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REVIEW

Effects of psychotherapy on brain activation during negative emotional processing in patients with posttraumatic stress disorder: a systematic review and meta-analysis

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Abstract

Post-traumatic stress disorder (PTSD) is a debilitating condition which has been related to problems in emotional regulation, memory and cognitive control. Psychotherapy has a non-response rate of around 50% and understanding the neurobiological working mechanisms might help improve treatment. To integrate findings from multiple smaller studies, we performed the first meta-analysis of changes in brain activation with a specific focus on emotional processing after psychotherapy in PTSD patients. We performed a meta-analysis of brain activation changes after treatment during emotional processing for PTSD with seed-based *d* mapping using a pre-registered protocol (PROSPERO CRD42020211039). We analyzed twelve studies with 191 PTSD patients after screening 3700 studies. We performed systematic quality assessment both for the therapeutic interventions and neuroimaging methods. Analyses were done in the full sample and in a subset of studies that reported whole-brain results. We found decreased activation after psychotherapy in the left amygdala, (para)hippocampus, medial temporal lobe, inferior frontal gyrus, ventrolateral prefrontal cortex, right pallidum, anterior cingulate cortex, bilateral putamen, and insula. Decreased activation in the left amygdala and left ventrolateral PFC was also found in eight studies that reported whole-brain findings. Results did not survive correction for multiple comparisons. There is tentative support for decreased activation in the fear and cognitive control networks during emotional processing after psychotherapy for PTSD. Future studies would benefit from adopting a larger sample size, using designs that control for confounding variables, and investigating heterogeneity in symptom profiles and treatment response.

Keywords Posttraumatic stress disorder · Meta-analysis · Seed-based *d* mapping · Psychotherapy

Introduction

Many people experience a traumatic event during their lifetime (around 70%), and around 5% subsequently develop post-traumatic stress disorder (PTSD; Koenen et al., 2017). Patients with PTSD suffer from re-experiencing symptoms, hypervigilance to possible threats, avoidance of trauma-related situations and feelings, negative alterations in cognitions and mood, as well as alterations in arousal and reactivity (American Psychiatric Association, 2013). PTSD is a debilitating condition which has

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been related to problems in emotion regulation and cognitive control and this is reflected in recent neuroimaging studies. Meta-analyses on fMRI studies using paradigms that elicit fear or other aversive emotions (such as the emotional faces task, conditioned fear paradigm or symptom provocation) have shown altered activation in PTSD patients compared to healthy controls in the amygdala, insula, striatum, and temporal gyrus (Schulze et al., 2019; Suarez-Jimenez et al., 2020). The level of activation was also partly found to be positively associated with PTSD severity (Thome et al., 2020).

Neurobiological models of emotion dysregulation in PTSD have evolved over time. Rauch et al. (2006) based the first model on fear conditioning models, where amygdala hyperactivation fails to be regulated by (medial) prefrontal regions and the hippocampus, while hippocampus overaction leads to impairments in fear contextualization/generalization. Lanius et al. (2010) later described two subtypes of PTSD with their own model of emotion dysregulation. The original re-experiencing/hyperarousal subtype, with failing inhibition of limbic areas such as the amygdala accompanied by the lower activation in medial prefrontal regions (e.g. the ventromedial prefrontal cortex (vmPFC) and rostral anterior cingulate cortex (rACC)) is specified as the "undermodulation" of emotions (Lanius et al., 2010). The dissociative subtype, on the other hand, shows an unusually high activation in emotion regulation areas such as the dorsal ACC and medial PFC, and is specified as the "overmodulation" of limbic areas (Lanius et al., 2010).

Later neurocircuitry models of PTSD and have been extended to include the salience and central executive networks as well as the fronto-limbic circuit (Patel et al., 2012). The salience network is involved in emotion regulation, conflict management and reward processing and is overactive in PTSD (Patel et al., 2012). Important regions in the salience network are the amygdala, insula and dorsal ACC. Conceptually the salience network overlaps partly with the fear network (LeDoux & Daw, 2018; LeDoux & Pine, 2016). The central executive network is involved in attentional control and working memory and has been found to be hypoactive in patients with PTSD (Patel et al., 2012). The central executive network overlap with the cognitive control network (LeDoux & Daw, 2018; LeDoux & Pine, 2016). Important brain regions involved in this network are the dorsolateral PFC and lateral parietal cortices. Patients with PTSD show less activation in the default mode network, which includes areas such as the medial PFC, posterior cingulate cortex and parahippocampal gyrus and is involved in internal processes such as self-referential thinking (Patel et al., 2012).

