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Hippocampal and amygdala volumes in adults with posttraumatic stress disorder secondary to childhood abuse or maltreatment: A systematic review

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ABSTRACT

We systematically reviewed differences in hippocampal and amygdala volumes between adults with childhood maltreatment-related posttraumatic stress disorder (PTSD) and healthy controls. Using the terms "adults", "MRI", "magnetic resonance imaging", with "posttraumatic stress disorder" "PTSD", "child abuse", and "child maltreatment", we conducted searches on several electronic databases. We identified 10 studies that met our inclusion criteria; 7 of which were included in a meta-analysis of hippocampal volume and 4 that were included in a meta-analysis of amygdala volume. Mean hippocampal and amygdala volumes were used to determine effect sizes. We found bilateral reduction of both the hippocampus and amygdala in the PTSD group compared to healthy controls, with effect sizes of −0.66 and −0.67 for the left and right hippocampus ($p < 0.00001$ and $p = 0.002$) and −1.08 and −1.15 for the left and right amygdala, ($p = 0.013$ and $p = 0.003$), respectively. Confidence intervals were −0.93, −0.39 and −1.26, −0.29 for the left and right hippocampus, respectively. For the amygdala, confidence intervals were −1.92, −0.23 and −1.19, −0.39 for the left and right amygdala. The relatively few studies available for analysis is a limitation. Additionally, sex diverse MRI studies in PTSD are needed to determine whether sex plays a significant role in the hippocampal effects associated with childhood-onset trauma.

Contents

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1. Introduction

Posttraumatic Stress Disorder (PTSD) is a debilitating condition that, by virtue of its symptom profile and chronicity, causes substantial work impairment (Blanchard et al., 1996; Davidson et al., 1991; Greene et al., 2016; Breslau et al., 2004; Goldberg et al., 2014) and social dysfunction (Zatzick et al., 1997; Blanchard et al., 1998; Brunello et al., 2001; Davidson, 2000; Ramchand et al., 2015). The disorder is also associated with detrimental cognitive effects (Elzinga et al., 2002; Sapolsky et al., 2000). There is now a fairly substantial body of literature detailing the effects of trauma exposure and PTSD on brain morphology, with most studies evaluating the impact on hippocampal, followed by amygdala, structure and function. The hippocampus plays a central role in memory and learning. Dysfunction of the hippocampus may be associated with aberrant fear extinction processes characteristic of PTSD (Admon et al., 2013a). There is a growing body of evidence that supports the theoretical foundation that the hippocampus underpins a number of endophenotypic disturbances in PTSD, via its role in memory function (McEwen, 2007). The amygdala also has a key role in the pathophysiology of PTSD through fear conditioning and extinction processes (Hartley et al., 2010; Godsil et al., 2013; Van Elzakkera et al., 2014). Patients with PTSD demonstrate amygdala hyperactivity in response to affective and trauma related cues, with this activation correlated with PTSD symptom severity (Shin et al., 2006; Hayes et al., 2012; Rauch et al., 2006).

Previous meta-analyses and systematic reviews of studies including participants with heterogeneous types of trauma exposure have consistently documented reduced hippocampal size in adults with PTSD compared to trauma exposed and trauma unexposed controls (Kitayama et al., 2005; Woon and Hedges, 2011; Hedges and Woon, 2010; Smith, 2005). Smaller hippocampal volume has also been correlated with PTSD symptom severity (Gilbertson et al., 2002), PTSD duration (Felmingham et al., 2009) and memory impairments (Douglas et al., 1995). Hippocampal volume reduction may be a consequence of trauma exposure, independent of PTSD status, given that two meta-analyses have demonstrated smaller hippocampal size in trauma exposed individuals compared to trauma unexposed controls (Woon et al., 2010 and Li et al., 2014), with a greater reduction in those with PTSD (Kitayama et al., 2005; Smith, 2005; Li et al., 2014). A question that arises is whether hippocampal differences in PTSD and controls are a consequence of trauma exposure or a pre-existing vulnerability factor which, following trauma exposure, predisposes individuals to PTSD (Jatzko et al., 2006). A study by Gilbertson et al. (2002) demonstrated that non-combat exposed twins had hippocampal volumes that were comparable to their combat veteran brothers with high severity PTSD. Hippocampal reduction was greater than that of combat exposed twins without PTSD suggesting that smaller hippocampal volume may be a heritability risk factor, already present during early development and pre-dating trauma exposure. Conversely another study of hippocampal size and connectivity prior to and following combat exposure found that reduced hippocampal size following trauma exposure, but not prior to exposure, was related to PTSD symptoms as well as to reduced hippocampal ventromedial prefrontal cortex connectivity (Admon et al., 2013a). It appears that reduced hippocampal size may be a premorbid vulnerability factor for PTSD in some individuals while in other individuals develop secondarily to PTSD (Admon et al., 2013a).

