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Review

Post-traumatic stress influences the brain even in the absence of symptoms: A systematic, quantitative meta-analysis of neuroimaging studies

E.A. Stark[a,b,c], C.E. Parsons[a,b,c,e], T.J. Van Hartevelt[a,b,c], M. Charquero-Ballester[a,b,c], H. McManners[a,b], A. Ehlers[d], A. Stein[a], M.L. Kringelbach[a,b,c,e,*]

[a] Department of Psychiatry, University of Oxford, Oxford, United Kingdom
[b] The Scars of War Foundation, The Queen's College, Oxford, United Kingdom
[c] Center of Functionally Integrative Neuroscience (CFIN), Aarhus University, Aarhus, Denmark
[d] Department of Experimental Psychology, University of Oxford, Oxford, United Kingdom
[e] Center for Music in the Brain, Department of Clinical Medicine, Aarhus University & The Royal Academy of Music Aarhus/Aalborg, Denmark

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ABSTRACT

Stress affects brain function, and may lead to post-traumatic stress disorder (PTSD). Considerable empirical data for the neurobiology of PTSD has been derived from neuroimaging studies, although findings have proven inconsistent. We used an activation likelihood estimation analysis to explore differences in brain activity between adults with and without PTSD in response to affective stimuli. We separated studies by type of control group: trauma-exposed and trauma-naïve. This revealed distinct patterns of differences in functional activity. Compared to trauma-exposed controls, regions of the basal ganglia were differentially active in PTSD; whereas the comparison with trauma-naïve controls revealed differential involvement in the right anterior insula, precuneus, cingulate and orbitofrontal cortices known to be involved in emotional regulation. Changes in activity in the amygdala and parahippocampal cortex distinguished PTSD from both control groups. Results suggest that trauma has a measurable, enduring effect upon the functional dynamics of the brain, even in individuals who experience trauma but do not develop PTSD. These findings contribute to the understanding of whole-brain network activity following trauma, and its transition to clinical PTSD.

Contents

* Corresponding author at: Department of Psychiatry, University of Oxford, Warneford Hospital, Oxford OX3 7JX, United Kingdom. Tel.: +44 1865613118; fax: +44 1865793101.
E-mail address: morten.kringelbach@psych.ox.ac.uk (M.L. Kringelbach).

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1. Introduction

After exposure to a traumatic event, many people will experience symptoms such as flashbacks, avoidance of trauma reminders and sleep difficulties (McFarlane and Papay, 1992). In the majority of individuals, these symptoms abate during the weeks post-exposure. However, some trauma-exposed survivors will not show spontaneous remittance of these symptoms, and develop post-traumatic stress disorder (PTSD) (Breslau et al., 1998). This disabling condition is characterised by re-experiencing symptoms, avoidance, arousal, and negative mood and cognition (DSM-5, APA, 2013). It remains as yet unclear how the PTSD symptom clusters can be explained by a coherent pathogenic model of neural function. It also remains unclear whether exposure to trauma per se leads to changes in brain function that persist even when initial symptoms abate.

1.1. Current neuroanatomical theories of PTSD

The neuroanatomy regulating both fear and memory has increasingly been recognised as core to PTSD. The prominent neuroanatomical theory of PTSD posits hyperresponsivity within the amygdala to stimuli related to threat (Liberzon and Sripada, 2007; Protopopescu et al., 2005; Rauch et al., 2006; Roozendaal et al., 2009; Shin et al.et al., 2005, 2006). Top-down regulation over the amygdala's affective responsiveness is then suggested to be inadequate from regions in the ventromedial prefrontal cortex (vmPFC), including the rostral anterior cingulate (rACC), medial prefrontal cortex (mPFC), subcallosal cortex (SC), and orbitofrontal cortex (OFC). Within this circuit, hyperresponsivity of the amygdala mediates symptoms of hyperarousal, and inadequate vmPFC top-down regulation leads to deficits in extinction learning, as well as aberrant suppression of attention and physiological response to trauma-related stimuli (Rauch et al., 2006). Consequently, 'executive' prefrontal regions are unable to regulate emotional processing within the 'salience network' involving the amygdalae, so that the individual remains constantly hypervigilant to cues that may signal an imminent threat. Decreased hippocampal function is also argued to account for deficits in mnemonic functioning such as the identification of 'safe' contexts, as well as involvement in difficulties with explicit memory (Bremner et al., 1995; Schwabe et al., 2012). This theory also predicts that 'chronic' cases of PTSD may involve progressive deterioration of both function and structure within these regions and inter-regional connections. The theory of prefrontal–limbic imbalance along a hypoactive–hyperactive gradient has strong support within the literature, with several meta-analytic reviews reporting consistent activity in these core regions across individual primary studies (Etkin and Wager, 2007; Hayes et al., 2012; Patel et al., 2012; Sartory et al., 2013; Simmons and Matthews, 2012).

More recently, several theories have explored PTSD in relation to disturbances in interactions between functional brain networks in the growing literature on resting state networks (Cabral et al., 2014; Zhang and Raichle, 2010). For instance, Sripada et al. (2012) argued that aberrant neural activity in PTSD is due, in part, to a disrupted equilibrium between certain important resting state networks such as the 'salience network' (SN) and the 'default mode network' (DMN). This view is based upon the suggestion by Menon (2011) that the SN 'arbitrates' between the DMN and the 'Central Executive Network' (CEN; associated with goal-directed behaviour and higher-level functions) to mediate the balance between externally oriented focus and internal mediation.

The network perspective for characterising functional neural activity in psychiatric disorders aims to identify aberrations across large-scale networks involving multiple brain regions. This approach is particularly relevant to the study of functional activity in a task-related context, as it allows us to consider the relative imbalance of regional activity and connectivity across the whole brain, and how this affects domain-general functions across social, affective, cognitive and perceptual faculties (Barrett and Satpute, 2013).

Yet, despite these recent developments in understanding the functional neuroanatomical networks of PTSD, there are also many inconsistencies across studies regarding the underlying networks. For example, there are many findings which are either inconsistent with the limbic–prefrontal imbalance theory, or which implicate important regions and/or connectivity not considered in previous theoretical accounts. Such findings support the reconceptualization of PTSD as a general imbalance of network activity, instead of assuming disorder-specific, encapsulated neuroanatomical networks.

1.2. Why do some individuals develop PTSD and others do not following a traumatic event?

The experience of a traumatic event is necessary but insufficient to account for the development of PTSD. One important question is

why, when exposed to the same traumatic event, not all individuals will develop PTSD. It is possible that additional factors relating to individual differences also affect risk for the development of PTSD.

This is particularly relevant to the study of the functional neuroanatomical networks underlying PTSD, as emerging evidence suggests that the final PTSD pathology results from both predisposed and acquired neural abnormalities. In particular, when analysing between-group differences in neural activity for PTSD compared to healthy controls, it is often unclear whether such functional differences correspond to pre-existing vulnerabilities, or acquired deficits specific to PTSD onset (Admon et al., 2013). A third possibility exists. Acquired deficits may be further separated by neural abnormalities specific to the disorder, and neural abnormalities resulting from the normal stress response to trauma exposure. The latter distinction may be teased apart by comparing individuals with PTSD to individuals without PTSD who experienced comparable traumatic events.

The need to compare adults with PTSD to trauma-exposed adults without PTSD, in addition to healthy, trauma-naïve controls, arises from the need to control for lasting effects of acute stressors such as trauma on the individual. There is a growing recognition that acute stressors may have durable impact upon the brain (McEwen, 2006; Roozendaal et al., 2009; Shonkoff et al., 2012; van Wingen et al., 2012). The neuroendocrine response associated with acute stress has been suggested to account for some pervasive changes in the brain following trauma. For example, stress hormones such as epinephrine may act to overconsolidate memory, supporting the development of the intrusive flashbacks common to PTSD (Pitman, 1989; Southwick et al., 1999). Studies of childhood trauma have also reported of 'toxic stress', which is the consequence of frequent, prolonged or strong activation of the body's stress response systems during development, in the absence of protective factors (Shonkoff et al., 2012). Toxic stress in young children can lead to permanent changes in brain structure and function (McEwen, 2005, 2006) which bear many similarities to PTSD pathology, including hyperactive amygdala, hippocampus atrophy, and reduced top-down regulatory control due to atrophy of the PFC. The effects of trauma on the brain can evidently be pervasive.