There is some evidence that the altered activation in areas in the salience, central executive and default mode networks might be normalized by psychological treatment. Current first-line psychological treatments for PTSD includes trauma-focused psychotherapies such as prolonged exposure therapy, eye-movement desensitization and reprocessing (EMDR), and cognitive processing therapy (Merz et al., 2019). Common elements in al therapies are exposure to the memory of the traumatic event, cognitive processing, targeting of emotions and emotion regulation skills (Schnyder et al., 2015). Trauma-focused psychological treatment for PTSD generally has clinically relevant positive effect (Lewis et al., 2020) with large effect sizes (Weber et al., 2021), but nonresponse rates can go up to 50% (Schottenbauer et al., 2008). Understanding how activation in the brain changes after therapy might help to improve treatment response, e.g. through transcranial magnetic stimulation (Harris & Reece, 2021).

So far, three systematic reviews have been published on the effect of psychotherapy on the brain in PTSD, both structural and functional. Thomaes et al. (2014) conclude that studies show a decrease in amygdala activation and an increase in dlPFC activation after therapy. Malejko et al. (2017) also conclude a decrease in amygdala activation after successful therapy, next to a decrease in the insula, and an increase in dorsal ACC and hippocampus activation. Manthey et al. (2021), on the other hand, conclude that change in amygdala activation is unclear and that there is some evidence of increased activation in the mPFC, albeit in different areas across studies and not in all studies. These diverging conclusions highlight the importance of meta-analysis for quantitatively assessing how robust the reported findings are (Button et al., 2013). A possible reason for the diverse conclusions from these reviews is the heterogeneity of included studies, which included a range of scanning paradigms and both pharmacological and psychotherapeutic interventions.

To overcome some of the limitations of the previous reviews, we performed a pre-registered coordinate-based meta-analysis of functional neuroimaging studies to identify the most consistent findings of change in brain activation patterns after trauma-focused psychotherapy for PTSD (PROSPERO CRD42020211039). As impaired negative emotion processing is a core symptom of PTSD and to improve homogeneity between the studies, we limited the inclusion of studies to those that probed emotional processing by directly comparing negative emotional and neutral stimuli using a pre- to post-treatment design.

Method

Study selection

A systematic literature search was conducted in PubMed, APA PsycInfo (EBSCO), Embase (Embase.com), and Web of Science (Clarivate), from inception until December 14th, 2021. Search terms were a combination of various forms of the terms: "PTSD" and "Imaging" (see supplementary

materials for the full list of search terms). To be as inclusive as possible, we chose not to include 'psychotherapy' as a search term but manually select the intervention studies during the screening procedure. To increase homogeneity between studies, we only included studies that used a negative versus neutral contrast. Inclusion criteria were that the studies: 1) included a sample of patients with PTSD according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) or the International Classification of Diseases (ICD); 2) used an emotional paradigm with a negative emotional and a neutral condition during functional neuroimaging (functional magnetic resonance imaging (fMRI), single-photon emission computed tomography (SPECT) or positron emission tomography (PET); 3) used this paradigm before and after trauma-focused psychotherapy; 4) reported activation data for a contrast of a negative emotional condition versus a neutral condition. We did not have any exclusion criteria.

After removing all duplicates, two authors (IA and ALT) independently screened all titles and abstracts through Rayyan (https://rayyan.qcri.org) followed by all remaining full texts. Disagreements were solved by consensus. This study was preregistered in PROSPERO (CRD42020211039).

Data extraction and quality assessment

Data were extracted from the papers by two authors (IA and ALT). We extracted information about patient demographics (age, sex), diagnosis (PTSD severity before and after treatment, type of trauma, comorbidity), treatment (type of treatment, number of sessions), and medication use in patients. We also extracted data on time between scans, type of scanner, scanning sequence parameters, software used to analyze the data, statistical methods and thresholds, coordinates of significant peak voxels where patients showed changes in brain activation during a negative versus neutral emotional condition, as well as the corresponding t-value. Finally, we extracted data about task design, stimuli presentation, and timing, as well as the contrasts being used.

All included papers were independently assessed for methodological quality (by IA and ALT), using a 22-item rating scale developed for psychotherapy studies (range: 0–44, Öst, 2008) and 15 items from the COBIDAS checklist for neuroimaging studies (See Supplemental Materials; range: 0–15, Nichols et al., 2017)). We determined the intraclass correlation between the raters with a two-way random model with absolute agreement while the final quality ratings were settled through consensus.

