Brief report

Post-traumatic stress disorder and declarative memory functioning: a review

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Declarative memory dysfunction is associated with post-traumatic stress disorder (PTSD). This paper reviews this literature and presents two frameworks to explain the nature of this dysfunction: that memory deficits are a product of neurobiological abnormalities caused by PTSD and/or that pre-existing memory deficits serve as a risk factor for the development of PTSD following trauma exposure. Brain regions implicated in declarative memory deficits include the hippocampus and prefrontal cortex, and imaging and biochemistry studies as they relate to memory dysfunction are described. Prospective and twin studies provide support for a risk factor model.

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Memory disturbances are predominant in the presentation of post-traumatic stress disorder (PTSD) and are part of the diagnostic criteria.[1] The re-experiencing symptom criteria of PTSD include intrusive memories of the traumatic event, and the avoidance symptom criteria include the inability to recall important aspects of the trauma. In addition, patients with PTSD often complain of experiencing everyday memory problems with emotionally neutral material, although these problems are not included in the diagnostic criteria. Documenting these types of memory deficits related to PTSD, and understanding the reasons underlying these deficits, has become a primary focus for researchers for the past 20 years, in part because memory problems can lessen a patient's engagement in, and response to, treatment. In this review, literature on declarative memory deficits (defined as the ability to consciously remember and reproduce emotionally neutral material) related to PTSD will be summarized. Some of the inconsistencies and complexities in these findings, with a focus on addressing the potential influence of comorbid psychopathologies, will be addressed. Then, these findings will be explored through two frameworks: (i) that memory dysfunction is a result of neurobiological abnormalities caused by trauma, and/or (ii) that memory dysfunction serves as a pre-existing risk factor for the development of PTSD.

Declarative memory dysfunction in PTSD

Multiple studies have demonstrated verbal declarative memory deficits related to PTSD, in samples of adult patients with PTSD related to combat,[2-9] childhood abuse,[10-11] rape,[12] political violence,[13] and the Holocaust.[14-15]

Studies have employed a variety of memory measures, including list-learning tasks such as the California Verbal Learning Test and the Rey Auditory Verbal Learning Test; paired associates learning, from the Wechsler Memory Scale (WMS); and narrative recall, such as the Logical Memory subtest of the WMS. Visual memory impairments appear to be less pronounced than verbal memory impairments.[16] Fewer studies have examined neuropsychological functioning in children with PTSD. There is some evidence of verbal memory deficits in samples of children exposed to intimate partner violence,[17] motor vehicle accidents,[18] and physical and sexual abuse.[19]

There are some exceptions to this fairly robust literature, with some studies failing to find memory impairments related to PTSD.[20-26] Conflicting methodologies across studies might account for these inconsistencies; the majority of studies examining memory in PTSD employ small sample sizes and a variety of instruments used to assess memory. In addition, confounds such as comorbid psychiatric conditions complicate interpretation of findings.

Meta-analysis is the most useful method to pool the results of individual studies, weight them for sample size, and generate an overall effect size to test the hypothesis that PTSD is associated with verbal declarative memory deficits. A meta-analysis of adult studies prior to 2006[27] showed a small-to-moderate effect size for memory deficits in PTSD. The 27 studies reviewed examined both verbal and visual memory and produced larger effects for verbal memory. The studies included both trauma-exposed and unexposed control groups with more pronounced differences occurring between PTSD patients and control groups not exposed to trauma. Similarly, Johnsen and Asbjensen,[28] in their recent meta-analysis, found a moderate effect size for verbal memory impairment, with stronger memory impairment in war veteran groups compared with civilian groups. The authors noted that the majority of studies reviewed included veterans from the Vietnam War with chronic, long-lasting PTSD. These findings could suggest that the memory impairments were related in part to illness duration.

It should be emphasized that overall, decrements in memory performance due to PTSD are subtle, with performance falling either in the low average range, or in the normal range yet significantly lower than controls. Still, the findings are clinically meaningful when they represent a change in functioning before and after trauma.

A closer examination of the pattern of memory deficits reveals that PTSD most significantly impacts the initial acquisition and learning phases of memory, as opposed to the retention phase. For example, when controlling for initial acquisition, several studies have failed to find PTSD-related deficits in delayed recall.[7,8,13,17,23,24,29] In Brewin et al's[27] meta-analysis, there was not an effect of immediate versus delayed recall, suggesting that any loss of memory over time is more likely accounted for by difficulties in immediate recall.

