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Review article

Magnetic resonance imaging predictors of psychotherapy treatment response in post-traumatic stress disorder: A role for the salience network

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ABSTRACT

The earliest neuroimaging studies in post-traumatic stress disorder (PTSD) utilized positron emission tomography (PET) to examine the brain's response to glucocorticoid administration given predominant neurobiological models of the stress response focusing on that neuroendocrine system. This work revealed that the anterior cingulate cortex and amygdala, which is now considered part of the salience network, play a role in treatment response, and set the stage for subsequent magnetic resonance (MR) imaging studies focused on understanding the role of the salience network in the neurobiology of treatment response in PTSD. This selective review discusses magnetic resonance (MR) imaging studies that have been used to predict treatment response to cognitive-behavioral therapy (CBT) or prolonged exposure (PE) in PTSD, which have demonstrated abnormalities in processing involving the salience network, including the amygdala, anterior cingulate cortex and insula. Increased attention to environmental cues may signal alarm resulting in hypervigilance and overactive action-monitoring for the detection of threatening stimuli and an inability to integrate concomitant emotional and sensory functions in PTSD. Successful psychotherapy treatment response in PTSD appears to involve the ability to downregulate amygdala activity to trauma-related stimuli through improved regulation of attention by the anterior cingulate cortex and concomitant internal emotional states mediated by the insula. In addition, the ability to better modulate (normalize) the salience network following psychotherapy in PTSD may be associated with better crosstalk between untargeted inner thought (i.e., task-negative network) and the ability to focus attention on stimulus-dependent demands (i.e., task positive network).

1. Introduction

Early neurobiological models of post-traumatic stress disorder (PTSD) focused on abnormalities in the neuroendocrine systems involved in stress. These studies, which predated neuroimaging work, demonstrated abnormal glucocorticoid receptor (GR) sensitivity as evidenced by enhanced negative feedback inhibition of cortisol in regions comprising the hypothalamic-pituitary-adrenal (HPA) axis in PTSD (Szeszko et al., 2018; Yehuda, 2009). These findings were at first counter-intuitive. Under the influence of threat the release of cortisol permits the body to mobilize and respond accordingly. During this initial fight or flight increased cortisol production at the level of the pituitary and/or hypothalamus occurs in conjunction with the sympathetic nervous system (SNS). In PTSD, cortisol release appeared to be attenuated, possibly resulting from alterations in glucocorticoid receptor responsiveness (Yehuda, 2002). Early biological studies of PTSD found cortisol levels to either be normal or even lower than normal among individuals with PTSD compared to those without PTSD (Mason et al., 1986; Yehuda et al., 2006). While several follow-up studies examining the HPA axis eventually pointed to glucocorticoid receptor sensitivity as a potential culprit, it was not possible to truly understand the functional implications of these findings without examining cortisol effects in the brain.

The earliest studies to understand brain neuroendocrine changes in PTSD were conducted by Dr. Monte Buchsbaum (Yehuda et al., 2009) using positron emission tomography (PET). One of these studies examined glucocorticoid effects by measuring glucose metabolic rate in the hippocampus, amygdala, and anterior cingulate cortex (ACC) during a randomized, double-blind, placebo-controlled study of metabolic response to hydrocortisone using 2-Deoxy-2-[(18) F] PET. Findings indicated that among individuals with PTSD hydrocortisone administration was associated with the restoration of a normal inverse relationship between regions comprising the anterior cingulate cortex and amygdala, now referred to as the salience network. This work also

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demonstrated that glucocorticoids may have different effects in different brain regions. Importantly, hydrocortisone appeared to be associated with improved memory performance in PTSD (Yehuda et al., 2007), suggesting potential treatment applications of glucocorticoid administration in PTSD. This early PET work set the stage for subsequent magnetic resonance (MR) imaging studies that have identified abnormalities in brain regions comprising the salience network that play a role in PTSD neurobiology and treatment response.

