Degree project

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The Neural Correlates of Cognitive Reappraisal Among Post-Traumatic Stress Disorder Patients – A Systematic Review

Bachelor Degree Project in Cognitive Neuroscience

First Cycle 22.5 credits

Spring term Year 2022-23

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Abstract

The ability to regulate emotions is essential for human well-being. Among posttraumatic stress disorder (PTSD) patients, the capability to control emotions is impaired. Trauma-focused cognitive behavioral therapy is a recommended treatment for patients diagnosed with PTSD. Usually, cognitive reappraisal is considered the primary regulation technique in cognitive behavioral therapy treatment. The strategy aims to decrease negative or increase positive emotions by changing the interpretation of an event to alter the meaning of the situation. The aim of this thesis was to conduct a systematic review of the neural correlates of cognitive reappraisal among post-traumatic stress disorder patients. Through a systematic search, screening, and selection process out of initial 545 articles, six studies were included for data extraction and discussion. Using functional magnetic resonance imaging, participants utilized the strategy of cognitive reappraisal during an emotion regulation task in the scanner. Using functional magnetic resonance imaging, the neural activity of the participants in the included studies was compared during a cognitive reappraisal task. The result revealed a tendency of decreased activity in prefrontal cortices in PTSD patients during reappraisal compared to controls, indicating deficient recruitment of prefrontal cortices in PTSD patients during reappraisal.

Keywords: emotion regulation, post-traumatic stress disorder, cognitive reappraisal, neural correlates, functional magnetic resonance imaging

The Neural Correlates of Cognitive Reappraisal Among Post-Traumatic Stress Disorder Patients – A Systematic Review

Introduction

Life is full of challenges and demanding situations. The capability to regulate emotions when facing hardships is important for physical as well as mental health (Ochsner et al., 2002). For people diagnosed with PTSD, emotional awareness and regulating function are impaired (Bonn-Miller et al., 2011).

Cognitive reappraisal, here referred to as reappraisal, is regarded to be a helpful approach to regulating emotions (Gross & John, 2003). The technique is considered a core ingredient in the most frequently used psychotherapy treatment for mood and anxiety disorders, cognitive behavioral therapy (Beck, 2005). Trauma-focused cognitive behavioral therapy treatment is recommended for PTSD patients (Institute of Medicine, 2008; National Institute of Clinical Excellence, 2005). However, some studies report that approximately one-third of the patients still fulfill the diagnostic criteria for PTSD after completing treatment (Bradley et al., 2005). This finding suggests further examination of why certain individuals with the disorder do not respond to the treatment, and if reappraisal is involved.

Emotions and Emotion Regulation

The two essential characteristics of what an emotion is are defined by when the emotion arises as well as the many-faceted character of the emotion (Gross, 2014). Behavior, personal experience, and physiology are linked to emotions (Mauss et al., 2005), and they can initiate actions based on personal experience, or refrain us from action. Furthermore, they involve alterations in bodily stance and facial expression (Ekman, 1972). Emotions last from seconds to minutes (Gross, 1998), and might be beneficial or damaging for the individual (Susskind et al., 2008). For example, fear could help us avoid dangerous

situations, or anger could result in the injury of someone dear to us or ourselves (Gross, 2015).

The research on emotion regulation arose in the mid-1990s and has increased remarkably ever since (Gross, 1998). Emotion regulation is now considered important in the main subareas of psychology. Emotion regulation means trying to affect which emotions are present, how they are expressed and experienced, and when (Gross, 1998). Emotion regulation can also be described as the process to impact the path of an emotion (Gross et al., 2011). Collecting the strategies individuals use to regulate emotions and evaluating if certain approaches are connected with certain results is the priority in the field of emotion regulation (Gross, 2015).

James Gross' process modal model of emotion (Gross, 1998), presents five different strategies for regulating emotions. Each strategy takes place at different times in the emotion-generative process. The strategies are situation selection, situation modification, attentional deployment, cognitive change, and response modulation (Gross, 2015). The efficacy of different emotion regulation strategies is varied (Webb et al., 2012). The most adaptive emotion regulation strategies are reappraisal, distraction, and perspective-taking (Gross & John, 2003).

Cognitive Reappraisal

Reappraisal is one of the most researched sorts of cognitive change (Gross, 2015). Reappraisal is an emotion regulation strategy that involves altering one's interpretation of an event to change its affective components and reformulate the meaning of a situation (Buhle et al., 2014). The aim could be to down-regulate negative emotions, or to increase positive emotions (Gross, 2015). The strategy is one of several change mechanisms responsible for the effectiveness of cognitive behavioral therapy (Clark, 2022), and is more long-lasting than other attention-focused strategies (e.g., distraction) (Kross & Ayduk, 2008; Ochsner et al., 2012; Ochsner & Gross, 2005; Silvers et al., 2013).

The neural correlates of reappraisal include increased activity in the posterior dorsal medial prefrontal, bilateral dorsolateral prefrontal, ventrolateral prefrontal, and posterior parietal cortices (Buhle et al., 2014). Bilateral amygdala activation has been found to decrease during reappraisal (Buhle et al., 2014), as well as reduced activity in the ventral striatum was found (Gross, 2015). Habitual use of reappraisal can lead to enhanced control of emotion, interpersonal functioning, and psychological and physical well-being (Goldin et al., 2008).

Posttraumatic Stress Disorder

PTSD is a chronic emotional dysfunctional disorder that is involved in intrusive re-experiencing (e.g., unpleasant memories or nightmares), avoidance of trauma-related stimuli, negative alterations in mood and cognition (e.g., feeling distant from others or trauma-related beliefs such as shame and guilt) and altered reactivity and arousal (e.g enhanced state of sensory sensitivity or heightened psychological startle reaction) (APA, 2013). About half of the population will experience trauma, as a result of major accidents, combat, or sexual harassment for example, during their life (Kessler et al., 1995). Although, only 5-10% of people will develop symptoms qualifying for the diagnosis of PTSD (Aupperle et al., 2012). This finding may contribute to the exploration of other factors than the trauma itself that has to do with the development, maintenance, or protection against PTSD symptoms. Neuropsychological research might provide insights by identifying cognitive functions that underlie PTSD and may influence the maintenance and development of the disorder (Aupperle et al., 2012).

