Brain Imaging in PTSD: History, Limitations, and Considerations

Neuroimaging research in PTSD has been ongoing for over 25 years. Bremner and colleagues (at the National Center for PTSD Clinical Neurosciences Division) published the first in human PTSD neuroimaging study (Bremner et al., 1995). Their work followed animal research showing detrimental effects of stress on hippocampal volume and smaller hippocampal volumes in Veterans with PTSD compared to controls without PTSD. The next major step for neuroimaging in PTSD was the ability to measure brain function in vivo by measuring the blood oxygen level dependent (BOLD) signal. The first functional magnetic resonance imaging (fMRI) paper in PTSD was published by Rauch and colleagues (Rauch et al., 2000), which showed greater amygdala reactivity in war Veterans with PTSD compared to combat controls.

These pioneering studies have greatly contributed to our understanding of the neurobiology of PTSD and paved the way for hundreds of neuroimaging studies. However, more recent developments in the neuroimaging field suggest caution when interpreting studies with small sample sizes typically seen in PTSD imaging studies to date. Likely related to these small sample sizes, neuroimaging findings in PTSD have been difficult to replicate, and reported effect sizes are probably overestimates.

More advanced imaging and harmonization methods now allow researchers to combine data from different research centers, providing the opportunity for large-scale consortium studies to have power to detect replicable effects. Other approaches might also increase power, such as the use of within-subjects designs with multiple MRI scans over time. Such studies have been used recently to address two main research questions: 1) predicting the development of PTSD using scans prior to or soon after trauma; and 2) investigating predictors for treatment response and post-treatment neurobiological changes.

In this quarterly, we will primarily focus on these large-scale and/or longitudinal studies, but also highlight smaller landmark studies that have significantly contributed to our current understanding of PTSD neurobiology.

Pathophysiology of PTSD

Studies comparing PTSD patients with trauma-exposed controls have been essential in helping the field learn more about the pathophysiology of PTSD. Following Bremner’s early work, subsequent structural MRI studies generally continued to show smaller hippocampal volumes in PTSD. Gilbertson et al. (2002) used a twin study design to show smaller hippocampal volume in trauma-exposed Veterans with PTSD and their unexposed twin compared to trauma-exposed Veterans without PTSD and their unexposed twins, providing the first evidence for the role of the hippocampus in the development of PTSD after trauma exposure (Gilbertson et al., 2002).

The worldwide Enhancing Neuroimaging Genetics through Meta-analyses (ENIGMA) consortium uses multisite neuroimaging data for large-scale
analyses and has shown structural differences between PTSD patients and controls. Logue et al (2018) showed smaller hippocampal volumes in 794 patients when compared with 1,074 controls from 16 cohorts [Logue et al., 2018]. Similarly, Wang et al (2021) showed smaller prefrontal regions important for regulation, including lateral orbitofrontal gyri and cortical regions implicated in sensory and emotion processing such as insular gyri in PTSD patients compared to controls [Wang et al., 2021].

After Rauch et al’s first fMRI study, many other studies investigated brain function in PTSD. Most have focused on fear neurocircuity, for example using a fear conditioning and fear extinction paradigm in the scanner. Milad et al (2009) were the first to employ this paradigm in the scanner and showed less activation of the hippocampus and ventromedial prefrontal cortex (vmPFC), but greater activation of the dorsal anterior cingulate cortex (dACC) during recall of fear extinction in participants with PTSD compared to trauma-exposed controls [Milad et al., 2009]. Several studies demonstrated greater amygdala reactivity in PTSD patients compared with controls and lower control by the vmPFC.

Where studies originally focused mostly on single brain regions, the emphasis in recent years has shifted more to how regions interact within circuits or networks. Studies specifically interested in brain networks often use a resting state paradigm where the participant is asked to either close their eyes or look at crosshairs on a screen and let their mind wander. Resting state networks that have been reliably identified across groups of individuals have been compared between PTSD patients and controls. Koch et al (2016) performed a meta-analysis of PTSD resting state fMRI studies and concluded that the salience network (SN) for orienting attention, consisting of the dACC, insula and amygdala showed greater within network functional connectivity (FC), whereas the default mode network (DMN) for self-referential processing, consisting of the precuneus, posterior cingulate cortex and vmPFC showed decreased connectivity [Koch et al., 2016]. FC is now also being used to estimate specific symptoms, such as trauma-related dissociative symptoms, distinct from PTSD and childhood trauma. In addition to FC, diffusion tensor imaging is used to determine the integrity of the white matter connections between brain regions in these networks, as well as relative strength of structural connectivity. Fani et al (2012) were the first to show decreased integrity of the posterior cingulum in women with PTSD compared to traumatized women without PTSD (Fani et al., 2012). The largest DTI study to date from the ENIGMA consortium comparing PTSD patients with controls showed disrupted white matter organization in the tapetum region in the corpus callosum region that connects the left and right hippocampus [Dennis et al., 2021].