Statistical analyses

Preprocessing and meta-analysis of significant peak coordinates from the included studies was performed using seed-based *d* mapping (SDM; https://www.sdmproject.com; Radua et al., 2012). SDM handles both positive and negative peak coordinates using reported t-values in a single map per study, leading to more nuanced statistical parametric maps. Hedge's g effect size was estimated per voxel, and the map was smoothed by an anisotropic Gaussian kernel using a gray-matter-specific template (Radua et al., 2014). The statistical parametric maps were then included in a random-effects meta-analysis weighted by sample size and within- and between-study heterogeneity. This resulted in a whole-brain map of changes in brain activation from pre- to post-treatment. First, we investigated changes in brain activation after psychotherapy using all available data, including studies with whole-brain analyses and those using regions of interest (ROIs, see Supplementary materials for full list of ROIs included in the studies). We included as a covariate whether a study included ROI findings (yes/no). To further ensure that findings were not driven by ROI-based studies with less stringent statistical thresholds we re-ran the analyses by including only whole-brain studies. We used a meta-regression to investigate the relationship between changes in activation after psychotherapy and the effect size of the treatment on clinical symptoms (Cohen's *d*), calculated as [PTSD severity pre-treatment—PTSD severity post-treatment)/SD pre-treatment]. We report results at an uncorrected statistical level (two-tailed $p < 0.05$ for the overall change in activation after therapy and $p < 0.005$ for the meta-regression) and corrected for multiple comparisons using threshold-free cluster enhancement (TFCE) correction ($p < 0.05$). Publication bias was assessed using Egger's test and I^2 as a measure of the heterogeneity.

Results

Characteristics of the included studies

Our search identified 3700 unique records. After title/abstract screening, 39 studies remained for full-text screening. We excluded 27 studies for the following reasons: absence of post-treatment scan ($n = 2$), absence of relevant negative emotional vs. neutral contrast ($n = 11$), absence of activation data ($n = 5$), patients not receiving treatment ($n = 4$), no PTSD sample ($n = 1$), or insufficient details e.g., on the statistics ($n = 4$). Attempts were made to contact the corresponding authors in cases where information was missing or ambiguous. Eleven fMRI studies and one PET study were included in the final analyses, where eight included data from whole-brain analyses (see Fig. 1 for the full flow chart). Four of the twelve studies did not report a t-value or statistics that could be converted to a t-value (Aupperle et al., 2013; Garrett et al., 2019; King et al., 2016; Simmons et al., 2013). We, therefore, coded peaks of increased activation

from pre- to post-treatment as "positive" and decreased activation as "negative", as is standard practice in SDM.

The 12 included studies included a total sample of 191 patients with PTSD with both pre- and post-treatment scans (See Table 1 for full information about the samples). Of the included studies, 11 included an adult sample (> 18 years) while one included an adolescent sample (Garrett et al., 2019). Since activation patterns for adolescents can be similar to adults (Herringa, 2017) we have included this study in our meta-analysis. Most studies used the Clinician-Administered PTSD Scale–DSM IV (CAPS-IV) as the main PTSD severity measure, while two studies (Garrett et al., 2019; Rousseau et al., 2019) used the self-reported UCLA PTSD Reaction Index for DSM-IV (PTSD-RI) or PTSD Checklist Scale (PCL-S), respectively. Two studies included patients with partial PTSD who did not all fulfill the full diagnostic criteria (Aupperle et al., 2013; Peres et al., 2011). In one study, 79% of patients had full PTSD but analyses were not reported separately for full and partial PTSD (Aupperle et al., 2013). In another study of working police officers all patients fulfilled the re-experiencing and hyperarousal criteria but not the numbing or avoidance criteria (Peres et al., 2011). Treatment duration ranged from a mean of 2.5 to 20 sessions. Eight studies used cognitive behavioral therapy/prolonged exposure (Aupperle et al., 2013; Felmingham et al., 2007; Fonzo et al., 2017; Garrett et al., 2019; Helpman et al., 2016; Peres et al., 2011; Simmons et al., 2013; Thomaes et al., 2012), two used mindfulness-based therapies (Bremner et al., 2017; King et al., 2016), and two used either EMDR or a mix of EMDR and cognitive behavioral therapy (Rousseau et al., 2019; van Rooij et al., 2016). (See Table 2 for estimated standardized mean difference changes in symptom severity after psychotherapy). Five studies used an emotional faces task (Felmingham et al., 2007; Fonzo

