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Altered resting-state functional activity in posttraumatic stress disorder: A quantitative meta-analysis

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Many functional neuroimaging studies have reported differential patterns of spontaneous brain activity in posttraumatic stress disorder (PTSD), but the findings are inconsistent and have not so far been quantitatively reviewed. The present study set out to determine consistent, specific regional brain activity alterations in PTSD, using the Effect Size Signed Differential Mapping technique to conduct a quantitative meta-analysis of resting-state functional neuroimaging studies of PTSD that used either a non-trauma (NTC) or a trauma-exposed (TEC) comparison control group. Fifteen functional neuroimaging studies were included, comparing 286 PTSDs, 203 TECs and 155 NTCs. Compared with NTC, PTSD patients showed hyperactivity in the right anterior insula and bilateral cerebellum, and hypoactivity in the dorsal medial prefrontal cortex (mPFC); compared with TEC, PTSD showed hyperactivity in the ventral mPFC. The pooled meta-analysis showed hypoactivity in the posterior insula, superior temporal, and Heschl's gyrus in PTSD. Additionally, subgroup meta-analysis (non-medicated subjects vs. NTC) identified abnormal activation in the prefrontal-limbic system. In meta-regression analyses, mean illness duration was positively associated with activity in the right cerebellum (PTSD vs. NTC), and illness severity was negatively associated with activity in the right lingual gyrus (PTSD vs. TEC).

Posttraumatic stress disorder (PTSD) is a psychiatric illness caused by traumatic events, characterized by traumatic event re-experiencing (e.g. flashbacks), avoidance of trauma-related events, hyperarousal (e.g. hypervigilance), and negative cognitions and mood[1]. Present understanding emphasizes the contribution of deficient cognitive and emotional processes to the symptoms of PTSD[2,3]. This implicates a variety of brain regions including the amygdala, prefrontal cortex, temporal cortex, insula, thalamus, anterior cingulate cortex (ACC) and hippocampus[4–6]. Neurocircuitry linking the increased activity of limbic regions such as amygdala and insula and the decreased medial prefrontal activation may also contribute to the anxiety and emotional dysregulation in PTSD[4,7].

Multiple neuroimaging modalities such as functional magnetic resonance imaging (fMRI), single-photon emission computed tomography (SPECT), and positron emission tomography (PET) have been employed to investigate the aforementioned altered brain activities in PTSD. In general terms, fMRI makes use of the blood oxygen level-dependent (BOLD) signal to show patterns of activity in the brain[4], either in response to specific tasks or in the so-called resting state; two analysis methods, amplitude of low-frequency (0.01–0.08 Hz) fluctuation (ALFF)[8] and regional homogeneity (ReHo)[9], have been used to quantify patterns of fMRI resting-state

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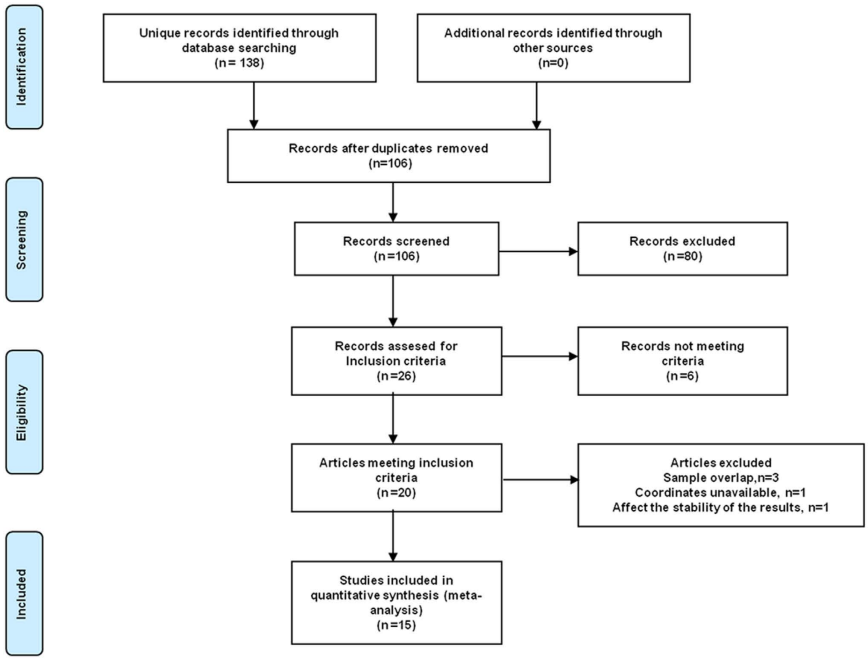

Figure 1. Meta-analysis of resting-state studies in PTSD.

activity. In addition, both regional cerebral blood flow (rCBF)/PET/SPECT and glucose metabolism (rCMglu)/PET can be used to visualize the activity of specific brain regions, and these have proved useful in studying PTSD[4,10]. The four different techniques of ALFF[11], ReHo[9], rCBF[12], and rCMglu[13] have generally been considered to reflect regional spontaneous neuronal activity in a similar manner, lending themselves to similar quantitative interpretation in terms of brain physiology; it therefore makes sense to combine them to explore the neural activity patterns of PTSD[14–17].

Resting-state neuroimaging, which evaluates regional interactions that occur when a subject is not performing an explicit task, has proved an informative and reliable research tool[18] which can provide insights into the pathophysiology of PTSD. Several studies have examined resting brain activity in PTSD[12,19–28], revealing significantly different spontaneous activity in the cerebral cortex (e.g. superior temporal gyrus, medial prefrontal cortex (mPFC), inferior parietal lobule and middle occipital gyrus), the limbic regions (e.g. the amygdala, hippocampus, insula, thalamus, and ACC), and even the cerebellum. However, the results have not been wholly consistent. For example, some studies have reported increased activation of the insula in PTSD[27,29,30], while others reported decreased[31,32] or absent activation[24,33] in the insula. There are several possible reasons for this variation. Published studies differ considerably in sample size, the demographic and clinical characteristics of the patients, differential levels in baseline activity and in the imaging protocols used. Another factor, often overlooked, is the use of different control groups: neuroimaging findings in PTSD may be compared to individuals without any history of trauma exposure ('non-trauma controls', NTC) or to individuals with a history of trauma exposure who have not developed PTSD ('trauma-exposed controls', TEC), and clearly these two comparisons have different pathophysiological implications.