This selective review of the literature provides an update and synthesis of the literature regarding the utility of MR imaging measures comprising the salience network to predict psychotherapy treatment response using cognitive-behavioral therapy (CBT) and prolonged exposure (PE) in PTSD. A role for the salience network, including the amygdala, anterior cingulate cortex and insula, in the neurobiology of PTSD is emphasized. Next, studies using baseline and longitudinal MR imaging measures (including brain structure and function) to predict symptom changes following psychotherapy are reviewed. The focus of this review will be on the use of CBT and PE as psychotherapeutic interventions given they are considered first-line treatments for PTSD. Lastly, an integrative model regarding how changes in brain regions comprising the salience network play a role in successful psychotherapy response in PTSD is described.

2. Salience in post-traumatic stress disorder and implications for treatment

The ability to quickly focus attention and initiate homeostatic mechanisms and concomitant motor functions in anticipation of threat is considered a critical survival function from an evolutionary perspective (Kotas and Medzhitov, 2015). These functions appear to be modulated, at least in part, by the salience network, which is primarily responsible for bottom-up processing, involving the integration of sensory information to inform behavior or cognition (Choi et al., 2018) and may be reliably identified using independent components analysis of resting state fMRI data (Biswal et al., 2010). This network processes attention, anticipation or “alarm” functions to maintain a state of hypervigilance to detect and integrate emotional and sensory functions in the context of threatening stimuli (Maren et al., 2013). The salience network also involves the detection and processing of the physiological significance of events between the anterior and posterior insula (Sridharan et al., 2008). The insula combined with the anterior cingulate cortex are responsible for “subjective salience” in the cognitive and emotional domains, as well as maintaining homeostasis (Menon and Uddin, 2010). Some PTSD symptoms (e.g., hypervigilance, irritability, aggression) often represent distortions in comprehending the social world that could conceivably arise from dysfunction of brain networks comprising the salience network.

The salience network facilitates switching between the default mode and task positive networks, and interaction of the anterior and posterior insula to identify the physiological significance of salient events (Sridharan et al., 2008). The default mode network, also known as the task negative network, demonstrates activation among individuals while at rest and unengaged in targeted inner thought in contrast to when individuals are engaged in goal-directed tasks linked to internally guided experiences that are regulated by the task-positive network. The default mode network is anticorrelated (i.e., negatively correlated) with the task positive network, which includes the dorsolateral prefrontal cortex, and plays a primary role in goal-oriented activity. These two networks maintain an “antagonistic” relationship with each other allowing individuals to shift between two distinct modes of information processing.

In the context of aberrant bottom up processing individuals with PTSD appear to be characterized by an overactive “action monitoring system” (Ursu et al., 2003) that assigns threat to stimuli in a disproportionate manner. In PTSD neural circuits associated with a bias toward threatening stimuli and hypervigilance may occur through aberrant “bottom-up” processing (Dunkley et al., 2018; Kimble et al., 2014), which occurs automatically by shifting attentional resources to salient sensory stimuli in the absence of preconceived ideas or expectations. There is some evidence that the treatment of trauma using a “bottom-up” approach, such as exposure therapy, may be an effective psychotherapeutic approach through the use of sensory awareness to regulate and integrate emotions (Grabbe and Miller-Karas, 2018). Truly testing this hypothesis, however, requires longitudinal assessment in a sample where some individuals remit from PTSD while others do not. The ideal scenario for examining potential brain changes in association with symptom exacerbation or recovery is a treatment study, particularly a psychotherapy trial.

The VA/DoD PTSD Clinical Practice Guideline for Posttraumatic Stress Disorder (2017) offers evidence-based recommendations for the treatment of PTSD with individual, manualized psychotherapies that focus on exposure or cognitive restructuring, such as prolonged exposure (PE) or cognitive behavioral therapies (CBT). These therapies emphasize confronting, rather than avoiding, trauma related memories, emotions, and cognitions. Exposure based therapies include exposure to memories and feelings related to the trauma, as well as *in-vivo* exposure to internal or external trauma related stimuli (such as people, places, or situations that function as distressing reminders). Cognitive processing therapy (CPT), a manualized form of trauma-focused CBT, includes identifying exaggerated or distorted beliefs about the trauma, and subsequent changes in beliefs about the self, others, and the world. Patients learn how to evaluate and challenge their beliefs to promote more balanced and realistic assessments.

