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Functional Neuroanatomy of Emotion and Its Regulation in PTSD

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Abstract

PTSD is a devastating disorder, linked to profound mental, physical, occupational, and functional impairment. In addition, it is a highly complex disorder, characterized by symptom heterogeneity across multiple domains. Nevertheless, emotion dysregulation arising from exaggerated response to threat and/or inability to regulate negative emotional states plays a defining role in the pathophysiology of PTSD. In order to improve our understanding of how emotion dysregulation manifests in this illness, functional neuroimaging research over the past 20 years provides great insight into underlying neuroanatomy of each component of emotion dysregulation in the context of PTSD. While prior reviews exist on the topic of neuroimaging findings in PTSD literature, the present review synthesizes this work through the lens of emotion and its regulation. Studies that employed tasks of emotional responding and symptom provocation, implicit regulation (e.g., emotional stroop and interference), explicit regulation (e.g., cognitive reappraisal), and fear conditioning/extinction studies were reviewed. Findings demonstrate that emotion dysregulation in PTSD arises from complications within a large neurocircuitry involving the amygdala, insula, hippocampus, anterior cingulate cortex, and prefrontal cortex. Although exaggerated response in the amygdala and insula to negative emotional triggers is pervasive, PTSD is also marked by deficient appraisal, resolution, and management of negative emotional states sub-served by the ACC and PFC during regulation. Together, this further supports the importance of studying emotion regulation deficits in tandem to exaggerated symptom provocation in order to better understand the constellation of symptoms present in those with PTSD.

Keywords

PTSD; fMRI; neuroimaging; emotion; emotion regulation; review

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1. Introduction

Posttraumatic Stress Disorder (PTSD) is a devastating disorder, linked to profound mental, physical, occupational, and functional impairment.[1] In addition, it is a highly complex disorder, characterized by symptom heterogeneity spanning the avoidance of trauma-related material, emotional blunting and distancing, hyper-vigilance, hyper-arousal, and persistent negative alterations in cognition and mood.[2] Although symptoms suggest a constellation of disturbances, emotion dysregulation is considered a core component of the disorder.[3–5] In particular, emotion dysregulation is thought to give rise to the presence of hypervigilance and attentional biases, enhanced startle response, hyper-arousal, emotional numbing, irritability, enhanced memories for traumatic events, difficulty in discriminating danger vs. safety, generalization of fear, and avoidance of emotional material or trauma reminders.[4] Given its relation to a wide array of signature symptoms, the investigation into how emotion dysregulation manifests itself is integral to the study of PTSD.

Yet, emotion dysregulation as a symptom is decidedly complex and may be defined by exaggerated emotional reactivity based on atypical “bottom-up” detection or appraisal of emotional triggers.[6] In contrast, emotion dysregulation may arise due to deficiency in “top-down” control of emotional response.[6] Further, deficiency in regulation may occur either implicitly (e.g., unconsciously) or explicitly (e.g., consciously), with each form of regulation relying on distinct cognitive processes.[7] For instance, deficits in implicit regulation result from impairment in the ability to unconsciously shift attention during an emotional experience that in turn modulates a response, while deficits in explicit regulation occur when trying to consciously change an emotional experience using cognitive strategies. While related, these sub-processes (e.g., emotional reactivity, implicit and explicit regulation attempt) are distinct, and emotion dysregulation may arise from complications within one or many of these processes. From the perspective of subjective experience or clinical observation, however, it is difficult to identify and isolate dysfunction specific to these domains.

Over the past 20 years, functional neuroimaging studies have provided the ability to examine brain functioning *in vivo* during tasks of emotion processing and implicit/explicit regulation. Functional magnetic resonance imaging (fMRI) has gained momentum over the last two decades as a neuroimaging technique as a way to non-invasively assess changes in metabolic activity in the brain in patients with PTSD by which to assess its clinical neuropathophysiology. Presently, a large number of fMRI studies have been published on the topic of emotion-specific brain dysfunction in those with PTSD and reviews of this literature are plentiful.[3,4,8–32] However, despite substantial literature on this topic, findings are synthesized specific to symptom provocation or fear conditioning, largely ignoring the study of how neural substrates during emotion regulation may be impaired. Other reviews at the intersection of emotion and cognition exist, but do not make the study of brain changes during emotion regulation a focus of their respective examinations.[33–38] Thus, there has yet to be a thorough review of fMRI findings that sufficiently explores ways in which emotion processing *and* its regulation are altered at the neural level in those with PTSD.

