The Relationship Between Cognitive and Brain Changes in Posttraumatic Stress Disorder

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Abstract
Preclinical studies show that stress is associated with changes in structure of the hippocampus, a brain area that plays a critical role in memory, inhibition of neurogenesis, and memory deficits. Studies in animals showed that both serotonin reuptake inhibitors (SSRIs) and the epilepsy medication phenytoin (dilantin) block the effects of stress on the hippocampus. Imaging studies in posttraumatic stress disorder (PTSD) have found smaller volume of the hippocampus as measured with magnetic resonance imaging (MRI) in patients with PTSD related to both combat and childhood abuse. These patients were also found to have deficits in memory on neuropsychological testing. Functional imaging studies using positron emission tomography (PET) found decreased hippocampal activation with memory tasks. In an initial study, we found that a year of treatment with paroxetine led to a 5% increase in hippocampal volume and a 35% increase in memory function. A second study showed that phenytoin was efficacious for symptoms of PTSD and led to a significant 6% increase in both right hippocampal and right whole brain volume, with no significant change in memory. These studies suggest that medications may counteract the effects of stress on the brain in patients with PTSD.

Keywords
PTSD; hippocampus; pharmacotherapy; stress; neurogenesis; paroxetine; depression

Patients with posttraumatic stress disorder (PTSD) exhibit a broad range of problems with memory, including gaps in memory, problems with declarative memory, attentional biases to trauma-related information, and intrusive memories. The past two decades of research have seen a convergence of findings from the clinical observations, and clinical and preclinical research.

Studies in animals exposed to stress showed deficits in hippocampal-based memory function1 and alterations in hippocampal morphology.2, 3 Stress interfered with hippocampal-based mechanisms of memory function, including long-term potentiation (LTP).1, 4 Mechanisms proposed for these findings include elevated levels of glucocorticoids released during stress,5, 6 stress-related inhibition of brain-derived neurotrophic factor (BDNF),7, 8 changes in serotonergic function,9 or inhibition of neurogenesis (or the growth of new neurons)10, 11 in the hippocampus. These effects are reversible with treatment with serotonin reuptake inhibitor (SSRI) medications, 12-14
tianeptine,\textsuperscript{15} and phenytoin.\textsuperscript{16} Antidepressant-induced promotion of neurogenesis may underlie the behavioral effects of these medications,\textsuperscript{17} although the relationship between the hippocampus and depression and PTSD is still not clear.\textsuperscript{18}

Studies have used neuropsychological testing as a probe of brain function in PTSD. Several studies have demonstrated verbal declarative memory deficits in PTSD\textsuperscript{19–22} using a variety of measures (including the Wechsler Memory Scale, the visual and verbal components of the Selective Reminding Test, the Auditory Verbal Learning Test, the California Verbal New Learning Test, and the Rivermead Behavioral Memory Test), found specific deficits in verbal declarative memory function\textsuperscript{23–36} (although see Refs. 37 and 38). These studies have been conducted in both patients with PTSD related to Vietnam combat,\textsuperscript{23, 25, 28–33, 35, 36} rape,\textsuperscript{26} adults with early childhood abuse,\textsuperscript{24} and traumatized children.\textsuperscript{27} Studies in women with PTSD showed that verbal declarative memory deficits are specifically associated with PTSD, and are not a non-specific effect of trauma exposure.\textsuperscript{26, 39} Other types of memory disturbances studies in PTSD include gaps in memory for everyday events (dissociative amnesia),\textsuperscript{40} deficits in autobiographical memory,\textsuperscript{41} false recall of material,\textsuperscript{42, 43} an attentional bias for trauma-related material,\textsuperscript{44–53} and frontal lobe-related impairments.\textsuperscript{54} These studies fairly consistently show that PTSD is associated with deficits memory that covers a range of categories.

Neuroimaging studies showed alterations in the hippocampus in PTSD. Magnetic resonance imaging (MRI) showed smaller volume of the hippocampus in PTSD; decreases in right hippocampal volume in the PTSD patients were associated with deficits in short-term memory.\textsuperscript{55} Findings of smaller hippocampal volume and/or a reduction in NAA in the hippocampus (a marker of neuronal integrity) in adults with chronic, long-standing PTSD have been replicated several times in the published literature.\textsuperscript{56–63} Studies in childhood\textsuperscript{64–66} and new onset\textsuperscript{67, 68} PTSD did not find hippocampal volume reduction, although reduced NAA (indicating loss of neuronal integrity) was found in medial pre-frontal cortex in childhood PTSD.\textsuperscript{69} In a recent meta-analysis we pooled data from all of the published studies and found smaller hippocampal volume for both the left and the right sides, equally in adult men and women with chronic PTSD, and no change in children.\textsuperscript{70} PTSD patients showed deficits in hippocampal activation while performing a verbal declarative memory task.\textsuperscript{63, 71} Both hippocampal atrophy and hippocampal-based memory deficits reversed with treatment with the SSRI, paroxetine, which has been shown to promote neurogenesis (the growth of neurons) in the hippocampus in preclinical studies.\textsuperscript{72} Treatment with phenytoin resulted in improved PTSD symptoms,\textsuperscript{73} a 6% increase in right cerebral volume and 5% increase in right hippocampal volume.\textsuperscript{74} These findings suggested that long-term treatment with paroxetine or phenytoin is associated with changes in brain structure that may underlie improvement in symptoms.\textsuperscript{72}

We hypothesize that stress-induced hippocampal dysfunction may mediate many of the symptoms of PTSD that are related to memory dysregulation, including both explicit memory deficits as well as fragmentation of memory in abuse survivors (FIG.1). It is unclear at the current time whether these changes are specific to PTSD, whether certain common environmental events (e.g., stress) in different disorders lead to similar brain changes, or whether common genetic traits lead to similar outcomes.\textsuperscript{75} Obviously, the increase in hippocampal volume with medication treatments known to promote neurogenesis in preclinical studies is not consistent with a pure genetic contribution to smaller hippocampal volume in PTSD.
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References


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FIGURE 1.
Lasting effects of trauma on the brain, showing long-term dysregulation of norepinephrine and cortisol systems, and vulnerable areas of hippocampus, amygdala, and medial prefrontal cortex that are affected by trauma.