Although many task-related neuroimaging meta-analyses, synthesizing a variety of symptom provocation and cognitive-emotional studies, have been performed to elucidate the neural underpinnings of PTSD[14–17,34], discrepancies between the results for different tasks have likely contributed to the heterogeneity of the conclusions[16,17,34]. Therefore, performing a meta-analysis of resting-state neuroimaging studies which observe the brain in the absence of overt task performance or stimulation should offer the technical advantage of greatly increased homogeneity of reported studies.

In the present study, we used a voxel-based meta-analytic technique, Effect Size Signed Differential Mapping (ES-SDM), to identify consistent functional brain alterations in PTSD by integrating the full range of studies reporting resting regional brain activity. We performed two individual pooled meta-analyses, comparing PTSD with TEC and with NTC respectively, to explore the different pathophysiological implications in PTSD. In addition, we used subgroup meta-analyses to control for comorbidity and medication. Finally, we performed meta-regression analysis to examine the potential effects of age, illness severity and illness duration of PTSD patients.

Results

Studies included in the meta-analyses. The search strategy identified a total of 138 papers (Fig. 1), of which 19 papers[12,19–24,26–33,35–38] met the inclusion criteria. No additional eligible articles were found in the reference lists of the selected studies. All these were in English except 4 papers[23,29,30,38] in Chinese, which were translated into English for assessment. For studies that reported results for multiple analysis methods such as ALFF

Study	Modality/Analysis	Trauma type	Group; no.(female)			Group; mean age(y)			MID	CAPS	DS	Thre	Co	QS
			PTSD	TEC	HC	PTSD	TEC	HC						
Baojuan *et al.*[19]	ASL-fMRI/rCBF	Mine disaster	10(0)	10(0)	–	41	34	–	6	79	Drug-naïve	uncorr	N	10
Bing *et al.*[20]	rs-fMRI/ALFF	MVC	20(7)	–	20(6)	33	–	3	7	52	Drug-free	corr	N	10
Bluhm *et al.*[21]	rs-fMRI/ALFF	SA	17(17)	–	15(15)	39	–	38	>6	77	Drug	corr	Y	9
Bonne *et al.*[12]	SPECT/rCBF	Mixed	11(7)	17(9)	11(6)	34	35	33	7	58	Drug-naïve	uncorr	Y	9
Huang *et al.*[23]	rs-fMRI/ALFF	Mixed	10(7)	–	10(7)	33	–	32	16	NA	Drug-naïve	uncorr	N	9
Kim *et al.*[35]	SPECT/rCBF	Subway fire	19(13)	–	19(7)	27	–	32	15	71	Drug-free	corr	Y	9.5
Kim *et al.*[24]	PET/rCMRglu	SA	12(12)	–	15(15)	36	–	38	10	NA	Drug	uncorr	N	9
Semple *et al.*[26]	PET/rCBF	Combat	7(0)	–	6(0)	43	–	34	>12	NA	Drug-free	uncorr	N	8.5
Shin *et al.*[33]	PET/rCMRglu	Combat	14(0)	19(0)	14(0)	58	57	58	>6	66	Drug	uncorr	Y	9
Song *et al.*[29]	rs-fMRI/ALFF	Burn	16(1)	16(1)	16(1)	38	36	39	9	68	Drug-free	corr	N	10
Yan *et al.*[27]	rs-fMRI/ALFF	Combat	52(0)	52(0)	–	33	34	–	>6	67	NA	corr	N	9.5
Yin *et al.*[31]	rs-fMRI/ALFF	Earthquake	54(39)	72(50)	–	42	42	–	8	64	Drug-naïve	corr	N	10
Zhang *et al.*[30]	rs-fMRI/ReHo	MVC	9(4)	–	15(7)	33	–	26	>6	NA	Drug-naïve	uncorr	N	9
Zhong *et al.*[36]	rs-fMRI/ReHo	Mixed	14(8)	–	14(8)	31	–	29	5	68	Drug-naïve	corr	Y	9
Zhu *et al.*[37]	rs-fMRI/ALFF	Earthquake	21(17)	17(12)	–	47	43	–	48	69	Drug-naïve	corr	Y	9.5

Table 1. Summary of studies included in the meta-analysis. TEC, trauma-exposed controls without PTSD; NTC, non-traumatized controls without PTSD; SA, sexual abuse/assault; MVA, motor vehicle accident; SPECT, single-photon emission computed tomography; PET, positron emission tomography; rs-fRMI, resting-state functional magnetic resonance imaging; ASL, arterial spin labeling; rCBF, regional cerebral blood flow; ALFF, amplitude of low-frequency fluctuation; ReHo, regional homogeneity; rCMRglu, regional cerebral glucose metabolic rate; CAPS, clinician-administered PTSD scale; MID, Mean illness duration (months); DS, Drug state; Thre, Threshold; Co, Comorbidity; QS, Quality score (out of 10); NA, not available; Y, yes; N, no.

and ReHo with the same group or overlapping groups of participants in different publications[28,31,32,37,38], the studies using ALFF were selected to decrease the heterogeneity of methodology (as more single-method studies used ALFF than ReHo). For 2 studies[32,37] which used ALFF with overlapping groups of participants, the study with the most participants was selected. For two studies[19,21] which reported between-group differences between in functional connectivity between multiple brain regions as well as in regional brain activities, we took only the regional brain activity results into account. One study[24] used two different modalities (SPECT and PET) with the same PTSD group but different control groups, and in this case we selected the larger control group. One study[22] which showed significant statistical heterogeneity ($p < 0.005$) was excluded. Finally 15 studies were included in the meta-analysis (Table 1). These included 6 studies[12,21,33,35–37] that recruited partial PTSD patients with comorbidity and 3 studies[21,24,33] that recruited partial PTSD patients taking medication at the time of study. Three studies[12,29,33] employing a three-group design contributed separately to the TEC and NTC analyses. One study[21] contributed no coordinates as no significant between-group differences in low-frequency oscillations were found.

Finally, our total sample comprised 286 patients with PTSD, 203 TECs and 155 NTCs. In the PTSD vs. TEC group were 7 studies comprising 178 PTSD and 203 TEC; controlling for comorbidity and medication there were 4 studies comprising 132 PTSD and 150 TEC, and 5 studies comprising 112 PTSD and 132 TEC. In the PTSD vs. NTC group were 11 studies comprising 149 PTSD and 155 NTC; controlling for comorbidity and medication there were 6 studies comprising 74 PTSD and 82 NTC, and 8 studies comprising 106 PTSD and 111 NTC, respectively. In no study was there any significant difference in age or sex between the PTSD and control groups.