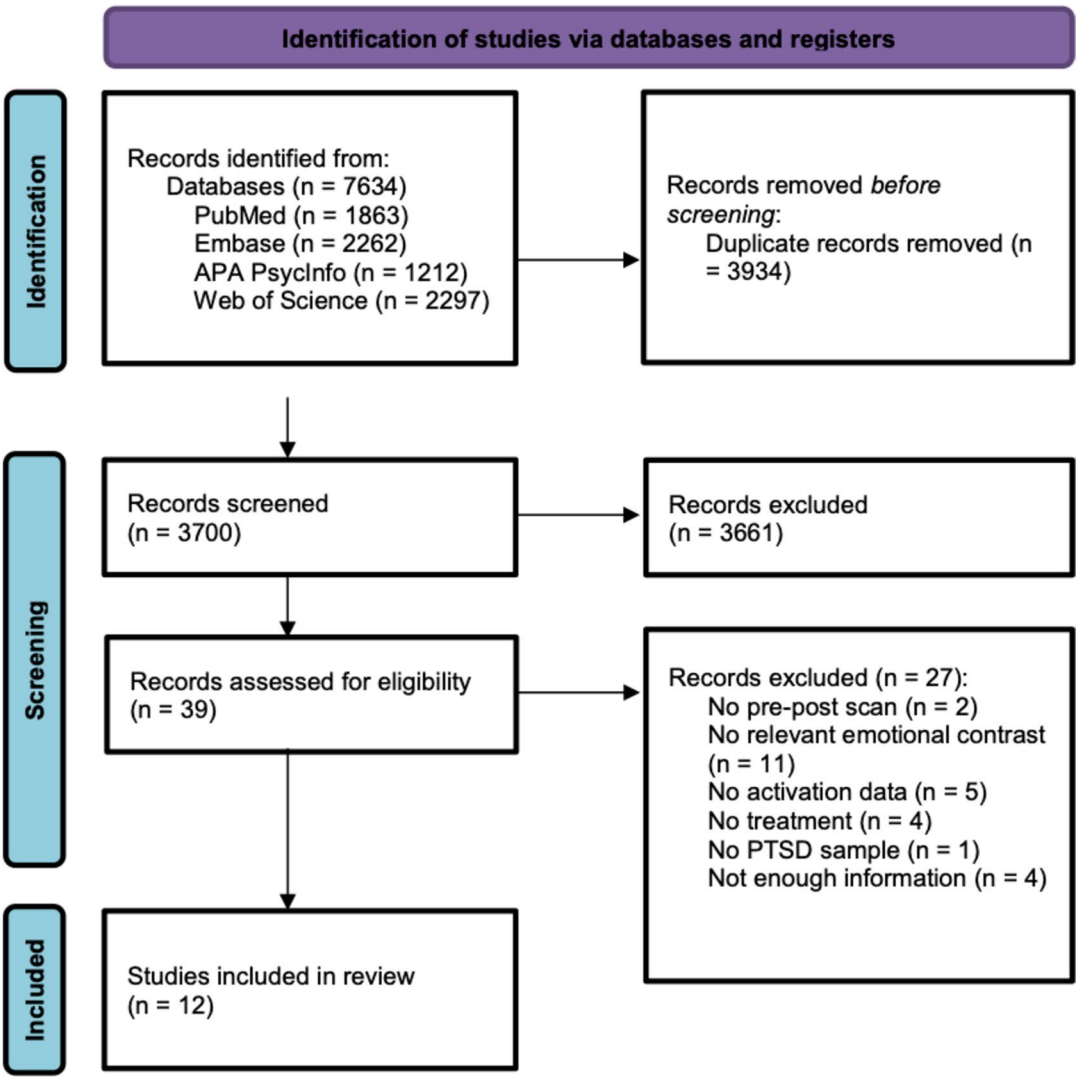

Fig. 1 Flow chart of included studies

Table 1 Characteristics of the included studies

Paper	N	Mean age (SD)	% Women	Type of trauma	% Comorbid depression	Other comorbidities	PTSD severity measure	Intervention (Mean number of sessions)	Control group	% Concurrent medication use	Imaging method	Task paradigm	Whole-brain contrast
Randomized controlled trials													
Bremner et al. (2017)	9	34 (7)	0	War (veterans)	Not reported	Not reported	CAPS-IV	Mindfulness-based stress reduction; MBSR (9)	Present-centered group therapy	0 (last four weeks)	PET	Symptom provocation (trauma related pictures & sounds)	No
Fonzo et al. (2017)	36	34.42 (14.72)	64	Not specified	50	Not reported	CAPS-IV	Prolonged exposure; PE (9–12)	Waitlist	8.3%	3 T fMRI	Emotional faces (fearful vs neutral)	Yes
King et al. (2016)[#]	14	32.43 (7.54)	0	War (veterans)	93	21% anxiety, 21% substance abuse	CAPS-IV	Mindfulness-based exposure therapy; MBET (13.5)	Present-centered group therapy	86%	3 T fMRI	Emotional face task (fearful vs shapes)	Yes
Thomaes et al. (2012)	16	35.20 (9.9)	100	Child abuse	62	76% anxiety, 75% personality disorder	CAPS-IV	Psychoeducation, skills training, CBT techniques and TAU (20)	TAU	66%	1.5 T fMRI	Emotional Stroop task (trauma words vs neutral words)	No
Pre-post design													
Aupperle et al. (2013)	14	40.07 (7.44)	100	Intimate partner violence	Not reported	Not reported	CAPS-IV	Cognitive therapy for battered women; CTT-BW (11.57)	No	0 (last four weeks)	3 T fMRI	Continuous performance task with trauma unrelated affective stimuli	Yes
Felmingham et al. (2007)	8	36.80 (8.8)	62.50	Assault or car accident	50	Not reported	CAPS-IV	Cognitive behavior therapy	No	25%	1.5 T fMRI	Emotional faces (fearful vs neutral)	Yes