Twin studies, genetic analyses and prospective studies have all been useful in elucidating the differential roots of neural abnormalities in PTSD. Abnormalities in amygdala reactivity to salient stimuli and dorsal ACC activity may represent predisposing risk factors for PTSD development following trauma exposure. The proposed mechanism for resulting vulnerability is abnormal fear generation and expression, therefore rendering individuals prone to greater fear responses to stress, and lower thresholds for successful coping both during and in the aftermath of the event (Admon et al., 2013). Contrastingly, dysfunctional interactions between the hippocampus and vmPFC may only become apparent following the development of PTSD, preventing typical fear extinction and the perpetuation of continued PTSD symptomology (Admon et al., 2013).

This knowledge can be applied to the use of meta-analytic analyses to synthesise available neuroimaging data concerning the functional neuroanatomical networks of PTSD. Here, the comparison between trauma-exposed and trauma-naïve control groups may be able to shed light on the matter. Comparisons between individuals with PTSD and control participants who have also experienced trauma, but do not have PTSD, offer an opportunity to explore neural abnormalities associated with PTSD while controlling for the brain response to acute stress among all individuals. Given that stress can have a profound impact on the brain in the absence of concurrent or subsequent psychopathology, there is a strong argument for including a trauma-exposed control group in neuroimaging studies of PTSD.

Of note, few existing meta-analyses have separated studies by the nature of the control group: whether they have also been exposed to trauma, but not developed PTSD, or whether they are trauma-naïve (Patel et al., 2012; Sartory et al., 2013). These analyses have hinted at key differences between trauma-exposed and trauma-naïve controls, such as hyperresponsive amygdalae in trauma-exposed controls without PTSD. Given that the control group acts as a baseline of measurement upon which to compare brain activity in PTSD, it is vital that we understand how the control group may differ as a function of trauma exposure, in response to general emotional processing as well as trauma-specific reactivity.

1.3. Addressing gaps in our existing knowledge

The presence of anomalies and inconsistencies in the functional neuroimaging literature continues to prompt further research into PTSD and the consequences of trauma on the brain. Crucially, the nature of the control group may prove pivotal in determining the apparent neural differences between individuals with PTSD and those without. To address the important question of why some individuals develop PTSD following trauma, and why some do not, meta-analytic syntheses of the literature must separate studies by the nature of the control group: whether they are trauma-exposed or not. Given the lack of existing data on this issue, we do not yet know whether a core network of regions is consistently differentially active in PTSD, and how functional brain activity differentiates these three groups.

It is possible that previous meta-analyses have found broad trends in spite of significant inconsistencies among individual research studies, due to amassing a large number of neuroimaging studies with different task parameters or subject groups. It is also possible that "functional differences (commonly proposed as causal in PTSD aetiology) may reflect the magnitude of responses within a common neurocircuitry across [anxiety] disorders, rather than activation of distinct systems" (Killgore et al., 2014), with more work needed to classify PTSD- and symptom-specific activity and connectivity.

We therefore conducted a meta-analysis of existing studies using fMRI to study brain activity in PTSD in comparison to control participants. As well as using quantitative coordinate-based meta-analysis to synthesise results from all studies, we aim to provide insight into how the nature of the control group (trauma-exposed or trauma-naïve) may be an important factor in determining relevant brain activity in PTSD.

2. Methods and materials

2.1. Primary literature search and selection

2.1.1. Search strategy

To identify appropriate studies, we conducted a literature search in April 2015 using Scopus, PsycINFO, and Web of Science (including MedLine). Search terms were used to identify the target population, adults with PTSD (e.g. "PTSD", "post-traumatic stress disorder" "trauma," "post-traumatic"), and brain activity measured by functional neuroimaging (e.g. "fMRI", "MRI", "functional", "neuroimaging"). We did not impose conditions related to the language of the article, but did specify that articles were published between 1st January 2000 and 31st April 2015, in an effort to ensure consistency of functional neuroimaging methodology. This initial search reached 2432 studies.

To identify further studies and studies from grey literature, we manually searched conference proceedings, and reference lists from original research articles and review papers identified in the earlier database searches. Subsequent selection of further articles was based upon title and abstract. These searches identified a

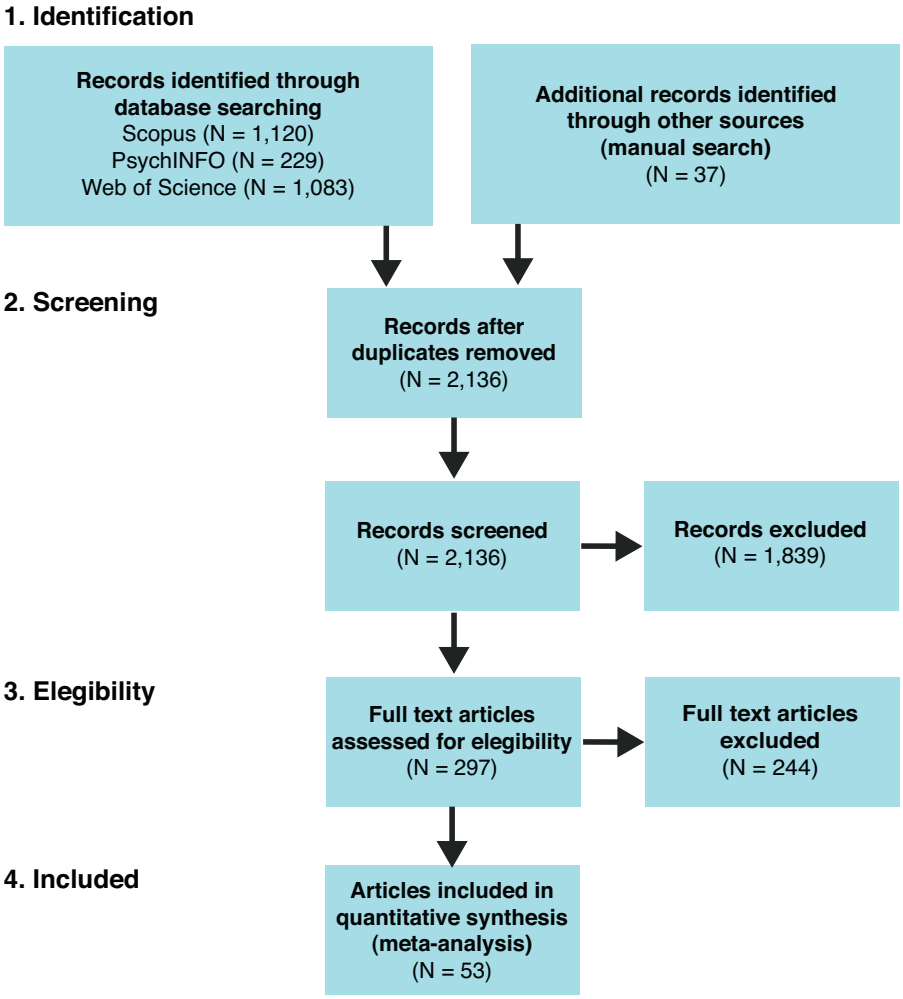

Fig. 1. PRISMA flowchart for literature search process.

further 37 unique articles for possible inclusion, which were added to the initial 2432 studies.

A total of 2469 records were obtained, which was reduced to 2136 following removal of duplicates. These records were screened and further reduced to 297 full text articles, which were assessed for eligibility (see Fig. 1). From these 297 studies, only 53 studies fulfilled criteria for eligibility and were therefore included in the meta-analysis.

2.1.2. Study eligibility

Studies were included if they met the following criteria for eligibility: (1) studies were original reports of task-dependent fMRI experiments; (2) included a PTSD patient group, and a control group (at this point there was requirement for either trauma-exposed or trauma-naïve controls), and (3) conducted between-group analyses using subtraction methodology; (4) stereotactic coordinates of neural activation made available (in Talairach or Montreal Neurological Institute, MNI, coordinates). If these were not reported in the paper, we contacted authors to retrieve this information; and (5) PTSD diagnosis was ascertained via clinical interview.

Studies were omitted based upon the following exclusion criteria: (1) review articles with no original, experimental data; (2) an overlap occurred between published studies reporting data from the same participant group. In this situation, the most appropriate study to our research question was kept; (3) reported neuroimaging data not conducted using fMRI (e.g. PET); (4) case studies; (5) studies involving a high degree of comorbidity between PTSD and other psychiatric disorders, without PTSD being confirmed as the principal diagnosis. An exception was here made for major depressive disorder (MDD) because of its high comorbidity with PTSD (Rytwinski et al., 2013); (6) patients in the 'acute' phase of illness (<2 months); (7) studies exploring PTSD in youth (<18 years old). Where the decision to exclude an article was irresolute, two independent reviewers (ES and CP) judged studies for suitability, and determined the appropriate action.