Meta-analysis of studies of PTSD vs. NTC. In the pooled whole-brain meta-analysis, in PTSD compared to non-trauma controls, resting-state activity was increased in the bilateral cerebellum, right insula (anterior part) and inferior frontal gyrus (IFG), and decreased in the dorsal medial prefrontal cortex (dmPFC) (including the bilateral medial superior frontal gyrus (mSFG) and anterior cingulate gyrus (ACC; BA32)), left insula (posterior part, BA 48) and adjacent left auditory cortex (including the superior temporal gyrus (STG; BA 48) and Heschl's gyrus (HG, BA 48)) (Fig. 2 and Table 2). The results were the same in the subgroup meta-analysis of 'non-comorbidity' studies compared to NTC. In the subgroup meta-analysis of 'non-medication' studies compared to NTC, resting-state activity in PTSD was increased in the right anterior insula, left amygdala, left parahippocampal gyrus and hippocampus, and right IFG, and decreased in the dmPFC (including the bilateral SFG and ACC).

Meta-analysis of studies in PTSD vs. TEC. In the pooled whole-brain meta-analysis, in PTSD compared to trauma-exposed controls, resting-state activity was increased in the ventral mPFC (vmPFC, including the bilateral mSFG, bilateral gyrus rectus (BA 11) and bilateral ACC), left SMG, and middle frontal gyrus (MFG), and decreased in the right posterior insula and adjacent right auditory cortex (including the right HG and STG) and right visual cortex (including the right lingual gyrus (LG) and calcarine fissure and surrounding cortex (CFC, BA 18)) (Fig. 2 and Table 3). In the subgroup meta-analysis of non-comorbidity studies, resting-state activity in PTSD compared to TEC was increased in the vmPFC and right MFG, and decreased in the right posterior insula. The results were the same in the subgroup meta-analysis of non-medication studies compared to TEC.

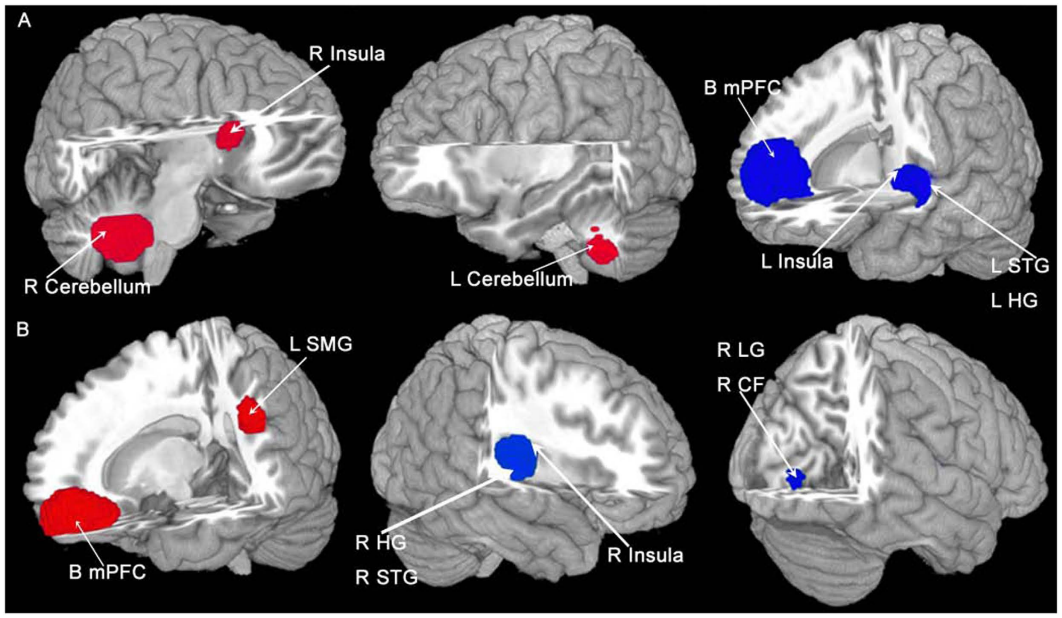

Figure 2. The areas of increased (red) and decreased (blue) resting-state brain activity in the meta-analyses of studies in PTSD patients compared with NTC (**A**) and TEC (**B**). R, right; L, left; (**B**), bilateral; mPFC, medial prefrontal cortex; SMG, supramarginal gyrus; STG, superior temporal gyrus; HG, Heschl's gyrus; LG, lingual gyrus; CFC, calcarine fissure cortex; PTSD, posttraumatic stress disorder; NTC, non-traumatized controls; TEC, trauma-exposed controls.

Reliability analysis. In a whole-brain jack-knife sensitivity analysis of PTSD vs. NTC (Table 4), the findings of decreased dmPFC activity in patients with PTSD were highly replicable, being preserved throughout all 11 combinations of the data sets. The results in the right cerebellum and left anterior insula were significant in all but 1 combination, and the results in the right posterior insula, right IFG, left cerebellum and left STG were significant in all but 2 combinations.

Whole-brain jack-knife sensitivity analysis of PTSD vs. TEC (Table 5) showed that the findings in bilateral vmPFC, bilateral gyrus rectus, and right posterior insula were highly replicable, being preserved in all 7 combinations of data sets. The results in left ACC, right MFG and right STG were significant in all but 1 combination, and the increased activity in left SMG and left STG was significant in all but 2 combinations.

Meta-regression. Variables explored by regression were age and the duration and severity of illness (Fig. 3). In meta-regression analyses of studies of PTSD vs. NTC the mean illness duration was positively associated with resting-state activity in the right cerebellum; no effect of age and illness severity was detected. In meta-regression analyses of PTSD vs. TEC age was positively associated with resting-state activity in the right SFG and negatively associated with activity in the left SMG; illness severity was negatively associated with activity of right LG; no effect of illness duration was detected.

Discussion

We used quantitative ES-SDM meta-analytic methods to synthesize findings from 15 resting-state functional neuroimaging studies of PTSD, in which patients with PTSD were compared to either TEC or NTC. The result confirmed a subset of regional differences that have frequently been reported in previous PTSD studies, including hyperactive anterior insula and hypoactive dmPFC in PTSD patients compared with NTC, and hyperactive vmPFC in PTSD compared with TEC. In addition differences were found in other regions, such as the auditory and visual cortex and cerebellum, that have hitherto been neglected in the modeling of trauma symptoms. Results were the same in subgroup meta-analysis of 'non-comorbidity' studies compared with NTC, and additional hyperactivity of the amygdala and hippocampus in the PTSD patients were identified in the subgroup meta-analysis of 'non-medication' studies compared with NTC.

