Cognitive and Hippocampal Abnormalities in Posttraumatic Stress Disorder

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Abstract

Context: Cognitive and hippocampal abnormalities have widely been observed in posttraumatic stress disorder (PTSD).

Objective: To determine whether cognitive and hippocampal abnormalities found in PTSD are familial vulnerability factors or acquired characteristics.

Design: Cross-sectional twin paradigm including monozygotic twins discordant for combat exposure.

Setting: Academic Medical Center

Participants: Male combat-exposed veterans with PTSD (n = 13) and their combat-unexposed co-twins (n = 13), as well as combat-exposed veterans without PTSD (n = 14) and their combat-unexposed co-twins (n = 14).

Main Outcome Measures: We used neurocognitive tests to measure verbal learning and memory, verbal fluency, and visuospatial copying ability. We used magnetic resonance imaging, positron emission tomography, and fluorodeoxyglucose 18 to examine hippocampal morphology, resting regional cerebral metabolic rate for glucose (rCMRglu), and activation during a recognition memory task.

Results: We found that combat veterans with PTSD and their identical co-twins (without combat exposure or PTSD) showed impaired declarative verbal memory compared to combat veterans without PTSD and their unexposed co-twins. Follow-up

analyses indicated that impairment in initial encoding, but not memory consolidation, drove the outcome. PTSD symptom severity in combat-exposed twins correlated negatively with verbal declarative memory performance in unexposed co-twins. We found no significant abnormalities in visuospatial copying ability, verbal fluency, or hippocampal structure or function.

Conclusions: Impairment in initial encoding of verbal declarative memory seems to represent a familial vulnerability factor for developing PTSD after exposure to psychological trauma.

Introduction

Posttraumatic stress disorder (PTSD) is an anxiety disorder that develops after exposure to traumatic events that threaten harm and/or death and induce intense feelings of fear, hopelessness, and horror. Individuals with PTSD report intrusive recollection of traumatic memories, avoidance of stimuli associated with traumatic events, general emotional numbing, and persistent physiological hyperarousal. To receive a PTSD diagnosis, symptoms must persist for a minimum of one month and disrupt daily functioning {American Psychiatric Association, 2000, #86914}.

An estimated 50-60% of people experience trauma at some point in their lives (Breslau, 2009; Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995), but only an estimated 3-9% of the US adult population currently has or has had PTSD (Breslau, 2009; Kessler, Petukhova, Sampson, Zaslavsky, & Wittchen, 2012; Roberts, Gilman, Breslau, Breslau, & Koenen, 2011). Because only a proportion of those traumatized

develop PTSD, this implies that pre-existing vulnerability or resiliency factors may increase or decrease the likelihood of developing PTSD after trauma exposure. By identifying cognitive and neurobiological characteristics of PTSD that are vulnerability or protective factors, researchers can create preventative screening measures for individuals who are at high risk for trauma. Furthermore, determination of characteristics that are acquired due to trauma exposure and PTSD onset will aid in the development of new approaches to clinical assessment and treatment for improving long-term outcomes of individuals with PTSD.

Cognitive and Biological Abnormalities in PTSD. Researchers have observed multiple areas of cognition that are dysfunctional in people with PTSD. Studies have reported deficits of general intelligence, executive functioning, working memory, attention, learning, memory, verbal fluency, and visuospatial function in comparison to trauma-exposed participants without PTSD (Bustamante, Mellman, David, & Fins, 2001; Brewin, Kleiner, Vasterling, & Field, 2007; Diener, Flor, & Wessa, 2010; Gilbertson, Gurvits, Lasko, Orr, & Pitman, 2001; Johnsen & Asbjornsen, 2008; Koso & Hansen, 2006; Lindauer, Olff, van, Carlier, & Gersons, 2006; Marx, Doron-LaMarca, Proctor, & Vasterling, 2009; Vasterling, Brailey, Constans, & Sutker, 1998; Vasterling et al., 2002) and healthy trauma-unexposed individuals (Bremner et al., 1995; Diener et al., 2010; Eren-Kocak, Kilic, Aydin, & Hizli, 2009; Uddo, Vasterling, Brailey, & Sutker, 1993).

A literature review of PTSD characteristics indicates that factors are more consistently found than others. A large number of studies have consistently reported memory impairments and abnormal hippocampal volumes in PTSD, while other

cognitive processes, such as visuospatial function, have more contradictory findings concerning their role in PTSD. Furthermore, the role of other possible factors has not yet been thoroughly assessed, such as verbal fluency and hippocampal function. The following is a brief literature review of the current research pertaining to the role of memory, verbal fluency, visuospatial function, and the hippocampus in PTSD. The review examines researchers' findings, assesses differences in methodology, and identifies gaps in the literature as a prelude to the current study.

Memory Impairments. Of the observed cognitive deficits in PTSD, declarative learning and memory dysfunction has been the most consistent finding. Brewin and colleagues (2007) conducted a meta-analysis of 27 studies that examined verbal and/or visual emotionally neutral memory impairment in participants with PTSD and healthy controls. They reported small to moderate effect sizes in the association between PTSD and memory impairment, with verbal memory having a larger effect size than visual memory. Another meta-analysis conducted by Johnsen and Asbjornsen (2008) examined 28 studies that investigated verbal memory in participants with PTSD and control samples. They reported a strong association between verbal memory impairment and PTSD, with a moderate effect size shown in comparison to non-PTSD trauma-exposed controls, and a large effect size shown in comparison to trauma-unexposed healthy controls. Furthermore, studies have reported negative correlations between verbal declarative memory and PTSD symptom severity (Lindauer et al., 2006; Vasterling et al., 2002).

However, findings have not been consistent with regard to the type of impairment in declarative learning and memory. Some studies have reported generalized memory impairments (Bremner, Vermetten, Afzal, & Vythilingam, 2004; Gilbertson et al., 2001) while others have observed impairments in specific memory processes, such as recall deficits in short and long delay trials (Bremner et al., 1993; Jenkins, Langlais, Delis, & Cohen, 1998; Yehuda, Golier, Tischler, Stavitsky, & Harvey, 2005; Yehuda, Keefe, Harvey, & Levengood, 1995) and impairment during initial acquisition (Diener et al., 2010; Johnsen, Kanagaratnam, & Asbjornsen, 2008; Uddo et al., 1993; Vasterling et al., 2002).

Hippocampal Abnormalities. In addition to cognition, researchers study the neurobiological abnormalities of PTSD by examining differences in brain structure and function in PTSD compared to controls. The hippocampus in particular has been thoroughly investigated due to its known involvement in declarative learning and memory processes (Desimone, 1992; Squire & Zola-Morgan, 1991). Several magnetic resonance imaging (MRI) studies have found diminished hippocampal volumes in chronic PTSD participants in comparison to trauma-exposed non-PTSD participants (Bremner et al., 2003; Gilbertson et al., 2002; Gurvits et al., 1996) and trauma-unexposed healthy participants (Bremner et al., 1995; Bremner et al., 1997; Villarreal et al., 2002; Wignall et al., 2004). A meta-analysis conducted by Kitayama and colleagues (2005) confirmed findings of smaller bilateral hippocampal volume in PTSD. Studies have also found hippocampal volume to be inversely correlated with PTSD symptom severity (Lindauer et al., 2006; Villarreal et al., 2002; Zhang et al., 2011) and trauma exposure

(Gurvits et al., 1996). However, other studies could not replicate findings of diminished hippocampal volumes in children with PTSD (Carrion et al., 2001; De Bellis, Hall, Boring, Frustaci, & Moritz, 2001; De Bellis et al., 1999) or participants with recent onset of PTSD (Bonne et al., 2001), suggesting that hippocampal volume differences may be limited to a specific subgroup (e.g., adult chronic PTSD).

While many studies have examined hippocampal morphology, not much is known about possible differences in hippocampal function in PTSD. In PET and functional MRI studies, researchers have reported decreased hippocampal activation in abused women with PTSD compared to abused female controls during a symptom provocation paradigm (Bremner et al., 1999), in abused women with PTSD compared to abused women without PTSD during a verbal memory task and retrieval of emotionally valenced words (Bremner, 2003; Bremner et al., 2003), and in firefighters with PTSD during a neutral word recall task (Shin et al., 2004). However, other studies have reported increased activation in the hippocampus in PTSD patients compared to healthy controls during encoding of items in an associative learning paradigm (Werner et al., 2009), in complex PTSD participants compared to controls during recall of negative words in a declarative memory task (Thomaes et al., 2009), and in veterans with PTSD compared to veterans without PTSD during a pain processing task using heat stimuli (Geuze et al., 2007). Conflicting results concerning the direction of hippocampal activation suggest that dysfunctional brain activity may in part be dependent upon the sample group tested, type of task given, and type of statistical analysis used.

In addition to using symptom provocation and cognitive tasks to assess activation, neuroimaging studies have examined the hippocampus during resting conditions. Researchers have monitored regional cerebral blood glucose metabolism at (rCMRglu) at resting state and found decreased glucose metabolism in veterans with chronic PTSD compared to veterans without PTSD (Molina, Isoardi, Prado, & Bentolila, 2010) and in women with recent PTSD due to sexual assault compared to healthy controls (Kim et al., 2012). One study found no differences in hippocampal rCMRglu between veterans with PTSD, their trauma-unexposed co-twins, or veterans without PTSD and their trauma-unexposed co-twins (Shin et al., 2009). Discrepancies between findings may be accounted for by subject group, as the samples from Molina et al. (2010) and Kim et al. (2012) were much younger (M = 37 years old, averaged across both studies) and had PTSD for a shorter length of time (M = 20 years of PTSD, Molina et al. (2010); M = 10 months of PTSD, Kim et al., 2012) than the sample examined by Shin et al. (2009) (M = 57.5 years old; M = 35 years of PTSD).

The relationship between memory impairment and hippocampal abnormalities in PTSD is not clear. Some studies have found inverse correlations between hippocampal volume and verbal memory (Bremner, 1999; Vythilingam et al., 2005). Others found no significant associations (Bremner et al., 1997; Lindauer et al., 2006; Woodward et al., 2009) or observed either memory deficits or hippocampal diminution, but not both (Gurvits et al., 1996; Nakano et al., 2002; Stein, Koverola, Hanna, Torchia, & McClarty, 1997). Inconsistency of results may be due to differences in participant

groups, type of memory impairment found, and presence of confounding factors, such as alcohol abuse and comorbidity.