Based upon these inclusion and exclusion criteria, 53 PTSD neuroimaging results remained in the analyses, amounting to results from 827 patients with PTSD and 864 control participants.

2.1.3. Data extraction

For each study, data for the PTSD group were extracted: number of participants included in final analyses, means of trauma (i.e. motor vehicle accident, or assault), and details of comorbidity and medication status. For the control group (or groups where multiple comparisons were used), data for the group were extracted: number of participants included in final analyses, comorbid Axis 1 diagnoses, medication status, and whether they were exposed to trauma or not. The selection of the control group and features by which they were matched to the PTSD group was also recorded.

Details of the fMRI paradigm were extracted, including the task paradigm, modality of stimuli, and whether or not the stimuli were specific to the trauma (i.e. pictures of warzones in the context of combat related PTSD).

For these meta-analyses, stereotactic coordinates where the BOLD response was reported to differ significantly between the PTSD participants and control group(s) were extracted.

2.2. Analysis and meta-analytic technique

Statistically significant foci from between-group contrasts were extracted and recorded for each study. Where necessary, coordinates were converted from Talairach coordinates to MNI space using the Lancaster transform (icbm2tal) in GingerALE (www.brainmap.org/).

Where comparisons occurred for multiple stages of the task design (pre- and post-conditioning procedure, for example), the most appropriate contrast was chosen based upon its relevance to the research question. In the event of the same participant group being used for multiple fMRI tasks and results reported in multiple papers, again we selected the most appropriate primary study in order to avoid overrepresentation of one sample group.

All meta-analyses were performed using activation likelihood estimation, implemented in GingerALE via BrainMap (ALE 2.3.3; http://www.brainmap.org; (Eickhoff et al., 2009)). This method extracts a set of spatial coordinates from all included studies in order to test for anatomical concordance between studies. The input coordinates are weighted according to the number of participants in each study, and these weightings contribute to overall weightings forming estimates of activation likelihood for each intracerebral voxel on a standardised map. Statistical significance of the ALE scores was determined by a permutation test using cluster level inference at $p < 0.05$ (FWE). We imposed no minimum cluster size of suprathreshold voxels initially, and therefore interpret clusters of small volume with caution.

We first synthesised all primary studies comparing brain activity in PTSD patients to control participants, using only whole-brain analyses. This meta-analytic process was subsequently conducted for all studies using ROI methodology. We subsequently used a logical overlay to explore the degree of convergence in activation coordinates between whole-brain and ROI analyses.

After conducting meta-analyses of all primary studies, we further divided the tasks into two categories based upon the nature of the control group: trauma-exposed controls and trauma-naïve controls. The trauma-exposed controls had all experienced a criterion 'A' stressor, defined by the DSM-IV (APA, 2003) comparable to the PTSD patients. Trauma-naïve control participants had not been exposed to traumatic events. Again, all analyses were repeated incorporating findings from studies using ROI analyses.

Subsequently, we performed a series of meta-analyses that removed studies using trauma-specific stimuli. All analyses were repeated incorporating findings from studies using ROI analyses.

Meta-analysis results, including overlap between ROI and whole-brain study subsets, were visualised using MRIcroS and MRIcroGL software (www.mricro.com).

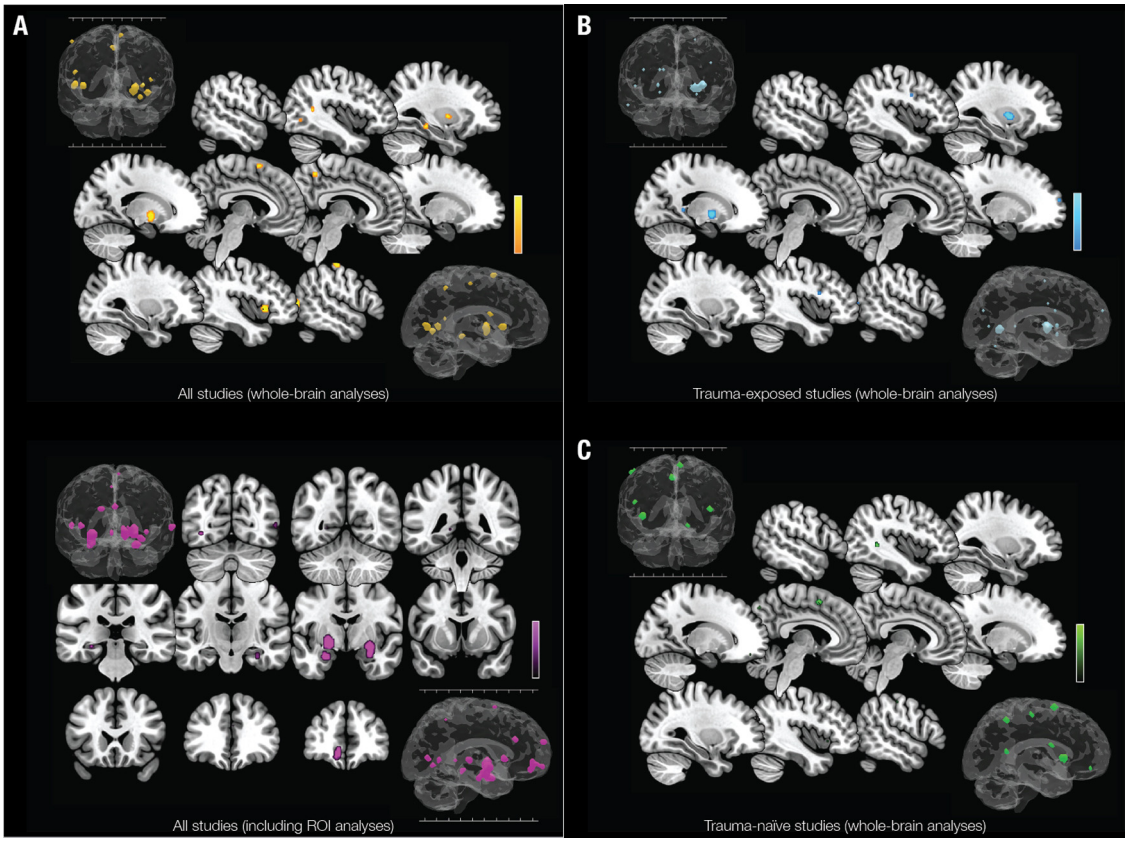

Fig. 2. Activation likelihood estimate analyses (GingerALE) of fMRI studies of PTSD. (A) *PTSD vs all controls* (*whole-brain analyses*) results are shown at the top with the significant differences in activity between adults with PTSD and all control participants from whole-brain analyses shown in yellow (cluster level $p < 0.05$, see Table 2). Front view of the glass brain is presented in the top left hand corner, with indications of the positions of 10 sagittal slices in between, and a sideview of the glass brain in the bottom right hand corner. *PTSD vs all controls* (*whole-brain and ROI analyses*) results are shown below with significant differences between PTSD and all control participants shown in magenta (see Table 3). The results are here shown on 10 coronal slices with their positions indicated on the sideview of the glass brain. (B) *PTSD vs trauma-exposed* results show the significant differences in activity between adults with PTSD compared with only trauma-exposed controls in blue from whole-brain analyses (see Table 4) (shown on glass brain and 10 sagittal slices). (C) *PTSD vs. trauma-naïve* results shows the significant differences between adults with PTSD compared with only trauma-naïve controls in green from whole brain analyses (see Table 6) (shown on glass brain and 10 sagittal slices). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3. Results

The analysis was threefold. First we combined all studies, collapsed across the nature of the control group (trauma-exposed or trauma-naïve), as in many previous meta-analyses of functional neuroimaging studies of PTSD. Second, we compared individuals with PTSD to trauma-exposed controls. Third, we compared individuals with PTSD to trauma-naïve controls. For each of the three analyses, we first included only studies using a whole-brain method of analysis. We subsequently included additional studies using a region-of-interest analysis. For the contrasts of PTSD compared to trauma-exposed and trauma-naïve controls, respectively, we also included a third synthesis of the data excluding trauma-specific stimuli to explore functional activity in response to general, emotionally valenced stimuli.