As such, the intent of this review was to survey fMRI studies through the dual lens of emotion *and* its regulation. Studies are summarized as they pertain to threat and emotion processing versus those that examine regulation of these processes at implicit and explicit levels. In addition, studies on fear conditioning and extinction are summarized as learning about and abolishing a fear response is highly relevant to the topic of controlling emotional states. Given the emphasis on the neural underpinnings of these processes, relevant neuroanatomy implicated within each study paradigm is also reviewed.

2. Functional Neuroimaging Studies of Emotion Processing

Most fMRI studies involving those with PTSD utilize tasks of passive emotion processing in the form of emotional faces that convey threat (e.g., angry, fearful), aversive imagery (e.g., mutilated bodies, images of violence), and trauma-specific cues, such as words, pictures, or autobiographical scripts. In healthy individuals, exposure to negative content activates the amygdala, insula, hippocampus, anterior cingulate cortex (ACC), and ventromedial prefrontal cortex (VMPFC), predominantly.[39] The amygdala, a dense set of nuclei within the medial and anterior portion of the temporal lobe[40], is involved in processing motivationally-salient stimuli.[41–43] While the amygdala is engaged in response to negative triggers and studied most commonly in this context, it is also activated in response to positive stimuli, such as happy faces[44], and stimuli that are novel.[45] In conjunction, the amygdala plays an important role in the consolidation of information from other brain regions during an emotional experience. These other regions include the insula, a portion of the cortex that is folded within lateral sulcus and responsible for the interoceptive awareness of an emotional state[46,47], and the hippocampus, situated within the temporal cortices that is involved in contextual learning and memory. Although the hippocampus and the parahippocampal gyrus, a region that directly surrounds the hippocampus and which is also instrumental for learning and memory, are traditionally studied in their role of encoding spatial information, events, facts, and autobiographical information[48], these regions are densely connected with the amygdala and send information regarding the probability that a stimulus is associated with danger based on prior experiences. The ACC, cortical tissue that surrounds the corpus callosum, is also active during appraisal of the emotional stimulus but is involved in inhibiting and controlling motor functioning associated with an emotional response.[40] Finally, the VMPFC, defined as cortical tissue located below the genu of the corpus callosum along the midline, is involved in emotional appraisal as well as linking this experience with a physiological response.[49]

2.1 Amygdala

In comparison to non-traumatized and traumatized controls, individuals with PTSD exhibit greater activation within the amygdala.[50–62] Although one study by Felmingham and colleagues did not find evidence of significant amygdala activation in response to negative images in a group of individuals with PTSD prior to treatment,[63] no comparison group was used in this study, making the lack of a significant amygdala effect difficult to interpret.[63] Although studies demonstrate that greater amygdala engagement occurs in PTSD compared to traumatized controls, individuals with a trauma history also exhibit elevated amygdala response in comparison to healthy, non-traumatized controls.[58] Therefore, elevated

amygdala response to negative triggers may be a result of trauma, or a pre-trauma feature. Much of the work that has found hyperactive amygdala response utilizes fearful or angry faces as probe to evoke threat[53,57–60], although elevated amygdala response occurs when individuals with PTSD are shown aversive images or cues intended to evoke autobiographical memory of the trauma[54,56,61] or when asked to recall a traumatic memory.[62] In addition, greater amygdala response is evident in those with PTSD when masked stimuli probes are used, as in the case of masked fearful faces[51,64–67] and stimuli that are inherently neutral (e.g., Chinese ideographs) but which were subconsciously primed with a masked negative face.[68] Thus, response of the amygdala to threat in those with PTSD is a robust finding, and does not depend on stimuli type or input from other brain regions that provide conscious perception of an emotional trigger.[69]

Although elevated amygdala response to negative stimuli is a consistent feature of PTSD, the implications of this characteristic in terms of subjective and behavioral response (e.g., feeling more negative; producing a physiological response) is not as clear. For instance, the vast majority of studies do not link elevated amygdala response with a behavioral/physical output[50–54,56,58–60,63], and while some studies found that individuals with PTSD rate images and faces as more negative[55,57], other work fails to find group differences in self-reported feelings of physiological response (e.g., heart pounding).[61] Therefore, elevated amygdala response in those with PTSD does not necessarily translate to increased experience of negative affect[70], although more work is needed in this domain.

Finally, although studied to a lesser extent, individuals with PTSD also display greater amygdala response to neutral faces compared to non-traumatized controls[71] and reduced amygdala response to happy faces compared to traumatized controls.[72] This latter finding correlates with symptoms of emotional numbing and reduced engagement of the ventral striatum, a region instrumental for reward processing.[72] These results suggest the possibility that PTSD is characterized by more pronounced deficits in salience detection that is not specific to negative content.