Rauch et al. (1998) first proposed a neurocircuitry model of PTSD and suggested medial prefrontal (including the anterior cingulate), ventromedial prefrontal, subcallosal, and orbitofrontal cortices to be hypoactivated compared to controls. This neurocircuitry model has been considered as widely adopted and useful in the understanding of PTSD, although it has been challenged by inconsistent findings in the literature (Patel et al., 2012). For instance, Patel et al. (2012) found less activity in the left angular gyrus, right posterior cingulate, and right medial prefrontal cortices in relation to the non-trauma controls. Also,

relative to the non-trauma controls, activity in the left supramarginal gyrus, left middle frontal gyrus, bilateral precentral gyrus, and right caudate nucleus was decreased among the PTSD participant. On the other hand, the PTSD group exhibited greater activation in the left amygdala, right hippocampus, bilateral anterior insula, and left putamen in PTSD patients compared to the non-trauma controls. The activity was also increased in the left precuneus, right middle frontal gyrus, right fusiform gyrus, and right postcentral gyrus in the PTSD group compared to the non-trauma controls (Patel et al., 2012).

Posttraumatic Stress Disorder and Cognitive Reappraisal

PTSD has been characterized in part as a disorder of emotional avoidance (Feeny & Foa, 2005; Marx & Sloan, 2005), which further suggests that emotion-regulation strategies, such as reappraisal, are underused by individuals with PTSD. Further, higher levels of PTSD symptom severity were associated with less frequent use of reappraisal (Eftekhari et al., 2009; Ehring & Quack, 2010).

Previous systematic reviews and meta-analyses of neural correlates of reappraisal among PTSD patients include other mood and anxiety disorders, with no results for PTSD patients separately reported (Picó-Pérez et al., 2017; Zilverstand et al. 2017). In clinical populations, a pattern of defective brain activation during reappraisal has been found (Picó-Pérez et al., 2017; Zilverstand et al. 2017). During reappraisal, individuals with clinical disorders showed insufficient recruitment of the dorsolateral and ventrolateral prefrontal cortex (dlPFC and vlPFC) (Zilverstand et al. 2017). Also, decreased activation in dorsomedial (dmPFC), left vlPFC, posterior cingulate cortex, and angular gyri were identified in individuals with mood and anxiety disorders during reappraisal, in comparison to healthy controls (Picó-Pérez et al., 2017).

The aim of this thesis was to investigate the difference in neural correlates of reappraisal among PTSD patients in comparison to healthy controls.

Method

Search Strategy

The databases Scopus, Web of Science, and Medline EBSCO were used to find relevant articles. The search was conducted 14th of March 2023, and the range of years covered was as far back as allowed in each database. The keywords used for the search were (PTSD OR "post-traumatic" OR "posttraumatic") AND (reapprais* OR (emoti* AND regulat*)) AND ("neural correlates" OR neural OR neuronal OR fMRI OR imaging) AND (PFC OR "pre-frontal" OR "prefrontal").

The two reviewers first identified the articles through database searching. The articles were then imported into the web application Rayyan. Rayyan is a web and mobile application manufactured to facilitate the process of filtering searches for systematic reviews, it assists in the screening of titles and abstracts (Ouzzani et al., 2016). The duplicates of the articles were removed, followed by the title and abstract screening which was performed individually by the two reviewers with the "blind mode" turned on (i.e., without seeing each other's choices while screening). Next the "blind mode" was switched off, and a comparison of the screening result was performed. Conflicting inclusion and exclusion decisions were discussed among the two reviewers until agreement upon a decision was made. Full texts of the selected articles were finally reviewed individually by both of the reviewers, the results discussed and the final included articles agreed on.

Inclusion and Exclusion Criteria

The inclusion criteria were: 1) Empirical studies in English that have been published in peer-reviewed journals. 2) PTSD patients and healthy controls. Only adult participants (over eighteen). 3) Studies that compare neural activation during reappraisal versus passive viewing of emotional stimuli in PTSD patients versus healthy controls. 4) Studies that use functional magnetic resonance imaging (fMRI) and examine activity in the prefrontal cortex (PFC). The exclusion criteria were: 1) Studies that use implicit emotion regulation. 2) Studies investigating trait (rather than state) emotion regulation.

Data Extraction

The primary region of interest in the included studies was PFC and its neural activity. The intervention performed by the PTSD patients and the healthy control group consisted of altering between passive viewing of emotional stimuli and cognitively reappraising negative stimuli. Focus was on comparing activity in PFC between the two groups, during passive viewing as well as during reappraisal. The intervention was performed during fMRI scanning.