Table 1 (continued)

Paper	N	Mean age (SD)	% Women	Type of trauma	% Comorbid depression	Other comorbidities	PTSD severity measure	Intervention (Mean number of sessions)	Control group	% Concurrent medication use	Imaging method	Task paradigm	Whole-brain contrast
Garrett et al. (2019)	20	15.30 (1.9)	90	Interpersonal trauma	50	35% anxiety	PTSD-RI	Trauma-focused Cognitive behavior therapy; TF-CBT (max. 20)	Healthy controls	0	3 T fMRI	Emotional faces (angry vs scrambled)	Yes
Helpman et al. (2016)	16	35.31 (9.89)	73.33	Not specified	0	Not reported	CAPS-IV	PE (10)	Trauma-exposed healthy controls	0 (last four weeks)	1.5 T fMRI	Fear conditioning – extinction recall	No
Peres et al. (2011)	12	31.20 (5.8)	0	Gunfire attack (police officers)	0	0%	CAPS-IV	Exposure based therapy and cognitive restructuring (15)	Trauma-exposed healthy controls and waitlist	0	1.5 T fMRI	Symptom provocation (trauma related sounds)	Yes
Rousseau et al. (2019)	16	35.40 (8.4)	43.75	Single traumatic event	56.25	12.5% social phobia, 37.5% generalized anxiety disorder, 18.75% panic disorder, 37.5% agoraphobia, 6.25% alcohol abuse	PCL-S	EMDR (2.5)	Healthy controls	25% antidepressants, 6.25% antidepressants and anxiolytics	3 T fMRI	Emotional faces (Fearful/angry vs shapes)	Yes
Simmons et al. (2013)	9*	32.90 (7.2)	0	War (veterans)	88	56% anxiety, 22% personality disorder	CAPS-IV	PE (12)	Non-responders	0 (last two weeks)	3 T fMRI	Continuous performance task with trauma related vs unrelated stimuli	Yes

Table 1 (continued)

Paper	N	Mean age (SD)	% Women	Type of trauma	% Comorbid depression	Other comorbidities	PTSD severity measure	Intervention (Mean number of sessions)	Control group	% Concurrent medication use	Imaging method	Task paradigm	Whole-brain contrast
Van Rooij et al., 2016	21*	35.20 (9.3)	0	War (veterans)	47.62	15% anxiety disorder	CAPS-IV	CBT/EMDR (duration unknown)	Non-responders	50%	3 T fMRI	Symptom provocation (trauma unrelated pictures)	No

CAPS-IV Clinician Administered PTSD Scale (DSM-IV), *CBT* cognitive behavior therapy, *EMDR* eye movement desensitization and reprocessing, *PCL-S* PTSD check list scale, *PFC* prefrontal cortex, *PTSD* posttraumatic stress disorder, *PTSD-RI* PTSD Reaction Index, *ROI* region of interest, *SD* standard deviation, *TAU* treatment as usual

Partial randomized controlled trial

*Remitters only

et al., 2017; Garrett et al., 2019; King et al., 2016; Rousseau et al., 2019), three used symptom provocation (Bremner et al., 2017; Peres et al., 2011; van Rooij et al., 2016), one used fear extinction (Helpman et al., 2016), and three used cognitive tasks with emotional stimuli (Aupperle et al., 2013; Simmons et al., 2013; Thomaes et al., 2012).