Findings in the pooled meta-analysis. In the meta-analyses, PTSD patients had increased resting-state brain activity in vmPFC compared with TEC, and decreased activity in dmPFC when compared with NTC. Alterations in mPFC have often been reported in PTSD studies using various imaging modalities including structural MRI[39], task-related MRI[40] and resting-state fMRI[31]. It therefore seems likely that mPFC is involved in the pathogenesis of PTSD. mPFC is a complex region, broadly divided into dorsal and ventral subdivisions, of which the dorsal part is involved in appraisal of negative emotion and detection of emotional conflict, while the ventral part has a regulatory role with respect to the limbic region in generating emotion responses[41]. MPFC is accepted as playing a critical role in cognitive and emotional dysregulation in the pathogenesis of PTSD[7,42]. Previous meta-analyses have often synthesized a variety of task-related studies, in which different task paradigms invoke different responses in the mPFC (such as decreased vmPFC activation in response to emotional vs. neutral scenes

Brain Regions	Maximum			Clusters	
	MNI coordinates, x, y, z	SDM value	p-value	No. voxel	Breakdown (no. of voxels)
Pooled meta-analysis					
PTSD > NTC					
R cerebellum	30, −38, −40	1.808	0.000372	714	R cerebellum, hemispheric lobule X (608)
					M cerebellar peduncle (106)
R insula, BA 48	32, 16, 2	1.563	0.001783	101	R insula, BA 48 (90)
					R external capsule (6)
					R lenticular nucleus, putamen, BA 48 (5)
L cerebellum	−32, −46, −46	1.449	0.003311	190	L cerebellum, hemispheric lobule VIII (183)
					M cerebellar peduncle (7)
R inferior frontal gyrus, BA 44	50, 12, 18	1.432	0.003644	40	R inferior frontal gyrus, opercular part, BA 44 (40)
PTSD < NTC					
R superior frontal gyrus, medial, BA 10	6, 50, 6	−1.327	0.000541	1496	R superior frontal gyrus, medial, BA 10 (374)
					L superior frontal gyrus, medial, BA 10 (502)
					R anterior cingulate/paracingulate gyri, BA 32 (402)
					L anterior cingulate/paracingulate gyri, BA 32 (216)
					R cingulum (cingulate gyrus) (2)
L rolandic operculum, BA 48	−44, −10, 6	−1.129	0.001809	411	L insula, BA 48 (89)
					L superior temporal gyrus, BA 48 (140)
					L rolandic operculum, BA 48 (106)
					L Heschl's gyrus, BA 48 (76)
Subgroup meta-analysis of studies without comorbidity					
PTSD > NTC					
R cerebellum	12, −92, −26	1.597	0.001193	204	R cerebellum, crus I (204)
R insula, BA 48	36, 20, 12	1.55	0.001577	384	R insula, BA 48 (175)
					R inferior frontal gyrus, BA 48 (195)
					R lenticular nucleus, putamen, BA 48 (9)
					R external capsule (3)
					R rolandic operculum, BA 48 (2)
R cerebellum	30, −36, −42	1.527	0.001779	237	R cerebellum (237)
PTSD < NTC					
R superior frontal gyrus, medial, BA 10	6, 62, 6	−1.528	0.000382	1443	R superior frontal gyrus, medial, BA 10 (457)
					L superior frontal gyrus, medial, BA 10 (674)
					R anterior cingulate/paracingulate gyri, BA 32 (246)
					L anterior cingulate/paracingulate gyri, BA 32 (60)
					R median cingulate/paracingulate gyri, BA 32 (5)
					R cingulum(cingulate gyrus) (1)
L insula, BA 48	−38, −6, 6	−1.432	0.000992	873	L insula, BA 48 (281)
					L superior temporal gyrus, BA 48 (248)
					L rolandic operculum, BA 48 (211)
					L Heschl's gyrus, BA 48 (107)
					L External capsule (19)
					L postcentral gyrus, BA 48 (7)
Subgroup meta-analysis of studies without medication					
PTSD > NTC					
R insula, BA 48	32, 14, 2	1.764	0.000693	228	R insula, BA 48 (146)
					R external capsule (50)

Continued

Brain Regions	Maximum			Clusters	
	MNI coordinates, x, y, z	SDM value	p-value	No. voxel	Breakdown (no. of voxels)
					R lenticular nucleus, putamen, BA 48 (18)
					R inferior frontal gyrus, BA 48 (14)
L amygdala, BA 34	−28, 0, −26	1.727	0.000865	333	L amygdala, BA 34 (115)
					L parahippocampal gyrus, BA 28 (83)
					L superior temporal gyrus, BA 38 (72)
					L uncinate fasciculus (19)
					L hippocampus, BA 36 (42)
					L fusiform gyrus, BA 36 (1)
					L fornix (cres)/Striaterminalis (1)
R inferior frontal gyrus, BA 44	52, 12, 18	1.602	0.001822	125	R inferior frontal gyrus, BA 44 (123)
					R precentral gyrus, BA 44 (1)
					R rolandic operculum, BA 48 (1)
PTSD < NTC					
R superior frontal gyrus, medial, BA 10	4, 40, 12	−1.459	0.000206	1828	R superior frontal gyrus, medial, BA 10 (492)
					L superior frontal gyrus, medial, BA 10 (637)
					R anterior cingulate/paracingulate gyri, BA 32 (463)
					L anterior cingulate/paracingulate gyri, BA 32 (234)
					R cingulum(cingulate gyrus) (2)
R thalamus	10, −28, 16	−1.147	0.001558	18	R thalamus (16)
					R hippocampus (2)
Genu_of_corpus_callosum	10, 22, −2	−1.098	0.002076	9	Genu of corpus callosum (7)
					R caudate nucleus, BA 11 (2)

Table 2. Brain regions showing greater and less activity in PTSD vs. NTC (voxelwise uncorrected $p < 0.005$ and FWHM 20 mm). L, Left; R, right; BA, Brodmann area; MNI, Montreal Neurological Institute; M, Middle; SDM, signed differential mapping.

in PTSD patients[43] but increased vmPFC activation during encoding of negative words[44]) that may increase the heterogeneity of the conclusions. In contrast, our results, reflecting intrinsic brain activity without the influence of external tasks, may provide more reliable information on neural patterns in mPFC and their possible roles in the pathophysiology of PTSD. However, the mPFC activity differences observed between PTSD patients and controls are not unambiguously interpretable in pathophysiological terms, and will need to be combined with results of task-related fMRI. In a self-referential cognition study, PTSD patients demonstrated less dmPFC response than did healthy controls[40]. Decreased dmPFC activity may be related to cognition in appraisal of negative emotion and resolution of conflict emotion in PTSD patients in the baseline state compared with the NTC[41]. However, increased vmPFC activity in PTSD relative to the TEC is inconsistent with the influential view that negative emotion regulation is lacking in PTSD patients owing to the hypoactive vmPFC, manifesting as failure to inhibit the hyperactive limbic regions (such as amygdala and insula)[7]. Lanius and colleagues have described a specific dissociative subtype of PTSD (defined as showing detachment from the overwhelming emotional content of the experience) that exhibits higher midline prefrontal inhibition of the limbic regions[45]. However, it is impossible to be clear about the subtype of the PTSD patients included in the present meta-analysis. Clearly the role of hyperactive dmPFC in PTSD merits further study.