Results reported were significant at cluster level $p < 0.05$ (FWE), providing an appropriately conservative criterion for significant differences in regional activity between groups. The results are shown in Fig. 2 and Tables 2–11. Brain regions are labelled according to the automated anatomical labelling (AAL) brain parcellation (Tzourio-Mazoyer et al., 2002) and Duvernoy (Duvernoy et al., 1991).

3.1. Primary literature

The meta-analysis of all fMRI studies of PTSD included 25 studies using whole-brain (WB) analyses, totalling 208 foci together, 418 participants with PTSD, and 426 control participants. For control participants, 33% ($n = 9$) of the studies included trauma-exposed individuals and the remaining 67% ($n = 18$) of the studies included trauma-naïve individuals. The mean sample size was 15 participants with PTSD, and 16 controls. Visual stimuli were used in 20 studies, two studies used auditory stimuli, and four studies used tactile stimuli.

A further 38 studies used region-of-interest (ROI) analyses, which were included in an additional set of meta-analyses. These 38 studies amounted to 155 foci together, 576 participants with PTSD, and 612 control participants. The mean sample size was 15 PTSD patients, and 16 controls. As control participants, 50% ($n = 19$) of the studies included trauma-exposed individuals, and the remaining 50% ($n = 19$) individuals who had not experienced a traumatic event. Visual stimuli were used in 24 studies, eight studies used auditory stimuli, and six studies used tactile stimuli.

Some studies were included in more than one meta-analysis if they included neuroimaging analyses of both whole-brain and region-of-interest, more than one type of control group, or stimuli presented in multiple modalities.

4. Part 1: All studies

4.1. *PTSD* vs. *all controls: Whole-brain analyses*

The meta-analysis of studies using a whole-brain analysis comparing patients with PTSD to control participants (both trauma-exposed and trauma-naïve) consisted of 25 primary studies.

The results show significantly different activation in PTSD patients relative to healthy controls in 7 clusters (see Table 2). These regions include the bilateral pallidum and putamen, right caudate, right insula—anterior part, right primary somatosensory cortex, right lateral occipital cortex, and left fusiform gyrus.

4.2. *PTSD* vs. *all controls: Whole-brain analyses and ROI analyses*

The meta-analysis of primary studies using both whole-brain and ROI analyses comparing patients with PTSD to control participants (both trauma-exposed and trauma-naïve) consisted of 49 primary studies.

Regions of significant differences in activity between participants with PTSD and controls include: bilateral amygdala, bilateral putamen, bilateral hippocampus, left parahippocampal gyrus, and left brainstem (red nucleus). We also observed significant differences in frontal regions such as the medial orbitofrontal cortex, ventromedial prefrontal cortex, left anterior cingulate, and the anterior part of the right insula. A more posterior cortical region showing significant differences between PTSD and all controls was observed in the right primary somatosensory cortex (see Table 3).

5. Different control groups

All studies were then separated by the nature of the control group being compared to individuals with PTSD: trauma-exposed, or trauma-naïve. Although there are slightly fewer studies comparing adults with PTSD to trauma-exposed control participants, as opposed to trauma-naïve control participants, the two groups of studies are broadly similar (see Table 1 for full study details).

6. Part 2: PTSD *vs.* trauma-exposed controls

The meta-analysis of primary studies where patients with PTSD were compared to trauma-exposed control participants consisted of 24 primary studies (Brohawn et al., 2010; Brunetti et al., 2010; Bryant et al., 2010; Diener et al., 2012; Falconer et al., 2008; Felmingham et al., 2010, 2014; Garfinkel et al., 2014; Geuze et al., 2007, 2008; Hou et al., 2007; Lanius et al., 2001, 2003, 2007; Linnman et al., 2011; Mickleborough et al., 2011; Milad et al., 2009; Offringa et al., 2013; Rauch et al., 2000; Rougemont-Bücking et al., 2011; Shin et al., 2001, 2005; Simmons et al., 2013; van Rooij et al., 2014). Due to overlap between participants used in multiple studies, the final meta-analysis of trauma-exposed controls compared to individuals with PTSD consisted of 7 primary studies (188 participants, 62 foci) for whole-brain analyses and 16 primary studies (490 participants, 80 foci) for ROI analyses.

6.1. Whole-brain analyses

When we compare PTSD against trauma-exposed controls, we observe differences in the basal ganglia (bilateral putamen and pallidum) and the left fusiform gyrus (see Table 4).

6.2. Whole-brain and ROI analyses

The meta-analysis of primary studies using both whole-brain and ROI analyses comparing patients with PTSD to trauma-exposed control participants consisted of 21 studies, totalling 616 participants and 125 foci.

Studies using ROI analyses were then included within the analysis. Regions of significant difference in activity between participants with PTSD and trauma-exposed controls include bilateral pallidum and putamen, extending to the caudate on the right, and the left fusiform gyrus. We also observed differences extending to the brainstem (red nucleus) on the left, and amygdala on the right. Further significant differences between PTSD and trauma-exposed participants when adding ROI analyses were located in the right superior frontal gyrus and the anterior cingulate cortex (see Table 5).

6.3. Trauma-unrelated stimuli

The PTSD *vs.* trauma-exposed whole-brain analyses were then repeated removing two of the seven studies, both of which used

Table 1
All studies included in final meta-analysis.

Authors	Date	Task paradigm	Means of trauma	Control group	Number of patients	Number of controls
Astur et al.	2006	Virtual reality Morris Water task, designed specifically to assess hippocampus function	Mixed	NX	12	12
Aupperle et al.	2012	Anticipation of negative and positive images	IPV-PTSD	NX	37	34
Bluhm et al.	2012	Self-referential processing task: responding yes or no to self-relevance of facts	Mixed	NX	20	15
Brohawn et al.	2010	Viewing negative, positive and neutral images	Mixed	TX	18	18
Bruce et al.	2013	Attentional interference task using emotional distracters (emotional faces)	IPV-PTSD	NX	32	21
Brunetti et al.	2010	Viewing negative and neutral faces	Bank robbery—'mild' trauma	TX	10	10
Bryant et al.	2005	Auditory Oddball Task	MVA & assault	NX	14	14
Bryant et al.	2008	Masked presentation of fear and neutral faces	MVA & assault	NX	15	15
Bryant et al.	2010	Masked presentation of fear and neutral faces	MVA & assault	TX	12	12
Diener et al.	2012	Painful stimulation while doing mental arithmetic	Mixed	TX	14	14
El Khoury-Malhame et al.	2011	Emotional face-matching	Mixed	NX	17	17
Elman et al.	2009	Passive viewing monetary reward task	Mixed	NX	20	26
Falconer et al.	2008	Response inhibition: Go/No-Go task	MVA & Assault	Both TX and NX	23	40
Felmingham et al.	2009	Auditory oddball task	MVA & Assault	NX	11	11
Felmingham et al.	2010	Masked presentation of fear and neutral faces	MVA & Assault	Both TX and NX	23	63
Felmingham et al.	2014	Passive viewing of neutral and happy faces	MVA & Assault	TX	23	20
Fonzo et al.	2010	Emotional face-matching	IPV-PTSD	NX	12	12
Frewen et al.	2012	Script-driven provocation paradigm, and association with emotional numbing symptoms	Women—childhood maltreatment	NX	14	16
Frewen et al.	2010	Script-driven imagery: social, non-social, positive and negative scripts	Women—childhood maltreatment	NX	14	20
Garfinkel et al.	2014	Fear acquisition and fear extinction recall	CR-PTSD	TX	14	14
Geuze et al.	2007	Painful stimulation	CR-PTSD	TX	12	12
Geuze et al.	2008	Encoding and retrieval of word-pairs	CR-PTSD	TX	12	12
Hou et al.	2007	Trauma-related short-term memory paradigm with symptom provocation	Accident	TX	10	7
Jatzko et al.	2006	Movie-induced positive emotional processing	Accident	NX	10	10
Kim et al.	2008	Same-different judgement with emotional distractors	Accident—fire	NX	12	12
Landré et al.	2012	Same/different judgement of words (n-back)	Women	NX	17	17
Lanius et al.	2001	Script-driven provocation paradigm	MVA & Assault	TX	9	9
Lanius et al.	2003	Script-driven provocation paradigm	MVA & assault	TX	10	10
Lanius et al.	2007	Script-driven provocation paradigm	General	TX	26	16
Linnman et al.	2011	Fear conditioning: electric shocks	CR-PTSD	TX	19	24
Mazza et al.	2012	Affective priming task: human faces	Natural disaster	NX	10	10
Mazza et al.	2013	Passive viewing of negative and neutral pictures	Natural disaster	NX	10	10
Mickleborough et al.	2011	Script-driven provocation paradigm and pain stimulation	Mixed	TX	17	26
Milad et al.	2009	Two-day fear conditioning and extinction paradigm	Mixed	TX	16	15
Offringa et al.	2013	Trauma-unrelated emotional interference task	Mixed	TX	17	18
Protopopescu et al.	2005	Presentation of trauma-related and non trauma-related emotional words	Assault	NX	9	14
Rauch et al.	2000	Masked presentation of fear and neutral faces	CR-PTSD	TX	8	8
Rougemont-Bucking et al.	2011	Two-day fear conditioning and extinction paradigm	Mixed	TX	18	16
Sailer et al.	2008	Decision-making task	Women	NX	13	13
Sakamoto et al.	2005	Presentation of traumatic images	Mixed	NX	16	16
Schechter et al.	2012	Viewing videos of own and unknown toddlers during separation and play	IPV-PTSD	NX	11	9
Shin et al.	2001	Emotional counting Stroop task	CR-PTSD	TX	8	8
Shin et al.	2005	Emotional face-matching	CR-PTSD	TX	13	13
Simmons et al.	2008	Anticipation of negative and positive images	IPV-PTSD	NX	15	15
Simmons et al.	2009	Anticipation of change in affective (interoceptive) state	IPV-PTSD	NX	15	15
Simmons et al.	2013	Anticipation of negative and pleasant images related to combat	CR-PTSD	TX	15	15
Steuwe et al.	2014	Effect of direct eye contact: virtual reality task	IPV-PTSD	NX	16	16
Strigo et al.	2010	Painful stimulation	IPV-PTSD	NX	23	15
Thomaes et al.	2009	Emotional declarative memory task	Women	NX	9	9
Van Rooij et al.	2014	Trauma-unrelated emotional processing	CR-PTSD	Both TX and NX	31	25
Werner et al.	2009	Face-profession match learning	Mixed	NX	12	12
Williams et al.	2006	Emotional face-matching	MVA & assault	NX	13	13
Zhang et al.	2013	Effect of negative emotional distraction on working memory	MVA	NX	20	20