Changes in brain activation after therapy

The main meta-analysis of all 12 studies found six significant clusters of decreased activation after psychotherapy at an uncorrected threshold ($p < 0.05$, two-tailed, see Table 3 and Fig. 2). The largest cluster (Fig. 2A) encompassed the left amygdala, putamen, hippocampus, parahippocampus, and medial temporal lobe. The second cluster (2B) included the right putamen, pallidum and posterior insula, the third cluster (2C) included the inferior frontal gyrus (pars orbitalis), the fourth cluster (2D) the right anterior cingulate cortex, the fifth cluster (2E) the left ventrolateral PFC, and the sixth cluster (2F) included the left anterior insula. No cluster survived TFCE correction for multiple comparisons. There were no brain areas that showed a significant increase in activation after psychotherapy. A meta-regression showed no significant relationship between change in symptom severity and change in brain activation after treatment. We also found no evidence for publication bias based on Egger's tests or funnel plots, and the I^2 suggested little to moderate heterogeneity in the findings.

Decreased activation in the left amygdala, medial temporal lobe cortex and left ventrolateral PFC after psychotherapy was also found when the meta-analysis was restricted to the eight studies that reported whole-brain results, but these were not significant after TFCE-correction for multiple comparisons.

Methodological quality

As shown by the psychotherapy methodology rating scales (see Supplementary Table 2), most studies used reliable and specific outcome measures in a well described and representative sample. Four studies (33%) were randomized controlled trials, while 8 studies (66%) did not include a treatment control group. Many studies did not use blinded evaluators, only measuring symptoms and/or brain function at two time points, while also not providing information about the therapist training and competence. Most studies did not perform a power analysis and did not describe how concominant psychological and pharmacological treatments were controlled.

With regard to neuroimaging information as assessed by an adaptation of the COBIDAS checklist, most studies reported the basic parameters about the type of scanner, scanning parameters and preprocessing pipeline. Most

Table 2 Changes in PTSD severity from pre- to post-treatment and treatment effect size

Study	Pre-treatment PTSD severity Mean (SD)	Post-treatment PTSD severity Mean (SD)	PTSD severity measure	Cohen's d*
Aupperle et al. (2013)	66.07 (16.78)	16.29 (16.81)	CAPS-IV	2.97
Bremner et al. (2017)	56 (29)	28 (20)	CAPS-IV	0.97
Felmingham et al. (2007)	78.1 (20)	28.9 (20.3)	CAPS-IV	2.46
Fonzo et al. (2017)	66.33 (15.17)	29.6 (21.26)	CAPS-IV	2.42
Garrett et al. (2019)	39.1 (10.6)	22.9 (9.5)	PTSD-RI	1.53
Helpman et al. (2016)	78.53 (16.31)	28.6 (Unknown)	CAPS-IV	3.06
King et al. (2016)	72.29 (18.32)	56.29 (Unknown)	CAPS-IV	0.87
Peres et al. (2011)	48 (3.62)	19 (5.03)	CAPS-IV	8.01
Rousseau et al. (2019)	59.7 (10.9)	26.3 (4.9)	PCL-S	3.06
Simmons et al. (2013)	86.7 (15.4)	25.8 (16.5)	CAPS-IV	3.95
Thomaes et al. (2012)	88.5 (13.9)	66.2 (22)	CAPS-IV	1.60
Van Rooij et al. (2016)	66.3 (12.6)	24.3 (14.1)	CAPS-IV	3.33

CAPS-IV Clinician Administered PTSD Scale (DSM-IV), *PCL-S* PTSD check list scale, *PTSD* posttraumatic stress disorder, *PTSD-RI* PTSD reaction index, *SD* standard deviation

*Cohen's D calculated as (PTSD severity pre-treatment – PTSD severity post-treatment)/SD pre-treatment

Table 3 Changes in brain activation after psychotherapy

Peak region	MNI (X/YZ)	SDM-Z	P-value	Number of voxels	I^2	Egger's test
Including all studies						
Left amygdala, putamen, (para)hippocampus, medial temporal lobe	-20,8,-18	-2.619	0.0044	216	19.88	n.s
Right putamen, pallidum, insula	28,-2,-4	-2.485	0.0065	77	7.62	n.s
Left inferior frontal gyrus (orbitalis)	-40,18,-16	-2.343	0.0096	20	10.40	n.s
Right anterior cingulate	12,40,22	-2.216	0.0134	6	34.41	n.s
Left ventrolateral prefrontal cortex	-56,4,10	-2.007	0.0224	2	4.67	n.s
Left insula	-36,12,-10	-1.996	0.0230	2	48.01	n.s
Including only studies assessing the whole brain						
Left amygdala, medial temporal lobe	-24,2,-20	-2.761	0.0029	79	8.25	n.s
Left ventrolateral prefrontal cortex	-56,2,12	-2.266	0.0117	17	6.76	n.s

MNI Montreal Neurological Institute, *SDM* seed-based d mapping

studies also provided an adequate description of the task parameters. However, not all studies provided information about the characteristics of the scan session, summary statistics for the task or information about randomization of the stimuli within the task. The intra-class correlation coefficient for the quality ratings between the two raters was high (0.88; 95% CI 0.55–0.97). The final consensus ratings can be found in Supplementary Table 2.