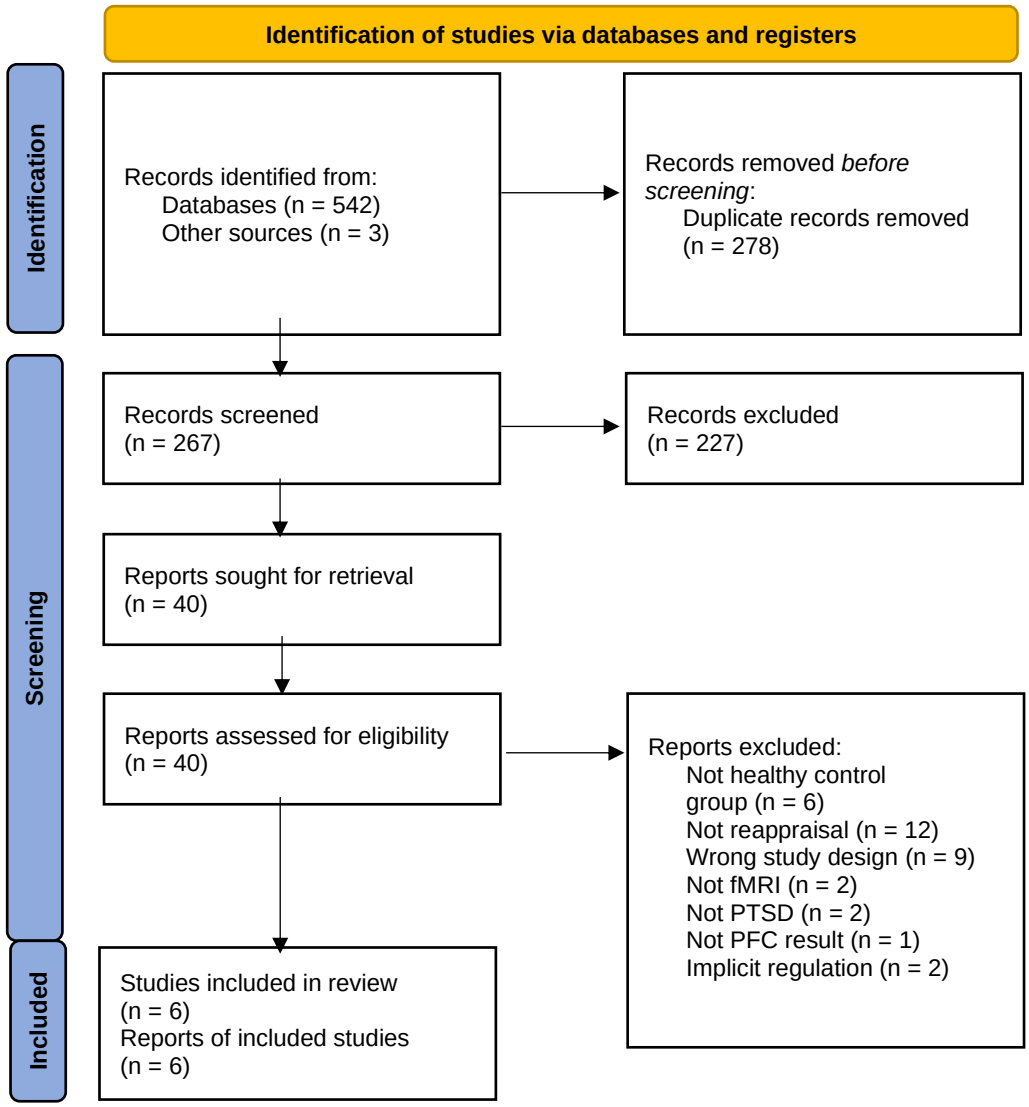
Results

Search Results

The initial search using the keywords detected 542 articles (see PRISMA flow chart, Figure 1). 278 duplicates were found and removed, leaving 264 articles to be reviewed by titles and abstracts. The two reviewers agreed on excluding 227 articles and performing a full-text review of the remaining 37 articles. In addition, systematic reviews and meta-analyses were manually searched for relevant articles. Three articles were identified, resulting in 40 articles for full-text review. Six articles were excluded because of a lack of a healthy control group, 12 articles did not use reappraisal, nine articles utilized the wrong study design, two of the articles did not use fMRI, two articles did not include PTSD patients, and one article did not report a result for PFC activity. Two, of the three articles found through manually reviewing relevant systematic reviews and meta-analyses, used implicit emotion regulation and were therefore excluded. Accordingly, a total of six articles met all of the eligibility criteria.

Figure 1

PRISMA Flow Chart



Methodology of Included Studies

Participants

Table 1 displays an overview of the methodologies of the studies. The studies had a total of 356 participants, although 307 were of interest for our literature review (161 PTSD patients and 146 controls). Importantly, three of the studies used trauma-exposed veterans (Joshi et al., 2020; Rabinak et al., 2014) and soldiers (Butler et al., 2019) without developed PTSD as control groups, while three of the studies used healthy control groups without trauma exposure (Bryant et al., 2021; Keller et al., 2022; New et al., 2009). For New et al. (2009) the cohort with trauma-exposed non-PTSD patients (14) were excluded. Additionally, for Keller et al. (2022) the group diagnosed with major depressive disorder (35) was eliminated. Three out of six studies had mixed gender distribution among the population (Bryant et al., 2021; Joshi et al., 2020; Keller et al., 2022). The other articles relied solely on men (Butler et al., 2018; Rabinak et al., 2014) or women (New et al., 2009). The mean age among the studies ranged from 28.3 (Butler et al., 2019) to 41.4 (Bryant et al., 2021) in the patient group, whereas among the control subjects, the mean age ranged from 31.7 (New et al., 2009) to 39.4 (Keller et al., 2022).

Studies defined PTSD using the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4th. Edition (Bryant et al., 2021; Keller et al., 2022; New et al., 2009; Rabinak et al., 2014) or ten criteria of the International Statistical Classification of Diseases (Butler et al., 2019). Joshi et al. (2020) did not clarify how they defined PTSD, they recruited only PTSD participants that have received the disease from combat exposure and the impairment has remained for at least three months. Participants were excluded if they had a history of neurological disorder (Bryant et al., 2021; Keller et al., 2022; New et al., 2009; Rabinak et al., 2014), traumatic brain injury (Bryant et al., 2021; Butler et al., 2018; New et al., 2009; Rabinak et al., 2014), loss of consciousness (Rabinak et al., 2014), psychosis (Bryant et al., 2021; Joshi et al., 2020), bipolar disorder (Bryant et al., 2021; Keller et al., 2022), major depression (Keller et al., 2022), substance dependence (Bryant et al., 2021; Joshi et al., 2020; Keller et al., 2022; New et al., 2009), a positive urine toxicology screen (Rabinak et al., 2014), acute somatic disorder (Keller et al., 2022), using psychotropic medication or previous comorbid Axis II psychiatric disorder (Butler et al., 2019) (American Psychiatric Association, 2000), other Axis I disorder except for symptoms of depression (New et al., 2009) or risk for suicide or alcohol dependence (Joshi et al., 2020).