Origin of Memory Impairments and Hippocampal Abnormalities in PTSD. The majority of research previously cited are post-trauma cross-sectional studies that can only establish correlations between observations and cannot determine the origin of cognitive and hippocampal abnormalities in PTSD. Observed abnormalities in individuals with PTSD could have been present prior to trauma-exposure or acquired after trauma-exposure or the development of PTSD symptoms. It is incredibly difficult to acquire pre-trauma data due to financial and logistical restrictions. Nevertheless, determining the origin of PTSD characteristics is pivotal in developing theoretical models for the onset and maintenance of this illness.

Several theories have been presented to explain the presence of declarative memory deficits and hippocampal abnormalities in PTSD. Pitman (2001) presented two possible explanations for why verbal memory deficits and hippocampal abnormalities may reflect vulnerability factors. First, individuals with verbal memory deficits and hippocampal abnormalities may be at increased risk to trauma exposure because they may not remember past experiences in which they encountered trauma (e.g., walking down the same dark alley at night in which he or she was assaulted) and are thus less likely to take precautions and avoid similar dangerous situations. Second, these pre-existing abnormalities may reflect vulnerability for PTSD development after trauma exposure. Because the hippocampus is known to modulate the extinction of conditioned fear responses (Myers & Davis, 2007; Phillips & LeDoux, 1992), it is possible that

hippocampal abnormalities result in a diminished ability to extinguish conditioned fear responses learned during traumatization.

On the other hand, declarative memory deficits and hippocampal abnormalities may reflect acquired characteristics of trauma exposure and PTSD development. For example, stress hormones associated with trauma exposure and PTSD may be toxic to brain functioning and structure (Buckley, Blanchard, & Neill, 2000; Sapolsky, 2000). Evidence for this proposal is provided by animal studies that examined mice under situations of extreme stress and found subsequent hippocampal damage (e.g., Sapolsky, 1996; Sapolsky, 2000). Additionally, Sandi and Pinelo-Nava (2007) proposed in a literature review that under situations of high stress, acquisition of declarative memory decreases. It is possible that experiencing high stress during trauma exposure results in long-term memory impairment. However, it is also possible that because PTSD symptoms themselves are inherent stressors (i.e., hyperarousal and re-experiencing of trauma result in continued stress on the body), the sustained high stress from chronic PTSD causes and maintains memory impairment.

Studies examining whether verbal declarative memory deficits in PTSD are vulnerability factors or acquired characteristics have predominantly found that differences in verbal memory performance predate trauma exposure. Parslow and Jorm (2007) investigated the cognitive performance of 1,599 young adults who participated in a longitudinal epidemiological study between 1999 and 2000. Participants' cognitive performance was assessed a second time between 2003 and 2004, after they all experienced one or more traumatic events related to a widespread fire in January 2003.

Parslow and Jorm (2007) found that PTSD symptoms of re-experiencing the trauma and hyperarousal were associated with poorer pre-trauma performance on measures of immediate and delayed word recall, digit span, coding speed and vocabulary. In a sample of male monozygotic twins discordant for combat trauma (which is identical in design to the current study), Gilbertson et al. (2006) found verbal declarative memory impairment in both combat-exposed participants with PTSD and their combat-unexposed co-twin in comparison to combat-exposed participants without PTSD and their combat-unexposed co-twin. Shared impaired performance in PTSD twin pairs suggests that poor verbal declarative memory is a familial vulnerability factor for PTSD.

Studies examining the origin of reduced hippocampal volume in PTSD have been inconsistent. Gilbertson et al. (2002) found that combat-exposed participants with PTSD and their combat-unexposed co-twins had significantly smaller hippocampal volumes than combat-exposed participants without PTSD and their combat-unexposed co-twins. This finding suggests that diminished hippocampal volume reflects a familial vulnerability factor for PTSD. Another study found an increased incidence of large cavum septum pellucidum in individuals with PTSD and their unexposed co-twins (May, Chen, Gilbertson, Shenton, & Pitman, 2004). The presence of large cavum septum pellucidum is associated with abnormal limbic system development, of which the hippocampus is a constituent (Sarwar, 1989).

The results of other neuroimaging studies have suggested that trauma exposure and PTSD affect hippocampal volume. A meta-analysis maintained that participants with PTSD have smaller hippocampal volumes than trauma-exposed controls and

trauma-unexposed healthy controls (Woon, Sood, & Hedges, 2010). However, the authors also found that trauma-exposed controls have smaller hippocampal volumes than trauma unexposed healthy controls. The gradation of hippocampal volume suggests that diminished volume may be at least partially an acquired characteristic of trauma exposure that can be exacerbated by chronic PTSD.

A review of the research literature yielded no studies that have examined whether abnormal hippocampal function represents a vulnerability factor or an acquired characteristic of PTSD. More research is needed to assess the origin hippocampal dysfunction in PTSD.

Verbal Fluency and Visuospatial Functioning. Because memory impairment has been consistently found in PTSD, researchers have focused on replicating these findings and developing theories concerning PTSD based upon memory impairment and its associated brain structures, such as the hippocampus. Alternatively, other cognitive processes have not been examined as thoroughly. Verbal fluency and visuospatial functioning are two processes that have relatively few and contradictory findings reported in PTSD. Due to the lack of consistent findings, it is important to establish whether theses two processes are truly characteristics of PTSD because if so, they could contribute to developing accurate theories concerning PTSD pathogenesis.

Verbal fluency tasks assess the speed at which participants can access lexical and semantic information. Verbal fluency also assesses executive function by requiring participants to retain words in the short-term without repetition. Uddo et al. (1993) studied Vietnam combat veterans with PTSD and Army National Guard enlistees

without PTSD and found that the PTSD group produced significantly fewer animal names than the control group but performed similarly to the controls when tested on producing words beginning with the same letter. Eren-Kocak et al. (2008) found that participants with current PTSD due to a natural disaster performed significantly worse than past PTSD and healthy control groups in the production of typical names of people. Furthermore, both current PTSD and past PTSD groups performed significantly worse than healthy controls on the production of animal names. Bustamante et al. (2001) examined a sample of participants in a Level I Trauma Center recovering from recent trauma and found a significant negative correlation between verbal fluency on words beginning with specific letters at initial assessment and PTSD symptom severity assessed 6 weeks later. However, Crowell et al. (2002) and Vasterling et al. (1998) did not find verbal fluency impairment in samples of combat veterans with PTSD compared to control groups. Inconsistencies in findings may be due to task used, as tests involving animal name production yield more robust impairment than tests measuring words produced according to the beginning of a specified letter.

Studies investigating visuospatial functioning have also been mixed. Gilbertson et al. (2001) and Crowell et al. (2002) found no significant differences in visuospatial and visuoconstructive ability in combat veterans with and without PTSD. Gilbertson et al. (2006) investigated visuospatial ability in a sample of monozygotic twins discordant for combat exposure and found no differences in overall visuospatial skill. However, Gurvits et al. (2000, 2002) found that combat veterans with PTSD performed significantly worse on a measure of visuospatial copying ability than combat veterans

without PTSD. Furthermore, the authors found a positive correlation between visuospatial copying ability and PTSD symptom severity, but not combat exposure.

Visuospatial tasks are complex measures that necessitate different levels of fine motor coordination, visual encoding and recall, and spatial processing according to the specified test, so inconsistencies in studies may be due differences in how visuospatial ability was measured. Gilbertson et al. (2007) suggested that individuals with PTSD show impairment in allocentric encoding of configural cues; allocentric mediation is the processing of configural relationships among distal environmental cues in contrast to processing in reference to one's midline axis (ie., egocentric mediation). They found allocentric processing to be impaired in individuals with PTSD in a study examining monozygotic twins discordant for combat exposure and PTSD, and they suggest that the impairment reflects a vulnerability factor for PTSD.

Little research has been conducted to examine the origin of verbal fluency and visuospatial abnormalities. No longitudinal or twin studies have reported abnormalities in verbal fluency. It is unclear the lack of reporting is due to failure to measure verbal fluency at all or findings of non-significant abnormality in PTSD samples. For visuospatial impairment, only one study determined that abnormal visuospatial ability reflects a familial vulnerability factor for PTSD using a twin paradigm (Gilbertson et al., 2007; see above). Furthermore, no studies have examined associations between verbal fluency hippocampal factors or visuospatial function and hippocampal factors. Because the hippocampus is primarily associated with memory function, hippocampal factors have not been examined in association with other cognitive processes. Therefore, it

would be worthwhile to determine whether verbal fluency and visuospatial function are associated with hippocampal structure and function.

The Current Study. To address these gaps in the PTSD literature, the current study sought to examine cognitive impairment and hippocampal abnormalities. We studied the most recent data collected from a sample of monozygotic twins discordant for trauma exposure and PTSD utilizing the identical twin case control paradigm described in previous studies (Gilbertson et al., 2002; Gilbertson et al., 2001; Gilbertson et al., 2006; Gilbertson et al., 2007; Shin et al., 2009; Shin et al., 2011). Each twin pair consisted of a combat veteran and his identical combat-unexposed co-twin. In half of the twin pairs, the combat-exposed twin had chronic PTSD; in the other half, the combat-exposed twin did not have PTSD. Given that identical twins have the same genetic makeup, any differences between a participant and his identical co-twin in cognitive performance or brain structure and function would suggest an influence of environmental factors, such as combat exposure or PTSD. Such differences would therefore reflect acquired characteristics. Alternatively, if veterans with PTSD and their identical co-twins perform similarly to each other but significantly different from veterans without PTSD and their identical co-twins, abnormalities are likely to represent familial vulnerability factors.

Using this unique model, we sought to replicate previous observations of neurocognitive and hippocampal differences in PTSD, determine the origin of found differences, and investigate any relationships between neurocognitive performance and hippocampal structure and function. We included cognitive performance measures of

visuospatial copying ability, verbal declarative memory, and verbal fluency. Hippocampal structure and function were measured using volumetric analysis, neuroimaging of activity during a memory recognition task, and regional cerebral metabolic rate for glucose (rCMRglu) during resting condition. In line with previous research, we expected to find abnormalities in verbal declarative memory, visuospatial copying ability, and hippocampal volume in veterans with PTSD and their identical co-twins, which would reflect familial vulnerability factors. We also predicted abnormal verbal fluency and hippocampal function; however, because the origin of verbal fluency and hippocampal function has not been thoroughly assessed in PTSD, we had no predictions for the direction or origin of the deficits. Additionally, we predicted associations between verbal declarative memory and PTSD symptom severity, hippocampal volume and function and PTSD symptom severity, and verbal declarative memory and hippocampal volume and function.