We found hyperactive right anterior insula in PTSD patients compared with NTC at rest. Hyperactivity in the anterior insula has been reported in resting-state functional neuroimaging studies of PTSD[27,30] as well as in multiple task-based studies[46,47], which seems to be a consistent pattern across different brain states. The functions of the anterior insula include not only the generalization of interoceptive anxiety but also perception of internal states[48]. Hyperactivity in anterior insula at rest may suggest an elevated detection of and response to internal and external salient stimuli[49]. In addition, we also found hypoactivity in posterior insula and its adjacent sensory-related regions including the STG and HG in PTSD patients compared with both TEC and NTC. This is not inconsistent with the previously-mentioned hyperactivity in anterior insula, because there are well-documented structural connectivity and functional differences between the anterior and posterior insula[50–52], the anterior insula being more related to self-awareness, salience detection, cognition, and other emotional/social behaviors, while the posterior part is related more to sensory perception and motor-related functions[51,53]. Moreover, we found hypoactivity in some sensory-related regions including the STG, HG (auditory cortex), and LG (visual cortex). Previous resting-state studies also revealed hypoactivity in the LG, cuneus[31], and STG[54] in PTSD. In a study investigating the resting-state network using independent component analysis, PTSD patients showed abnormal functional connectivity in the auditory and visual network, suggestive of low-level perceptual deficits[55]. Thus, hypoactivity in the posterior insula as well as these sensory-related cortices at rest may reflect decreased perception of the

Brain Regions	Maximum			Cluster	
	MNI coordinates x, y, z	SDM value	p-value	No. of voxel	Breakdown (no. of voxels)
Pooled meta-analysis					
PTSD > TEC					
L superior frontal gyrus, medial orbital, BA 11	−2, 48, −10	2.915	1.45E-05	1407	R superior frontal gyrus, medial orbital, BA 11 (448)
					L superior frontal gyrus, medial orbital, BA 11 (431)
					L gyrus rectus, BA 11 (214)
					R gyrus rectus, BA 11 (180)
					L anterior cingulate/paracingulate gyri, BA 10 (118)
					R anterior cingulate//paracingulate gyri, BA 11 (16)
L supramarginal gyrus, BA 48	−54, −28, 32	1.745	0.001651	169	L supramarginal gyrus, BA 48 (117)
					L superior temporal gyrus, BA 42 (51)
					L rolandic operculum, BA 48 (1)
R middle frontal gyrus, BA 46	40, 42, 36	1.676	0.002254	59	R middle frontal gyrus, BA 46 (59)
PTSD < TEC					
R Heschl's gyrus, BA 48	38, −22, 8	−1.681	0.000941	370	R insula, BA 48 (141)
					R rolandic operculum, BA 48 (104)
					R Heschl's gyrus, BA 48 (85)
					External_capsule_R (29)
					R superior temporal gyrus, BA 48 (11)
R calcarine fissure/surrounding cortex, BA 18	14, −78, 2	−1.874	0.000476	362	R calcarine fissure/surrounding cortex, BA 17 (259)
					R lingual gyrus, BA 18 (67)
					R cuneus cortex, BA 17 (34)
					L calcarine fissure/surrounding cortex (1)
					R superior occipital gyrus, BA 18 (1)
R fusiform gyrus, BA 37	38, −56, −14	−1.69	0.000904	88	R fusiform gyrus, BA 37 (83)
					R cerebellum, BA 37 (5)
R caudate nucleus	8, 6, 8	−1.48	0.004387	5	R caudate nucleus (5)
Subgroup meta-analysis of studies without comorbidity					
PTSD > TEC					
L superior frontal gyrus, medial orbital, BA 11	−2, 48, −12	3.425	9.29E-06	2012	R superior frontal gyrus, medial orbital, BA 11 (612)
					L superior frontal gyrus, medial orbital, BA 11 (545)
					L gyrus rectus, BA 11 (347)
					R gyrus rectus, BA 11 (242)
					L anterior cingulate/paracingulate gyri, BA 10 (210)
					R anterior cingulate/paracingulate gyri, BA 11 (52)
					L anterior corona radiata (3)
					L olfactory cortex (1)
R middle frontal gyrus, BA 46	42, 42, 34	1.522	0.00243	100	R middle frontal gyrus, BA 46 (100)
PTSD < TEC					
R fusiform gyrus, BA 37	42, −58, −18	−1.743	0.000846	307	R cerebellum, BA 37 (154)
					R fusiform gyrus, BA 37 (151)
					R inferior temporal gyrus, BA 37 (2)
R calcarine fissure/surrounding cortex, BA 18	16, −98, 0	−1.739	0.00086	542	R calcarine fissure/surrounding cortex, BA 17 (338)
					R lingual gyrus, BA 18 (104)
					R cuneus cortex, BA 17 (68)