2.2 Insula

During exposure to negative faces[53,58,59], trauma-specific imagery[73] and anticipation of negative images[74,75], individuals with PTSD exhibit greater activation in the insula compared to trauma-exposed and healthy controls. In addition, greater insula response occurs in those with PTSD in response to masked negative faces[65] and neutral symbols that have been unconsciously paired with negative faces[68], suggesting that regions involved in interoceptive awareness of emotional state are active without ability to consciously perceive. The insula is also over-engaged in those with PTSD during a relaxation period when individuals were previously told to re-imagine their trauma[76], suggesting that individuals with PTSD may be incapable of disengaging from feelings spurred by their trauma when instructed to.[76] The presence of exaggerated insula response during exposure to negative stimuli has been specifically tied to symptoms of re-experiencing[73], hyper-arousal[75] and the occurrence of flashbacks.[77] Therefore, the extent to which individuals with PTSD re-experience physical reminders of their traumatic experience may be directly tied to over-active insula engagement during emotion processing.

2.3. Hippocampus

In terms of the state of hippocampal/parahippocampal gyrus findings in PTSD, several studies find evidence of enhanced engagement in PTSD during exposure to trauma-specific images.[78–81] As individuals with PTSD experience trauma-specific images as more personally relevant[36], over-engagement of regions responsible for encoding autobiographical information is not altogether surprising. However, the finding of enhanced hippocampal/parahippocampal activation in PTSD extends to studies utilizing stimuli that are not intended to serve as reminders of trauma, such as generally aversive images[50,82], emotional faces[83], and negative words.[84] To note, over-engagement of the hippocampus in PTSD is not present across all emotional stimuli types, as there is *less* engagement of the hippocampus in response to positive images.[85] Therefore, individuals with PTSD may over-generalize their personal relevance to negative stimuli in particular.

In several instances, greater hippocampal engagement during exposure to negative stimuli[50,83] and trauma-specific cues[61] correlates with greater amygdala engagement in those with PTSD. In some instances co-activation of the hippocampus and amygdala when individuals are exposed to negative images is related to accurately recalling this content at a later time.[50] Therefore, salience detection encoded by the amygdala alongside memory formation may therefore help individuals remember emotional content. In contrast, other work finds that increased hippocampal engagement during the encoding of negative words is related to the occurrence of false positives (e.g., falsely stating that a subject has encountered a stimulus before[84]). Taken together, this suggests that greater hippocampal engagement during encoding of negative content may be related to better recall, but this phenomenon may be over-generalized. In addition, other work finds that greater hippocampal/parahippocampal engagement during the encoding of *trauma-specific* images is related to *worse* memory performance, qualified by inability to correctly recall seeing this content before.[85] Discrepancy across studies in terms of whether enhanced hippocampal engagement boosts or hinders performance mirrors results from behavioral studies, which demonstrate that PTSD patients possess an advantage in remembering emotional content compared to healthy peers, but that memory distortions are prevalent.[87–90] Therefore, memory disturbances in PTSD may be best qualified as enhanced, but over-generalized, alongside a failure to recall this material if related to the trauma. The clinical significance of enhanced hippocampal functioning and altered memory accuracy may be central to understanding the existence of the over-generalization of fear as a central feature of PTSD pathophysiology.[91]

2.4 Anterior Cingulate Cortex

Although diverse in its functioning, the ACC is involved broadly in the integration of information from multiple sources to assign value and resolve conflict, along with motoric response to inhibit or engage in a behavioral response.[92] Specifically the ACC is involved in resolving the extent to which threat is attended to, based on the integration of external and internal clues.[92,93] Further, the ACC helps modulate the extent to which the amygdala is engaged based on updating the likelihood of threat.[92,94,95] The most widely-recognized sub-division of the ACC involves dichotomizing the region along a dorsal (dACC) and ventral (vACC) boundary.[93] The vACC includes the subgenual ACC (sgACC) and rostral ACC (rACC) and is involved in detection of emotion[30,96] based on its strong connections with the

amygdala.[97] The dACC, in contrast, is involved in conflict control, response selection, and error detection[92,93] and forms little direct connection to the amygdala.[97]

During emotion processing, several studies find that individuals with PTSD under-engage the ACC[57,58,60,73,78,79,98], although some of this work did not localize deficits to dorsal or ventral sub-regions. Nevertheless, under-engagement of the vACC[57] and dACC[58] or under-engagement of both regions in the same study are reported[60,73,78,79,98], suggesting that deficits within the ACC are pervasive. As a consequence, both direct emotional appraisal (sub-served by vACC) and conflict resolution of emotional states (sub-served by dACC) are likely to be altered in PTSD. In addition, deficits in engaging the vACC and dACC is evident across studies of negative face processing[57,58,60] and trauma-specific imagery[73,78,79,98], suggesting that altered appraisal of negative emotion is not specific to any one type of negative stimulus.