Key: CR-PTSD—combat-related PTSD; MVA—motor vehicle accident; IPV-PTSD—intimate partner violence PTSD; NX—not exposed to trauma; TX—exposed to trauma.

Table 2
Activation likelihood estimation meta-analytic results for studies comparing PTSD to all controls using only whole brain-based analysis, at cluster level inference $p < 0.05$.

Cluster number	Volume (mm^3)	ALE	MNI coordinates			Side, region
			X	*Y*	*Z*	
1	1752	0.01756	−22	0	−8	L Pallidum
		0.01291	−32	0	−4	L Putamen
2	1304	0.01821	36	18	−4	R Insula (anterior)
3	968	0.01511	48	−22	50	R Primary somatosensory cortex
4	912	0.01336	20	8	4	R Pallidum/putamen
		0.00970	10	12	12	R Caudate
5	688	0.01664	48	−68	−4	R Lateral occipital cortex
6	640	0.01476	−24	−56	−6	L Fusiform gyrus
7	400	0.0151	−36	−62	−12	L Fusiform gyrus

Table 3
Activation likelihood estimation meta-analytic results for studies comparing PTSD to all controls using whole brain-based analysis and ROI analysis, at cluster level inference $p < 0.05$.

Cluster number	Volume (mm^3)	ALE	MNI coordinates			Label
			X	*Y*	*Z*	
1	4400	0.02607	−20	−2	−12	L Amygdala
		0.02014	−26	2	−26	L Parahippocampal gyrus (anterior)
		0.01303	−32	0	−4	L Putamen
		0.01303	−8	−12	−10	L Brainstem (red nucleus)
2	2776	0.02360	24	0	14	R Amygdala
		0.01502	28	−12	−26	R Hippocampus
		0.01047	18	10	−1	R Putamen
3	1128	0.01792	−12	50	−10	L Medial orbitofrontal cortex
4	1112	0.01495	2	60	−12	R Medial orbitofrontal cortex
		0.01318	0	52	0	Ventromedial prefrontal cortex
5	1040	0.01821	36	18	−4	R Insula (anterior)
6	792	0.01537	−30	−30	−18	L Parahippocampal gyrus/hippocampus
7	728	0.01511	48	−22	50	R Primary somatosensory cortex
8	616	0.01385	20	6	4	R Putamen/pallidum
9	520	0.0154	−2	30	18	L Anterior cingulate

Table 4
Activation likelihood estimation meta-analytic results for studies comparing PTSD to trauma-exposed controls using whole brain-based analysis only, at cluster level inference $p < 0.05$.

Cluster number	Volume (mm^3)	ALE	*x*	*y*	*z*	Label
1	1688	0.01618	−22	−2	−6	L Pallidum
		0.01282	−32	0	−4	L Putamen
2	1560	0.01334	20	8	4	R Putamen/pallidum
3	740	0.0126	−26	−56	−8	L Fusiform gyrus

trauma-specific stimuli in the experimental paradigm (Hou et al., 2007; Simmons et al., 2013). The remaining paradigms consisted primarily of emotional processing tasks using trauma-unrelated stimuli such as negative and neutral pictures from the IAPS database, or facial expressions (see Table 1 for details of individual study characteristics).

After removing trauma-related stimuli from the analysis, significant differences between PTSD and trauma-exposed participants remained in the bilateral basal ganglia (bilateral pallidum and putamen) extending further into the ventral putamen. Additional clusters were found in the left cerebellum, left upper brainstem, left inferior temporal gyrus, left superior temporal gyrus, left hippocampus/parahippocampal gyrus, left lingual gyrus, left thalamus, as well as lateral occipital cortex, right caudate, right primary visual cortex, and superior frontal gyrus (see Table 6).

The analysis was then repeated including PTSD *vs.* trauma-exposed studies using ROI analysis, but removing 5 of the 21 studies, which used trauma-specific stimuli in the experimental paradigm (Hou et al., 2007; Lanius et al., 2001; Lanius et al., 2003; Mickleborough et al., 2011; Simmons et al., 2013). The remaining paradigms consisted primarily of emotional processing tasks using trauma-unrelated stimuli such as negative and neutral pictures from the IAPS database, or facial

Table 5
Activation likelihood estimation meta-analytic results for studies comparing PTSD to trauma-exposed controls using whole brain-based analysis and ROI analysis, at cluster level inference $p < 0.05$.

Cluster number	Volume (mm^3)	ALE	*x*	*y*	*z*	Label
1	3736	0.02152	−22	−2	−8	L Pallidum
		0.01294	−32	0	−4	L Putamen
		0.01147	−8	−10	−8	L Brainstem (red nucleus)
2	1728	0.01584	24	0	−14	R Amygdala
		0.01027	18	10	−12	R Putamen
3	1032	0.01334	20	8	4	R Putamen/pallidum
		0.00939	12	8	4	R Caudate
4	536	0.01604	14	62	14	R Superior frontal gyrus, medial
5	424	0.0126	−26	−56	−8	L Fusiform gyrus
6	376	0.01043	2	32	16	R Anterior cingulate

Table 6
Activation likelihood estimation meta-analytic results for studies comparing PTSD to trauma-exposed controls using whole brain-based analysis only, excluding studies presenting trauma-related stimuli, at cluster level inference $p < 0.05$.