Continued

Brain Regions	Maximum			Cluster	
	MNI coordinates x, y, z	SDM value	p-value	No. of voxel	Breakdown (no. of voxels)
					L calcarine fissure/surrounding cortex (22)
					R superior occipital gyrus, BA 18 (9)
					L cuneus cortex, BA 18 (1)
R rolandic operculum, BA 48	50, −12, 12	−1.524	0.00188	207	R rolandic operculum, BA 48 (68)
					R insula, BA 48 (54)
					R Heschl's gyrus, BA 48 (30)
					R external capsule (27)
					R superior temporal gyrus, BA 48 (25)
					R lenticular nucleus, putamen, BA 48 (3)
Subgroup meta-analysis of studies without medication					
PTSD > TEC					
R gyrus rectus, BA 11	4, 46, −18	2.026	0.000549	648	R superior frontal gyrus, medial orbital, BA 11 (322)
					L superior frontal gyrus, medial orbital, BA 11 (156)
					R gyrus rectus, BA 11 (95)
					L gyrus rectus, BA 11 (53)
					L anterior cingulate/paracingulate gyri, BA 10 (22)
R middle frontal gyrus, BA 46	40, 40, 30	2.024	0.000569	147	R middle frontal gyrus, BA 46 (147)
PTSD < TEC					
R Heschl's gyrus, BA 48	44, −16, 10	−2.024	0.000249	381	R insula, BA 48 (133)
					R rolandic operculum, BA 48 (115)
					R Heschl's gyrus, 0.000249 (76)
					R external capsule (36)
					R superior temporal gyrus, BA 48 (21)
R calcarine fissure/surrounding cortex, BA 18	12, −92, 8	−2.389	1.03E-05	405	R calcarine fissure/surrounding cortex, BA 18 (270)
					R lingual gyrus, BA 18 (76)
					R cuneus cortex (53)
					R superior occipital gyrus, BA 18 (3)
					L calcarine fissure/surrounding cortex, BA 17 (3)
R fusiform gyrus, BA 37	38, −56, −14	−2.123	0.000135	145	R fusiform gyrus, BA 37 (125)
					R lingual gyrus, BA 19 (16)
					R cerebellum, BA 37 (3)
					R inferior temporal gyrus, BA 37 (1)

Table 3. Brain regions showing greater and less activity in PTSD vs. TEC (voxelwise uncorrected $p < 0.005$ and FWHM 20 mm). L, Left; R, right; BA, Brodmann area; MNI, Montreal Neurological Institute; SDM, signed differential mapping.

external environment in PTSD patients compared with both TEC and NTC. Furthermore, hypoactivity of posterior insula and its adjacent sensory-related regions was reliably present in both pooled meta-analyses of PTSD vs. TEC and PTSD vs. NTC, which may suggest that this is a true disease-related pattern. However, it is also possible that the hypoactivity in these sensory-related regions may be related to differing responses to the confining environment of the MRI scanner. Further study is warranted.

Our finding of cerebellar hyperactivity in PTSD is consistent with reports of elevated cerebellum rCBF activity in PTSD at rest[12]. Cerebellum has been implicated in the pathophysiology of PTSD, some studies reporting altered functioning[20,56] and even structure[57] of the cerebellum in PTSD. The cerebellum, traditionally associated with motor control, is increasingly implicated in cognitive processing and emotion mediation[58,59], and intimate afferent and efferent connections to the prefrontal cortex provide a neuroanatomical substrate[60,61]. Patients with cerebellar lesions manifest a constellation of cognitive, affective and behavioral abnormalities included distractibility, disinhibition, anxiety, as well as aggression and irritability[62]. Kipping and colleagues[63] investigating the negative affective responses to positive events in PTSD, found that negative affective interference scores positively predicted response within the right cerebellum, left amygdala, and right middle frontal gyrus. Furthermore,

Discarded studies	Hyperactivation regions				Hypoactivation regions					
	R cerebellum	R insula	R IFG	L cerebellum	R mSFG	L mSFG	L ACC	R ACC	L insula	L STG
Bing *et al.*[20]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Bluhm *et al.*[21]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Bonne *et al.*[12]	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
Huang *et al.*[23]	Y	Y	Y	Y	Y	Y	Y	Y	N	N
Kim *et al.*[35]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Kim *et al.*[24]	N	Y	Y	N	Y	Y	Y	Y	N	N
Semple *et al.*[26]	Y	N	N	Y	Y	Y	Y	Y	Y	Y
Shin *et al.*[33]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Song *et al.*[29]	Y	N	N	Y	Y	N	N	Y	Y	Y
Zhang *et al.*[30]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Zhong *et al.*[36]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

Table 4. Sensitivity analyses of studies in the meta-analysis of PTSD vs. NTC. L, left; R, right; IFG, inferior frontal gyrus; mSFG, medial superior frontal gyrus; ACC, anterior cingulate gyri; STG, superior temporal gyrus; Y, yes.

Discarded studies	Hyperactivation regions								Hypoactivation regions	
	L mSFG	R mSFG	L GR	R GR	L ACC	L SMG	L STG	R MFG	R insula	R STG
Baojuan *et al.*[19]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Bonne *et al.*[12]	Y	Y	Y	Y	Y	N	N	Y	Y	Y
Shin *et al.*[33]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Song *et al.*[29]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Yan *et al.*[27]	Y	Y	Y	Y	Y	N	N	Y	Y	Y
Yin *et al.*[31]	Y	Y	Y	Y	N	Y	Y	N	Y	N
Zhu *et al.*[37]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

Table 5. Sensitivity analyses of studies in the meta-analysis of PTSD vs. TEC. L, left; R, right; mSFG, medial superior frontal gyrus; GR, gyrus rectus; SMG, supramarginal gyrus; ACC, anterior cingulate gyri; STG, superior temporal gyrus; MFG, middle frontal gyrus; Y, yes; N, no.

resting-state functional connectivity across the cerebellum has been mapped to the cerebral cortex, covering prefrontal, motor, somatosensory, posterior parietal, visual, and auditory cortices[64]. Taken together, the evidence suggests that the hyperactive cerebellum at rest may cooperate with the cerebral cortex in contributing to internal activity in PTSD.

Findings in the subgroup meta-analysis. In the subgroup meta-analysis of non-medication studies, increased activity in the left amygdala, parahippocampal gyrus and hippocampus was observed in PTSD compared to NTC which was not identified in the pooled meta-analysis. The amygdala participates in the enhancement of startle[65], and the hippocampus is involved in the memory retrieval[66]. Many task-based functional neuroimaging studies with non-medicated PTSD patients have shown increased activation of limbic and paralimbic structures, mainly in the amygdala, hippocampus and parahippocampus[7,67]. The present results might therefore suggest that activation of amygdala, hippocampus, and parahippocampus may be different in non-medicated PTSD patients. A longitudinal study in PTSD which directly investigates the relation between medication and activation of limbic structures would clearly be of interest.

Findings in the meta-regression analyses. Meta-regression analyses of PTSD vs. NTC studies showed that the mean illness duration was positively associated with resting-state activity in the right cerebellum. This is the first study to our knowledge to report this positive relationship. Partially consistent with this, a longitudinal fMRI study found increased activation in cerebellum in acute PTSD patients and decreased cerebellar activation in symptoms-improved PTSD patients after 2 years of follow-up, which suggested the cerebellum may reflect symptom improvement[68]. Thus, we suggest that the altered cerebellar activity might accompany the development of PTSD and be some degree of restored if symptoms are improved in PTSD patients. Further studies are warranted.