2.5 Prefrontal Cortex

Unlike the amygdala, insula, hippocampus, and ACC – which suggest uniform direction of aberrant activation in PTSD (e.g., either over- or under-engaged) – there is discrepancy across studies regarding the PFC. A heterogeneous structure, the PFC contains functional sub-divisions based on dorsal/ventral and lateral/medial locations, partitioning the structure into dorsomedial prefrontal cortex (DMPFC), ventromedial prefrontal cortex (VMPFC), dorsolateral prefrontal cortex (DLPFC) and ventrolateral prefrontal cortex (VLPFC) regions. In general, medial portions of the cortex are active in response to emotional triggers. For instance, activation in the DMPFC occurs during exposure to negative content[99,100] and may be generally involved in evaluation of one's own emotional experience.[101,102] Individuals exhibit activation in DMPFC during self-focused regulation of emotion, theorized to play an important role in emotional self-monitoring as it serves emotion regulation goals.[103] In contrast, the VMPFC forms heavy reciprocal connections with the amygdala and other sub-cortical structures as well as with the lateral cortex; therefore, function of the VMPFC is viewed as a relay-station for "bottom-up" information from limbic and sub-cortical structures signaling emotion detection, and lateral PFC signaling response selection and control.[104] Owing to dense projections with the amygdala, the VMPFC is involved more so in the implicit, automatic regulation of emotion.[30,96]

During processing of fearful faces and script-driven imagery, several studies find that individuals with PTSD under-engage the DMPFC[57,60,76] and VMPFC.[57,62,66,98] Deficiency in recruiting the midline PFC suggests that emotional appraisal and automatic emotion regulation are both compromised in PTSD during passive viewing. Some studies have found that under-engagement of both regions is related to greater amygdala engagement[57], suggesting that failure to engage these regions may be directly related to hyper-reactivity of the amygdala. In contrast, other work has found *increased* engagement of the VMPFC[60], DMPFC[105] and MPFC generally, without specification as to dorsal versus ventral boundaries[53,59,73,106] and in response to negative faces and script-driven imagery. In addition, VMPFC activation in PTSD is *positively* related to amygdala reactivity in response to emotional faces and greater symptom severity.[107] Therefore, over-engagement of the MPFC also appears linked to greater amygdala response in those with PTSD, making the

role of the MPFC as it relates to PTSD illness unclear. As many studies involving those with PTSD do not qualify specific sub-regions that are altered (e.g., DMPFC v. VMPFC) and given the diversity of functions within this region, we conclude that more work is needed to fully qualify the nature of altered MPFC engagement in response to negative stimuli in this population.

3. Functional Neuroimaging Studies of Emotion Regulation

Exaggerated threat detection and negative emotional responding, as outlined above, may be borne from "bottom-up" aberrations specific to aberrant appraisal of emotion. Alternatively, they may accompany and/or result from altered "top-down" regulation of affect that occurs through attentional control and emotional coping strategies. As the neurocircuitry that underlies unconscious and conscious regulation of negative affect is distinct from appraisal of emotion, it deserves closer inspection as it relates to the pathophysiology of PTSD.

Unlike tasks of passive emotion processing, in which participants are shown emotional content without instruction to cognitively engage in this material, tasks of *implicit emotion regulation* test capacity for completing a cognitive task in light of emotional triggers. Individuals' ability to accurately and/or rapidly complete the cognitive task in light of these emotional "distractors" that are irrelevant for cognitive performance, or changes in engagement of cortical regions in this process, provides clues as to the strength of emotion regulation capacity. Tasks of emotional interference most commonly include stroop tasks, in which participants are asked to carry out an information-processing task that contains both congruent and incongruent trials. For example, in a stroop task in which individuals are asked to identify the quantity of written numbers displayed on a screen, congruent trials are those without conflict between the numbers as written and quantity listed (e.g., two "2's). On incongruent trials, a mismatch is present, such as three "4's". Emotional distractors are used throughout the task, just before and after trials in most cases. In another version of implicit emotion regulation, individuals are asked to make a judgment about a non-emotional stimulus, such as whether two houses are the same or different, while emotional distractors are presented before or after trials or within the background. Finally, some studies employ attention bias paradigms, which show participants a set of stimuli, one aversive and one neutral. Immediately following the display of these stimuli, one image is replaced by a dot-probe and the latency towards directing attention to this probe provides a measurement of attentional bias towards the preceding emotion.[108] In most cases, negative faces are used as emotional triggers and greater attentional bias towards the dot-probe that replaces these faces indicates impaired regulation of negative affective states.