Rabinak et al. (2014) included comorbidity (n= 2 major depressive disorder, n= 1 alcohol abuse) and psychotropic medication usage (n=7).

Stimuli

The majority of the studies used emotional pictures from the International Affective Picture Set as emotional stimuli. Only Butler et al. (2019) used images provided by the German armed forces, taken by soldiers during active duty displaying war-related scenes (e.g. explosions, destroyed vehicles, or soldiers under enemy fire). Four studies utilized stimuli of both negative and neutral valance (Bryant et al., 2021; Joshi et al., 2020; New et al., 2009; Rabinak et al., 2014) and two entirely negative (Butler et al., 2018; Keller et al., 2022).

The mean valence ratings for the negative pictures in Bryant et al. (2021) were 2.18 and the mean arousal rating was 6.91. The neutral pictures had a mean valence of 5.05 and a mean arousal of 3.2. In Butler et al. (2019) images of unpleasant valence and medium arousal were selected for negative stimuli (no neutral images were involved). No valence or arousal ratings regarding the images were presented by Joshi et al. (2020), the pictures were described as either "aversive" or "neutral". Keller et al. (2022) used only negative stimuli and the images ranged from 2.0-3.5 in valence and 5.1-6.8 in arousal ratings. New et al. (2009) did not present any valence and arousal ratings of the images (neutral and negative). Neither Rabinak et al. (2014) presented ratings regarding valence and arousal, the images were described as "unpleasant" or "neutral".

The Procedure of Emotion Regulation Task During fMRI

Bryant et al. (2021) arranged two task runs with three blocks (Think, Neutral, and Watch), consisting of ten image trials each. For each trial, the word "think" or "watch" appeared on the screen for 1.5 s, followed by 3.5 s rating how negative the participant felt on a scale of 1 to 5 where 1 is not negative and 5 means extremely negative. The "think" trial referred to the downregulation of emotional responses by using the strategies of reappraisal. The "watch" and "neutral" condition was referred to as simply watching the stimuli. Negative images appeared on the "think" and "watch" trials, whereas neutral pictures appeared on the "neutral".

In Butler et al. (2019) emotion regulation task, sixty images were presented, and arranged in twenty trials per condition (feel, reappraise, and suppress). The conditions were randomly interspersed and images were counterbalanced across participants to ensure that images were not presented with the same emotion regulation condition. Prior to each image, the instruction “feel”, “reappraise” or “suppress” was presented for 1 s. The image was then displayed for 10 s. Participants were asked to rate how much they were affected by the image on a scale from 1 to 4 where 1 indicated not affected and 4 strongly affected. The “feel” condition was referred to allow the image to trigger an emotional response and experience it. For “reappraisal” participants were instructed to think objectively in order to decrease emotional reactivity. During the “suppress” condition, the participants were instructed to not display any emotions outwards. Although, no “suppress” condition result was included in our study.

Joshi et al. (2020) participants completed three sets of the emotion regulation task. The task consisted of 80 unpleasant and 80 neutral pictures presented in blocks of five images over 20 s. Prior to each block, instructions of “look”, “maintain” or “reappraise” were presented. Negative images were accompanied by guidance of “maintain” or “reappraise” and neutral images appeared along with “look” instructions. For “maintain” blocks, participants were instructed to passively view photos and experience emotions. In “reappraise” blocks, participants were guided to decrease the intensity of their negative emotional response by using the cognitive strategy of reappraisal (e.g., reinterpret a man crying in front of a church as expressing tears of joy at a wedding).

In the Keller et al. (2022) study subjects were presented with 19 pictures with negative valence. Each individual completed one set of nine reappraise-view cycles (approximately seven minutes). Pictures were randomly arranged, but the occurrence was similar for the view and regulate condition. The sign "x" signaled to the subject to view the image, while "+" required the participant to reappraise the content of the picture. In the "view" condition, participants were instructed to maintain the negatively evoked emotions. During the reappraisal condition, participants were instructed to change their interpretation of the negative stimuli. For example, imagine that the situation (1) is better than it looks or (2) is not real or (3) will improve in the future or (4) taking the perspective of a professional. Before and after the reappraise-view cycle, participants rated their current arousal and valence level from 1 to 7.

Via headphones, subjects in the New et al. (2009) study received auditory instructions to either "diminish", "enhance" or "maintain" their response to negative images before each trial. "Diminish" was referred to as a decrease in the intensity of negative affect by imagining a less negative outcome. Instructions for "enhance" were to imagine a more negative outcome. In "maintain", participants were instructed to maintain their emotional response. Pictures were randomly distributed on regulation conditions. Every trial consisted of 2 s fixation, 12 s picture onset (with regulation instructions after 4 s) subjective rating for 4 s where participants were asked to rate how negative they felt (1 = very negative, 2 = negative, or 3 = neutral), ending with a 6 s intertrial interval. All participants completed four trials each. In each trial, participants viewed 15 negative and 5 neutral images. Neutral pictures were presented only with "maintain" instructions whereas negative images were accompanied by either "enhance", "reappraise" or "diminish" exhortation, five pictures per condition. Negative pictures were matched for valance and arousal and distributed across emotion regulation conditions.