We also found that PTSD symptom severity was negatively associated with activity of the right LG in the meta-regression analyses of PTSD vs. TEC studies. A previous voxel-based morphometry analysis demonstrated reduced gray matter volume in the lingual gyrus in the chronic PTSD group compared with the symptoms-improved group[39]. The result suggested a close association between the LG and PTSD symptoms which merits further study.

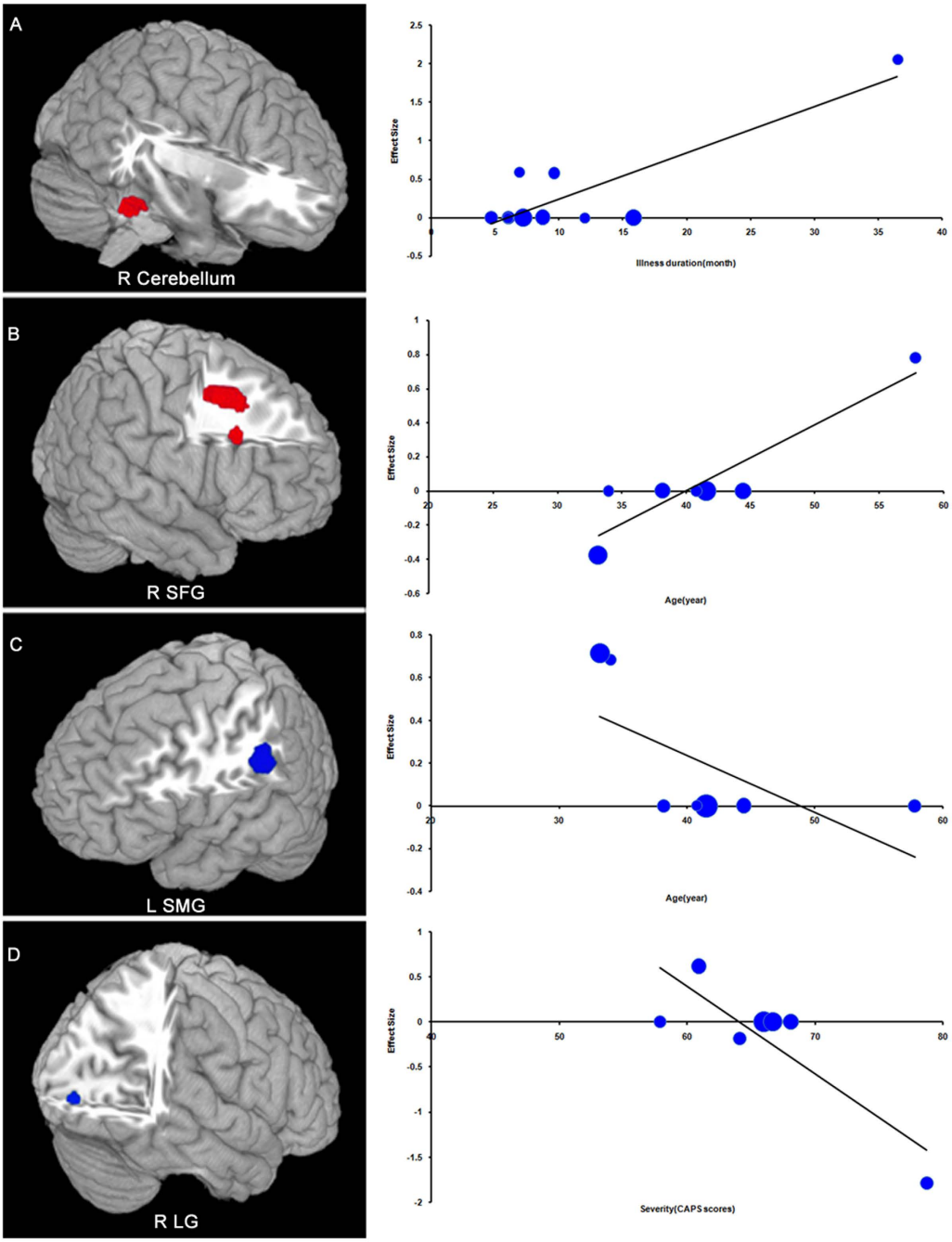

Figure 3. Results of meta-regression analyses of studies of PTSD patients compared with NTC (**A**) and TEC (**B–D**). (**A**) Illness duration is positively associated with the resting-state activity in the L cerebellum; (**B**) Mean patient age is positively associated with resting-state activity in the R SFG; (**C**) Mean age is negatively associated with resting-state activity in the L SMG; (**D**) Illness severity is negatively associated with resting-state activity in the R LG. Each study is represented as a dot, with larger dots symbolizing larger sample sizes. The regression line (meta-regression signed differential mapping slope) is shown as a straight line. R, right; L, left; SFG, superior frontal gyrus; SMG, supramarginal gyrus; LG, lingual gyrus; PTSD, posttraumatic stress disorder; NTC, non-traumatized controls; TEC, trauma-exposed controls.

Limitations. This meta-analysis has some limitations. One constraint was the availability of studies that met our criteria for inclusion. The exclusion of studies that did not report stereotaxic coordinates or used functional connectivity approaches likely reduced our power to detect less-robust activations. Further, the small number of studies precluded separate meta-analyses for some moderator variables, such as the characteristics of patients (trauma type, gender), imaging method (fMRI, PET, SPECT), and analysis method (ALFF, ReHo, rCBF, rCMRglu). Although we conducted subgroup meta-analyses of 'non-comorbidity' and 'non-medication' studies in

PTSD compared with TEC, these included only 4 studies and 5 studies, respectively, and had limited power; further investigation will needed to determine their relative contributions to PTSD pathology.

In addition, like all coordinate-based methods, ES-SDM assumes that effect sizes originate from homogeneous t-value contrasts; in fact they might originate from different covariate models or from different raw statistics, and this limitation could be controlled by SDM covariate analyses, if relevant. Finally, all neuroimaging data are highly sensitive to common artifacts such as head motion and breathing effects that may influence the results[69,70].

Conclusions

The present meta-analyses provide a unique opportunity to assess altered intrinsic brain activities across individual PTSD studies during rest. The results confirmed a subset of consistent regional differences often reported in previous PTSD studies, including the vmPFC, insula, and limbic regions (including the amygdala and hippocampus). Additional regions were found, such as the auditory and visual cortex and cerebellum, that have received less attention. It is noteworthy that different parts of mPFC and insula may have different pathophysiological implications in PTSD, and future PTSD studies should subdivide these regions, especially in functional connectivity analysis. Differential brain regions and activities found in two individual pooled meta-analyses revealed differential pathophysiological implications in two different comparisons. Further studies are needed to determine whether the findings reported here are disease-related or stress-related. Subgroup analyses also suggested an influence of medication and co-morbidity on the pathophysiology of PTSD, which will need to be verified by further study.