In contrast to studies of implicit emotion regulation are those of *explicit emotion regulation*, defined as when individual consciously and with intention attempt to alter their emotional reactions using cognitive control strategies. Multiple volitional strategies exist for regulating emotional experiences, such as distancing, distraction, and suppression. By far, the most widely-used technique to study explicit regulation is cognitive reappraisal, a strategy used to re-interpret the meaning of an emotional stimulus to alter one's own affective experience.[109] For example, cognitive reappraisal is used when individuals re-evaluate the scene of women

crying outside a church as one that depicts tears of joy at a wedding, rather than sorrow at a funeral.

In healthy individuals during implicit regulation, numerous regions of the PFC are engaged including VMPFC, DMPFC, VLPFC, and DLPFC in addition to the ACC[110,111], while explicit regulation relies on engagement of these regions alongside middle temporal, superior temporal, and parietal cortices.[112–115] In particular, both tasks of implicit and explicit regulation rely on functioning of the DLPFC and VLPFC, which differ from medial portions of the PFC that are heavily involved in emotional appraisal. In contrast, the VLPFC is attributed to motor inhibition[116], spatial attention and re-orienting attention to objects[117–119], semantic processing[120], categorization of objects[118,119], and memory for semantic information.[121–123] During emotion processing, the VLPFC is involved in the generation of inner speech[124–126], which helps individuals categorize emotions for appraisal and reappraisal.[113] Functionally, the DLPFC forms numerous connections with other brain regions, predominantly with sensory cortices and regions involved in the integration of sensory information, such as the inferior parietal lobe.[127] The DLPFC does not form direct connections with sub-cortical regions involved in emotional response, such as the amygdala, and must receive this information through the involvement of intermediate brain regions, predominantly the VMPFC and ACC.[128–130] The DLPFC is involved in executive functioning broadly-defined, including working memory[131–133], decision making[134], attentional control[135], and response selection.[136] Given these functions, DLPFC's role may be described as the active generation of strategies in order to execute goal-directed behavior, including emotion regulation.[118,119]

3.1. Prefrontal Cortex

In individuals with PTSD undergoing tasks of implicit regulation, the direction of aberrations within the PFC are mixed and discrepancies across studies may depend on the location of aberration within the cortex, as well as the type of emotional distractor used. For instance, during a stroop task in which participants indicated whether the quantity of numbers displayed on a screen was congruent to the number as written (e.g., two "2's") while negative emotional images were shown prior to each trial, individuals with PTSD exhibited *less* engagement of the VLPFC in comparison to traumatized and healthy controls.[137] During incongruent trials (e.g., when the quantity of numbers did not match the number displayed), individuals with PTSD displayed less engagement of the DLPFC in comparison to traumatized controls.[137] As trauma-exposed individuals engaged the DLPFC to a greater extent compared to healthy controls, over-engagement of this region during difficult trials may reflect compensatory functioning that is not necessary in the absence of a trauma history.[137] Less engagement of the VLPFC and *greater* engagement of the VMPFC also corresponds to greater PTSD symptom severity when participants are instructed to press a button in response to a salient stimulus while also viewing negative emotional images.[138] Less VLPFC and greater VMPFC activation also corresponded to greater amygdala engagement in this task[138], suggesting that exaggerated VMPFC response does not translate to successful regulation. Therefore, in those with PTSD there is less reliance on lateral PFC regions known to be involved in regulation, alongside greater engagement of VMPFC that is likely recruited for emotional appraisal.[138]

In contrast, other work finds that PTSD symptom severity *positively* relates to engagement of the VLPFC and VMPFC during an emotional interference task in which individuals were instructed to indicate via button-press the occurrence of a non-emotional 'target' stimulus amidst emotional distractors.[139] As this study utilized emotional distractors that were trauma-specific, discrepancy in terms of whether the PFC is over- versus under-engaged during implicit regulation may depend stimulus type. Over-engagement in this case may signal the need for compensatory functioning when emotional distractors are personally relevant.

In terms of exploring altered engagement of the PFC during explicit regulation of negative affect in those with PFC, limited studies have been completed in this domain. First, New and colleagues demonstrated that individuals with PTSD were less effective at reappraisal in reducing negative affect (as evidenced by subjective ratings) and exhibited reduced engagement of the DMPFC and lateral PFC compared to healthy controls when using reappraisal to make negative images appear less negative, although this pattern was also observed in traumatized controls.[140] Subsequently, Rabinak and colleagues found focal deficits in the DLPFC in those with PTSD, again when using reappraisal to make images appear less negative.[141]

3.2. Anterior Cingulate Cortex

During an implicit regulation same-different task in which individuals are instructed to make a judgment about a non-emotional scene when emotional distractors were used, and when individuals are participating in a stroop task in which participants viewed faces that matched a superimposed emotional word, participants with PTSD exhibit less activation in the vACC.[142,143] Less engagement of the vACC is correlated with avoidance symptoms[142] and re-experiencing symptoms[143], suggesting that vACC deficiency during implicit regulation is linked to more than one symptom domain.