Methods

Participants

Participants were recruited through a variety of avenues. The majority of participants were contacted through the Vietnam Era Twin Registry (VETR) using the methods described in a previous study (Orr et al., 2003). Additional twin pairs were recruited via letters sent to Vietnam veterans receiving disability compensation for PTSD from the Veterans Benefits Administration in Washington, DC. The letters asked whether the recipient had an identical twin brother unexposed to combat and, if so,

whether the recipient and his twin might be willing to join the study (Orr et al., 2003). An additional pair was recruited via an advertisement posted on www.military.com during August 2012. The Institutional Review Board (IRB) at Partners Healthcare System, Boston, Massachusetts approved this study. Each participant provided written informed consent after receiving a full explanation of study procedures.

Participants were 27 male monozygotic twin pairs, in which one brother served in combat whereas his co-twin did not. Participants were separated into four experimental groups. Participants who were combat veterans with chronic PTSD made up the exposed PTSD (P) group (n=13). Their combat-unexposed co-twins without PTSD made up the PTSD Co-twin (PC) group (n=13). Participants who were combat veterans but did not develop chronic PTSD made up the Control (C) group (n=14). Their unexposed co-twins without PTSD made up the Control Co-twin (CC) group (n=14). Twin pairs in which the combat-exposed brother has PTSD were referred to as the "PTSD twin pairs." Twin pairs in which the combat-exposed brother does not have PTSD were referred to as the "Control twin pairs." Participants with combat exposure were collectively referred to as the "Exposed" group and their unexposed co-twins were the "Unexposed" group.

An experienced licensed psychologist interviewed all participants using (1) the Clinician-Administered PTSD Scale (CAPS; (Weathers, Keane, & Davidson, 2001)) to diagnose PTSD and determine symptoms severity and (2) the Structured Clinical Interview for *DSM-IV* (SCID; First, Spitzer, Gibbon, & Williams, 1995) to determine the

presence of comorbid Axis I disorders. Current comorbid disorders among participants included dysthymia (2 P, 1 PC), alcohol abuse/dependence (1 P, 2 PC), panic disorder (2 P), MDD (3 P), eating disorder (1 P), substance abuse/dependence (2 P, 1 C), GAD (1 P), and simple phobia (1 P, 2 PC, 1 C). Participants with comorbid major depressive and substance use disorders were not excluded from the study due their high prevalence rates in the PTSD population. To measure alcohol use history, participants completed the Michigan Alcoholism Screening Test (MAST; Selzer, 1971). Current psychotropic medication use among participants include antidepressants (7 P, 2 PC, 1 C, 3 CC), antipsychotics (2 P, 1 PC), anticonvulsants (1 PC), acetylcholinesterase inhibitors (1 P), and anxiolytics (1 P).

Neurocognitive Data Acquisition

Participants completed a battery of neurocognitive tests administered according to standardized test-specific procedures. The administrator was a licensed neuropsychologist blind to exposure and PTSD status. All tests were completed in one block in the afternoon of the second day of data collection.

Visuospatial Copying Ability. The Neurologic Soft Signs (NSS) Figure Drawing task assessed visuospatial copying ability and thus demanded visual perceptual acuity, fine motor coordination, organization, and planning. This task required the participant to copy the image of three 3-Dimensionally drawn shapes: cube, pyramid, and truncated pyramid. We scored each figure on a rating scale of 0 -3: 0 = near perfect replication, 1 = mild distortion, 2 = moderate distortion or loss of three-dimensionality,

3 = severe distortion of basic shape to the extent that it's near unrecognizable. Gurvits et al. (2006) showed that the average score across drawings are related to PTSD status and trauma exposure.

Verbal Fluency. The Controlled Oral Word Association Test (COWAT) evaluated the spontaneous production of words pertaining to a category and thus demands verbal initiation, short-term memory, planning, and organization (Benton, Hamsher, & Sivan, 1994). This test required the participant to say as many novel words beginning with a given letter as possible within 60 seconds. In three trials, participants produced words beginning with the letters F, A, and S, respectively. The total number of novel words produced across the three trials was used for statistical analysis.

Verbal Learning and Memory. The California Verbal Learning Test (CVLT) measured initial registration of neutral learning material, retention of material over short and long delays, encoding strength, and interference effects through oral communication (Delis, Kramer, Kaplan, & Ober, 1987). The CVLT consists of a primary neutral word list (List A) and an interference neutral word list (List B) presented verbally to the participant, and it measures 20 separate indices of verbal learning and memory. We consolidated the indices into a single composite measure based on the combined performance of the two strongest factors of the CVLT (General Verbal Learning and Response Discrimination), as determined by previous factor analytic models (see Delis, Kramer, Freeland, & Kaplan, 1988). The validity of and procedure for

computing the CVLT composite score have been reported in a prior study (Gilbertson et al., 2006).

The General Verbal Learning Factor includes the following subtests: List A Total Recall, List B Total Recall, Short-Delay Free Recall (SDFR), Short-Delay Cued Recall (SDCR), Long-Delay Free Recall (LDFR), Long-Delay Cued Recall (LDCR), Recall Consistency, Percent Recency Recall, Semantic Clustering, Recognition Hits, and Short-Delay Free Recall Versus List A Trial 5. The General Verbal Learning Factor represents generalized declarative verbal learning and memory. The Response Discrimination Factor includes the following subtests: Total Free Recall Intrusions, Total Cued Recall Intrusions, and False Positives. The Response Discrimination Factor represents inhibition and cognitive control.

We computed the standardized z scores for each subtest making up the two factors and reported the average *z* score of these measures as the CVLT composite score. We also calculated the *z* score of both individual factors by determining the average *z* score of the subtests composing the factors; any potential differences between the two factors can thus be determined in secondary analyses. The difference in z scores for Trial 5 versus Long-Delay Free Recall and Trial 5 versus Long-Delay Cued Recall were also analyzed as a measure of memory consolidation, which is thought to be hippocampus-dependent (Golomb et al., 1994; Diener et al., 2010). Additional analyses of variance were conducted on each aforementioned subtest using its average *z* scores.

Hippocampal Data Acquisition

Fluorodeoxyglucose F18 – PET Procedures. We used positron emission tomography (PET) and Fluorodeoxyglucose F18 (FDG) to measure resting regional cerebral metabolic rate for glucose (rCMRglu). PET equipment and procedures are described in previous studies (e.g. Deckersbach et al., 2006; Shin et al., 2009). Immediately prior to PET scanning, subjects fasted for a minimum of 6 hours. A 40-minute uptake period was required after FDG administration (185 MBq, 5 mCi) during which each subject was instructed to sit quietly with his eyes closed in a dedicated waiting room. The subject was then escorted to the CTI/Siemens Medical Solutions HR+ PET scanner located in the adjacent room. The HR+ PET scanner had an in-plane and axial resolution of 4.5mm full-width at half-maximum intensity, 63 contiguous slices with 2.5-mm separation, and a sensitivity of 200 000 cps/μCi/mL (2-dimensional) and 900 000 cps/μCi/mL. Each subject was aligned in the scanner relative to the canthomeatal line. Expandable cushions were fitted around his head to limit movement (Shin et al., 2009). PET scans were conducted 1 day prior to functional magnetic resonance imaging (fMRI) scans, and both imaging scans were conducted an average of 8 years before the neurocognitive measures.

Functional Magnetic Resonance Imaging Procedures. Participants were scanned using a Siemens Medical Systems Symphony/Sonata 1.5-T whole-body high-speed fMRI scanner with a 3-axis gradient head coil (Shin et al., 2011). Expandable foam pillows cushion the subjects' heads within the coil limited head movement. An automated scout image was acquired and shimming procedures were performed in

order to optimize field homogeneity before high-resolution structural MRI images with a 1.33-mm slice thickness were collected. Structural MRI images were 3-dimensional magnetization-prepared rapid gradient-echo; repetition time/echo time/ flip time was equal to 73 seconds/3.31 milliseconds/7°. Volumetric analysis methods have been described in previous studies (Shin et al., 2009).

Hippocampal activation was determined by measuring changes in blood oxygen level dependent (BOLD) signal while the participant was within the fMRI undergoing a recognition memory task. The memory task described in Weiss et al. (2004) was shown to produce hippocampal activation in participants with no history of mental illness (Stark & Squire, 2000). The task consists of eighty words presented during the study phase and again during the testing phase (Old Words). An additional eighty words that were not presented during the study phase served as new foils during the testing phase (New Words). During the study phase outside of the scanner, participants read aloud each of the eighty Old Words for two cycles with instructions that there would be a subsequent memory test. The testing phase occurred approximately fifteen minutes after the study phase, during which fMRI data was collected. Test items were divided into eight blocks consisting of 20 words, which were either primarily old (18 Old Words, 2 New Words) or primarily new (18 New Words, 2 Old Words). The sequence of Old Word and New Word blocks was counterbalanced across subjects. Participants indicated via button press whether they believed each item was an Old Word or New Word. Between each block of words, a fixation cross was shown for 30 seconds (Fixation

Period). To assess learning and recognition, the difference between hippocampal activation during presentation of Old Words (O) and during low-level fixation (F) baseline was calculated and is referred to throughout the paper as "hippocampal OvF."

Statistical Analyses

All statistical analyses were performed using two-tailed tests with a significance threshold of $p<.05$. Using SPSS Software, analyses of variance were conducted on each dependent variable. We used 2x2 mixed ANOVAs for group comparisons. When a significant main effect or interaction was found, follow up *t*-tests were conducted to further explore the findings. We treated combat exposure as the repeated measure, because within each pair one twin had been exposed to combat while the other had not. We treated the presence or absence of PTSD diagnosis in the combat-exposed brother as the between-subjects factor. Following this statistical model, a significant difference between PTSD and Control twin pairs (main effect of Diagnosis) in the absence of an interaction would show that the dependent variable reflects a familial vulnerability factor. A significant difference between Exposed and Unexposed participants (main effect of Exposure) in the absence of an interaction would indicate that the dependent variable reflects an influence of trauma exposure. The presence of an Exposure x Diagnosis interaction in which the combat-exposed PTSD group (P) exhibits a significant difference in comparison to the PC, C, and CC groups would suggest that the dependent variable reflects an acquired characteristic of chronic PTSD.