Comorbidities

It is important to establish that any memory deficits observed in patients with PTSD are related to PTSD and not to psychiatric conditions commonly comorbid with PTSD, particularly depression, substance use disorders, and traumatic brain injury. For example, Neylan et al[20] failed to find PTSD-related memory deficits when veterans with psychiatric comorbidities were excluded. Barrett et al[30] found that veterans with PTSD alone did not exhibit impairments in neurocognitive functioning, whereas veterans with PTSD and a concurrent diagnosis of depression, anxiety, or substance abuse did. To further address the comorbidity issue, researchers have matched PTSD and control subjects on comorbidity status,[2,11,12] statistically controlled for alcohol use or depression,[6] or examined subgroups with and without comorbid disorders[8] and continued to find PTSD-related neuropsychological deficits. Our group[9] systematically examined the independent and interactive contributions of PTSD and alcohol abuse history using a four-group design and found verbal memory deficits specific to PTSD.

The majority of neuropsychological studies with patients with PTSD excluded subjects with traumatic brain injury (TBI), which could represent a confound as it is also associated with memory deficits and commonly comorbid with PTSD. In their meta-analysis, Brewin et al[27] determined that a confounding effect of a history of head injury is not likely: studies reviewed that excluded subjects with head injury actually showed larger effect sizes for memory impairments than did studies that failed to state whether they excluded subjects with head injury. A current focus of PTSD research is to examine independent and interactive effects of PTSD and TBI on neurocognitive functioning and to attempt to distinguish patterns of impairment between the two disorders. This

is challenging, as the diagnosis of mild TBI cannot be easily made when PTSD is present as clinicians are unsure of the cause of many of the cognitive symptoms.

Memory and PTSD frameworks

There are two primary frameworks for understanding memory impairment in PTSD. The first posits that memory deficits are a product of neurobiological abnormalities caused by PTSD. The second framework posits that preexisting memory deficits serve as a risk factor for the development of PTSD following trauma exposure. Each model represents either end of the nature vs nurture paradigm—either that the environment impacts neurobiology or that genetics influence one's predisposition to PTSD.

Neurobiological abnormalities in PTSD

Researchers have established multiple neurobiological systems and structural and functional abnormalities involved in PTSD.[31,32] Here, key systems and structures and their relationship to declarative memory will be briefly summarized. Memory deficits appear to be most related to abnormalities in the hippocampus and hypothalamic-pituitary-adrenal (HPA) axis, and the prefrontal cortex and catecholamine system.

Over 15 years of PTSD research has focused on the role of the hippocampus, a brain area particularly sensitive to the effects of stress. Studies showing glucocorticoid toxicity in the hippocampus and memory dysfunction in animals under stress[33,34] led to the hypothesis that severe stress, in particular traumatic stress, may result in similar changes in humans. Meta-analyses[35,36] of adults with PTSD reveal smaller hippocampal volume in both the left and right sides. Functional imaging studies have demonstrated abnormal cerebral blood flow to the hippocampus[37,38] during declarative memory tasks. Other studies have found reductions in N-acetyl aspartate (NAA), a marker of neuronal integrity.[39,40] In addition, dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis is associated with PTSD.[41-45]

In contrast, meta-analysis[36] did not demonstrate hippocampal volume loss in children. Two possible explanations are that hippocampal alterations associated with PTSD may change over time or that there may be more sensitive markers of hippocampal pathology than volume loss with children. There is some limited evidence pointing to hippocampal dysfunction in children. Carrion and colleagues[46] found that PTSD symptoms and cortisol levels predicted hippocampal reduction over time. And in a functional imaging study, this group[47] found decreased activity in the hippocampus during a verbal memory task in children with PTSD symptoms from interpersonal trauma.

The relationship between declarative memory and hippocampal functioning is well established within studies of elderly subjects, both with and without dementia.[48-51] Given that line of research, as well as repeated documentation of both declarative memory deficits and hippocampal abnormalities in PTSD, it would follow that there would be a correlation between hippocampal dysfunction and declarative memory performance in individuals with PTSD. However, few studies have examined and demonstrated this relationship. Two research studies have found expected correlations between hippocampal volume loss and declarative memory performance,[52,53] whereas three other studies have not.[54-56]

Although the hippocampus was the early focus of research in understanding declarative memory deficits related to PTSD, the discrepant findings described above suggest that it should not be the only focus. To summarize, first, research does not consistently show a correlation between declarative memory performance and hippocampal function. Second, there is limited evidence showing hippocampal dysfunction in children. Finally, the pattern of memory impairments in PTSD demonstrates that PTSD is less associated with problems with retention, a process mediated by the hippocampus, and much more associated with problems with acquisition and learning, processes more associated with prefrontal system dysfunction.[57]