With regard to the dACC, greater symptom severity is related to more differential activation in the dACC during trials in which emotional versus non-emotional distractors were used during target-detection (e.g., colored shape indicating need for button press).[138] In other words, engaging the dACC preferentially *more* during emotional distraction as opposed to non-emotional distraction suggests increased monitoring of potential conflict in those with more symptoms. PTSD may therefore be associated with exaggerated need for conflict monitoring during cognitive control when emotion is present. Other work has found that individuals with PTSD, compared to TECs, exhibit greater dACC activation during emotional counting stroop task when trauma-specific words were used[144] and when emotional distractors were used in the form of images.[145] However, there is also evidence that PTSD symptom severity is *negatively* associated with the dACC while *positively* related with the vACC during an attentional control task when distractors were trauma-specific.[139] Less activation in the dACC is also associated with greater threat bias in those with PTSD[146], suggesting that greater orienting to threat occurs when findings are reversed (e.g., less dACC/greater vACC). Therefore, greater dACC and less vACC responding during implicit regulation that is more evident in the PTSD literature may signal compensatory engagement necessary for the functional resolution of emotional conflict.

4. Studies of Fear Conditioning and Extinction

Related to the topic of symptom provocation and regulation is the process by which fear is conditioned and subsequently extinguished, studied using classical (Pavlovian) fear conditioning paradigms that allow for the study associating environmental cues with aversive events. Neural disruptions in both processes (e.g., conditioning and extinction) are pertinent to PTSD as this disorder is commonly associated with the over-learning of a fear response and difficulty in extinction, suggesting that fear is readily acquired and difficult to extinguish.[147] During classical fear conditioning, a neutral stimulus (e.g., conditioned stimulus/CS, a light) is paired with an aversive stimulus (e.g., unconditioned stimulus/US, electrical shock) and a fear response based on associative learning develops to the neutral stimulus.[148] This fear response, similar to passive emotion processing, is associated with engagement of the amygdala, insula, and ACC in humans.[149] Related, fear generalization following conditioning occurs when stimuli other than the CS, but which share similarities with the CS, elicits a fear-related response.[150] In healthy individuals, amygdala engagement is increased during fear conditioning and decreases over time during extinction, suggesting proper “learning” of a fear response and ability to implicitly regulate this fear response once the stimulus no longer signals threat.

Similar to implicit regulation, fear extinction occurs unconsciously, during which time a fear response is regulated as individuals re-learn to identify a CS as safe.[148,151] Fear extinction recall is also used, in which individuals are brought back into the laboratory to test retention of extinction learning.[152,153] This process studies the extent to which memory systems that encoded safety and accompanying control of fear are intact. Fear extinction and its retention are thought to be instantiated by a discrete group of regions including the hippocampus, amygdala, VMPFC, and vACC.[152,154] In particular, the hippocampus is both necessary for activation of remembered fear based on exposure to a stimulus previously, and for re-learning contingencies about the potential for danger based on contextual encoding. In contrast, the VMPFC and vACC are essential for fear extinction and play an important role in retention of an extinguished response over time.[148]

The possibility of atypical neural functioning during fear conditioning and extinction in PTSD is likely given behavioral and physiological research. For instance, individuals with PTSD display elevated sweat response during threat of shock and this response remains elevated when individuals are shown the CS-, indicating safety.[155] Enhanced sweat response also occurs during extinction, suggesting impaired implicit regulation of a learned fear response.[155] In addition, there is evidence that individuals with PTSD self-report expecting to be shocked to a greater extent than controls (e.g., abnormal US expectancy in relation to the CS), indicating underlying deficits in differentiating threat from safety.[156]

4.1. Amygdala

Despite evidence of altered response to fear conditioning and extinction using peripheral and self-report measures, evidence of elevated amygdala response during this process is mixed.[157–159] For instance, some work shows less engagement of the amygdala during conditioning when a negative image is treated as the CS in comparison to healthy and traumatized peers.[160] Other work shows that amygdala activation does not differentiate

between stimuli that have been conditioned to be aversive (CS+) and those that have been conditioned to signal safety (CS-), while amygdala activation does show differentiation in traumatized controls.[105] Finally, others have found that individuals with PTSD exhibit greater engagement of the amygdala in response to the US (e.g., the shock) outside the conditioning process.[161] Therefore, underlying aberrations in amygdala engagement in response to aversive stimuli may make it difficult to isolate elevated response in this region during the conditioning process. In addition, there may be differences in direction of effects (e.g., hyper versus hypo response of the amygdala) based on differences in aversive stimuli type (shock versus negative imagery), with greater engagement of the amygdala in response to shock, and less engagement of the amygdala in response to negative images.