Pearson product-moment bivariate correlational analyses were conducted to assess the relationship between neurocognitive measures, hippocampal functional and volumetric data, and PTSD symptom severity. Analyses assessing the relationship between neurocognitive data and hippocampal data were conducted across all subjects. Analyses involving PTSD symptom severity were computed by separately correlating the CAPS scores of Exposed participants to their own neurocognitive and hippocampal data, as well as to the neurocognitive and hippocampal data of their Unexposed co-twins. If a given dependent variable reflects a familial vulnerability factor, then those measures in the Unexposed co-twins should predict (correlate with) PTSD symptom severity in their Exposed twins.

Not all participants who completed the neurocognitive measures also underwent fMRI and PET scanning. For analyses involving hippocampal volume, the dataset included 9 PTSD pairs and 11 Control pairs. For analyses involving hippocampal FDG data, the dataset included 4 PTSD pairs and 6 Control pairs. For analyses involving hippocampal fMRI data, the dataset included 4 PTSD pairs and 9 Control pairs. Because repeated measures analyses were used, both members of a twin pair were excluded if either member had missing values.

Alcohol abuse, psychotropic medication use, and comorbidity are known confounding factors in brain and cognitive studies in PTSD (Hedges & Woon, 2010; Horner & Hamner, 2002; Vasterling et al., 2012). Potentially confounding medications include beta-blockers, anticonvulsants, antidepressants, neuroleptics, benzodiazepines,

sedatives, hypnotics, cerebral stimulants, and other psychotherapeutic agents (Shin et al., 2009). Covariates were screened as potential confounders of dependent variables using preliminary correlational analyses with a screening threshold of p <.20 (Shin et al., 2009). Identified potential confounders were controlled for in subsequent analyses. MAST scores were used as a measure of alcohol abuse. Current psychotropic medication use and comorbidity were scored as either present or absent for each group (e.g., 0 = not present, 1= present in P, 2 = present in PC, 3 = present in C, 4 = present CC).

Results

Demographic Characteristics

Group mean demographic data for PTSD twin pairs and Control twin pairs are shown in Table 1. The PTSD and Control twin pairs did not differ on mean age (t(26) = .769, p = .449). A 2x2 repeated measures ANOVA on years of education showed no significant main effects or interaction (all ps > .193). A 2x2 repeated measures ANOVA on lifetime alcohol abuse symptoms (MAST scores) showed a significant Exposure x Diagnosis interaction (F(25) = 4.658, p = .041). Follow-up t-tests indicate no significant differences between P & C groups and PC & CC groups (all ps > .148) An independent samples t-test on P and C groups' total CAPS score showed a significant difference in reported PTSD symptom severity (t(26) = 6.931, p = < .001), indicating more severe PTSD symptoms in the P group compared to the C group.

Table 1. Descriptive Statistics of Demographic Data

Variable	PTSD Twin Pairs (N=13)				Control Twin Pairs (N=14)			
	Exposed		Unexposed		Exposed		Unexposed	
	M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
Age (Years)	62.47	2.344	62.47	2.344	61.71	3.451	61.71	3.451
Education (Years)	13.571	2.6808	13.929	3.4298	15.46	3.565	14.79	2.785
MAST[a]	4.31	4.973	2.38	4.073	2	2.418	2.21	2.723
CAPS (total symptom score)	53.71	23.769	-	-	6.14	9.718	-	-

PTSD = Posttraumatic stress disorder; MAST = Michigan Alcoholism Screening Test; CAPS = Clinician-Administered PTSD Scale
df = 1, 26 unless otherwise noted
[a] 1 PTSD twin pair was excluded due to missing data (df=1, 25).

Group Comparisons of Neurocognitive Data

Group means of the neurocognitive data for PTSD twin pairs and Control twin pairs are shown in Table 2. A 2x2 repeated measures ANOVA on COWAT total score showed neither significant main effects nor a significant interaction for verbal fluency (all *p*s >.285). A 2x2 repeated measures ANOVA on NSS Figure Drawing average score showed no significant main effects nor a significant interaction for visuospatial copying ability (all *p*s > .184).

Table 2. Means of Neuropsychological Measures

Variable	PTSD Twin Pairs (N=13)				Control Twin Pairs (N=14)			
	Exposed		Unexposed		Exposed		Unexposed	
	M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
CVLT								
List A Total Recall[a]	47.8	12	44.8	12.9	60	11	65	6.5
List A Trial 5 Recall[a]	0.17	1.03	-0.2	1.19	1	1	1.3	0.6
List B Recall[a]	0.67	1.15	0	1.48	1.1	0.9	1.1	1.1

Short Delay Free Recall	-0.2	0.99	-0.6	0.1	0.9	0.9	1	1
Short Delay Cued Recall	-0.2	1.14	-0.7	0.75	0.6	0.8	0.8	0.8
Long Delay Free Recall	0.15	0.8	-0.3	1.03	0.8	0.7	0.9	0.6
Long Delay Cued Recall	0.23	1.01	-0.5	1.13	0.8	0.7	0.7	0.7
Free Recall Intrusions	-0.4	0.65	0.23	1.36	0	0.9	0.3	1.1
Cued Recall Intrusions	-0.4	0.96	0.31	1.38	0	0.7	0	1.1
Recognition Hits	-0.1	0.76	0.23	0.83	0.6	0.6	0.6	0.5
False Positives	0.46	1.05	0.23	0.73	0	0.6	0	0.5
Semantic Clustering	-0.4	0.77	0.15	0.8	0	1.5	1.1	1.4
Recall Consistency	-0.6	1.19	-0.7	1.03	0.4	0.9	0.4	1.1
Percent Recency	-0.3	1.03	-0.2	0.9	0	0.9	0	0.6
Trial 5 Minus SDFR[a]	0.33	0.65	0.5	0.8	0.1	0.5	0.3	0.7
Trial 5 Minus LDFR[a]	0	0.74	0.17	0.94	0.2	0.8	0.4	0.7
Trial 5 Minus LDCR[a]	-0.1	0.79	0.33	1.15	0.2	0.6	0.6	0.8
General Verbal Learning	4.2	1.39	3.53	1.81	5.9	1.3	6.5	0.9
Response Discrimination	-0.1	0.79	0.26	1.05	0	0.6	0.2	0.7
Composite Score	2.05	0.67	1.89	1.13	2.8	0.6	3.2	0.5
COWAT								
Total	36.2	9.8	35.7	9.78	41	8.4	40	9.5
NSS Figure Drawing								
Average	1	0.67	1.13	0.63	0.8	0.6	1	0.7

PTSD = Posttraumatic Stress Disorder; CVLT = California Verbal Learning Test; SDFR = Short Delay Free Recall; SDCR = Short Delay Cued Recall; LDFR = Long Delay Free Recall; LDCR = Long Delay Cued Recall; COWAT = Controlled Oral Word Association Test; NSS Figure Drawing = Neurologic Soft Signs Figure Drawing Task

[a] 1 PTSD twin pair was excluded due to missing values (df = 1, 24).

A 2x2 repeated measures ANOVA on the single CVLT Composite score showed a significant main effect of Diagnosis ($F(25) = 32$, $p < .001$) in the absence of a main effect

of Exposure and a Diagnosis x Exposure interaction (*p*s > .82). Participants in PTSD twin pairs had lower CVLT Composite scores (M = 1.97, SD = .90) than participants in Control twin pairs (M = 3.00, SD = .55). See Figure 1.

Preliminary correlational analyses of potential confounders for this DV indicated that history of alcohol (MAST) use met our threshold for a potential confound ($r(52) = -.207$, $p = .132$), but the results of the previous ANOVA were not changed when we controlled for MAST scores.

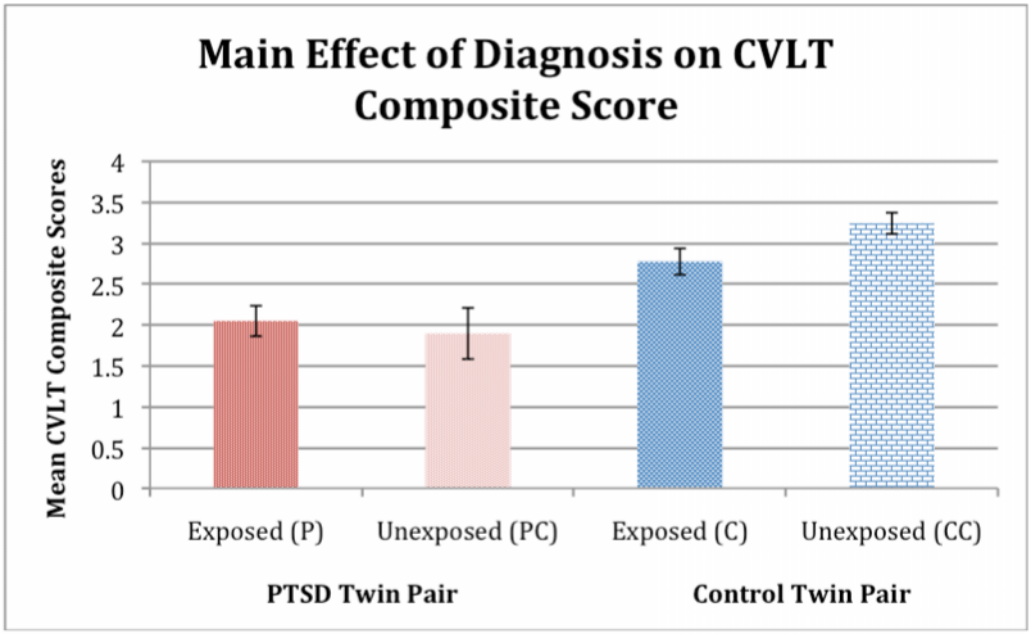

Figure 1.

In additional analyses using a 2x2 repeated measures ANOVA, we found a significant main effect of Diagnosis for the CVLT General Verbal Learning Factor ($F(25) = 32.914$, $p = <.001$), in the absence of significant main effect of Exposure or Exposure x Diagnosis interaction (all *p*s > .088). PTSD twin pairs had lower CVLT General Verbal

Learning Factor scores (M = 3.87, SD = 1.60) than Control twin pairs (M = 6.20, SD = 1.10), see Figure 2.