Discussion

We conducted the first coordinate-based meta-analysis on trauma-focused psychotherapy-induced changes in brain activation during emotional processing in PTSD. Our findings tentatively suggest that PTSD patients show decreased activation in several regions of the fear and cognitive control networks after therapy, including the amygdala, (para)hippocampus, putamen, pallidum, insula, inferior frontal gyrus, anterior cingulate cortex, and ventrolateral PFC, although these findings did not survive correction for multiple comparisons. Decreased activation in the left amygdala and ventrolateral PFC was also found when only studies assessing the whole-brain were included, but these findings were not significant after correction for multiple comparisons.

The emotional tasks used in the included studies are designed to induce distress, fear and trauma memories. A core component of trauma-focused psychotherapy is to learn how to manage distress and intrusive memories, address negative trauma-related cognitions, and discriminate traumatic memories from the present (Olff et al., 2020). In general, patients in the included studies responded well

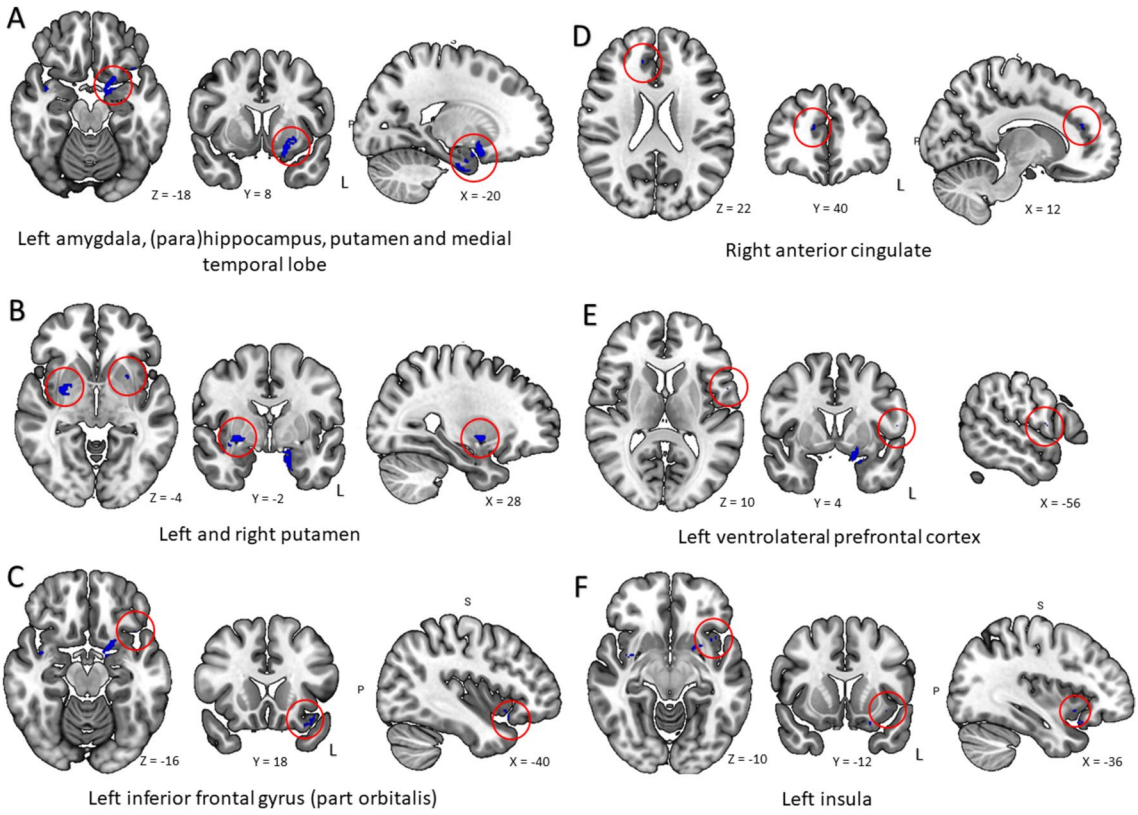

Fig. 2 Changes in brain activation after psychotherapy. Results show a decrease of activation after psychotherapy in the **A**) left amygdala, (para)hippocampus, putamen, and medial temporal lobe; **B**) left and right right putamen; **C**) left inferior frontal gyrus (pars orbitalis); **D**) right anterior cingulate; **E**) left ventrolateral prefrontal cortex; **F**) left insula