Cluster number	Volume (mm^3)	ALE	*x*	*y*	*z*	Side, Region, Brodmann Area (BA)
1	1352	0.01598	−22	0	−6	L Pallidum
		0.00981	−32	2	−4	L Putamen
2	1056	0.00984	20	10	−4	R Putamen
3	504	0.00984	−8	−46	−38	L Cerebellum
4	496	0.00783	−8	−54	−16	L Cerebellum
5	296	0.00972	−24	10	−14	L Putamen
6	288	0.00971	−8	−54	−50	L Cerebellum
7	288	0.00755	−6	−56	−30	L Cerebellum
8	288	0.00754	−2	−82	−18	L Cerebellum
9	288	0.00759	−6	−8	−6	L Thalamus
10	280	0.00755	−6	−70	−14	L Cerebellum
11	272	0.00744	−26	−56	−10	L Fusiform gyrus
12	272	0.00766	−42	−50	−10	L Inferior temporal gyrus
13	272	0.00971	−18	−38	−4	L Parahippocampal gyrus/hippocampus
14	264	0.00938	46	−68	−4	R Lateral occipital cortex
15	264	0.00764	−18	−14	−2	L Thalamus
16	264	0.00838	10	8	4	R Caudate
17	264	0.00938	18	−74	14	R Primary visual cortices
18	264	0.00938	14	62	14	R Superior frontal gyrus, medial
19	264	0.00971	−22	−4	48	L Superior frontal gyrus
20	256	0.00761	−44	−56	−30	L Cerebellum
21	256	0.00741	−28	−26	−14	L Parahippocampal gyrus/hippocampus
22	256	0.00766	−18	−86	−6	L Fusiform gyrus
23	256	0.00771	−52	−2	−4	L Superior temporal gyrus
24	256	0.00765	−8	−52	0	L Lingual gyrus
25	248	0.00774	−52	−10	−20	L Middle temporal gyrus
26	248	0.00776	−18	−16	−12	L Brainstem (upper)
27	248	0.00779	−38	−64	−12	L Lateral occipital cortex
28	240	0.00783	−32	−46	−28	L Cerebellum
29	240	0.00788	−48	−26	−18	L Inferior temporal gyrus

Table 7
Activation likelihood estimation meta-analytic results for studies comparing PTSD to trauma-exposed controls using whole brain-based analysis and ROI analysis, excluding studies presenting trauma-related stimuli, at cluster level inference $p < 0.05$.

Cluster number	Volume (mm^3)	ALE	*x*	*y*	*z*	Label
1	3624	0.02137	−22	−2	−8	L Pallidum
		0.01147	−8	−10	−8	L Brainstem (red nucleus)
		0.00992	−32	2	−4	L Putamen
2	1952	0.01584	24	0	−14	R Amygdala
		0.01027	18	10	−12	R Putamen
3	640	0.01604	14	62	14	R Superior frontal gyrus, medial
4	432	0.01039	−48	−10	26	L Primary somatosensory cortex
5	416	0.01041	36	0	−2	R Putamen
6	416	0.01090	−10	−50	4	L Primary visual cortices
7	328	0.00923	−36	−30	−18	L Parahippocampal gyrus

Table 8
Activation likelihood estimation meta-analytic results for studies comparing PTSD to trauma-naïve controls using whole brain-based analysis only, at cluster level inference $p < 0.05$.

Cluster number	Volume (mm^3)	Extrema Value	*x*	*y*	*z*	Label
1	1056	0.01767	36	18	−4	R Insula (anterior)
2	752	0.01501	48	−22	50	R Primary somatosensory cortex
3	440	0.01373	2	−48	40	R Precuneus
4	416	0.01351	−6	8	54	L Supplementary motor area
5	408	0.01275	−40	−48	4	L Superior temporal gyrus
5	408	0.01032	−4	10	24	L Anterior cingulate (premotor)
6	408	0.01205	−4	−72	46	L Precuneus
7	400	0.01202	44	4	12	R Rolandic operculum
8	336	0.01155	−16	48	−16	L Mid-anterior orbitofrontal cortex
9	312	0.0107	−54	−4	16	L Primary somatosensory cortex

expressions (see Table 1 for details of individual study characteristics).

The results were again different compared to the results including trauma-related stimuli. There were no longer significantly different clusters of activation in the left fusiform gyrus, right anterior cingulate and the most dorsal part of the right putamen and pallidum extending to the right caudate. We found additional clusters in left primary somatosensory cortex, left primary visual cortex and left parahippocampal gyrus (see Table 7).

7. Part 3: PTSD *vs.* trauma-naïve controls

The meta-analysis of primary studies where patients with PTSD were compared to control participants who had not experienced

Table 9
Activation likelihood estimation meta-analytic results for studies comparing PTSD to trauma-naïve controls using whole brain-based analysis and ROI analysis, at cluster level inference $p < 0.05$.

Cluster number	Volume (mm^3)	Extrema Value	*x*	*y*	*z*	Label
1	3488	0.01558	−2	52	0	L Anterior cingulate and paracingulate gyri
2	1176	0.01582	24	0	−14	R Amygdala
		0.01469	28	−12	−26	R Hippocampus
3	784	0.01766	36	18	−4	R Insula (anterior)
4	688	0.0302	−26	0	−26	L Amygdala
5	624	0.01501	48	−22	50	R Primary somatosensory cortex
6	616	0.01276	−32	−16	8	L Putamen
		0.01109	−40	−12	6	L Insula (posterior)
7	576	0.01443	2	60	−12	R Medial orbitofrontal cortex
		0.01051	0	52	−12	R Ventromedial prefrontal cortex
8	536	0.01149	−8	10	32	L Anterior cingulate
		0.01058	−4	10	24	L Anterior cingulate (premotor)
9	456	0.01623	4	−82	20	R Visual cortex
10	392	0.01409	−54	36	−12	L Mid-anterior orbitofrontal cortex

Table 10
Activation likelihood estimation meta-analytic results for studies comparing PTSD to trauma-naïve controls using whole brain-based analysis only, excluding studies presenting trauma-related stimuli, at cluster level inference $p < 0.05$.

Cluster number	Volume (mm^3)	ALE	*x*	*y*	*z*	Label
1	1024	0.01740	36	18	−4	R Insula (anterior)
2	488	0.01373	2	−48	40	R Precuneus
3	480	0.01032	−4	10	24	L Anterior cingulate (premotor region)
4	456	0.01275	−40	−48	4	L Superior temporal gyrus
5	80	0.01184	−4	−72	46	L Precuneus
6	16	0.01070	50	−18	46	R Primary somatosensory cortex

Table 11
Activation likelihood estimation meta-analytic results for studies comparing PTSD to trauma-naïve controls using whole brain-based analysis and ROI analysis, excluding studies presenting trauma-related stimuli, at cluster level inference $p < 0.05$.

Cluster number	Volume (mm^3)	ALE	*x*	*y*	*z*	Label
1	3248	0.01558	−2	52	0	L Anterior cingulate and paracingulate gyri
2	1272	0.01582	24	0	−14	R Amygdala
		0.01469	28	−12	−26	R Hippocampus
3	744	0.01740	36	18	−4	R Insula (anterior)
4	704	0.01149	−8	10	32	L Anterior cingulate (premotor)
5	688	0.01276	−32	−16	8	L Putamen
		0.01109	−40	−12	6	L insula (posterior)
6	632	0.01443	2	60	−12	R Medial orbitofrontal cortex
		0.01048	0	52	−12	R Ventromedial prefrontal cortex
7	488	0.01623	4	−82	20	R Visual cortices
8	416	0.01409	−54	36	−12	L Mid−anterior orbitofrontal cortex
9	376	0.01443	−34	−18	−12	L Hippocampus
10	376	0.01205	−4	−72	46	L Precuneus
11	352	0.01373	2	−48	40	R Precuneus

traumatic events consisted of 32 studies (Astur et al., 2006; Aupperle et al., 2012; Bluhm et al., 2012; Bruce et al., 2013; Bryant et al., 2005, 2008; El Khoury-Malhame et al., 2011; Elman et al., 2009; Falconer et al., 2008; Felmingham et al., 2009, 2010; Fonzo et al., 2010; Frewen et al., 2010, 2012; Jatzko et al., 2006; Kim et al., 2008; Landré et al., 2012; Mazza et al., 2012, 2013; Protopopescu et al., 2005; Sailer et al., 2008; Sakamoto et al., 2005; Schechter et al., 2012; Simmons et al., 2008, 2009; Steuwe et al., 2014; Strigo et al., 2010; Thomaes et al., 2009; van Rooij et al., 2014; Werner et al., 2009; Williams et al., 2006; Zhang et al., 2013). Due to overlap between participants used in multiple studies, one study was excluded from each group, leaving the final meta-analysis of trauma-exposed controls compared to individuals with PTSD comprised of 18 studies (577 participants, 145 foci) for whole-brain analyses; and 20 studies (609 participants, 93 foci) for ROI analyses. Some studies used both whole-brain and ROI and the foci from these are therefore split up for the meta-analysis.