Rabinak et al. (2014) experimental task consisted of three conditions. The “look” condition, where participants simply viewed the neutral images. The “maintain” condition, where subjects were instructed to naturally experience the unpleasant stimuli. Lastly, the “reappraise” conditions were explained as “use the cognitive strategy of reappraisal to decrease negative affect evoked by unpleasant images” (Rabinak et al., 2014, p.853). Two strategies of reappraisal were presented, either re-interpret the scenario in a less negative way (e.g. crying outside a church could be a wedding rather than a funeral) or objectify the content of the image (e.g. man with bleeding wounds could be an actor in a movie). Participants viewed two 20 s blocks of each condition (look, maintain, and reappraise). Every block consisted of emotional regulation instruction (look, maintain, and reappraise) followed by four images presented for 5 s each interspersed with 20 s baseline blocks consisting of an image of a fixation cross on black background. During baseline blocks, participants were asked to relax and reset their minds. Following the scanning session, subjects viewed all 96 previously seen images and rated these pictures on arousal (1= not at all arousing, 5= somewhat arousing, 9= extremely arousing) and valence (1= most unpleasant, 5= neutral, 9= most pleasant).

Study Design

All studies have a between-subject design. Although some studies report within-subject results (Butler et al., 2019; Keller et al., 2022; New et al., 2009; Rabinak et al., 2014). The regions of interest included in Bryant et al. (2021) were dlPFC, dmPFC, bilateral amygdala, insula, and hippocampus defined from the Automated Anatomical Labelling (AAL) atlas (Tzourio-Mazoyer et al., 2002). The subgenual anterior cingulate cortex and pregenual anterior cingulate cortex were also included and defined in Kober et al. (2008) meta-analysis. Joshi et al. (2020) regions of interest were dmPFC, dlPFC, and amygdala. Those were defined using the Montreal Neurological Institute atlas. Keller et al. (2022) selected regions of interest were: the posterior cingulate cortex (extended into the precuneus), bilateral dmPFC, bilateral angular gyrus, left vlPFC, bilateral inferior frontal gyrus, left middle temporal cortex, bilateral precentral gyrus, and supplementary motor area. Those regions were defined using the MarsBaR toolbox (version 0.44) (Brett et al., 2002). Rabinak et al. (2014) regions of interest were defined based on (Buhle et al., 2014) meta-analysis of 48 neuroimaging studies on reappraisal. However, the meta-analysis did not observe any activity in vmPFC, the coordinates for that area were taken from Diekhof et al. (2011) meta-analysis instead. The regions of interest in Rabinak et al. (2014) are dorsomedial, dorsolateral, ventrolateral, ventromedial prefrontal cortices and anterior cingulate cortex. No specifications regarding the regions of interest were defined in Butler et al. (2019) and New et al. (2009).

Table 1

Article, Sample, Age, Stimuli, Instructions, Design

Article	Participants	Mean age *(SD)*	Emotion stimuli	Instructions for CR	Instructions for contrast condition
Bryant et al., 2021	*n*= 61 37 PTSD patients (17 women, 20 men), 24 HC (12 women, 12 men)	PTSD = 41.4 (11.1), HC = 35.0 (13.9)	40 Pictures from IAPS, 20 negative, 20 neutral	"Down-regulate emotional responses by using the strategies of cognitive reappraisal."	"Simply view the image."
Butler et al., 2019	*n*=45 18 PTSD soldiers (men), 27 CEC (men)	PTSD = 28.3 (6.4), HC = 32.7 (5.9)	60 Combat images (images with unpleasant valence and medium arousal)	"Think objectively while viewing the images in order to decrease emotional reactivity."	"Allow the image to trigger an emotional response."
Joshi et al., 2020	*n*=77 51 PTSD veterans (46 men, 5 women), 26 CEC (men)	PTSD = 33.07 (8.70), HC = 35.73 (8.32)	160 Pictures from IAPS, 80 aversive, 80 neutral	"Use cognitive strategy to decrease intensity of negative emotional response."	"Passively view negative images and experience emotions."
Keller et al., 2022	*n*= 89 35 MDD (18 men, 17 women), 20 PTSD (10 men, 10 women), 34 HC (17 men, 17 women)	MDD = 37.3 (13.5), PTSD = 43.4 (13.0), HC = 39.4 (12.1)	19 Pictures from IAPS, pictures with negative valence	"Reappraise the content of negative emotion by changing your interpretation of the negative stimulus."	"Maintain the negative emotion elicited by the image."
New et al., 2009	*n*=42 14 PTSD patients (women), 14 TE non-PTSD (women), 14 HC (women)	PTSD = 38.7 (11.2), TE non-PTSD = 38.5 (10.8), HC =	Pictures from IAPS, neutral and negative	"Decrease intensity by imagining a less negative outcome."	"Maintain response."

		31.7 (10.3)			
Rabinak et al., 2014	*n*=42 21 PTSD veterans (men), 21 CEC (men)	PTSD = 30.24 (7.29), CEC = 34.81 (9.54)	96 Pictures from IAPS, 64 unpleasant, 32 neutral	"Use reappraisal to decrease negative affect."	"Passively process e.g. experience naturally unpleasant pictures."

Note. PTSD = posttraumatic stress disorder, HC = healthy controls, MDD = major depressive disorder, TE = trauma-exposed, CEC = combat exposed controls, IAPS = International Affective Picture Set, CR = cognitive reappraisal.

Neural Activation When Watching Negative Stimuli Versus Passive Viewing

The contrast condition of watching negative stimuli compared to watching neutral stimuli is presented here to illuminate what is regulated in this condition versus the reappraisal condition. However, two of the studies did not report this result (Joshi et al., 2020, Keller et al., 2022).

Rabinak et al. (2014) discovered no significant group differences in PFC activation for emotional reactivity. Both groups showed increased activation in ventrolateral, dorsomedial, ventromedial, and dorsolateral prefrontal cortices. Although, in PTSD patients left dlPFC was activated, in contrast to right dlPFC in the control group in an within-group comparison. Bryant et al. (2021) neither found any significant group differences in dlPFC and dmPFC. New et al. (2009) identified increased activation in the supplementary motor area in both the control group as well as in PTSD patients in a within-group comparison during passive viewing. During regulation instructions to enhance responses to negative pictures, New et al. (2009) detected a difference between groups in the activation of medial PFC, in particular the supplementary motor area. The control group had greater activation in medial PFC than the PTSD group.