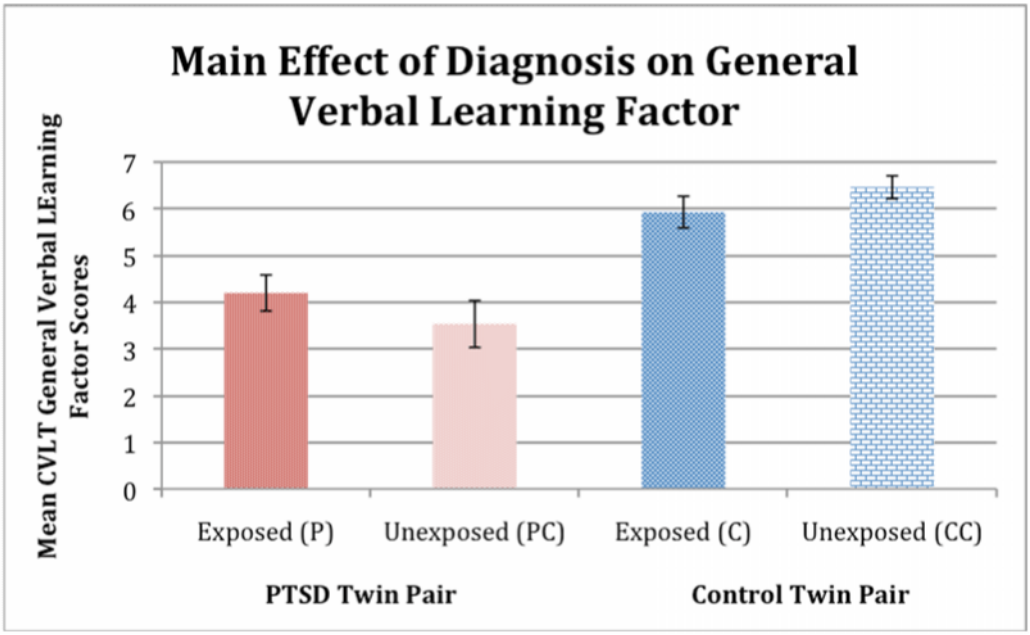

Figure 2.

Preliminary correlational analyses of potential confounders for this DV indicated that history of alcohol abuse (MAST) and comorbidity met our threshold for a potential confound ($r(52) = -.236$, $p = .085$; ($r(52) = -.238$, $p = .083$, respectively). To control for the effects of MAST scores and comorbidity, we conducted univariate analyses of the DV and covariates in Exposed and Unexposed groups separately. We found a significant effect of comorbidity ($F(26) = 4.663$, $p = .042$), but no significant effect of alcohol abuse ($F(26) = .327$, $p = .573$) in the Exposed group. Results of the repeated measures ANOVA did not change after adjustment for comorbidity, which showed a main effect of

Diagnosis of the General Verbal Learning Factor (F(26) = 9.101, *p* = .006). No significant results were found in covariate analyses for the Unexposed participants (all *p*s >.136).

For the DV of CVLT Response Discrimination Factor, a 2x2 repeated measures ANOVA revealed a significant main effect of Exposure (F(25) = 1.093, *p* = .046), in the absence of a significant main effect of Diagnosis or Exposure x Diagnosis interaction (all *p*s >.306). This significant main effect suggests that Exposed participants had lower CVLT Response Discrimination scores (M = -.15, SD = .97) than Unexposed participants (M = .23, SD = .875) (Figure 3). However, the standard errors for these means are quite large, so a bigger sample size is needed to determine whether this main effect would hold up with greater statistical power.

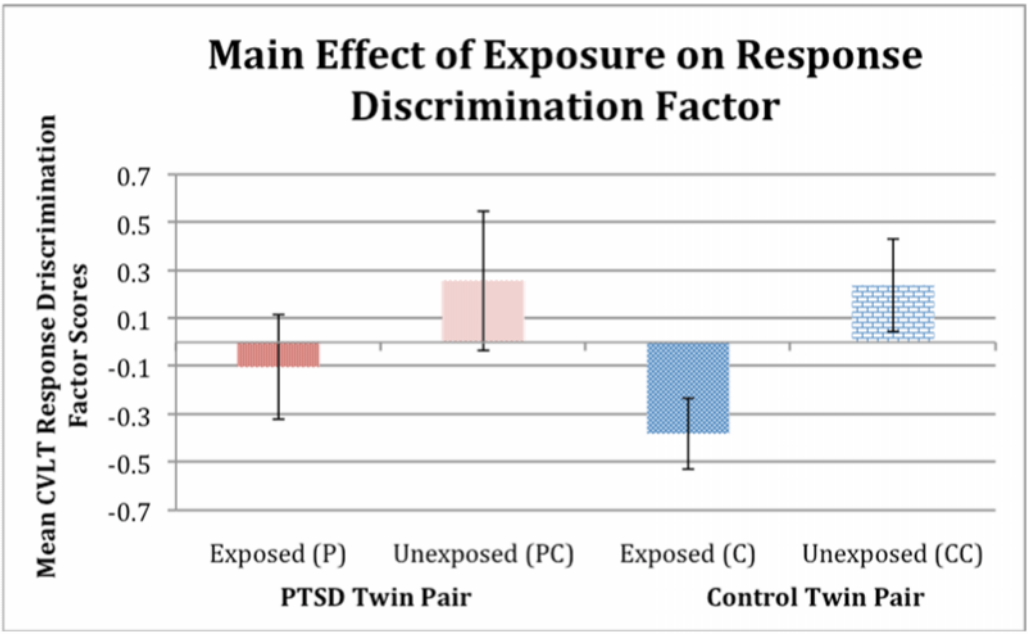

Figure 3.

Preliminary correlational analyses of potential confounders for this DV indicated that comorbidity and antidepressant use met threshold for potential confound ($r(52)$ = .221, p = .109; ($r(52)$ = .239, p = .082, respectively). To control for comorbidity and antidepressant use, we conducted univariate analyses of the DV and covariates and Exposed and Unexposed individuals separately. We found a a significant effect of antidepressant use (F(26) = 4.661, p = .042), but no significant effect of comorbidity (F(26) = .884, p = .357) in Exposed individuals. Results of the repeated measures ANOVA did not change after adjustment for antidepressant use, which showed no significant main effect of Diagnosis of the Response Discrimination Factor in Exposed groups alone (F(26) = .073, p = .790). No significant effects were found in covariate analyses of Unexposed groups alone (all ps > .112).

We ran additional 2x2 repeated measures ANOVAs for each CVLT subtest and found no significant main effects or interactions for Cued Recall Intrusions, Percent Recency, Trial 5 Minus SDFR, Trial 5 Minus LDFR, or Trial 5 Minus LDCR (all ps > .092). However, analyses showed that PTSD twin pairs performed significantly worse than Control twin pairs on the following CVLT subtests (i.e., there were significant main effects of Diagnosis for these subtests): List A Total Recall ($F(24)$ = 29.503, p < .001; PTSD: M = 46.3, SD = 12.45; Control: M = 62.5; SD = 8.75); List A Trial 5 Recall ($F(24)$ = 18.062, p < .001; PTSD: M = .065, SD = 1.11; Control: M = 1.15, SD = .80); List B Recall ($F(24)$ = 4.474, p = .045; PTSD: M = .335, SD = 2.63; Control: M = 1.1, SD = 1); SDFR ($F(25)$ = 27.113, p < .001; PTSD: M = -.40, SD = .545; Control: M = .95, SD = .93); SDCR

($F(25) = 18.505$, $p < .001$; PTSD: M = -.45, SD = .945; Control: M = .7, SD = .8); LDFR ($F(25) = 17.022$, $p < .001$; PTSD: M = -.075, SD = .915; Control: M = .85, SD = .65); LDCR ($F(25) = 9.045$, $p = .006$; PTSD: M = -.135, SD = 1.07; Control: M = .75, SD = .70); Recognition Hits ($F(25) = 5.913$, $p = .023$; PTSD: M = .065, SD = .795; Control: M = .60, SD = .55); False Positives ($F(25) = 6.991$, $p = .014$; PTSD: M = .345, SD = .89; Control: M = 0, SD = .55); and Percent Recall ($F(25) = 14.445$, $p = .001$; PTSD: M = -.25; SD = .965; Control: M = 0, SD = .75). The standard errors for many of these means are quite high, especially in PTSD twin pairs, so a bigger sample size is needed to examine whether the main effect of Diagnosis would remain with greater statistical power.

In contrast, 2x2 repeated measures ANOVAs showed significant main effects of Exposure in the absence of significant main effects of Diagnosis or Exposure x Diagnosis interactions (all ps >. 099) for the CVLT subtests of Semantic Clustering ($F(25) = 10.360$, $p = .004$; Exposed: M = -.20, SD = 1.135; Unexposed: M = .625, SD = 1.1;see Figure 4) and Free Recall Intrusion ($F(25) = 8.291$, $p = .008$; Exposed: M = -.2, SD = .775; Control: M = .265, SD = 1.23; see Figure 5).