7.1. Whole-brain analyses

Regions of significant difference in activity between participants with PTSD and trauma-naïve controls include the right anterior insula, bilateral somatosensory cortex, bilateral precuneus, left supplementary motor area, left superior temporal gyrus, left anterior cingulate cortex (premotor), right Rolandic operculum and the mid-anterior orbitofrontal cortex (see Table 8).

7.2. Whole-brain and ROI analyses

The meta-analysis of primary studies using both whole-brain and ROI analyses comparing patients with PTSD to trauma-naïve control participants consisted of 31 studies, totalling 998 participants and 206 foci.

Regions of significant difference in activity between participants with PTSD and trauma-naïve controls include extensive regions of the anterior cingulate and paracingulate gyri, left anterior cingulate (premotor region), bilateral insula (anterior for the right and posterior for the left), bilateral amygdala extending to the hippocampus on the right, right primary somatosensory cortex, right medial orbitofrontal cortex, left mid-anterior orbitofrontal cortex, right ventromedial prefrontal cortex and right visual cortex (see Table 9).

7.3. Trauma-unrelated stimuli

This analysis of whole-brain studies only was then repeated removing 3 of the 18 studies, which used trauma-specific stimuli in the experimental paradigm (Mazza et al., 2013; Sakamoto et al., 2005; Zhang et al., 2013). The remaining paradigms consisted primarily of emotional processing tasks using trauma-unrelated stimuli such as negative and neutral pictures from the IAPS database, or facial expressions (see Table 1 for details of individual study characteristics).

In this analysis the comparison between PTSD and trauma-naïve controls was no longer significant in the following regions: left primary somatosensory cortex, left supplementary motor area, right Rolandic operculum and left mid-anterior orbitofrontal cortex (see Table 10).

The analysis comparing adults with PTSD and trauma-naïve controls (now including ROI analyses as well as whole-brain analyses) was then repeated removing four of the 31 studies, which used trauma-specific stimuli in the experimental paradigm (Mazza et al., 2013; Protopopescu et al., 2005; Sakamoto et al., 2005; Zhang et al., 2013). The remaining paradigms consisted primarily of emotional processing tasks using trauma-unrelated stimuli such as negative and neutral pictures from the IAPS database, or facial expressions (see Table 1 for details of individual study characteristics).

Following removal of studies incorporating trauma-related stimuli, there were no longer significant differences in activation between adults with PTSD and trauma-naïve controls in the following brain regions: left amygdala and right primary somatosensory cortex. Additional regions with significant differences in activation were the bilateral precuneus and left hippocampus (see Table 11).

8. Discussion

This meta-analysis was undertaken to explore differences in functional brain activity between healthy adults and adults with PTSD. We hypothesised that trauma, even in the absence of symptoms, may have an enduring effect on brain function and therefore compared the brain activity between individuals with PTSD to control groups of both trauma-exposed and trauma-naïve participants.

Whole brain and ROI analyses showed distinct patterns of differences in functional activity depending on whether controls had been exposed to trauma or not. This suggests that the experience of trauma, whether or not it leads to clinically significant symptoms of PTSD, may have long-lasting effects on functional brain activity. This raises the important question as to whether we should conceptualise negative effects of trauma on brain function only in terms of a diagnosis of PTSD, or consider sub-syndromal brain states following trauma, which may be represented in the form of a gradient. It also raises the question of how sustained exposure to trauma affects the brain longitudinally and whether sub-syndromal trauma-resultant brain states are endemic in survivors of prolonged or repeated trauma such as veterans and refugees from warzones or survivors of repeated interpersonal violence such as childhood sexual abuse (Anda et al., 2006; Papageorgiou et al., 2000; Sutker et al., 1991).

In addition, we found evidence to support the importance of prefrontal–limbic–basal ganglia interactions in the pathology of PTSD. We discuss this in terms of its putative relation to our emerging understanding of the spontaneous dynamics of the brain's functional networks, and how trauma may lead to state changes perturbing the balance of the networks.

8.1. Brain networks in PTSD compared to control groups whether trauma-exposed or trauma-naïve

Overall, comparing individuals with PTSD to those without PTSD, we found the hypothesised differences in prefrontal regions, temporal regions, parahippocampal and amygdala regions as well as in regions of the basal ganglia. These findings fit well with previous reports of core brain regions associated with PTSD, which have been further explored in precedent studies and meta-analyses, and suggested to work according to a prefrontal–limbic imbalance along a hypoactive–hyperactive gradient in PTSD (Etkin and Wager, 2007; Hayes et al., 2012; Patel et al., 2012; Sartory et al., 2013; Simmons and Matthews, 2012). However, our analyses cannot offer direct confirmation of the hypoactive-hyperactive gradient in PTSD, and further research will be needed in order to further characterise the relationship within the brain network most strongly affected by PTSD.

Crucially, however, when we compared individuals with PTSD separately to trauma-exposed and trauma-naïve control groups, we found differential activity in different networks. Most significantly, we found differential involvement of basal ganglia regions (pallidum and putamen) in individuals with PTSD compared to trauma-exposed controls, while these regions were not involved when comparing PTSD with the trauma-naïve control group. In contrast, we found differential involvement of regions in bilateral precuneus, anterior cingulate (premotor area), right insula, primary somatosensory cortex, orbitofrontal cortices and supplementary motor area when comparing PTSD with the trauma-naïve control group (and not the trauma-exposed control group). Differences in activity in the insula when comparing PTSD and trauma-naïve participants are found to be right lateralised and anterior. Interestingly, a recent fMRI study has reported differential activity in the right anterior insula of people who had been previously exposed to a painful stimulus and were subsequently looking at pictures displaying that same painful stimulus in contrast to participants who had not been exposed to the painful stimulus prior to observing the pictures (Preis et al., 2013). These results suggest that the right anterior insula could be a core region of the network undergoing changes after experiencing a traumatic or painful event but may not be specifically involved in the development of PTSD.

In addition, we also found significant common activity when comparing PTSD patients with *both* control groups in the right amygdala. The amygdala is a key region of the 'salience network' and has been widely implicated in the pathology of PTSD, generally attributed to a heightened fear response, although the relative importance of this region remains under debate. It is interesting to note that the amygdala was only found to display differential activity following the inclusion of studies using ROI analysis where its importance would have been predetermined by the authors. This may in part be linked to the diminished sensitivity and potential dropout of signal in the temporal regions with fMRI unless acquisition protocols are specifically tailored for detecting activity in amygdala and orbitofrontal cortex.

The significant differences in active networks when comparing individuals with PTSD to the trauma-exposed and trauma-naïve control groups suggest that the experience of trauma may have long-lasting effects on functional brain activity, even in the absence of clinically significant symptoms of PTSD. It is interesting that we find a lack of differential activity in emotionally salient regions such as precuneus and orbitofrontal cortices between the PTSD and trauma-exposed control groups, all of which have been implicated in emotional regulation (Adolphs, 2002; Barrett and Satpute, 2013; Berridge and Kringelbach, 2013). Whether this corresponds to a marker of resilience, or subdromal post-traumatic symptoms is as yet unclear. As expected, these regions are differentially active when comparing PTSD with the trauma-naïve control group.

It is of potential interest to note the significant differential responses in regions of basal ganglia when comparing PTSD with the trauma-exposed group. This could indicate that the transition to the clinical syndrome of PTSD could be dependent on basal ganglia involvement. The differences in the amygdala between PTSD and both control groups could suggest that the changes in activity in the basal ganglia need to be coupled to dysregulation in these regions involved in memory and emotion.

Despite these important findings, the meta-analytic approach employed here has some limitations. Ultimately, our interpretation of the results depends on whether (1) the brain in PTSD is in a more 'normal' state, with no widespread dysregulation or pathological brain activity, or, alternatively, (2) both the trauma-exposed brain and the brain in PTSD may be displaying an imbalance of neural activity, leading to a lower incidence of differential brain activity in key brain regions. Without a direct comparison with a third, trauma-naïve, control group, these possibilities cannot yet be teased apart.

However, given existing knowledge of general emotional processing in PTSD and in the aftermath of trauma, the second alternative of 'brain imbalances in PTSD and trauma-exposed groups' would seem more plausible.

This is principally supported by the significant advances in whole-brain computational modelling which have shown that neuropsychiatric disorders can lead to imbalances in functional and structural brain networks (Deco and Kringelbach, 2014). The normal brain is thought to operate best when the network is critical (i.e. at the border of a dynamical bifurcation point), so that, at that operating point, the system defines a meaningful dynamic repertoire that is inherent to the neuroanatomical connectivity (Cabral et al., 2014; Deco et al., 2013).

