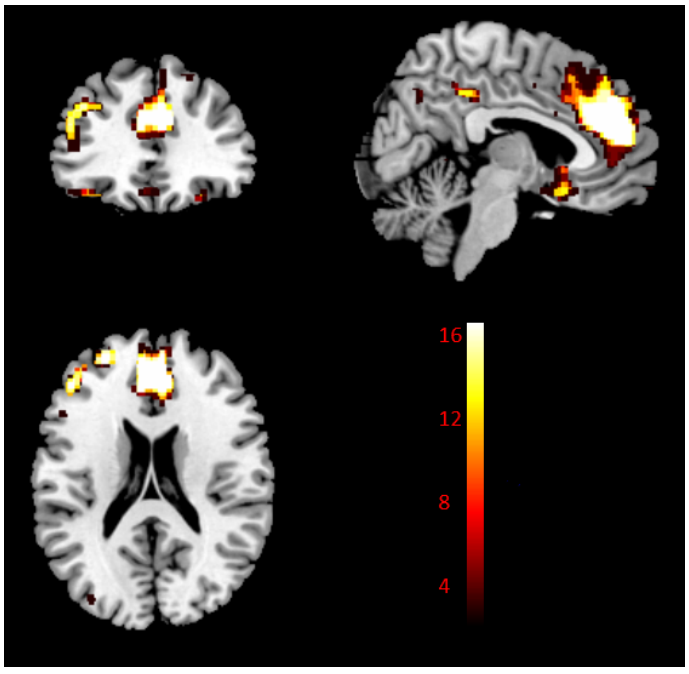


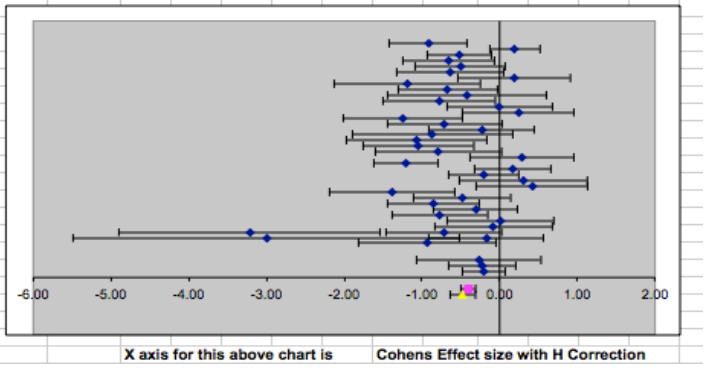
Figure S14. Binarised map of Jackknife Analyses (PTSD vs all contros – including pediatric data). The overlaid colored regions indicate the number of sensitivity analyses reporting volume reductions in the same region. Thus the higher the value the more consistent the results.

Region	Number of ROI studies (from table 2)	Hedges g ROI meta-analysis (from table 2)	Number of VBM studies	Hedges g Extracted region from VBM meta-analysis
R Insula	3	**-0.53 (-0.89 to -0.16)**	13	-0.11 (-0.31 to 0.10)
L Insula	3	**-0.78 (-1.29 to -0.28)**	13	-0.14 (-0.34 to 0.07)
R Anterior Cingulate	6	-0.14 (-0.43 to 0.14)	13	**-0.28 (-0.48 to -0.07)**
L Anterior Cingulate	6	**-0.40 (-0.69 to -0.11)**	13	**-0.28 (-0.51 to -0.05)**
R Hippocampus	38	**-0.42 (-0.59 to -0.26)**	13	-0.13 (-0.31 to 0.06)
L Hippocampus	38	**-0.38 (-0.55 to -0.22)**	13	-0.15 (-0.33 to 0.04)
R Amygdala	19	-0.24 (-0.52 to 0.03)	13	**-0.20 (-0.38 to -0.02)**
L Amygdala	19	-0.28 (-0.57 to 0.00)	13	**-0.20 (-0.38 to -0.02)**

Table S13. Region of interest meta-analysis compared to VBM meta-analysis (Seed-based d Mapping (SDM)). When comparing the methodologies it is important to note that effect sizes are calculated differently in each method. For example the inclusion of coordinates results in the SDM meta-analysis tends to reduce the magnitude of effect sizes as non-significant findings are assumed to be zero, furthermore SDM calculates the average effect size of a number of voxels rather than effect size of a single region. Note that the right column of this table is different from the clusters shown in table S11. In this table effect sizes are given for an entire structure, while table S11 shows clusters or 'hot spots' within a structure. Thus while a significant small cluster was found in the left hippocampus in table S11, when the entire structure was considered there was no overall difference in volume.