to treatment and showed improvement in PTSD symptoms. These symptoms include hyper responsivity to threats and avoidance. We theorize that this is associated with the reduced activation we found in regions of the fear network after successful therapy due to the reduced need for detecting threats and engaging in defensive behaviors. This is supported by previous research highlighting the role of the amygdala in the processing of immediate threats and intrusive memories and the putamen in the preparation and execution of defensive behaviors (Jahanshahi et al., 2015; LeDoux & Daw, 2018; LeDoux & Pine, 2016). Reduced activation in regions of the cognitive control network after therapy may reflect a decreased demand for processes such as the conscious evaluation of threat using working memory and integration with previous experiences mediated by the regions of the PFC and hippocampus (Belyk et al., 2017; Brohawn et al., 2010; LeDoux & Daw, 2018; LeDoux & Pine, 2016), or the integration of body signals involving the insula (Critchley et al., 2004; LeDoux & Daw, 2018; LeDoux & Pine, 2016). Despite the common elements of the different types of treatment, precise working mechanisms differ. For example, EMDR works through taxing working memory and prolonged exposure through reevaluation of negative cognitions (Schnyder et al., 2015; Shapiro, 2001). This might result in different changes in brain activation and might therefore lead to our current non-significant result. Because some studies compared responders to non-responders (for these studies we could not include the whole sample in our analyses) and other studies reported data for all patients (responders and non-responders together), it is unclear how change in activation pattern is related to clinical improvement. Our metaregression did not give an indication for an association between treatment effect size and change in brain activation.

An important limitation of the current meta-analysis is that only twelve studies could be included, which limits the power and generalizability of the findings. Our results should therefore be seen as preliminary evidence of changes in brain activation after treatment. The patient samples in the included studies differed on many clinical characteristics, including type and duration of traumatic events, comorbidity, medication status, and type and duration of treatment. Although the variation in these clinical characteristics reflects the diversity in the causes, presentations, and consequences of having PTSD,

it likely also leads to less consistent patterns of altered brain activation at the group level (Benfer et al., 2018; Guina et al., 2018). Dissociation was not assessed in most of the studies, while dissociative symptoms in PTSD have been linked to less amygdala activation and more anterior cingulate and medial PFC activation (Roydeva & Reinders, 2021).

There were also some important methodological differences and shortcomings in the included studies, which should be taken into account when interpreting the results from the meta-analysis. The studies used different emotional processing tasks such as symptom provocation, cognitive tasks with emotional stimuli or fear extinction. While all studies were designed to elicit a negative emotional response, the tasks might invoke slightly different circuits in the brain. Unfortunately, we do not know of any studies that compare these different task directly. Most studies were small, which makes it unlikely to detect moderate to small changes in brain activation. A minority of studies also did not report data at the whole-brain level but only for specific ROIs, which may increase the probability of both false positive and negative findings (Müller et al., 2018). Less statistical power due to more stringent thresholds in studies using whole-brain contrasts likely resulted in the difference between our results when including all studies versus when only including studies assessing the whole-brain.

We recommend researchers to report not only ROI results but include whole-brain analysis in their studies, to aid future meta-analyses. The majority of studies used a non-randomized pre-post treatment design without a control group or with only a healthy control group to adjust for the passage of time or repetition effects in task-related distress and brain activation. Furthermore, many studies did not report on essential elements of the training of therapists and raters which makes it hard to properly rate the quality of the treatments. The few available studies make it difficult to run meaningful meta-regressions investigating the impact of comorbidity, medication, task paradigms, or specific treatments. Future studies should include information about these clinical characteristics to aid interpretation and comparison of results.

Conclusion

Studying the neural correlates of effective treatment for PTSD is vital to identify the brain regions and mechanisms of recovery. The present meta-analysis suggests that there is tentative support for decreased activation in the fear and cognitive control networks during emotional processing after psychotherapy for PTSD. Our findings are in line with prevailing models highlighting the role of normalized threat detection, monitoring, and action preparation in clinical recovery, but fail to provide evidence for increased prefrontal activation related to cognitive control and emotion regulation (LeDoux & Daw, 2018; LeDoux & Pine, 2016; Wen et al., 2022). There are several limitations in the studies that influence the interpretability of these findings, the most important one the limited number of includable studies. Future studies would be strengthened by adopting a larger sample size, using designs that control for confounding variables, and investigating heterogeneity in symptom profiles and treatment response.

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Declarations

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