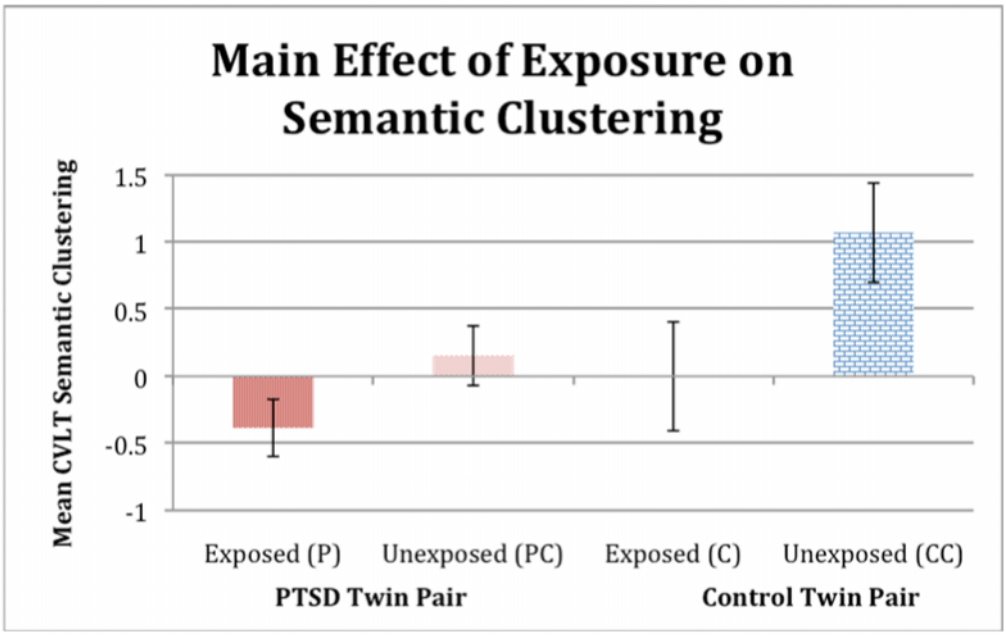

Figure 4

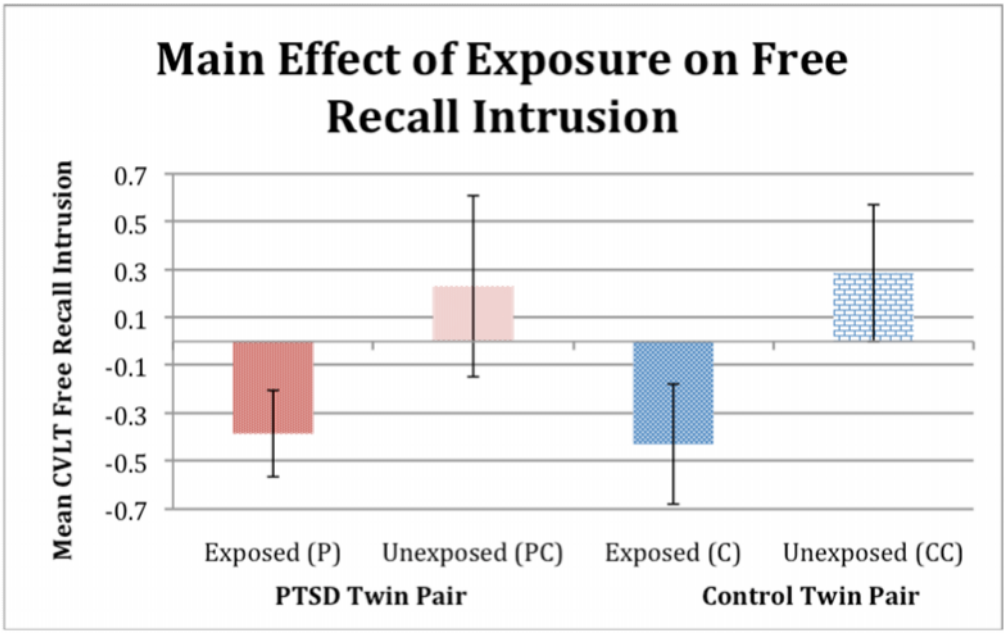

Figure 5

Group Comparisons of Hippocampal Data

Separate 2x2 repeated measures ANOVAs conducted on whole-brain-volume-adjusted left and right hippocampal volumes showed neither significant main effects nor significant interactions. Preliminary correlational analyses between potential confounding factors and hippocampal volume showed no significant associations (p > .437).

A separate 2x2 repeated measure ANOVA conducted on hippocampal rCMRglu showed neither significant main effects nor a significant interaction. Preliminary correlational analyses between potential confounding factors and hippocampal rCMRglu showed no significant associations (p >.291).

A separate 2x2 repeated measures ANOVA conducted on hippocampal OvF showed neither significant main effects nor a significant interaction. Preliminary correlational analyses between potential confounding factors and hippocampal OvF indicated that history of alcohol use (MAST) (r(30) = -.249, p = .184) and antidepressant use (r(30) = -.281, p = .123) met our threshold for potential confounders. However, the results of the analyses remained unchanged after controlling for MAST scores and antidepressant use.

Group Correlations of PTSD Symptom Severity, Neurocognitive Data and Hippocampal Data

Neurocognitive Data and Symptom Severity. We found a significant negative correlation between the Exposed group's PTSD symptom severity (CAPS scores) and

the Exposed group's CVLT Composite score ($r(25) = -.566$, $p = .002$; see Figure 6). To determine if a specific factor drove the significant correlation, secondary analyses were conducted. We found a significant relationship between the Exposed group's PTSD symptom severity (CAPS scores) and the Exposed group's General Verbal Learning Factor ($r(25) = -.662$, $p < .001$; see Figure 7), but no significant relationship between the Exposed group's PTSD symptom severity and their Response Discrimination Factor ($r(25) = .325$, $p = .098$).

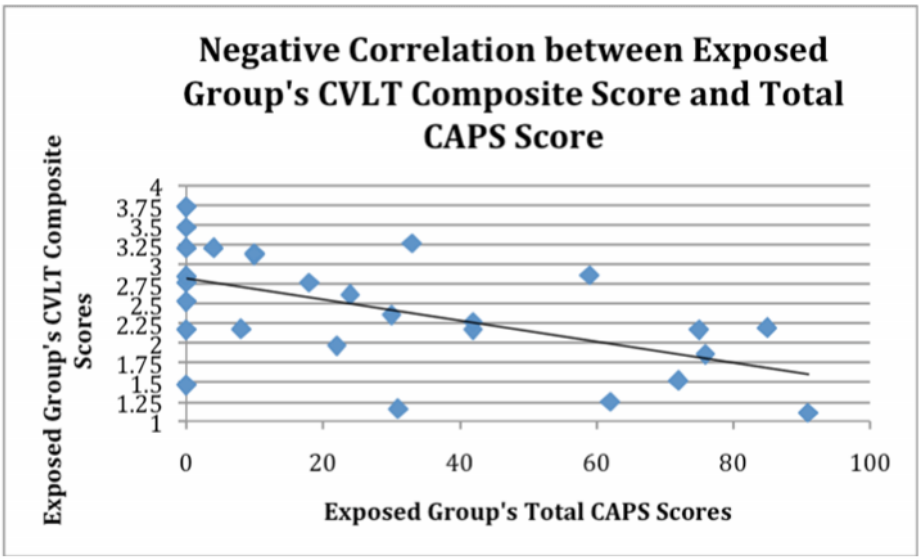

Figure 6

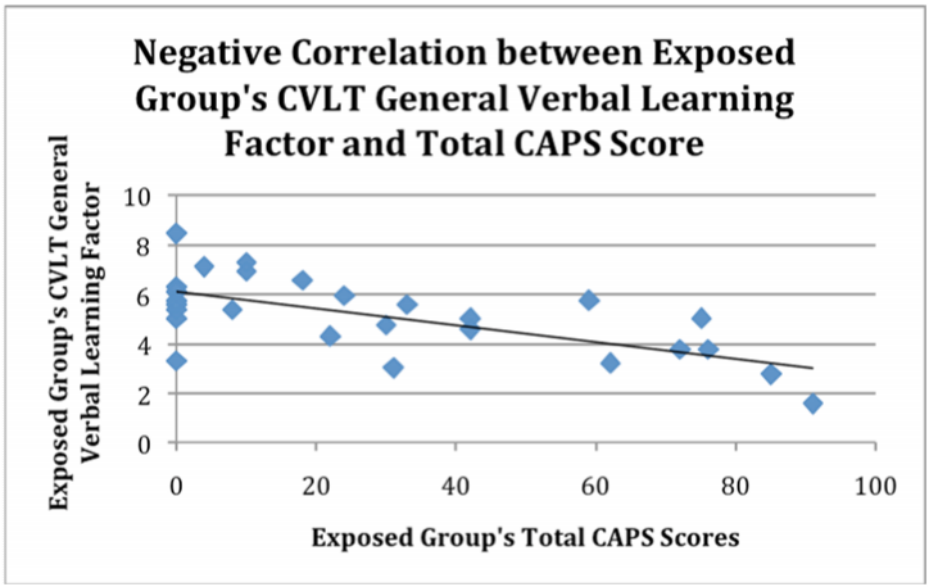

Figure 7

We also found a significant negative correlation between the Exposed individuals' PTSD symptom severity (CAPS scores) and the Unexposed individuals' CVLT Composite score ($r(25) = -.592$, $p = .001$; see Figure 8). Additional analyses revealed a significant negative relationship between the Exposed individuals' PTSD symptom severity (CAPS scores) and the Unexposed individuals' General Verbal Learning Factor ($r(25) = -.711$, $p < .001$; see Figure 9), but no significant relationship between the Exposed group's PTSD symptom severity (CAPS scores) and their Response Discrimination Factor ($r(25) = .183$, $p = .361$). An additional correlational analysis was conducted between Exposed individuals' Response Discrimination Factor and combat exposure, which showed no significant relationship ($r(23) = .205$, $p = .349$.