First Author	Year	Link to paper	Number of Patients (PTSD)	Number of Controls (NTC unless ony a TC group is present)	Diagnosis	CAPS scores	Regions measured	Age patients	SD Age patients	Age Controls	SD Age Controls	Female patients	Female controls
Bremner JD	1995	http://ajp.p	26	22	DSM-III-R	ns	left hippocampus, right hippocampus, left ten	46	1.8	44.5	7.3	0	0
Gurvits TV	1996	http://dx.d	7	8	DSM-III-R	70.3	intracranial cravity, whole brain, subarachnoi	44.4	1.7	38.1	10	0	0
Bremner JD	1997	http://dx.d	17	17	DSM-III-R	ns	left hippocampus, right hippocampus, left ten	40.1	5.7	42.4	7.3	5	5
De_Bellis MD	1999	http://dx.d	44	61	DSM-III-R	ns	intracranial volume, cerebral volume, cortical	12.2	2.4	12	2.3	19	25
Bonne O	2001	http://ajp.p	10	27	DSM-IV	57.9	left hippocampus, right hippocampus, left am	33.7	8.9	29.8	10.1	7	12
Carrion VG	2001	http://dx.d	24	24	DSM-IV	ns	total brain, right brain, left brain, total cerebr	11	ns	11	ns	10	10
De_Bellis MD	2001	http://dx.d	9	9	DSM-IV	ns	cerebral volume, temporal lobe, total amygda	10.6	1.6	10.5	1.6	4	4
Schuff N	2001	http://dx.d	18	19	DSM-IV	63.1	left hippocampus, right hipocampus, left ento	51.2	2.5	51.8	3.2	0	0
De_Bellis MD	2002	http://dx.d	28	66	DSM-IV	ns	intracranial volume, cerebral volume, cortical	11.47	3	11.58	2.83	14	35
De_Bellis MD	2002	http://dx.d	43	61	DSM-IV	ns	total superior temporal gyrus (STG), total righ	12.2	2.4	12	2.3	18	25
Fennema-Notest	2002	http://dx.d	11	17	DSM-IV	58	bilateral mesial temporal lobe (MTL) gray, left	33.35	10.3	35.3	12.5	11	17
Gilbertson MW	2002	http://www	12	23	DSM-IV	72.2	total brain volume, total hippocampus, right h	ns	ns	ns	ns	0	0
Villarreal G	2002	http://dx.d	12	10	DSM-IV	87	right hippocampus, left hippocampus, right hi	43	9.3	44	11.4	10	8
Bremner JD	2003	http://ajp.p	10	11	DSM-IV	ns	left hippocampus, right hippocampus, total br	35	6	32	8	10	11
De_Bellis MD	2003	http://dx.d	61	122	DSM-IV	ns	intracranial volume, cerebral volume, cerebra	11.74	2.63	11.71	2.56	30	60
Hedges DW	2003	http://jouri	4	4	DSM-IV	ns	total brain volume, total hippocampal volume	54.5	6	54.3	7.09	0	0
Rauch SL	2003	http://www	9	9	DSM-IV	70.8	total cortical volume, pregenual anterior cingu	52	1.9	51.7	1.9	9	9
Yamasue H	2003	http://dx.d	9	16	CAPS	62.2	VBM gray, VBM white	44.6	16	44.4	14	4	6

Hippocampus			Summary
SD for Effect size	1	input=	Pooled SD
Measure (L,R,T)	total	input=	Total
Hedges Correction	1	input=	H Correction
Volume effect size	0	input=	Cohens Effect size
Number of studies	41		
Number patients	909	Correlation	0.8
Number of controls	991		
Heterogeneity (Q)	105.32	**Publication Bias**	
I2 %	62.0		
p value	0.000	p value	0.012
Fixed Effects	-0.402		
(-95% to +95%)	-0.496	-0.308	
FFX p	0.000		
Random Effects	-0.473		
(-95% to +95%)	-0.635	-0.311	
RFX p	0.000		



Intracranial Volume			Summary
SD for Effect size	1	input=	Pooled SD
Measure (L,R,T)	Total	input=	Total
Hedges Correction	1	input=	H Correction
Volume effect size	0	input=	Cohens Effect size
Number of studies	13		
Number patients	224	Correlation	0.8
Number of controls	248		
Heterogeneity (Q)	16.70	**Publication Bias**	
I2 %	10.2		
p value	0.337	p value	0.112
Fixed Effects	-0.238		
(-95% to +95%)	-0.415	-0.060	
FFX p	0.009		
Random Effects	-0.244		
(-95% to +95%)	-0.432	-0.055	
RFX p	0.012		

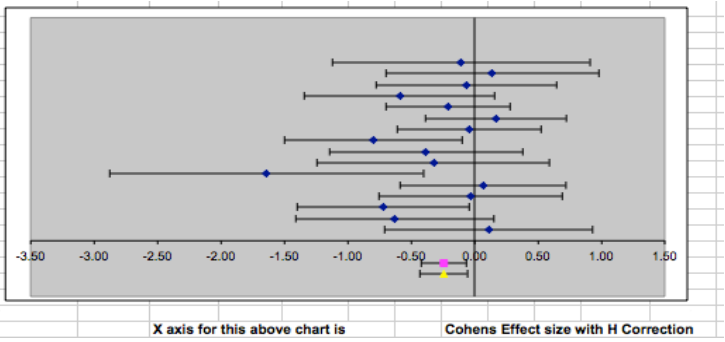


Figure S15: Screenshot of online database available at and meta-analysis available at www.ptsdmri.uk. The top part of the database is shown followed by a section of the meta-analysis page of the hippocampus and Intracranial volume showing forest plots and results.

References for Supplementary Materials and Papers Included in Database

References 1- 8 are citations from the supplementary materials while paper and subsequent references are papers included in the database.

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