Based on published neuroimaging studies as well as the extant animal literature, Shalev et al (2017) reviewed the neurobiology of PTSD and created a model consisting of four main neurocircuits: 1) emotion regulation and executive function circuit consisting of the medial, dorsolateral and ventrolateral prefrontal cortex (PFC), 2) threat and salience detection circuit consisting of the amygdala, insula and anterior cingulate cortex, 3) the contextual processing circuit that consists of the medial PFC, hippocampus, thalamus and locus coeruleus, and 4) the fear learning circuit, consisting of the different nuclei of the amygdala [Shalev et al., 2017]. Clinical observations and psychophysiological assessments have characterized PTSD as a disorder of fear responses and hyperarousal, emotion processing, and decreased regulation of emotions and unwanted reminders of the trauma. The research on the pathophysiology of PTSD has provided strong evidence for PTSD-related impairments in emotion processing and prefrontal regulation regions, both structurally and functionally, and showed reduced functional and structural connectivity suggesting impaired prefrontal control over subcortical emotion processing.

Prediction of PTSD Risk

One of the key questions in PTSD research has centered around PTSD risk following exposure to trauma. The identification of individuals at risk and mechanisms related to PTSD development versus resilience are essential for the development and implementation of prevention and early intervention strategies. Longitudinal studies have collected data in high-risk individuals (e.g., policemen in training) or recently traumatized individuals (recruited in the Emergency Departments [ED]). Roeckner et al (2021) recently reviewed studies predicting stress resilience and concluded that individual differences in the processing of threat cues, and post-trauma adaptions to the stressor that encompass multiple mechanisms and circuits contribute to different clinical response profiles after trauma exposure (Roeckner et al., 2021). Structural studies showed soldiers with decreased hippocampal volume following military service displayed more PTSD-related symptoms (Admon et al., 2013). In a large ED study, Ben-Zion et al recently demonstrated that lower hippocampal volume was a predictor for persistence of PTSD symptoms 14 months post-trauma and did not change in the first year post-trauma, supporting the vulnerability trait hypothesis of smaller hippocampal volume as a risk for PTSD development (Ben-Zion et al., 2022).

In a prospective fMRI study of police recruits, higher baseline anterior PFC, dorsal and medial frontal pole activity was related to lower PTSD symptoms after trauma exposure (Kaidewaj et al., 2021). The first fMRI studies following patients brought to the ED showed that PTSD symptoms 6-12 months post-trauma were predicted by greater amygdala and lower hippocampal activation 1-month post-trauma (Stevens et al., 2017; van Rooij et al., 2018). Several other ED studies followed with the largest ED study to date (AURORA) collecting data of 3,000 recently traumatized civilians with 2-week post-trauma MRI data available for about 500. Stevens et al (2021) used the AURORA data to define the first neuroimaging-based biomarkers reflecting threat reactivity, reward reactivity and inhibitory engagement to characterize heterogenous stress responses shortly after trauma; this was the first study to suggest that neuroimaging-based biotypes can be used for predicting symptom development in the aftermath of trauma (Stevens et al., 2021).

Prospective studies have shown predictive value of resting state neural network connectivity for the development of PTSD. Most notably, Harnett et al (2021) showed in the AURORA study that connectivity of the right inferior temporal gyrus with the DMN was positively related to PTSD symptoms 3 months post-trauma (Harnett et al., 2021). Sheynin et al (2021) used a computational method to identify fMRI predictors for PTSD status, severity and
symptom clusters. They were the first to use this so-called deep learning approach to predict PTSD diagnosis at three timepoints using different imaging modalities. They concluded that the resting state modality, as it does not have different conditions, was the most pertinent predictor (Sheynin et al., 2021).