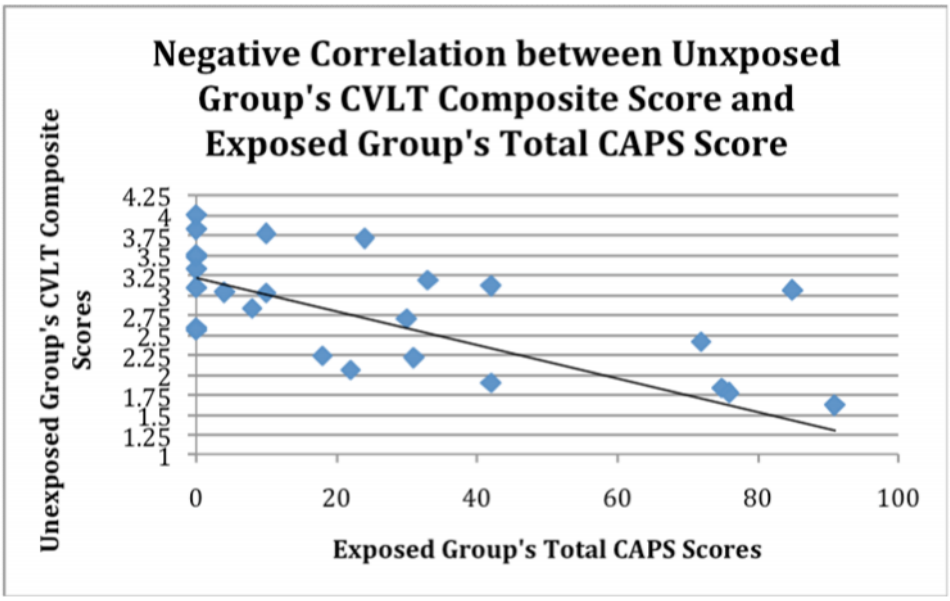

Figure 8

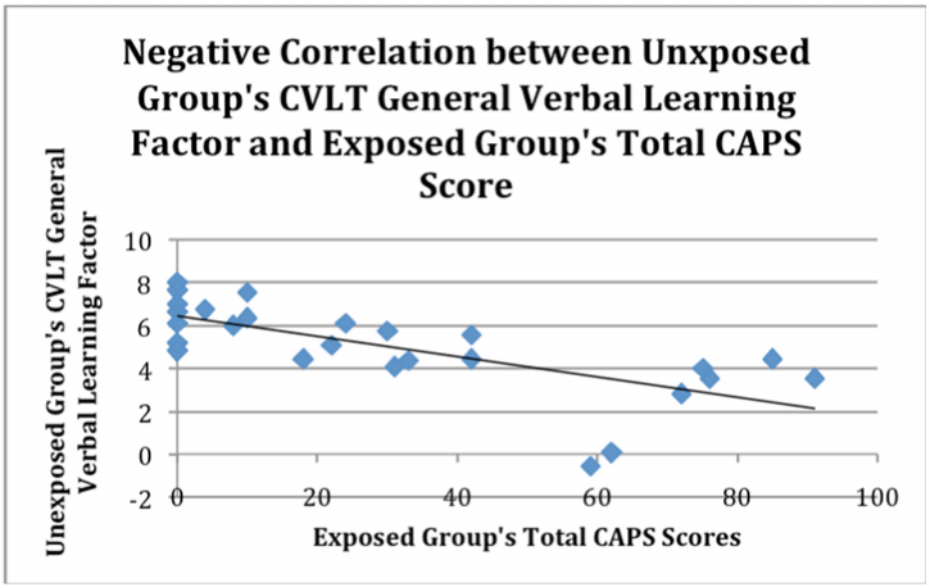

Figure 9

Finally, we found no significant correlations between the Exposed group's PTSD symptom severity (CAPS scores) and the Exposed individuals' verbal fluency nor between the Exposed individuals' PTSD symptom severity and Unexposed individuals' verbal fluency. We found no significant correlations between the Exposed group's PTSD symptom severity (CAPS scores) and the Exposed individuals' visuospatial copying ability, nor between the Exposed individuals' PTSD symptom severity (CAPS scores) and the Unexposed individuals' visuospatial copying ability (all *p*s > .217).

Hippocampal Volume and Symptom Severity. We found no significant correlation between the Exposed participants' PTSD symptom severity (CAPS scores) and whole-brain-volume-adjusted left and right hippocampal volumes There was also no correlation between the Exposed participants' PTSD symptom severity and Unexposed individuals' whole-brain-volume-adjusted left and right hippocampal volume (all *p*s > .247)

Hippocampal Function and Symptom Severity. We found no significant relationship between the Exposed group's PTSD symptom severity and the Exposed group's hippocampal rCMRglu. Additionally, no significant relationships were found between the Exposed group's PTSD symptom severity and the Exposed group's hippocampal OvF. We found no significant relationship between the Exposed group's PTSD symptom severity and the Unexposed group's hippocampal rCMRglu. Additionally, no significant associations were found between the Exposed group's symptom severity and the Unexposed group's hippocampal OvF (all *p*s >.268).

Neurocognitive Data and Hippocampal Volume. We found no significant relationship between neurocognitive measures and hippocampal volume (all *p*s >.148) across all subjects.

Neurocognitive Data and Hippocampal Function. Across all subjects, we found no significant relationship between declarative verbal memory and hippocampal rCMRglu, nor between declarative verbal memory and hippocampal OvF. We found no significant relationship across all subjects between verbal fluency and hippocampal rCMRglu, nor between verbal fluency and hippocampal OvF (all *p*s >.281).

We found a significant positive relationship across all subjects between visuospatial copying ability and hippocampal rCMRglu ($r(20) = .585$, $p = .007$; see Figure 10). We suspected that the observed correlation may have been driven by the highest performing subject. However, a significant positive relationship remained after exclusion of the highest performer, ($r(19) = .483$, $p = .036$; see Figure 11). In addition, we found no significant relationship between visuospatial copying ability and hippocampal OvF ($r(19) = -0.327$, $p = .09$).

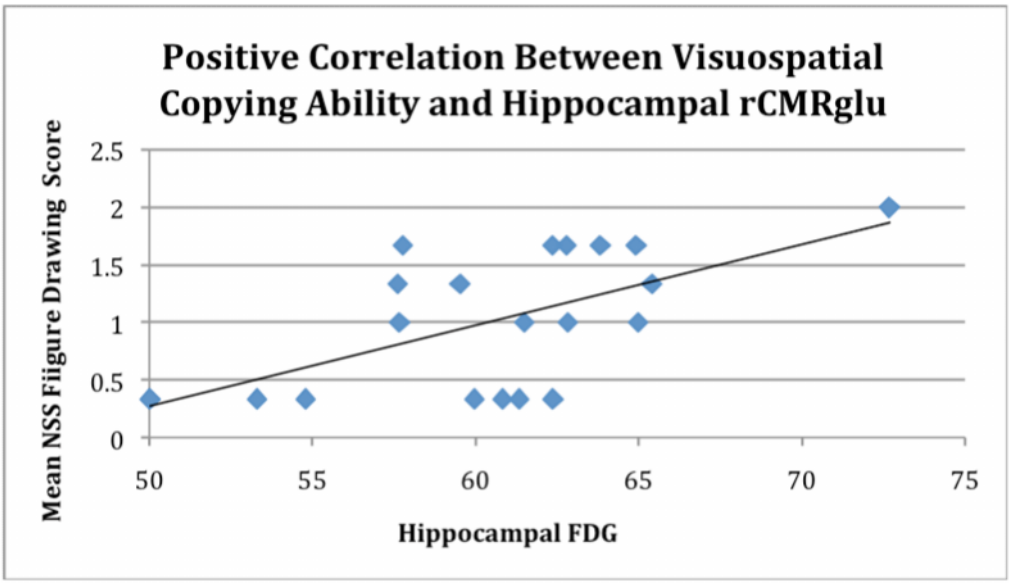

Figure 10

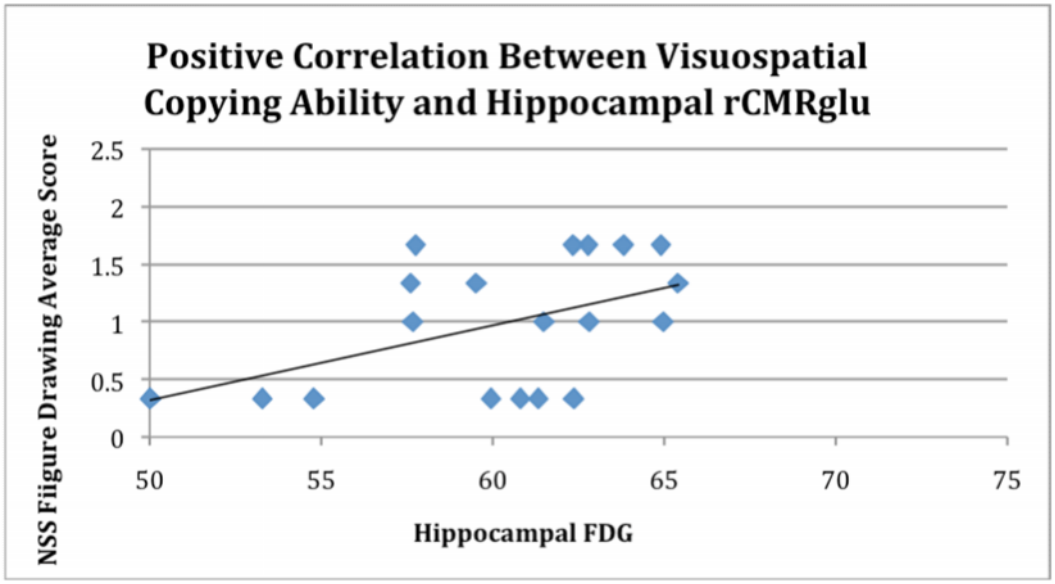

Figure 11. Correlational analysis between visuospatial copying ability and hippocampal rCMRglu excluding one subject (1 PC).

Discussion

This study sought to confirm neurocognitive deficits and hippocampal abnormalities in PTSD and to determine whether these abnormalities are familial vulnerability factors or acquired characteristics of PTSD using a sample of male monozygotic twins discordant for combat exposure. We also investigated whether any associations exist between cognitive deficits and hippocampal abnormalities. We hypothesized that impaired verbal declarative memory, poor visuospatial copying ability, and small hippocampal volume would reflect familial vulnerability factors for PTSD. We also predicted associations between PTSD symptom severity and all of the dependent variables, with the exception of verbal fluency and visuospatial copying ability.

We found a main effect of Diagnosis for the General Verbal Learning Factor and Composite score of the CVLT, suggesting that total declarative verbal learning and memory impairment is a familial vulnerability factor in PTSD. However, no significant group differences were found in analyses of measures of memory consolidation (i.e., Trial 5 Minus SDFR, Trial 5 Minus LDFR, Trial 5 Minus LDCR). This suggested that impaired initial encoding processes might have driven the observation of total memory impairment in PTSD twin pairs. In other words, fewer words recalled after delay in the PTSD pair compared to the Control twin pair appears to be due to poorer word acquisition during the first five trials of the CVLT in PTSD pairs. These findings are consistent with other studies that have reported deficits in initial learning, but not long-term memory retention (Diener et al., 2010; Golier, Harvey, Legge, & Yehuda, 2006;

Johnsen & Asbjornsen, 2009; Vasterling et al., 1998; Vasterling et al., 2002). Thus, our findings suggest that impaired initial encoding processes, rather than total overall learning per say, reflect a familial vulnerability factor for PTSD. In a study with a design identical to the present study, Gilbertson et al. (2006) also found verbal declarative memory impairment to be a familial vulnerability factor.

Studies of other anxiety disorders have also found declarative memory impairment. Airaksinen, Larsson, and Forsell (2005) administered a neutral free recall and cued recall memory test in population based samples comprising of participants affected by panic disorder, social phobia, generalized anxiety disorder, obsessive compulsive disorder (OCD), specific phobia, and healthy controls. They found that the use of semantic cues and the magnitude of gain between free and cued recall trials were similar amongst all groups. From these findings, the authors concluded that declarative memory impairments occur during initial encoding rather than retrieval. Other studies have also found memory deficits in specific anxiety disorders such as OCD (Savage et al., 2000; Zitterl et al., 2001), panic disorder (Lucas et al., 1991; Asmundson et al., 1995), and social phobia (Asmundson et al., 1995). As all anxiety disorders, including PTSD, share categorical symptoms of maintained high stress, it is possible that individuals with anxiety disorders share similar pathogenesis, symptomatology, and neurocognitive abnormalities. Thus, research investigating the origin of cognitive impairment in other types of anxiety disorders should be conducted to determine if

impairments may be shared familial vulnerability factors that manifest into different forms of the same condition.