Results of previous meta-analyses evaluating amygdala volume in PTSD stemming from heterogenous types of trauma have been more mixed. The first meta-analysis performed demonstrated smaller left, but not right, amygdala volume in patients with PTSD compared to trauma-exposed and unexposed controls, however the authors included studies of child and adolescent participants in their analysis (Karl et al., 2006). A subsequent meta-analysis by Woon and Hedges (2009) demonstrated no differences in amygdala size between adults with PTSD compared with trauma-exposed and unexposed controls. A more recent meta-analysis in adults with PTSD also reported no differences in right and left amygdala volume between patients with PTSD and trauma exposed and unexposed controls, but found that combined left and right amygdala volumes were reduced in PTSD patients compared to trauma unexposed controls (O'Doherty et al., 2015).

Changes in amygdala volume could potentially be a feature of trauma exposure or of comorbid psychopathology and not PTSD per se. For instance, one meta-analysis reported reduced hippocampal and amygdala volumes in individuals with Borderline Personality Disorder (BPD) and these results were not influenced by a history of abuse or PTSD comorbidity (Ruocco et al., 2012). However, another meta-analysis found that BPD patients without comorbid PTSD, unlike BPD patients with comorbid PTSD, had smaller amygdala volumes than healthy controls (De-Almeida et al., 2012). Similarly, female patients with dissociative identity disorder and comorbid PTSD demonstrated significantly smaller left amygdala volumes than controls (Vermetten et al., 2006). Amygdala dysfunction may also be a predisposing factor for the development of PTSD as increased amygdala responsivity prior to combat exposure predicted increased PTSD symptomatology following exposure (Admon et al., 2009, 2013b). Kuo et al. (2012) showed that increased volume of the amygdala may be apparent following trauma exposure in adulthood, irrespective of exposure to early life trauma or the severity of trauma.

Childhood abuse or childhood maltreatment (defined as neglect, physical abuse, sexual abuse and emotional maltreatment during childhood and adolescence) has deleterious morphological effects on the developing brain (De Bellis et al., 1999; Navalta et al., 2006; Anda et al., 2006). Childhood abuse is also associated with long term adverse physical and mental health outcomes, through emotional, behavioural, cognitive and social pathways (Conte and Schuerman, 1987; Kendall-Tackett, 2002; Wegman and Stetler, 2009). In addition to the risk of PTSD from early life stress or trauma, there is robust evidence of risk for the development of other psychiatric disorders and for brain morphological alterations following exposure to childhood trauma (Navalta et al., 2006). In animal studies, early maltreatment has been associated with an accelerated loss of neurons (Edwards et al., 1990; Smythies, 1997), delays in myelination (Dunlop et al., 1997) and consequent detrimental neurodevelopmental effects. Synaptic pruning is a very important step in the maturing brain and during childhood and adolescence leads to a refinement of over-produced synapses and to improved brain efficiency (Seeman, 1999). Elevated cortisol levels associated with childhood maltreatment may lead to abnormalities in age-appropriate pruning (Todd, 1992), long-lasting psychiatric sequelae, and brain morphological changes. Children suffering from maltreatment-related PTSD, for example, have