While four of the studies used stimuli of both negative and neutral valence (Bryant et al., 2021; Joshi et al., 2020; New et al., 2009; Rabinak et al., 2014), two studies used stimuli of solely negative valance (Butler et al., 2018; Keller et al., 2022). Butler et al. (2019) reported increased activation in the medial orbitofrontal cortex in both groups. No significant differences in neural activity between the groups were discovered. For activation in other areas see Appendix A.

Neural Activation When Using Cognitive Reappraisal

Neural activation when using reappraisal during exposure to negative stimuli compared to watching negative stimuli was presented in Table 2.

During fMRI, several studies found decreased activity in bilateral (Bryant et al., 2021) and right (Keller et al., 2022) dmPFC among PTSD patients during reappraisal. Joshi et al. (2020) also found decreased activation in dmPFC. Increased activity in the dmPFC was additionally found bilaterally among the healthy control group (Bryant et al., 2021) and in the right (Keller et al., 2022). Likewise, increased activity was found in Joshi et al. (2020) control cohort during reappraisal versus passive viewing.

Decreased activity was found in dlPFC bilaterally among the patients and increased bilaterally among the healthy participants (Bryant et al., 2021). Rabinak et al. (2014) also found decreased activity in the left dlPFC among the PTSD participants, but the activity was increased in the left dlPFC among the healthy cohort.

Butler et al. (2019) found increased activity in the dorsal anterior cingulate cortex among the patients and decreased activity within the same area among the controls. New et al. (2009) found decreased left inferior orbitofrontal activity among the PTSD group and increased activity in the healthy controls during reappraisal. No difference in amygdala activity was found between groups (Butler et al., 2018; New et al., 2009; Rabinak et al., 2014). Also, Rabinak et al. (2014) found no difference in the activity of dmPFC, anterior cingulate cortex, vmPFC, or vlPFC between the two groups. For more activity details, see Appendix B.

Table 2

Neural Activation in Region of Interest When Using Cognitive Reappraisal During Exposure to Negative Stimuli Compared to Watching Negative Stimuli

Article	PTSD Patients	Healthy Controls
Bryant et al., 2021	BL dmPFC ↓ BL dlPFC ↓	BL dmPFC ↑ BL dlPFC ↑
Butler et al., 2019	dACC ↑	dACC ↓
Joshi et al., 2020	dmPFC ↓	dmPFC ↑
Keller et al., 2022	R dmPFC ↓	R dmPFC ↑
New et al., 2009	L iOFC ↓	L iOFC ↑
Rabinak et al., 2014	L dlPFC ↓	L dlPFC ↑

Note. L = left, Right, dmPFC = dorsomedial prefrontal cortex, dlPFC = dorsolateral prefrontal cortex, dACC = dorsal anterior cingulate cortex, iOFC = inferior orbitofrontal cortex, ↓ = decreased activation in relation to the other group, ↑ = increased activation in relation to the other group.

Discussion

This systematic review aimed to investigate the differences in neural correlates of reappraisal between PTSD patients and healthy controls. The neural correlates of reappraisal in healthy individuals included dmPFC, dlPFC, vlPFC, and posterior parietal lobe (Buhle et al., 2014; Ochsner et al., 2012). Four studies included in this systematic review confirm activity in dmPFC during reappraisal (Bryant et al., 2020, Joshi et al., 2020, Keller et al., 2022, Rabinak et al., 2014). Three of these studies show decreased activity in dmPFC in PTSD patients during reappraisal compared to increased activity in the healthy control group, during a between-group comparison (Bryant et al., 2020, Joshi et al., 2020, Keller et al., 2022). In a within-group comparison, Rabinak et al. (2014) report increased activation of dmPFC and vlPFC in both PTSD patients and the control group, with no group differences. A

decreased activity in dlPFC in the PTSD group compared to the control group is also confirmed in two studies (Bryant et al., 2021; Rabinak et al., 2014). Decreased activity in dlPFC in the PTSD group is consistent with former literature that individuals with clinical disorders show deficient recruitment of dlPFC (Zilverstand et al. 2017).

There was a pattern of decreased activity in prefrontal cortices in PTSD patients compared to healthy controls in the findings of the included studies in this systematic review (Bryant et al., 2020; Joshi et al., 2020; Keller et al., 2022; New et al., 2009; Rabinak et al., 2014), with the exception of Butler et al. (2019) where in contrast the activity in the dorsal anterior cingulate cortex is increased in PTSD patients compared to controls. Previous research has found less activation in PTSD patients compared to healthy controls in medial prefrontal regions (Rauch et al., 1998). A tendency in the findings of the included studies is that PTSD patients show hypoactivation in medial prefrontal regions (Bryant et al., 2021; Joshi et al., 2020; Keller et al., 2022; New et al., 2009), in line with earlier research.

Within PFC there are a variety of functions, divided into the functional sub-areas dmPFC, vmPFC, dlPFC, and vlPFC (Fitzgerald et al., 2019). Medial regions are considerably entailed in reappraisal (Aron et al., 2004), and generally, the function of the medial areas of the cortex is that they respond to emotional triggers (Britton et al., 2006; Hariri et al., 2003). Consequently, four out of the six studies included (Bryant et al., 2020; Joshi et al., 2020; Keller et al., 2022; New et al., 2009) reported activity in the medial regions during reappraisal. Three of the studies (Bryant et al., 2020; Joshi et al., 2020; Keller et al., 2022) reported decreased activity in dmPFC in PTSD patients compared to the control group during reappraisal. During presentation of negative stimuli, dmPFC is activated (Britton et al., 2006; Hariri et al., 2003), as well as during self-conscious emotion regulation (Ochsner et al., 2004). Banks et al. (2007) reported that the interplay between prefrontal cortices and the amygdala is a significant neural mechanism behind emotion regulation. They found that the robustness in the connection between orbitofrontal cortex/dmPFC and amygdala anticipated efficacious reduction in negative affect. The decreased activation of dmPFC in PTSD patients

compared to controls suggest that PTSD patients' ability to self-regulate and reappraise in the presence of negative stimuli is impaired in relation to healthy individuals.

