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Review Article

Neuroimaging genetic approaches to Posttraumatic Stress Disorder

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ABSTRACT

Neuroimaging genetic studies that associate genetic and epigenetic variation with neural activity or structure provide an opportunity to link genes to psychiatric disorders, often before psychopathology is discernable in behavior. Here we review neuroimaging genetics studies with participants who have Posttraumatic Stress Disorder (PTSD). Results show that genes related to the physiological stress response (e.g., glucocorticoid receptor and activity, neuroendocrine release), learning and memory (e.g., plasticity), mood, and pain perception are tied to neural intermediate phenotypes associated with PTSD. These genes are associated with and sometimes predict neural structure and function in areas involved in attention, executive function, memory, decision-making, emotion regulation, salience of potential threats, and pain perception. Evidence suggests these risk polymorphisms and neural intermediate phenotypes are vulnerabilities toward developing PTSD in the aftermath of trauma, or vulnerabilities toward particular symptoms once PTSD has developed. Work distinguishing between the re-experiencing and dissociative sub-types of PTSD, and examining other PTSD symptom clusters in addition to the re-experiencing and hyperarousal symptoms, will further clarify neurobiological mechanisms and inconsistent findings. Furthermore, an exciting possibility is that genetic associations with PTSD may eventually be understood through differential intermediate phenotypes of neural circuit structure and function, possibly underlying the different symptom clusters seen within PTSD.

Contents

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Posttraumatic Stress Disorder (PTSD) is a debilitating disorder associated with increased suicide risk, educational dropout, unemployment, relationship instability, and the development of comorbid psychiatric disorders (Kessler, 2000). The majority of individuals in the US will experience a traumatic event in their lifetime, yet not all will develop PTSD (Kessler, 2000; Kessler et al., 1995; Koenen et al., 2013). There is evidence that genetic and epigenetic factors account for 30–70% of these individual differences (Afifi et al., 2010; Pitman et al., 2012), but the mechanisms by which they exert this influence are not well understood. In the long run, understanding these mechanisms will greatly inform both how to identify those at risk for certain clusters of PTSD symptoms, and how to tailor individual treatments for the best recovery outcomes. Brain structure and function, along with genetics, have emerged as important biological markers of PTSD, helping to identify risk for this disorder and further linking a complex cluster of behaviors to mechanisms of dysfunction and recovery (Greco and Liberzon, 2016; Michopoulos et al., 2015; Peterson et al., 2014; Stark et al., 2015). Combining the two methodologies of neuroimaging and genetics, however, offers an opportunity for an even more nuanced mechanistic understanding of PTSD (Bogdan et al., 2016). In addition to briefly outlining the current findings in the neuroimaging and genetics of PTSD, we focus on how the combination of these techniques has led to further insight into the vulnerabilities and patterns of PTSD dysfunction and recovery.

1. Classic findings in the neurobiology of PTSD

1.1. Brain structure overview

By examining the structural composition of brain regions we can identify potential dysfunctions. Reductions or increases in volume could point toward under or overuse, respectively, of that brain region or dysregulated communication between regions. PTSD research has consistently implicated abnormal structure in a number of brain regions involved in memory, emotion regulation and production (Fig. 1). Several studies have found decreased hippocampal (HP) volume in participants with PTSD (Gurvits et al., 1996; Stein et al., 1997; Kitayama et al., 2005; Wang et al., 2010; Smith, 2005; Karl et al., 2006). Reduced volume has also been widely observed in the rostral ventromedial prefrontal cortex (vmPFC) and in the dorsal anterior cingulate cortex (dACC) (Kasai et al., 2008; Kitayama et al., 2006; Carrion et al., 2010; Schuff et al., 2008; Karl and Werner, 2010; Sekiguchi et al., 2013). Work has yet to definitively determine whether these structural abnormalities are risk factors for developing PTSD or a consequence of the

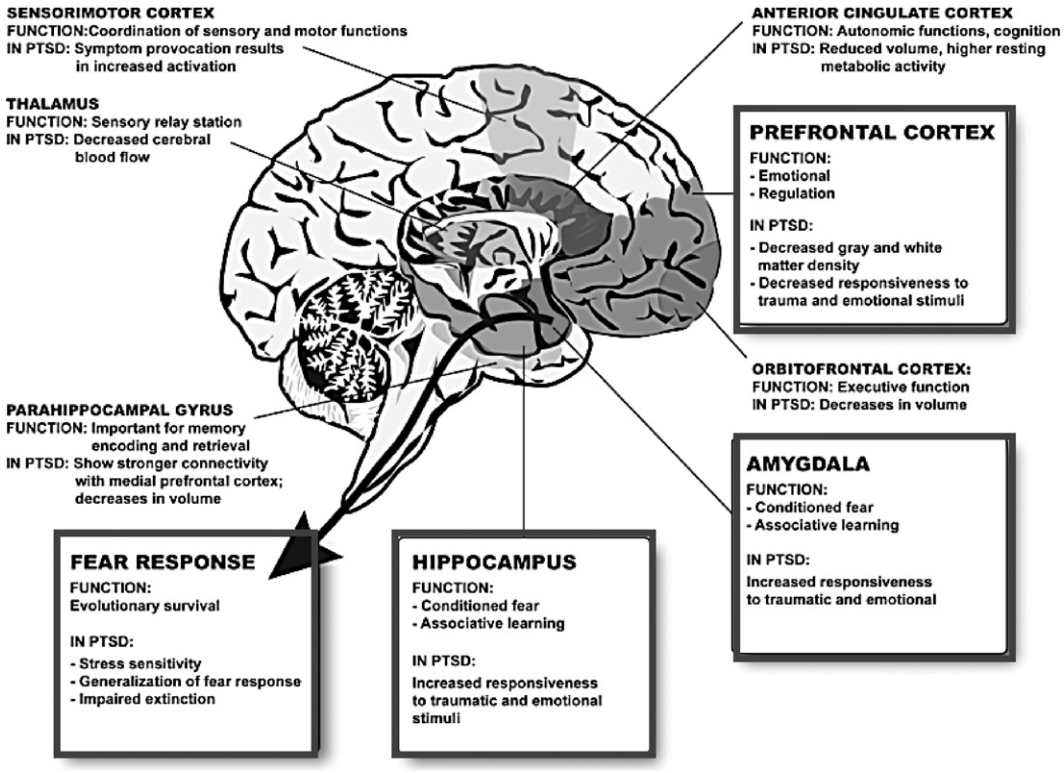

Fig. 1. Brain regions most frequently associated with Posttraumatic Stress Disorder. This diagram of the human brain illustrates some of the most frequent brain regions associated with PTSD in two decades of work related using fMRI approaches to understand brain activation in PTSD. The prefrontal cortex (PFC) and the hippocampus have strong connections to the amygdala, which is important for conditioned fear and associative emotional learning. The PFC is involved in emotion regulation and is hypoactive in PTSD with some studies showing decreased gray matter density. The hippocampus is thought to play a role in explicit and contextual memories of traumatic events and in mediating extinction of conditioned fear. In PTSD, the hippocampus is decreased in volume. The amygdala is the most well-known area in regulating fear responses, involved in conditioned fear and recovery from fear. Hyperactivation of the amygdala to fearful cues is a robust intermediate phenotype in patients with PTSD. The end result of these neuroanatomical alterations is increased stress sensitivity, generalized fear responses and impaired extinction. Other regions including the anterior cingulate cortex, the orbitofrontal cortex, the parahippocampal gyrus, the thalamus and the sensorimotor cortex also play a secondary role in the regulation of fear and PTSD.
(Figure adapted from Mahan and Ressler, 2012.)