Given the complications of performing prospective neuroimaging studies, there is much progress to be made on the definition of neurobiological predictors for the development of PTSD. The increasing number of (large) studies will be essential in these efforts. The current published findings suggest an important role for regions of the threat neurocircuitry, including the amygdala, hippocampus and PFC, and show great promise for the use of biotypes and resting state FC in predicting post-trauma risk versus resilience.

Treatment of PTSD

Several longitudinal neuroimaging studies have been conducted to identify neurobiological predictors for treatment and nonresponse in PTSD. Structural studies have again showed an important role for the hippocampus, such that smaller hippocampal volume was observed in treatment non-responders (van Rooij et al., 2015), suggesting it is not only a predictor for the development of PTSD, but also for persistence of symptoms and treatment non-response.

Functional studies have consistently shown that greater amygdala prior to trauma-focused therapy predicts poor treatment outcome (for example Fonzo et al., 2017). Moreover, Fonzo et al showed that greater dorsolateral prefrontal cortex (DLPFC) activation and better inhibition of the amygdala induced by transcranial magnetic stimulation predicted better treatment response. Further supporting the critical role of the amygdala function in PTSD maintenance, ablation of the right amygdala in two patients with epilepsy and comorbid PTSD improved PTSD symptoms and biomarkers (Bijanki et al., 2020). Etkin et al (2019) used a novel approach combining a verbal memory task with a resting state scan to show that aberrant FC within the ventral attention network (VAN) and impaired executive function was related to poor psychotherapy response (Etkin et al., 2019). However, while a second study also identified an impaired executive functioning subtype of PTSD, the original treatment prediction was not replicated.

Brain regions implicated in fear learning an extinction have been related to trauma-focused therapy treatment response, i.e., hippocampus, amygdala, regions of the salience and default mode network. This is not surprising given the premise of extinction processes for trauma-focused therapy. An important next step in our field is the individualization of treatments to increase treatment response rates. The identification of neurobiological treatment predictors will help augment the treatment protocols by, for example, the use of focal neuromodulation. A recent review of treatment studies and the identification of potential neurostimulation targets concluded that downregulating the fear learning and threat and salience detection circuits and upregulating the emotion regulation and executive function and contextual processing circuits may mediate PTSD treatment response (van Rooij et al., 2021).

Other Studies, Future Directions and Conclusions

Neuroimaging research has greatly advanced our understanding of the neurobiology of PTSD and mechanisms underlying PTSD risk and persistence of symptoms after treatment. It may help guide us towards strategies for predicting which individuals are most likely to develop PTSD following a traumatic experience, as well as which individuals with PTSD may be more likely to respond to specific treatments, and the development of such early interventions or novel treatment approaches.

However, there are clear limitations for most of the existing literature. To date, research emphasis has largely been on fear neurocircuitry and, due to lack of power in most studies, often focused on hypothesis-based regions of interest (in the threat neurocircuitry) that may miss the relevance of other brain regions. Only more recently have studies using large samples and multimodal methods begun to show consistent involvement of other areas or networks, such as the ventral visual stream, in the development of PTSD. Furthermore, neuroimaging cannot (yet) be used as a diagnostic tool to diagnose PTSD or define PTSD risk in a single individual. Going forward, increased research emphasis should be devoted to relating neuroimaging findings to easy-to-collect measures to better identify individuals at risk immediately post-trauma.

There are many developments in the neuroimaging field addressing these concerns. The large consortium and multisite neuroimaging studies will be essential in detecting replicable effects and will allow for unbiased whole brain assessment as well as the identification of smaller more precise regions needed for interventions. Furthermore, there is an increased emphasis on network-level and multimodal analyses rather than assessments of individual regions, which will be essential in relating different measures to move the field forward. There are also novel developments in imaging techniques that hold great promise, such as measuring peripheral immune activation and its association with deficient brain microglial activation, which challenged the prevailing hypotheses regarding neuroimmune activation as central to stress-related psychopathology. Another interesting approach includes the use of neuromelanin-sensitive MRI. This is an approach that, like positron emission tomography-based measures, could reflect neurobiological processes relevant to illness and their treatment, but would be more scalable and easier to implement. Finally, imaging is now being used to guide transcranial magnetic stimulation (TMS) treatment targeting in individual patients with major depressive disorder and research is underway studying this in PTSD as well. This means an important application of neuroimaging as a tool to improve treatment for psychiatric disorders.