Additionally, we found impaired inhibition and cognitive control in Exposed individuals compared to Unexposed individuals, reflecting an acquired characteristic of trauma exposure. Findings of impaired inhibition and cognitive control are consistent with Vasterling et al. (1998) and Johnsen & Asbjornsen (2009) who report an increased number of intrusive responses during recall in PTSD. Similarly, Gilbertson et al. (2006) also found significant disinhibition in Exposed individuals, which was interpreted as an adaptive response style during combat stress because hyperresponsivity may increase survival.

We did not find impairment on visuospatial copying ability and verbal fluency in PTSD, unlike Gurvits et al. (2002) and Uddo et al. (1993). The findings are not surprising as the PTSD literature has so far been inconsistent on this issue, with some studies reporting no differences in visuospatial function (Crowell, Kieffer, Siders, & Vanderploeg, 2002; Eren-Kocak et al., 2009; Gilbertson et al., 2001; Gilbertson et al., 2006; Zalewski, Thompson, & Gottesman, 1994) and one study reporting no differences in verbal fluency (Crowell et al., 2002). Only one previous study (Gurvits et al., 2002) used the Neurologic Soft Signs Figure Drawing Task as a measure of visuospatial function and found only a marginal association between figure copying ability and PTSD after adjusting for pre-trauma variables in correlational analyses. Additionally, Gurvits et al. analyzed visuospatial copying ability using the mean performance of

seven items. The current study's figure drawing task used only three of the original seven items, which may have reduced the task's ability to accurately assess visuospatial copying ability.

The inconsistency between the current study's lack of findings and some previous research concerning verbal fluency may be due differences in how verbal fluency was measured. Evidence from dementia research suggests that it is possible that variability in verbal fluency measures across studies account for inconsistency of results. Monsch et al. (1992) found that in patients with dementia of the Alzheimer type, categorical fluency (e.g., animal names) is superior to human name and letter (i.e. COWAT) fluency tests in discriminating impairment due to its dependence on an intact structure of semantic knowledge. Consistent with this hypothesis, Eren-Kocak et al. (2009) reported that participants with current and past PTSD provided significantly fewer words than healthy controls in a verbal fluency test using animal names. However, only participants with current PTSD (and not past PTSD) produced significantly fewer words in the verbal fluency test using human names. The authors reasoned that because human names are commonly used in daily life and thus are easier to remember than animal names, increasing difficulty makes deficits in participants with past PTSD more visible. Alternatively, Uddo et al. (1993) found significant verbal fluency impairment in PTSD participants requiring word production according to letters, but no impairment in the word production of animal names. The current study utilized the COWAT, a letter verbal fluency measure; which is thought to

not be as effective in discriminating impairment. Thus, the poorer discriminatory ability of the COWAT may have masked verbal fluency abnormalities that are actually present in our sample. Additional research comparing different verbal fluency measures in PTSD need to be conducted in order determine whether verbal fluency impairment is a characteristic of PTSD.

No significant differences in hippocampal volume were observed between groups. Gilbertson et al. (2002) previously reported diminished hippocampal volume to be a familial vulnerability factor for PTSD. Failure to replicate findings of main effect of Diagnosis in the current study may be due to the advancing age of our participants. In a literature review examining memory performance and hippocampal structure in aging populations, Golier et al. (2006) reported no association between hippocampal volume and PTSD in aging combat veterans or Holocaust survivors. It is possible that a floor effect, reflecting hippocampal volume diminution due to normal aging, is masking any differences between groups (Stoub et al., 2012). Additionally, Golier et al. (2005) studied aged combat veterans with and without PTSD and found no significant differences in hippocampal volume between PTSD and non-PTSD groups. However, the authors conducted additional analyses within the PTSD group and found that veterans who developed PTSD due to their first trauma exposure had significantly smaller hippocampal volumes than veterans who developed PTSD after their second traumatic experience or beyond. We do not have the data available to conduct similar analyses at this time, but it is possible that previous reports of hippocampal volume diminution

had a higher concentration of participants who developed PTSD immediately after first trauma exposure. Furthermore, it has been previously suggested that hippocampal abnormality is visible only in participants with high current PTSD symptom severity (CAPS score > 65; Felmingham et al., 2009; Gilbertson et al., 2007). Within our sample, only 3 PTSD twin pairs have CAPS > 65, and we therefore do not have enough statistical power to determine the significance of high current PTSD symptom severity on hippocampal volume.

Analysis of functional hippocampal data revealed no significant differences between groups. Molina et al. (2010) found reduced basal cerebral glucose metabolism in the right hippocampus at resting state in war veterans with chronic PTSD in comparison to war veterans without PTSD. Kim et al. (2012) found similar results in the left hippocampus of participants with recent PTSD due to sexual assault in comparison to healthy control subjects. Age may explain the lack of differences in basal cerebral glucose metabolism at resting state in the current study. Molina et al. and Kim et al. studied much younger samples than the current study (M = 37.5 years old across both studies vs. M = 62 years old). Similar to the discussion concerning hippocampal volume, the normal aging process may induce abnormal functioning in control comparison groups that present similarly to PTSD induced abnormalities. This may produce a floor effect that obscures any PTSD related abnormalities in older populations that are visible in studies examining younger populations. Furthermore, brain structural and functional data was gathered an average of 8 years prior to

neurocognitive data collection. The large gap between the two assessments may account for the lack of significant associations between neurocognitive and hippocampal abnormalities.

No other study has specifically investigated hippocampal activation by measuring the difference of BOLD signal between the recognition phases of neutral "Old" words and resting state. The lack of significant differences may be because the cognitive task is based on memory recognition. Memory recognition impairment has not been observed in previous research. Furthermore, the current study found no impairment in recognition, but in initial encoding. (Diener et al., 2010; Golier et al., 2006; Johnsen & Asbjornsen, 2009; Vasterling et al., 1998; Vasterling et al., 2002). Thus, it would be worthwhile to repeat the study of hippocampal activation using a cognitive task that involves initial recall.

Correlational analyses indicate a direct relationship between PTSD symptom severity in the Exposed group and verbal declarative memory impairment in the Exposed and Unexposed group. Our findings are consistent with Gilbertson et al. (2002), who found that the overall verbal memory measure of both Exposed groups and Unexposed groups to be predictive of the combat-exposed group's PTSD symptom severity. Our finding that the unexposed co-twins' verbal memory performance is predictive of the combat exposed twins' PTSD symptom severity supports the repeated measures ANOVA finding that indicates verbal memory impairment as a familial vulnerability factor.

No significant correlations were found between PTSD symptom severity and measures of verbal fluency, visuospatial copying ability, hippocampal volume, basal cerebral glucose metabolism, and activation during a recognition task. These results are consistent with analyses of variance that found no significant differences between groups for the aforementioned measures.

Correlational analyses between cognitive measures and hippocampal regional basal cerebral glucose metabolism found a significant positive correlation between visuospatial copying ability and hippocampal rCMRglu. No previous studies have determined an association between visuospatial copying ability and hippocampal rCMRglu. As neither variable showed significant differences between groups nor were associated with PTSD symptom severity, it is likely that the correlation is representative of a factor not characteristic of PTSD or trauma exposure. More research examining visuospatial ability and hippocampal rCMRglu is needed in order to determine whether the association between the two variables is a characteristic of PTSD. Correlational analyses between cognitive measures and hippocampal volume and cognitive measures and hippocampal activation showed no significant associations.

A general limitation to cognitive and brain studies in PTSD is the significantly higher rates of alcohol and substance abuse and comorbidity, especially major depressive disorder, among participants with PTSD in comparison to controls. In the current study, we statistically controlled for potential confounders and determined that all significant findings remained significant after adjustment for covariates. It is possible

that our nonsignificant findings were due to lack of statistical power, and additional group differences might have been found if a larger sample size had been used. However, due to the nature of the identical twin paradigm, few people were qualified to participate in our study, thereby limiting our ability to increase our power with a larger sample.

Additionally, the current study's findings are limited to combat-exposed adults with chronic PTSD. Studies that have included participants with recent onset PTSD (Carrion et al., 2001; De et al., 1999; De, Hall, Boring, Frustaci, & Moritz, 2001) or children with PTSD (Bonne, 2001) have provided results inconsistent with the general trends observed in adults with chronic PTSD. Furthermore, the current study's sample is composed of monozygotic twins only. Factors unique to identical twins, such as the splitting of one zygote during embryo formation, may contribute to differences in cognitive performance and brain structure and function. It should also be noted that in the absence of dizygotic twins, the twin case-control design cannot differentiate genetic and environmental factors of familial vulnerability. Finally, current medication use, but not past treatment history, has been accounted for in this study. It is possible that previous treatment of PTSD, via a combination of pharmacological and psychotherapeutic interventions, may have reduced the presence of cognitive impairments and brain abnormalities that were subject to the effects of PTSD symptomatology. For example, Vermetten et al. (2003) found that long-term treatment

with paroxetine improved declarative memory deficits and increased hippocampal volumes in PTSD.

Conclusion

The finding of verbal declarative memory impairment, specifically in initial encoding, support conclusions that specific cognitive processes associated with PTSD represent familial factors that contribute to the likelihood for the development of PTSD after exposure to trauma. The lack of significant group differences in analyses on the dependent variables of verbal fluency, visuospatial copying ability, hippocampal volume, and hippocampal function suggests that these measures are not associated with PTSD or trauma exposure. Previous studies have suggested that the presence of PTSD characteristic may be mutable and subject to environmental factors. Thus, possible explanations for lack of findings include the contributions for progressive aging and symptom severity reduction. To determine the influence of age and symptom severity, researchers should conduct longitudinal studies the examine long-term PTSD presentation in samples with chronic, severe PTSD in comparison to samples with low PTSD symptom severity or samples with past PTSD. The current study's finding that initial encoding impairment is a familial vulnerability factor for chronic PTSD is beneficial to the development of preventative screening assessments for environments that are high risk for trauma exposure.

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