Clinically, individuals with PTSD often display generalisation of fear to contexts in which they are safe (Rothbaum and Davis, 2003). Although this process is excessive and maladaptive in PTSD (overgeneralisation), it could be adaptive after trauma to avoid re-exposure to trauma by monitoring the environment for cues that might indicate its imminence. Therefore, we might expect hypervigilance and some degree of generalisation to exist in some trauma-exposed individuals without PTSD. A quantitative gradient in PTSD symptomology among trauma-exposed survivors (those with PTSD and those without) may therefore lead to the changes in functional neural activity in response to emotional stimuli that we find in our meta-analysis. As stress can enhance mnemonic recall for emotionally salient information, and also impair memory for neutral information within the same stressful episode (Payne et al., 2006; Qin et al., 2012), it is possible that traumatic events lead to memory distortion in all individuals who experience trauma, not just those who develop PTSD. The key to understanding how PTSD might lead to severe functional impairment and distress may therefore lie in the more subtle dynamics of where the key neural differences are between PTSD and trauma-exposed individuals.

8.2. *Comparison of trauma-naïve* vs. *trauma-exposed controls*

Ideally, we would be able to contrast trauma-exposed and trauma-naïve controls, to further explore whether there are significant differences in functional activity dependent upon trauma exposure in the absence of PTSD. However, it has not been commonplace within the literature to include the three groups in studies of brain activity, which should therefore be vital for future neuroimaging studies.

What we can discern is that the overall pattern of differences in neural activity between PTSD and the two control groups, trauma-exposed and trauma-naïve, is markedly different. Indeed, we see less differential activity between PTSD and trauma-exposed controls in the typical 'PTSD neuroanatomical networks' encompassing frontal regions, reward-related regions and structures implicated in memory. These core neuroanatomical networks, replicated across many neuroimaging studies to date (Rauch et al., 2006), are far more consistent when comparing PTSD to trauma-naïve controls. Whereas this could be due to the higher number of studies comparing PTSD to trauma-naïve participants, it could also be that these regions are not that strongly involved in the pathophysiology of PTSD *per se* but rather reflect the impact of trauma in the brain. The differences might also reflect a more resilient response to trauma in those who have experienced trauma without developing PTSD. Furthermore, recent research in rodents has shown that some of the regions arising in our meta-analysis as part of the network differentially affected in PTSD versus trauma-exposed participants (e.g. caudate, putamen, medial prefrontal cortex) contain specialised neuronal cell types thought to regulate resilience (Russo et al., 2012). Overall, our results highlight the importance of conducting more studies looking at the three different groups, trauma-exposed, trauma-naïve and PTSD, in order to redefine and further understand the neural mechanisms involved in resilience, response to trauma, and PTSD.

8.3. *Consequences of trauma exposure in the absence of PTSD*

Differences in neural activity do not necessarily correspond to cognitive or behavioural differences. However, existing research does indeed suggest that there may be enduring consequences of traumatic experiences, even in the absence of PTSD (Cerqueira et al., 2007; Shonkoff et al., 2012; Tzourio-Mazoyer et al., 2002). A resulting question is whether the acute stress response has an impact on the brain, independent of, but perhaps a precursor for the development of PTSD.

First, there is existing evidence that trauma measurably affects cognition, even in the absence of PTSD. While some cognitions, such as an individual's 'world view' distinguish between trauma-naïve individuals and all trauma-exposed individuals, others are specifically related to PTSD, and are not found in traumatised controls without PTSD (Foa et al., 1999). This again supports the idea of a gradient in terms of durable, measurable effects of trauma upon exposed individuals.

Second, there is existing evidence for neural changes following trauma, in the absence of PTSD. In a longitudinal study of the effect of deployment-related combat stress on the brain, mesofrontal circuits and midbrain–prefrontal coupling were altered following stress in a cohort of soldiers (van Wingen et al., 2012). Crucially for the purpose of teasing apart the contribution of PTSD, all but one of these soldiers did not meet criteria for PTSD, and although some functional brain changes remitted by 1.5 years, midbrain–prefrontal coupling abnormalities did not. Sustained suboptimal cortical regulation may confer susceptibility to subsequent environmental stressors, increasing the risk of such individuals developing PTSD if again exposed to trauma. Of note, people who are exposed to traumatic events, may be populations of particular concern, such as refugees, armed forces combatants and emergency workers (Bazarian et al., 2013).

8.4. *The difference between whole-brain studies and ROI analyses*

A comprehensive consideration of the relative merits of whole-brain and ROI analytical methods is beyond the scope of this review. However, it is important to highlight the impact of these two methods of analysis on the activation likelihood estimation.

We first included studies that only used whole-brain analyses, and subsequently repeated the analysis including ROI analyses. As would be expected with an increase in the number of studies, we found a greater number of clusters denoting significantly different neural activity. Of interest, however, many brain regions that

only became apparent through the second step of this analysis were those that currently exist in functional neuroanatomical network models of PTSD (Liberzon and Sripada, 2007; Rauch et al., 2006; Sailer et al., 2008). For instance, when comparing individuals with PTSD to trauma-exposed controls, amygdala activity only becomes apparent when including studies using ROI analyses.

8.5. Comments on the primary literature

The 53 primary studies included in our meta-analysis represent several heterogeneous features corresponding to: means of trauma, status of psychiatric comorbidity, experimental task paradigm, modality of stimuli, the nature of the control group, and method of statistical analysis (whole-brain contrast or selection of a priori region(s)-of-interest). All of these factors may correspond to important functional differences in neural activity.

It is difficult to distinguish trauma severity and chronicity from type of trauma exposure. For example, individuals exposed to combat may well have experienced a greater number of traumatic sequelae compared to those who have experienced a motor vehicle accident. Similarly, individuals who have suffered from intimate partner violence (IPV-PTSD) may have endured trauma of greater severity and chronicity. The nature of this meta-analysis has permitted synthesis of brain activity across types of trauma, finding common areas of differential activity. However, functional neuroimaging studies have yet to directly contrast the neural activity related to trauma of different means (combat-related, intimate partner violence, motor vehicle accident, assault) or of different degrees of severity or chronicity. Further, given a high comorbidity between PTSD and depression in the included studies, it is possible that some functional activity in the brain corresponds to depressive pathology.

The task paradigm differs considerably between studies. Differences include active versus passive involvement in response to stimuli, masked or overt presentation of stimuli, and executive tasks compared to perceptual tasks (see Table 1). The modality of stimuli used in such paradigms is also of interest to understanding the functional neuroanatomy underlying the most debilitating PTSD symptoms, such as flashbacks. Here, we noticed a large imbalance in the literature favouring visual stimuli, in line with the predominance of visual intrusive memories in PTSD, followed by auditory stimuli, with occasional tactile stimuli, and total absence of olfactory stimuli. Future studies across all of the sensory modalities may provide us with a more complete understanding of the functional neuroanatomy underlying PTSD. This data may be informatively combined with resting-state neuroimaging. Of note, the bulk of data is currently cross-sectional in nature, with comprehensive longitudinal studies of brain activity pre- and post-trauma yet to be conducted. Whole-brain computational models may provide an important means to move beyond correlations in cross-sectional studies and to begin to understand causal mechanisms (Deco and Kringelbach. 2014).

9. Conclusions

This meta-analysis suggests that trauma, even in the absence of symptoms, may have an enduring effect on brain function. There were differential patterns of group differences when comparing the brain activity between individuals with PTSD to control groups of both trauma-exposed and trauma-naïve participants. Critically, we found that regions of the basal ganglia were differentially active when comparing PTSD with the trauma-exposed but *not* the trauma-naïve group. In contrast, when comparing PTSD with the trauma-naïve control group (and not the trauma-exposed control group), there was a differential involvement of regions in precuneus, cingulate, right insula and orbitofrontal cortices known to be involved in emotional regulation. Finally, when comparing PTSD with *both* control groups, we only found common changes in activity in the amygdala. Taken together, this suggests that the transition to clinical PTSD could be linked with imbalances specifically in the basal ganglia coupled with imbalances in a larger network. This fits well with new evidence from whole-brain computational modelling of neuropsychiatric disorders that these disorders lead to specific imbalances in specific topological brain networks. Our meta-analysis also identified the need to directly compare trauma-exposed and trauma-naïve control groups such that potential biomarkers may be identified that could help early diagnosis and potentially novel interventions.

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