The function of dlPFC is that it creates connections with other brain areas. Primarily connections with areas engaged in the inclusion of sensory information, and the sensory cortex, for example, the inferior parietal lobe (Hoshi, 2006). Moreover, dlPFC executes goal-oriented conduct, inclusive regulation of emotion (Corbetta et al., 2008), the decision-making process (Lee et al., 2007), selection of response (Yamagishi et al., 2016), and working memory (Arnsten & Jin, 2014). Two of the included studies (Bryant et al., 2021; Rabinak et al., 2014) confirm activity in dlPFC during reappraisal. PTSD patients showed decreased activity in dlPFC compared to the control group indicating deficient emotional awareness and regulation in PTSD patients compared to healthy individuals.

Rabinak et al. (2014) on the other hand, reported increased activation of dmPFC and vlPFC in both groups, with no significant group differences detected. vlPFC assists individuals to sort emotions for reappraisal since vlPFC is engaged in the production of inner speech (Geva et al., 2011). The result of Rabinak et al. (2014) indicates that there is no difference between the groups in this regard.

In contrast to the other studies, Butler et al. (2019) found increased activity instead of decreased activity in prefrontal cortices in PTSD patients during reappraisal compared to controls. The specific location of the increased activity detected by Butler et al. (2019) was the dorsal anterior cingulate cortex. The function of the anterior cingulate cortex is that it is engaged in incorporating information from various origins, with the purpose to solve conflict and to indulge in or prevent responses in behavior. The anterior cingulate cortex adjusts to what degree the amygdala is employed (Etkin et al., 2011). The result of Butler et al. (2019) distinguishes it from the result of other studies, it suggests that the anterior cingulate cortex is more activated in PTSD patients and therefore they are more efficient at regulating the amygdala than healthy controls.

Methodological Issues

Essential aspects of the methods were similar across the studies included in our systematic review. Although, the instructions of reappraisal among the studies varied from "down-regulate" (Bryant et al., 2021) or "decrease intensity" (Joshi et al., 2020; New et al., 2009) of emotional responses or "decrease negative affect" (Rabinak et al., 2014) to "think objectively" or "change your interpretation" when viewing the emotional stimuli (Butler et al., 2018; Keller et al., 2022). The different reappraisal instructions could be a factor contributing to the varied neural activation result. The instructions for the contrast condition were similar. For the contrast conditions, the instructions were more comparable. All studies, in some way, instructed the participants to "simply" or "passively" view images (Bryant et al., 2021; Joshi et al., 2020; Rabinak et al., 2014), "allow" or "maintain" the emotional response (Butler et al., 2018; Keller et al., 2022; New et al., 2009).

An additional difference was that two of the studies included the treatment of sertraline and Enhanced Medication Management (EMM) (Joshi et al., 2020) and trauma-focused cognitive behavioral therapy (Bryant et al., 2021) in order to assess differences in PTSD symptoms and neural response pre- to post- treatment. Only pretreatment results for these studies were included in our review to minimize falsely displayed results. Furthermore, gender distribution in the studies was heavily biased toward males. With all studies included, 71% of the participants consisted of men, this was general for both the PTSD patients and the control group.

Limitations

Various limitations of this systematic review should be considered. Foremost, the low number of studies requires careful consideration in drawing general conclusions from the result.

Bao et al. (2021) state that whether trauma causes symptoms of PTSD or not, trauma affects the function of the default-mode network and affective network. The importance of choosing a control group with caution when examining changes in PTSD networks was

consequently emphasized by Bao et al. (2021). Stark et al. (2015) confirmed that trauma without PTSD symptoms can affect brain function permanently. Furthermore, New et al. (2009) used both a trauma-exposed control group as well as a healthy control group. They reported a difference in results by the two control groups during enhancement of emotional stimuli, trauma-exposed non-PTSD participants activated areas of PFC to a higher extent than both PTSD patients and healthy controls. This suggests that the fact that three of our studies included trauma-exposed controls (Butler et al., 2019; Joshi et al., 2020; Rabinak et al., 2014) and three studies included healthy controls (Bryant et al., 2021; Keller et al., 2022; New et al., 2009) is a weakness. Only healthy control cohorts would contribute to a more distinct result.

Future Directions and Societal Aspects

To avoid contradictions in neural and subjective measures of emotion regulation, behavioral and psychophysiological measures of emotional arousal, e.g. skin conductance should be an included measurement for a more valid result (Lanius et al., 2012).

The linkage between the prefrontal cortices and the amygdala is significant for emotion regulation (Banks et al., 2007; Cisler et al., 2014; Goldin et al., 2013). During reappraisal, efficient regulation of emotions is dependent on the negative functional interconnection between the medial frontal cortex and amygdala (Uchida et al., 2015). Bryant et al. (2021) investigated the effects of trauma-focused cognitive behavioral therapy and reported that a prerequisite to efficient response to trauma-focused cognitive behavioral therapy is the ability to impede the amygdala during reappraisal. The pattern of the result of the studies in this systematic review indicates impaired recruitment of medial prefrontal cortices in PTSD patients during reappraisal, suggesting PTSD patients are less capable of down-regulating the amygdala than healthy individuals during reappraisal. Kozel et al. (2018) proposed that transcranial magnetic stimulation aiming at dlPFC can be a method to improve the effect of trauma-focused cognitive behavioral therapy (Kozel et al., 2018). It is of

great importance to unravel the conditions for PTSD patients undergoing trauma-focused cognitive behavioral therapy to enable improvement of response to the therapy.