Exposure and cognitive therapies do not appear to have any differential effect on specific PTSD symptom clusters and both treatments reduce symptom severity in patients with either high or low baseline levels of intrusion, avoidance and hyperarousal (Horesh et al., 2017). Based on reviews of research, all major traumatic stress societies in the U.S. and Europe recommend these therapies as first line treatments for PTSD. However, it is widely acknowledged that although these treatments lead to improvement in most patients, many continue to experience clinically significant symptoms, and only a minority experience full remission of the disorder. Using neuroimaging to predict and track changes associated with clinical responses to psychotherapy could provide information on potential subgroups and mechanisms of change in association with treatment, and facilitate investigation of the functioning of brain circuits that are associated with symptom recrudescence and remission.

3. Amygdala

The amygdala sits in the anterior portion of the temporal lobe and is comprised of several individual nuclei that maintain afferent and efferent connections with other brain regions that play a role in fear regulation (Sah et al., 2003). Incoming information reaches the amygdala rapidly and well in advance of the cerebral cortex. The amygdala is biased for action and in PTSD (and other anxiety disorders) does not appear to be easily “turned off” once activated in response to feared stimuli that are perceived to be outside of an individual's control. This “hard wiring” likely serves a critical evolutionary survival function so that potential threats can be quickly acted on and communicated to the rest of the brain possibly in advance of conscious awareness. In this regard the amygdala plays a critical role in how individuals react to feared (i.e., trauma-related) stimuli that are perceived as threatening or dangerous. More specifically, the amygdala is believed to play a role in the acquisition, expression, and regulation of fear and traumatic memories, as well as fear conditioning and generalization (Fragkaki et al., 2016) that is associated with abnormal connectivity to the hippocampus (Sripada et al., 2012) . Several studies demonstrate that fear extinction is impaired in PTSD and that alterations in amygdala activity may partially mediate fear-extinction learning (Milad et al., 2009).

Evidence for involvement of the amygdala in the neurobiology of PTSD is supported by structural and functional neuroimaging data. In the most recent meta-analysis of amygdala volume, which included 14 studies of individuals with PTSD (O'Doherty et al., 2015), there was a medium effect size for bilateral amygdala volume reduction compared to healthy controls. However, there were no significant differences in amygdala volume between individuals with PTSD and trauma-exposed controls. Using activation likelihood estimation analysis Stark and colleagues (Stark et al., 2015) reported that amygdala functional activity changes distinguished individuals with PTSD from both healthy controls and trauma exposed controls without PTSD. These findings are consistent with those of Nooner and colleagues (Nooner et al., 2013) who found that even mild trauma was associated with functional abnormalities within brain regions connected to the amygdala.

Structural or functional abnormalities in the amygdala may represent the neuroanatomic substrate that perpetuates hyperarousal (but not trauma experience, re-experiencing, or avoidance symptoms) in PTSD (Stevens et al., 2013). Exaggerated amygdala activation has been reported during the encoding of emotionally negative stimuli in PTSD (Hayes et al., 2012; Xiong et al., 2013), which is associated with symptom severity (Brohawn et al., 2010). Amygdala reactivity to negative emotional information could represent a biomarker of vulnerability to traumatic stress and potentially be a risk factor for PTSD (McLaughlin et al., 2014). While undergoing fMRI prior to military service soldiers with the greatest amygdala response during risk anticipation while playing an interactive competitive game were at greatest risk for developing PTSD and stress associated disorders (Admon et al., 2013). Taken together, these findings suggest that amygdala alterations may predispose an individual to experiencing the long-lasting effects of even a mild traumatic experience.