During extinction, individuals with PTSD display greater amygdala engagement.[158] Elevated amygdala response is also evident in PTSD during extinction recall when extinguished stimuli are presented 24-hours after conditioning.[157] In contrast, other work has found no differences in amygdala response during extinction between PTSD and traumatized controls.[159] Again, discrepant findings may be due to underlying differences in amygdala engagement that is changed in the conditioning process, as even more work demonstrates *hypo*-activation of the amygdala during fear renewal (e.g., when the CS+ is shown again after extinction) in those with PTSD.[157] That is, PTSD is associated with atypical response of the amygdala across all phases of fear conditioning, extinction, and recall.

4.2. Hippocampus

Consistent with the finding that individuals with PTSD exhibit greater hippocampal activation during emotion processing, greater engagement of the hippocampus is also evident during exposure to the US.[161] During extinction, however, individuals with PTSD do not exhibit significant engagement of the hippocampus, while trauma-exposed controls do, suggesting that individuals with PTSD failed to contextualize safety cues.[158] In another study, individuals with PTSD exhibited less activation in the hippocampus during fear renewal.[157] Less activation within the hippocampus coincided with less activation within the amygdala in this same study, suggesting deficiency in the detection of salient stimuli that may be driven by inability to recall that this stimuli was previously associated with danger.[157]

4.3. Anterior Cingulate Cortex

During fear conditioning and fear extinction, individuals with PTSD display elevated dACC engagement.[158,159,161,162] Elevated recruitment of a region responsible for error detection and monitoring when forming a fear response suggests greater attention paid to conflict resolution in this process. Further, as elevated dACC is evident in both conditioning and extinction in those with PTSD, accurate dissociation between real versus imagined threat that occurs during conditioning may carry over and lead to deficiency in regulation during extinction.

Other work, however, finds *decreased* engagement of the ACC in response to trauma-specific images used as the US in individuals with PTSD during conditioning without

specification as to location of this finding (e.g., dorsal versus ventral distinction).[160] In this study, decreased engagement of the ACC in PTSD in comparison to healthy controls did not carry over into extinction, while patients in this sample possessed significant dissociation symptoms.[160] Therefore, decreased functioning of the ACC during conditioning in response to trauma-specific content may relate to the presence of specific symptoms or be driven by the use of trauma-specific cues.

4.4. Prefrontal Cortex

During extinction, individuals with PTSD display less engagement of the VMPFC[158,162] and DLPFC.[160] In addition, reduced engagement in VMPFC during extinction is associated with greater fear-potentiated startle response in those with PTSD when conducting response inhibition outside the scanner in a Stop-Go task using stimuli that are not affective.[163] That is, deficits during inhibition of affective stimuli may be related to inability to inhibit motoric responses to non-affective stimuli as well.

In contrast, other work has found *greater* activation in these same regions that was also associated with greater generalization of a CS.[91] In this study, there was more activation within the VMPFC and DLPFC in individuals with PTSD as a novel stimulus dynamically changed to resemble the original CS+ in characteristics (e.g., shape and size) to a greater extent.[91] Although more activation in the VMPFC and DLPFC was evident in trauma-exposed controls and patients with sub-threshold PTSD as well, the correlation between how similar each stimulus was rated and fMRI activation in the VMPFC and DLPFC regions was strongest for those with PTSD.[91] Therefore, while most work suggests that individuals with PTSD possess deficient recruitment of the VMPFC and DLPFC during fear conditioning, these regions may be involved with identifying whether a stimulus predicts threat or safety based on stimulus composition. Under-engagement in the VMPFC and DLPFC during fear conditioning in those with PTSD may thus be driven by underlying deficits in capacity to *correctly* identify stimulus characteristics in order to accurately anticipate threat.

5. Conclusions

Emotion dysregulation is not a unitary construct, nor do all of its forms share the same neurocircuitry.[6] Nevertheless, the importance of emotion dysregulation as an underlying mechanism for PTSD psychopathology is gaining traction.[164–166] This is particularly salient and timely given that emotion regulatory function and dysfunction cuts across multiple disorders[167] and may explain the heterogeneity of symptoms in PTSD (e.g., intrusive reminders, emotional numbing, avoidance, negative cognitions and mood, hyperarousal). As such, this review provided an overview of aberrant brain functioning in the contexts of negative emotional responding and its regulation. In surveying the available literature on these topics, we draw conclusions regarding the nature of underlying neural perturbations that may be responsible for the manifestation of emotion dysregulation as a central feature of PTSD.

