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Increased activation of the left hippocampus region in Complex PTSD during encoding and recognition of emotional words: A pilot study

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Abstract

To gain insight into memory disturbances in Complex Posttraumatic Stress Disorder (Complex PTSD), we investigated declarative memory function and medial temporal lobe activity in patients and healthy non-traumatized controls. A case-control study was performed in nine patients with Complex PTSD and nine controls. All respondents performed a declarative memory task with neutral and emotional, negative words during functional magnetic resonance imaging. Memory performance of neutral words was impaired in Complex PTSD with a relative conservation of recall of negative words. Deep encoding of later remembered negative words, as well as correct recognition of negative words and false alarms, was associated with an enhanced Blood Oxygenation Level Dependent (BOLD) response in the left hippocampus extending into the parahippocampal gyrus of Complex PTSD patients compared with controls. Post-hoc volumetric comparisons did not reveal significant anatomical differences in the medial temporal lobe between Complex PTSD patients and controls. We conclude that in Complex PTSD preferential recall of negative words is associated with increased activation in the left hippocampus and parahippocampal gyrus during both successful and false recall. These findings support a model of an abnormally functioning hippocampus in Complex PTSD.

Keywords: Medial temporal lobe; Functional brain imaging; Memory; Emotional stimuli; Posttraumatic Stress Disorder; DESNOS; Childhood abuse

1. Introduction

Sexual and physical childhood abuse appears to be a crucial etiological factor in the development of several psychiatric disorders such as posttraumatic stress disorder (PTSD). Sexual abuse affects 10% of Dutch women (Draijer, 1990). The risk of PTSD following exposure to

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any type of trauma is 10 to 20% with the highest risk associated with assaultive violence (Breslau et al., 1998). Terr (1991) divides trauma into two basic types: Type I trauma refers to a single non-interpersonal traumatic event; type II trauma refers to repeated and interpersonal traumatic events, such as childhood abuse. More severe symptoms are associated with type II trauma (Green et al., 2000). After type II trauma "classic" PTSD (re-experiencing, numbing and hyper arousal) can be complicated by additional features such as impaired affect regulation, dissociation and memory disturbances, disturbances of self-image and relational problems (Herman, 1992; Van Der Kolk et al., 1996; Zlotnick et al., 1996). This syndrome has been brought under the heading of 'PTSD with associated features' in DSM-IV-TR (American Psychiatric Association, 2000) or 'Disorders of Extreme Stress Not Otherwise Specified' (DESNOS) and is also known by clinicians as 'Complex PTSD'. In a student population prevalence of Complex PTSD was found to be 1% (Ford et al., 2006). It is associated with severe psychiatric symptoms, high co-morbidity and social maladjustment, and it tends to run a chronic course in spite of considerable use of medical and psychiatric services (Höing, 2003).

Memory dysfunction is a central feature of PTSD. On the one hand, memories of traumatic events can be intrusive in PTSD patients, as in flashbacks and nightmares, disturbing normal daily activities. On the other hand, memory fails during periods of numbing and dissociation. In several neuropsychological studies, PTSD has been associated with impaired performance on memory tests (Sutker et al., 1992; Vasterling et al., 1998) with a preference for remembrance of trauma-related material compared with neutral material (Chemtob et al., 1999; McNally, 2006).

Animal studies have shown that stress, particularly early in life, during a 'window of susceptibility', may have profound and enduring effects on the regulation of stress later in life. A history of childhood abuse is related to increased neuro-endocrine stress reactivity, which is further enhanced when additional trauma is experienced in adulthood (Heim et al., 2002). Early adverse events are associated with structural and functional changes in brain areas involved in emotion processing and long-term declarative memory functioning, especially parts of the medial temporal lobe (MTL) such as the amygdala, the hippocampus and the parahippocampal gyrus (Elzinga and Bremner, 2002; Sapolsky, 2000). The hippocampus is a key structure associated with declarative memory function and receives extensive inputs from brain regions involved in emotion processing (Rolls and Kesner, 2006).

A meta-analysis on 21 structural imaging studies (Karl et al., 2006) revealed a significantly smaller volume of the right and left hippocampus in adult subjects with (chronic) PTSD compared with both traumatized and non-traumatized controls without PTSD. Stronger effect sizes were found in male versus female PTSD patients. Moreover, effect sizes increased with PTSD severity. Effect sizes increased with age as well, but in older patients with PTSD a smaller hippocampal volume has not been found (Freeman et al., 2006; Golier et al., 2005; Yehuda et al., 2007). So, not all magnetic resonance imaging (MRI) studies on chronic PTSD revealed a decreased hippocampal volume; negative results have been reported both with manual segmentation methods and automated techniques (Jatzko et al., 2006).

Smaller hippocampal volumes have been found in patients with major depressive disorders (MDD) as well, especially associated with repeated episodes (see meta-analysis: Videbech and Ravnkilde, 2004). However, a study with a specific comparison of MDD patients with early childhood abuse versus non-traumatized MDD patients found volume losses exclusively in the trauma-exposed group (Vythilingam et al., 2002). Furthermore, hippocampal volumes appeared to be smaller in patients with trauma-related Dissociative Identity Disorder (DID) as well (Vermetten et al., 2006; Ehling et al., 2007) and in traumatized borderline patients (Driessen et al., 2000). So, we may conclude that a smaller hippocampus may not be specific for PTSD; nevertheless it has been found especially in psychiatric disorders related to early trauma.

Functional imaging studies have shown conflicting results with regard to the hippocampus in PTSD (for review, see Francati et al., 2007). Blood flow in the hippocampus was found to be diminished during retrieval of negative word pairs in female PTSD patients with childhood sexual abuse ($n=10$) compared with non-exposed controls ($n=11$) (Bremner et al., 2003b) and during encoding of a (neutral) paragraph in women with child sexual abuse and PTSD ($n=10$) compared with abused controls without PTSD ($n=12$), suggesting that hippocampal dysfunction is related to the diagnosis of PTSD and not to the abuse itself (Bremner et al., 2003a). In line with these findings, intrusive memories of childhood sexual abuse were associated with decreased blood flow in the right hippocampus in women with PTSD ($n=10$) relative to abused women without PTSD ($n=12$) (Bremner et al., 1999). Decreased hippocampal function was also found using the hippocampus-dependent virtual Morris water task during functional MRI (fMRI) in PTSD patients (Astur et al., 2006). In contrast, increased perfusion of the left