Finally, it must be acknowledged that differences observed between PTSD and controls during resting-state fMRI are still not easily interpreted, because diverse interpersonal differences (e.g. drugs, smoking, mental state, and many other confounders) may influence the neuroimaging result. Transcending this limitation will require innovative methodological approaches. This is a developing field and our results should be considered provisional.

Methods

Study selection. A systematic search strategy was used to select studies published between January 1995 and April 2015. A combination search strategy of Mesh terms and text words was conducted in PubMed, Web of Knowledge, Embase and Science Direct, China National Knowledge Infrastructure (CNKI), National Technical Information Service, and System for Information on Grey Literature. The terms used were as follows: ALFF <or> ReHo <or> rCBF <or> rCMRglu <or> ASL <or> amplitude of low frequency fluctuations <or> low frequency fluctuations <or> regional homogeneity <or> regional cerebral perfusion <or> regional cerebral metabolic <or> arterial spin labeling; PTSD <or> posttraumatic stress disorder; baseline <or> resting-state <or> rest <or> resting. We assessed all search results for potential suitability. The abstracts were all in English; articles in Chinese were translated into English for assessment. Studies were selected according to the following inclusion criteria: 1) the study had used at least one of the functional imaging techniques of fMRI, PET, or SPECT to analyze altered spontaneous brain activity in patients with PTSD; 2) the study included comparison of PTSD patients with NTC or TEC; 3) 3-dimensional coordinates in stereotactic space of the activation areas were clearly reported. Studies were excluded if they were case reports, reported only region of interest (ROI) findings or used seed-voxel-based analysis procedures, if the participants were not classified using current diagnostic criteria for PTSD, if the data contributed to another publication (in which case the publication with the largest group size was selected), or if the data, when added in, tipped the balance into significant heterogeneity ($p < 0.005$). The reference lists of the identified articles were searched for additional studies. Two authors (T.W and J.L) independently conducted the literature search. The results were compared, any inconsistent result was discussed, and a consensus decision was reached.

Study quality assessment. Individual study quality was assessed using a 10-point checklist, which focused on the clinical and demographic aspects of the study samples and the imaging methodology (see supplementary material, Table S1). The checklist was based on previous meta-analytic studies[71,72]. The assessment included the quality of the diagnostic procedures, the demographic and clinical characterization, the sample size, the MRI acquisition parameters, the analysis method and the quality of the reported results. Though the checklist was not designed as an assessment tool, it provides some objective indication of the rigor of individual studies. At least two authors reviewed every paper and independently determined a quality rating. These ratings were compared, any disagreement was discussed, and a consensus score was obtained. The study quality scores are presented in Table 1.

Voxel-wise meta-analysis. Papers were divided into two based upon the nature of the control group, TEC or NTC (i.e. with and without trauma exposure, as defined in the Introduction). Two individual meta-analyses were performed comparing PTSD with TEC and with NTC. Additional subgroup meta-analyses were performed to control for comorbidity and medication. The meta-analyses were performed using ES-SDM (Effect Size Signed Differential Mapping; http://www.sdmproject.com/software)[73–75] which uses peak coordinates to recreate, for each study, a map of the effect sizes of the differences between patients and controls, and then conducts a standard random-effects variance-weighted meta-analysis in each voxel[75]. Specifically, first peak coordinates and effect-sizes (e.g. t-values or z-scores) of all functional differences that were statistically significant at the whole-brain level between patients and controls were extracted from each dataset. We checked that each included study used the same statistical threshold throughout the whole brain, to avoid potential bias toward liberally-thresholded regions. For studies that reported only z-scores, these were converted to t-values using the online converter (www.sdmproject.com/utilities/?show=Statistics). For studies not reporting any measure related

to effect size (t-values, z-scores, p-values or similar), we write a "p" for positive peaks (i.e. patients > controls) and an "n" for negative peaks (i.e. patients < controls), according to the SDM tutorials. Second, peak coordinates and their t-values were used to recreate a standard Montreal Neurological Institute (MNI) map of the differences for each study by means of a non-normalized Gaussian kernel, which assigns higher effect sizes to the voxels more correlated with peaks. In the assignment, a relatively large full-width at half-maximum (FWHM, 20 mm) was used to control false positive results[74]. Unlike earlier meta-analytic methods such as activation likelihood estimation[76] and multilevel kernel density analysis[77], both positive and negative coordinates are reconstructed in the same map to avoid any voxel erroneously appearing to be positive and negative at the same time[73]. Third, the mean map was obtained by voxel-wise calculation of the random-effects mean of the study maps, weighted by the sample size and variance of each study and the between-study heterogeneity. Finally, statistical significance was calculated using standard randomization tests[75], creating null distributions from which the p-values were obtained directly. Default ES-SDM kernel size and thresholds were used (FWHM = 20 mm, voxel $p = 0.005$, peak height $Z = 1$, cluster extent = 10 voxels)[74].

Reliability analysis. Systematic whole-brain voxel-based jack-knife sensitivity analysis was conducted to test the robustness of the results of the two main meta-analyses, PTSD vs. NTC and PTSD vs. TEC. Briefly, jack-knife sensitivity analysis consists of repeating the analysis discarding just one study each time, and is used to assess the reproducibility of the results across different studies[74]. The rationale is that if a previously significant brain region remains significant in all or most of the combinations of studies, it can be concluded that this finding is highly replicable[78].

Meta-regression analysis. The potential effects of age, illness severity and illness duration of PTSD patients were examined by simple linear regression, weighted by the square root of the sample size and restricted to predict only possible SDM values (i.e. from −1 to 1) in the observed range of values of the variable. The main output for each variable was a map of the regression slope[78]. As in previous meta-analyses, to minimize the detection of spurious associations we decreased the probability threshold to 0.0005, required abnormalities to be detected both in the slope and in one of the extremes of the regressor, and discarded findings in regions other than those detected in the main analyses. Finally, regression plots were visually inspected to discard fits driven by too few studies[78].

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Author Contributions

J.Z. and H.Z. contributed to the conception of the study. T.W., J.L., L.L., M.W., W.Z. and H.H. contributed significantly to analysis and manuscript preparation; T.W. and J.L. performed the data analyses and wrote the manuscript. Q.G. and G.J.K. contributed to the interpretation and discussion of the results of the analysis.

Additional Information

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