In a series of studies investigating brain changes in adolescent girls with PTSD related to either physical or sexual assault, Cisler and colleagues investigated the neural correlates of treatment response following trauma focused CBT(Cisler et al., 2015, 2016). They reported that better ability to suppress functional connectivity between the amygdala and insula during a cognitive reappraisal task was associated with greater post-treatment symptom reduction. In a related study these girls were engaged in an implicit threat processing task while they viewed faces with either fearful or neutral expressions. Adolescents with less symptom reduction demonstrated greater amygdala activation while viewing both threat and neutral images in contrast to the adolescents with greater symptom reduction who demonstrated amygdala activation only to threat images. Studies conducted by Roy and colleagues reported that Veterans with PTSD demonstrated either improvement, or normalization of amygdala activation following exposure therapy among individuals with PTSD during an affective Stroop response task (Roy et al., 2010, 2014). Similarly, individuals with PTSD who had the greatest symptom reduction (compared to a waiting list group) demonstrated less amygdala activation during emotional reactivity/regulation at the time of a baseline scan (Fonzo et al., 2017).

4. Anterior cingulate cortex

The anterior cingulate cortex wraps around the corpus callosum and is considered to be a central hub for the integration of cognitive-behavioral, emotional-autonomic, and motor neural networks (Devinsky et al., 1995). The anterior cingulate cortex is known to be heterogeneous and there is evidence that it may be comprised of several cytoarchitecturally and functionally distinct regions (Bush et al., 2000; Devinsky et al., 1995). The region surrounding the genu contains afferent connections from the amygdala (Vogt and Pandya, 1987) and has been linked to affective processing (Whalen et al., 1998) that is highly relevant to emotion dysregulation in PTSD. This rostral-ventral "affective division" is distinct from a dorsal "cognitive division" that is activated during tasks tapping error-monitoring and response inhibition to nonemotional stimuli (Bush et al., 1998; Whalen et al., 1998).

The anterior cingulate cortex has been hypothesized to play an important role in detecting and signaling conflict during information processing (van Veen and Carter, 2002), especially when there is a high likelihood of making errors (Brown and Braver, 2005)and/or when this information does not match internal standards (Gehring and Knight, 2000; Ursu et al., 2003; van Veen and Carter, 2002). The anterior cingulate cortex may attempt to resolve this conflict (van Veen and Carter, 2002; van Veen et al., 2001) and adjust brain activity to minimize and/or eliminate confusing aspects during information processing (Bush et al., 2000). Thus, activity within the anterior cingulate cortex may play an important role in abnormal conflict detection as part of an overactive "action monitoring system" (Ursu et al., 2003; van Veen and Carter, 2002). The anterior cingulate cortex has also been hypothesized to play a role in the "expected value of control" such that it integrates payoffs with the associated costs regarding the identity and intensity of control signals to maximize this expected value (Shenhav et al., 2013). These processes balance performance monitoring and are highly sensitive to the detection of mismatch (i.e., error) in the environment based on models of cognitive control.

MR imaging studies have implicated anterior cingulate cortex abnormalities in detecting and managing conflict in PTSD. Greater activity in the dorsal anterior cingulate cortex was observed in complex PTSD, which was associated with fast reaction time to negative compared to neutral words consistent with an inability to divide attention from negative words (Thomaes et al., 2013). Similarly, compared to PTSD patients and healthy controls, combat controls demonstrated increased functional connectivity between the rostral anterior cingulate cortex and the precentral gyrus (extending into the middle frontal gyrus) suggesting the brain may be successfully inhibiting cognitions related to trauma (Kennis et al., 2015). Less rostral anterior cingulate cortex activity during exposure to trauma reminders in PTSD may represent the neuroanatomic substrate of an inability to mediate distress and arousal (Shin et al., 2001).

Several studies support a role for the anterior cingulate cortex in successful psychotherapeutic treatment response in PTSD. Helpman and colleagues (Helpman et al., 2016a) scanned individuals with PTSD prior to and then following PE in the context of a 2 day behavioral fear conditioning, extinction, and recall paradigm. Individuals with PTSD demonstrated reductions in rostral anterior cingulate cortex activation during extinction recall, and a concomitant increase in functional coherence between the rostral anterior cingulate cortex and the ventromedial prefrontal cortex and subgenual anterior cingulate cortex. Moreover, reductions in symptom severity from pre- to post-treatment were associated with lower subgenual anterior cingulate cortex activation. Studies investigating error detection and emotional arousal using the classic and emotional Stroop tasks examined fMRI activity in a cohort of child abuse-related complex PTSD patients compared to non-trauma exposed healthy controls (Thomaes et al., 2012). In a subgroup of patients, they examined treatment effects of psychoeducation and CBT added to treatment as usual (experimental group) versus treatment as usual. Individuals in the experimental group demonstrated a reduction in dorsal anterior cingulate cortex and left anterior insula activation following treatment. During the emotional Stroop contrast clinical improvement was associated with a reduction in dorsal anterior cingulate cortex and left anterior insula activation.