There are a number of studies further elucidating the impact of PTSD on the prefrontal cortex (PFC). Stress exposure releases glucocorticoids and catecholamines in the PFC,[58-59] which impair functions mediated by the PFC including working memory, executive function, and the regulation of behavior and emotion.[60] Deficits in these areas are also associated with PTSD.[5-8,12,61-65] Several magnetic resonance imaging (MRI) studies have reported decreased frontal cortex volume in PTSD[66-68] and decreased volume in medial prefrontal regions, namely the anterior cingulate and subcallosal cortex.[69-72] A functional imaging study revealed underactivation of the frontal cortex during a paired-associates learning task in patients with PTSD.[73] Particularly in children, findings of

frontal dysfunction are more robust than findings of hippocampal dysfunction.[66,67,74]

Cognitive risk and protective factors in PTSD

PTSD is a unique psychiatric disorder in that it is the result of a traumatic life event. As such, it would be assumed that all neuropsychological and neurobiological abnormalities associated with PTSD are also caused by that event. However, prospective and twin studies offer compelling support for the model that pre-existing memory and learning deficits, and related hippocampal dysfunction, increase one's vulnerability to developing PTSD. Gibertson et al[75] studied monozygotic twin pairs who were discordant for combat exposure and found that the identical co-twins of combat veterans with PTSD, who had not experienced combat exposure or PTSD themselves, showed similar deficits in verbal memory. In addition, both combat veterans with PTSD and their co-twins exhibited smaller hippocampi,[76] suggesting that a smaller hippocampus and memory impairments in PTSD represent a pre-existing, genetic factor. Further support for this framework has come from a recent longitudinal study, where researchers examined the extent to which poorer neurocognitive functioning prior to a major natural disaster predicted the development of PTSD symptoms.[77] Development of PTSD symptoms was inversely associated with word recall, as well as working memory, processing speed, and verbal intelligence performance assessed pretrauma.

Conclusions

It is likely that memory dysfunction is both a pre-existing risk factor for the development of PTSD as well as a consequence of the disorder. Vasterling and Brailey[78] propose a potential "downward spiral" (p 192) in which pre-existing neurocognitive deficits lead to an increased risk of PTSD through ineffective coping or fewer resources, and the development of PTSD, in turn, engenders greater cognitive dysfunction. Regardless of the origin of memory deficits, their effects on daily functioning and treatment are of primary concern. Memory problems reduce the resources available to PTSD patients when coping with life's demands and more specifically, can impact patients' ability to engage in and respond to psychological treatment. Indeed, a recent study found that verbal memory impairment predicted poorer outcome in patients receiving cognitive behavioral therapy for PTSD.[79] To address this concern, future research should examine the effects of cognitive rehabilitation training on neuropsychological deficits related to PTSD. ❑.

Trastorno por estrés postraumático y funcionamiento de la memoria declarativa: una revisión

La disfunción de la memoria declarativa se asocia con el trastorno por estrés postraumático (TEPT). Este artículo revisa la literatura y presenta dos propuestas para explicar la naturaleza de esta disfunción: que los déficit de memoria son producto de anormalidades causadas por el TEPT y/o que los déficit de memoria preexistentes constituyen un factor de riesgo para el desarrollo de un TEPT a continuación de la exposición a un trauma. El hipocampo y la corteza prefrontal son las regiones cerebrales que participan en los déficit de memoria declarativa. Se describen los estudios de imágenes y bioquímicos que se han realizado y la manera en que ellos se relacionan con la disfunción de memoria. Los estudios prospectivos y de gemelos proporcionan apoyo para un modelo de factor de riesgo.

Etat de stress post-traumatique et fonctionnement de la mémoire déclarative

L'état de stress post-traumatique (ESPT) s'associe à un trouble de la mémoire déclarative. Cet article analyse la littérature et présente deux grands axes pour expliquer la nature de ce trouble : tout d'abord, ces déficits mnésiques résultent d'anomalies dues à l'ESPT, de plus, la préexistence de déficits mnésiques jouent le rôle de facteur de risque de développement de l'ESPT après exposition à un traumatisme. L'hippocampe et le cortex préfrontal sont les régions cérébrales impliquées dans les déficits de mémoire déclarative. Nous décrivons ici les études de biochimie et d'imagerie liées au trouble mnésique, les études prospectives et de jumeaux servant de base à un modèle de facteur de risque.

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