Considering the fact that half of the population will experience trauma during their lifetime (Kessler et al., 1995), and that 5-10% of the trauma-exposed individuals will develop PTSD symptoms it is vital to acquire more knowledge about the mechanisms behind PTSD in order to relieve suffering (Aupperle et al., 2012). It is essential to have insight into why trauma-focused cognitive behavioral therapy might not be appropriate for some PTSD patients in order to provide alternative treatments. Further research on neural correlates in PTSD patients during reappraisal is consequently required.

Conclusion

In this systematic review, the differences in neural correlates of reappraisal between PTSD patients and healthy controls were explored. Previous systematic reviews in this domain have included PTSD patients in a clinical cohort, with no results separately reported for PTSD patients (Zilverstand et al. 2017). Also, there is currently a limited amount of studies in this area (Fitzgerald et al., 2019). These two facts imply that more research is needed. The limited amount of studies included in this systematic review needs to be considered when interpreting the result. Considering this, the result of the included studies showed that there was a pattern of decreased activity in prefrontal cortices in PTSD patients during reappraisal compared to controls, indicating deficient recruitment of prefrontal cortices in PTSD patients during reappraisal.

Word count: 6400

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Appendix A

Neural Activation Watching Negative Stimuli Compared to Watching Neutral Stimuli

Article	PTSD Patients	Healthy Controls
Bryant et al., 2021	L Hippocampus ↑ [a]	R Insula ↓ [a] L Hippocampus ↓ [a]
Butler et al., 2019	Occipital cortex ↑ [b] mOFC ↑ [b]	Occipital cortex ↑ [b] mOFC ↑ [b] Caudate ↑ [b]
Joshi et al., 2020	No comparison was found.	No comparison was found.
Keller et al., 2022	No comparison was found.	No comparison was found.
New et al., 2009	mPFC SMA ↑ [b] L Insula ↑ [b] Superior occipital gyrus ↑ [b] L & R middle frontal gyrus ↑ [b] Inferior frontal gyrus ↑ [b] Middle occipital gyrus ↑ [b] Inferior occipital gyrus ↑ [b] Superior parietal lobe ↑ [b] Precentral gyrus ↑ [b]	mPFC SMA ↑ [b] Calcarine sulcus ↑ [b] L Insula ↑ [b] Superior occipital gyrus ↑ [b]
Rabinak et al., 2014	L dlPFC ↑ [b] R vlPFC ↑ [b] R dmPFC ↑ [b] M vmPFC ↑ [b] L Midbrain ↑ [b] L Middle occipital gyrus ↑ [b] Caudate ↑ [b] BL Amygdala ↑ [a]	R dlPFC ↑ [b] R vlPFC ↑ [b] R dmPFC ↑ [b] M vmPFC ↑ [b] R Fusiform gyrus ↑ [b] Midbrain ↑ [b] L PCC ↑ [b] L Middle temporal gyrus ↑ [b] BL Amygdala ↑ [a]

Note. L = Left, R = Right, mOFC = medial orbitofrontal cortex, mPFC = medial prefrontal cortex, SMA= supplementary motor area, PFC= prefrontal cortex, vmPFC = ventromedial prefrontal cortex, vlPFC = ventrolateral prefrontal cortex, dmPFC = dorsomedial prefrontal cortex, dlPFC = dorsolateral prefrontal cortex, PCC = posterior cingulate cortex, ↓ = decreased activation, ↑ = increased activation.

[a] = between group analysis. [b] = within-group analysis

Appendix B

Neural Activation in Whole-Brain When Using Cognitive Reappraisal During Exposure to Negative Stimuli Compared to Watching Negative Stimuli

Article	PTSD Patients	Healthy Controls
Bryant et al., 2021	BL dmPFC ↓ [a] BL dlPFC ↓ [a]	BL dmPFC ↑ [a] BL dlPFC ↑ [a]
Butler et al., 2019	OFC ↑ [b] Occipital cortex ↑ [a] dACC ↑ [a]	dlPFC ↑ [b] Occipital cortex ↓ [a] dACC ↓ [a]
Joshi et al., 2020	dmPFC ↓ [a]	dmPFC ↑ [a]
Keller et al., 2022	R dmPFC ↓ [a] R IFG ↓ [a]	R dmPFC ↑ [a] R IFG ↑ [a] R Precental gyrus ↑ [a] BL IFG (pars triangularis) ↑ [b] BL Middle frontal gyrus ↑ [b] L Precentral gyrus ↑ [b] BL SMA ↑ [b] BL Temporal gyrus ↑ [b] R Caudate ↑ [b] R Thalamus ↑ [b] R Insula ↓ [b]
New et al., 2009	Middle temporal gyrus ↑ [a] L Superior temporal gyrus ↑ [a] Rolandic operculum ↑ [a] L IFG ↑ [a]	BL Posterior cingulate ↑ [a] L Inferior OFC ↑ [a] R Superior frontal gyrus ↑ [a] L Middle frontal gyrus ↑ [a] Medial frontal gyrus ↑ [a] L IFG ↑ [a] Precentral gyrus ↑ [a] Inferior pari lobe ↑ [a]
Rabinak et al., 2014	L dlPFC ↓ [a] dmPFC ↑ [b] vlPFC ↑ [b] Middle temporal gyrus ↑ [b] Middle occipital gyrus ↑ [b] Calcarine fissure ↑ [b]	L dlPFC ↑ [a] dmPFC ↑ [b] vlPFC ↑ [b] Middle temporal gyrus ↑ [b]

Note. L = Left, R = Right, BL = bilateral, dmPFC = dorsomedial prefrontal cortex, dlPFC = dorsolateral prefrontal cortex, OFC = orbitofrontal cortex, vmPFC = ventromedial prefrontal cortex, dACC = dorsal anterior cingulate cortex, rACC = rostral anterior cingulate cortex,

SMA = supplementary motor area, IFG = inferior frontal gyrus, ↓ = decreased activation, ↑ = increased activation.

[a] = between group analysis. [b] = within-group analysis.