Given a strong role for fear conditioning in PTSD the majority of studies investigating treatment response using CBT have utilized affective stimuli such as fearful or angry faces while individuals with PTSD undergo functional magnetic resonance imaging (fMRI). Better symptom improvement following eight sessions of CBT that comprised education, imaginal and *in vivo* exposure, and cognitive restructuring was related to lower bilateral amygdala activation and lower ventral anterior cingulate cortex activation in response to masked fearful faces compared to neutral faces (Bryant et al., 2008a). Administration of fearful faces to individuals with PTSD following assault or car accidents revealed that successful imaginal exposure and cognitive restructuring

was associated with an increase in rostral anterior cingulate cortex and a reduction in amygdala activation (Felmingham et al., 2007). Using cognitive trauma therapy Aupperle and colleagues (Aupperle et al., 2013) focused on psychoeducation, skills training, exposure to trauma reminders, and correction of irrational beliefs in the treatment of battered women. Successful treatment was associated with greater anterior cingulate cortex and reduced anterior insula activation during anticipation of negative images, and decreased dorsolateral prefrontal cortex and amygdala activity while viewing negative minus positive pictures.

A few studies examined changes in anterior cingulate morphology following CBT or PE in PTSD. Following 10 weeks of PE treatment individuals who remitted from PTSD demonstrated cortical thinning and less left anterior cingulate cortex volume (Helpman et al., 2016b) compared to PTSD non-remitters and trauma-exposed healthy controls who were scanned 10 weeks apart, but did not receive treatment. In contrast, using CBT (Bryant et al., 2008b) reported that PTSD treatment responders had larger rostral anterior cingulate cortex volume compared to nonresponders. In addition, larger rostral anterior cingulate cortex volume was associated with symptom reduction with PTSD.

5. Insula

The insula plays an important role in monitoring internal body states and processing these states in the context of external emotional stimuli (Nicholson et al., 2016). The insula may be divided into a smaller posterior region that maintains connections with the somatosensory cortex and a larger anterior region that receives afferent and efferent connections to the amygdala (Craig, 2011) that are likely most relevant to PTSD phenomenology. In support of these connectivity patterns individuals with PTSD have demonstrated lower functional connectivity compared to healthy controls within the anterior insula (Zhang et al., 2016). Greater connectivity of the insula to the basolateral amygdala was found among individuals with PTSD and dissociative symptoms compared to patients without dissociative symptoms (Nicholson et al., 2016).

Cognitive trauma therapy was associated with a reduction in insula activation during anticipation of affective stimuli among battered women with PTSD (Aupperle et al., 2013). Also, in that study an increase in insula activity was associated with better treatment response. Using a task involving the anticipation of combat-related/negative images versus noncombat-related/positive images Simmons and colleagues (Simmons et al., 2013) examined changes in brain activity following PE treatment in Veterans with PTSD. Individuals who remitted from PTSD demonstrated a reduction in brain activation in the anterior insula during the anticipation of negative images from pre- to post-treatment. In contrast, individuals with PTSD who did not remit demonstrated greater activation during anticipation of positive images between the right cingulate and right mid-posterior insular region. Furthermore, among individuals who remitted from PTSD change in functional activation in the insula was associated with greater connectivity between this region and the right cingulate cortex. Taken together, these studies suggest that treatment response in PTSD is associated with lower functional activity within the anterior insula during the processing of aversive stimuli. This suggests the need to identify internal physiological signals within this region and tolerate the anxiety associated with successful exposure therapy.