First and in the case of emotion processing, findings from this review confirm the presence of a hyper-active amygdala and insula in response to stimuli that convey social threat (e.g., faces), aversive images, and cues that evoke personal trauma in those with PTSD. Without

specificity in terms of which types of stimuli produce over-activation in these regions is telling, suggesting that those with PTSD possess uniform exaggerated salience detection and – as a consequence – greater interoceptive awareness of negative emotional states. Elevated amygdala activation in response to stimuli that are innocuous, such as neutral faces, suggests that the processing of motivational-salience is fundamentally altered in those with PTSD. Second, greater hippocampal engagement in response to general negative content implies that learned responses to threat may be over-generalized. In addition, under-engagement of the ACC during negative emotion processing suggests deficiency in error detection, perhaps as it relates to conflict resolution in terms of whether emotional states should be inhibited based on probability of true threat. Finally, altered engagement of the MPFC responsible for appraisal of this experience and control of arousal may explain the dynamic fluctuations and variability of fear and negative emotion symptoms observed in PTSD patients.

These conclusions are consistent with those from prior published reviews on the topic of the neurobiology of PTSD in the context of negative emotion processing[4,11,14,20,29,36]; however, we also offer new insights particular to brain functioning in the context of regulation. Primarily, this review provides a more in-depth review on the functioning of the PFC and ACC during tasks of implicit and explicit emotion regulation that prior syntheses of the literature have not made their primary interest. We conclude that that PTSD is also characterized by under-engagement of the VLPFC, DLPFC, DMPFC, and DLPFC across both implicit and explicit regulation. Deficiency in more than one region of the PFC suggests that multiple domains of cognitive control are compromised in this process, with deficits likely spanning attention, working memory, semantic processing, and organization and selection of strategies for regulation.[117–120] Further, deficiency in recruiting overlapping cortical regions during tasks of implicit and explicit emotion regulation also suggests that aberrations are similar when regulation goals are made more or less obvious. In contrast, over-engagement of the VMPFC and vACC during implicit regulation suggests greater appraisal of emotional states when individuals are unconsciously trying to regulate, while aberrant engagement of the dACC suggests disturbances in filtering out task irrelevant emotional information and/or choosing which stimuli to respond to in light of competing cognitive demands and emotional triggers. Together, this provides significant evidence of deficient utilization of brain regions responsible for the complex act of resolving and managing emotional states in PTSD.

Evidence from studies of fear conditioning and extinction provide more evidence that PTSD is not wholly characterized by over-reactive response to fear, but rather that distinguishing threat versus safety is primarily impaired. Abnormal engagement of the amygdala is a consistent finding, but the direction of aberrations across the conditioning, extinction, and recall is mixed, suggesting confusion in deciphering which stimuli are motivationally relevant.[150,168] Atypical engagement of the hippocampus along with over-engagement of the dACC during conditioning suggests deficient ability contextualizing a fear response, alongside greater monitoring and resolution of the potential for harm. Under-engagement of the PFC during extinction, a form of implicit regulation, is also evident and may be related to complications in emotion regulation stemming from inability to discriminate threat from safety.

To note, many nuances of PTSD as a complex disorder make understanding its associated neurobiology difficult. At this forefront is the fact that PTSD is characterized by heterogeneity of symptoms. Therefore, variability in findings between studies may signal that a “one-size-fits-all” approach may not be applicable to the study of altered neural networks in PTSD. Similarly, the impact of a single traumatic event versus constant trauma exposure on brain functioning is not fully clear, and the impact of multiple traumatic events over a lifetime and/or early life trauma may have differential consequences for brain functioning. Nevertheless, the corpus of studies reviewed here suggest that threat and negative emotion processing and emotion regulation deficits at the neural level accurately classify most cases of PTSD. Altered engagement within the amygdala, insula, hippocampus, ACC, and PFC demonstrate that emotion dysregulation in PTSD arises from complications across a large neurocircuitry. In addition, although PTSD is characterized by increased detection of negative emotion, we emphasize that this principle disturbance exists alongside deficiency in the appraisal, resolution, and management of negative emotional states. Future research should aim at delineating whether certain brain circuits may reflect particular symptom clusters of PTSD to help refine the nosology of the illness.[169–172] Moreover, a more complete and precise understanding of the pathophysiology of PTSD is needed to test if existing and novel therapies can effectively target emotion dysregulation and its neural substrates.[173–175]

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