Neuroimaging research in PTSD has greatly informed us about underlying neurobiological mechanisms of PTSD, and more recently, risk for development of PTSD and treatment response. Novel developments in the field promote (unbiased) analyses of large datasets and longitudinal analyses to mitigate some of the concerns related to neuroimaging replicability. Future neuroimaging research is needed for the assessment of different subtypes of PTSD or the neurobiological characteristics of specific PTSD symptoms relative to other psychiatric disorders or stress-related symptoms. Future directions also include the use of neuroimaging data and related scalable measures to further define PTSD risk and understand heightened risk for PTSD in certain demographic groups such as women and minoritized populations, and the use of MRI to guide novel treatments for PTSD.
Peng, K. K., Weiss, M. E., Thompson, A. L., Zack, S. E., Lindley, S. E., Fonzo, G. A., Goodkind, M. S., Oathes, D. J., Zaiko, Y. V., Harvey, M., Jung, D., Keilp, J., Admon, R., Han, C. K., Motter, M. J., Rupe, Z. S., Wasserstein, A., Naar-King, M., Cai, H., Wiltse, B., Price, A. C., Behar, I. G., & et al. (2022). Longitudinal volumetric evaluation of hippocampus and amygdala subregions in recent trauma survivors. Molecular Psychiatry. Advanced online publication. doi:10.1038/s41388-022-01842-x This study measured hippocampal and amygdala volumes in 100 trauma survivors with PTSD brought to the ER 1-, 6- and 14-months post-trauma. Smaller right hippocampal was observed in 29/100 patients who still met for PTSD 14 months post-trauma. No change over time in hippocampal volume was observed in either the remission or non-remission group, supporting the vulnerability trait hypothesis for the hippocampus in PTSD.

Bremner, J. D., Randall, P., Scott, T. M., Bronen, R. A., Seibyl, J. P., Southwick, S. M., Delaney, R. C., McCarthy, G., Charney, R. C., & Innis, R. B. (1995). MRI-based measurement of hippocampal volume in patients with combat-related posttraumatic stress disorder. American Journal of Psychiatry, 152(7), 973-981. doi:10.1176/ajp.152.7.973 This is the first PTSD MRI paper. Combat Veterans with PTSD (N = 26) had an 8% smaller right hippocampal volume relative to controls without PTSD (N = 22). No smaller volumes of comparison regions (caudate, and temporal lobe) were observed. Furthermore, smaller right hippocampal volumes in PTSD patients were associated with short-term memory deficits.


observed in PTSD patients compared to healthy controls. Partly concordant with these findings, the systematic review on seed-based FC studies showed enhanced SN connectivity, but decreased DMN connectivity in PTSD.


The largest MRI study using data from 16 sites (N = 1,868) as part of the ENIGMA consortium. PTSD patients (N = 794) had significantly smaller hippocampal volumes compared to trauma-exposed controls. Amygdala volumes were also smaller but did not survive correction for multiple comparisons.


This is the first PTSD fMRI paper. PTSD patients with combat-related trauma (N = 8) showed greater amygdala responses to masked fearful versus masked happy faces when compared with individuals with combat-related trauma without PTSD (N = 8).


This review defines a model of brain regions implicated in PTSD based on the understanding of the diagnosis, prevalence, neurobiological characteristics, and treatment of PTSD, as well as the clinical implications of this knowledge.


This study represents the largest prospective neuroimaging study with recently trauma-exposed civilians brought to the ED (N = 146). Neuroimaging-based biomarkers reflecting threat reactivity, reward reactivity and inhibitory engagement are used to characterize heterogeneous stress responses shortly after trauma exposure.


This longitudinal study scanned Veterans with (N = 47) and without PTSD (N = 25) before and after trauma-focused therapy (or a 6–8-month interval). Smaller hippocampal volume was observed in treatment non-responders compared to treatment-responders and Veterans without PTSD and did not change with treatment, suggesting hippocampal volume as a predictor for persistence of PTSD symptoms.


This study compared regional volumes data of 68 cortical regions across both hemispheres from 1,379 PTSD patients to 2,192 controls without PTSD after data were processed by 32 international laboratories using ENIGMA standardized procedures. Volumes of left and right lateral orbitofrontal gyri, left superior temporal gyrus, and right insular, lingual, and superior parietal gyri were significantly smaller in PTSD patients compared to controls.

References (*indicate 15 featured articles)


disorder across 3047 adults: Results from the PGC-ENIGMA PTSD consortium. Molecular Psychiatry, 26(8), 4315–4330. doi:10.1038/s41380-019-0631-x