6. Summary and future directions

There is considerable heterogeneity in PTSD symptom presentation (Gilbertson et al., 2002) and no overarching model has been proposed to account for the complex symptom constellation of PTSD. With the advent of the DSM-V, there are now over 600,000 diagnostic permutations that could potentially yield a diagnosis of PTSD (Galatzer-Levy and Bryant, 2013). The use of MR imaging could provide quantitative biomarkers to conceptualize PTSD neurobiology and identify brain regions that play a role in successful psychotherapy treatment response. These effects could conceivably be amplified through the use of other interventions such as transcranial direct current stimulation (Dittert et al., 2018)

This review suggests that changes in a network of brain regions including the anterior cingulate cortex, amygdala and insula, which form part of the salience network, play a role in the neurobiology of PTSD and that changes in these regions predict psychotherapy treatment response using exposure therapies. The bulk of data indicate that greater amygdala activation prior to psychotherapy predicts worse psychotherapy treatment response. Better treatment response following psychotherapy is associated with reductions both in amygdala and insula activity along with increases in anterior cingulate cortex activity. In addition, neuroimaging studies examining both the amygdala and anterior cingulate cortex indicate that these changes may occur in tandem over the course of treatment. Given that structural and functional imaging studies provide different information they should be considered complementary and be better integrated in future studies examining treatment response in PTSD.

Successful psychotherapeutic treatment response in PTSD may be associated with greater ability to assert top down control of high amygdala responsivity by increasing activity in the anterior cingulate cortex to suppress attention to trauma related stimuli. In this context, individuals with PTSD may learn how to reduce high amygdala activity when habituating to distressing traumatic stimuli. The use of behavioral interventions to extinguish trauma related memories may therefore involve learning new associations in contrast to the “erasure” of traumatic memories. The inability to dampen amygdala reactivity during behavioral interventions may be indicative of difficulty managing anxiety during treatment and lead to less successful treatment outcome.

Connectivity abnormalities have been demonstrated in regions comprising both the task negative and task positive networks in PTSD (Daniels et al., 2010). The loss of anticorrelation between the default mode and task positive networks could play a role in PTSD phenomenology through the confusion of internally and externally focused states modulated by the salience network. For example, individuals with PTSD demonstrated “enhanced” coupling among regions comprising the salience network in response to direct versus averted gaze processing (Thome et al., 2014). Successful psychotherapeutic treatment may enable individuals to better modulate (normalize) the salience network resulting in better crosstalk between the task-negative and task positive networks.

A limitation of several studies examining the relationship between MR imaging and psychotherapy treatment response includes the use of discrete groups of patients with PTSD and the lack of individuals exposed to stress without PTSD. It is increasingly recognized that post-traumatic stress symptoms exist on a continuum with evidence that neural changes may occur below the diagnostic threshold for a diagnosis of PTSD. The use of an “extreme groups” approach can reduce statistical power and penalize the user on a number of grounds including reliability and interpretability of findings (Preacher et al., 2005). A possible solution to this problem is the use of a dimensional approach across trauma-exposed individuals that obviates the need for arbitrary thresholds.

Prior work investigating psychotherapy response in PTSD has focused mainly on affective stimuli in the context of fMRI paradigms. Therefore, better understanding changes in brain activity following psychotherapy could employ fMRI coupled with the use of dynamic causal modeling to identify causal mechanisms across distributed brain regions. Such approaches may improve our understanding regarding abnormal neural circuits in PTSD and the identification of targets for intervention. It should also be acknowledged that abnormalities in the salience network have been identified in a wide-range of processes and disorders other than PTSD such as schizophrenia (Gohel et al., 2018) suggesting that dysfunction within this network is not specific to PTSD. In addition, other treatments with efficacy in the treatment of PTSD

have yielded changes in brain structure and function such as mindfulness training (Greenberg et al., 2018; King et al., 2016) and eye movement desensitization and reprocessing (Bossini et al., 2017; Boukezzi et al., 2017) and the role of the salience network (and other brain regions) in mediating such changes will need to be clarified (Malejko et al., 2017).

Disclaimer

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