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Dissociation Between Working Memory Performance and Proactive Interference Control in Post-Traumatic Stress Disorder

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Abstract

Deficits in working memory (WM) and cognitive control processes have been reported in post-traumatic stress disorder (PTSD), in addition to clinical symptoms such as hypervigilance, re-experiencing, and avoidance of trauma reminders. Given the uncontrollable nature of intrusive memories, an important question is whether PTSD is associated with altered control of interference in WM. Some studies also suggest that episodic memory shows a material-specific dissociation in PTSD, with greater impairments in verbal memory and relative sparing of nonverbal memory. It is unclear whether this dissociation applies to WM, as no studies have used identical task parameters across material. Here we tested 29 combat Veterans with PTSD and 29 age-matched control Veterans on a recent probes WM task with words and visual patterns in separate blocks. Participants studied four-item sets, followed by a probe stimulus that had been presented in the previous set (recent probe) or not (nonrecent probe). Participants with PTSD made more errors than controls, and this decrement was similar for verbal and visual stimuli. Proactive interference from items recently presented, but no longer relevant, was not significantly different in the PTSD group and showed no relationship to re-experiencing symptom severity. These results demonstrate that PTSD is not reliably associated with increased intrusions of irrelevant representations into WM when non-emotional stimuli are used. Future studies that use trauma-related material may provide insight into the flashbacks and intrusive thoughts that plague those with PTSD.

Keywords

PTSD; verbal working memory; visual working memory; cognitive control; interference resolution

Introduction

Post-traumatic stress disorder (PTSD) is a serious psychiatric illness that can occur after experiencing or witnessing traumatic events. Symptoms include hyperarousal, negative affect, avoidance, and intrusive memories of the traumatic incident (DSM-5, American Psychiatric Association, 2013). In addition to these disturbances in mood and emotion, decrements in cognitive function are often reported (Vasterling et al., 1998; Gilbertson et al.,

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2001; Koso & Hanson, 2006; Nelson et al., 2009; but see Crowell et al., 2002; Neylan et al., 2004; Brenner et al., 2010). These alterations can go beyond exaggerated attentional bias to threat (Ashley et al., 2013) and impaired fear memories (Hayes et al., 2012) to include the processing of non-emotional information. Among the most consistent cognitive deficits in PTSD are impairments in memory and executive control functions (Vasterling et al., 2009; Polak et al., 2012). A recent meta-analysis of 60 studies found that verbal learning and memory, speed of processing, and attention/working memory showed the largest effect sizes (Scott et al., 2015).

Deficits in episodic memory have been most often observed using standardized measures to assess list learning and recall (Bremner et al., 1993; Yehuda et al., 1995; Scheiner et al., 2014). One review suggested that verbal memory is consistently impaired in PTSD (Johnsen & Asbjørnsen, 2008). Dissociations between verbal and visual memory have also been reported, with impaired performance on verbal memory tasks but intact (or relatively less impaired) performance on visual tasks (Bremner et al., 1993, 1995; Vasterling et al., 2002; Eren-Koçak et al., 2009; Woodward et al., 2009). But not all studies are in alignment, either because both forms of memory were impaired (Uddo et al., 1993; Vasterling et al., 1998; Gilbertson et al., 2001; Jelinek et al., 2006; Grigorovich et al., 2013) or both were intact (Zalewski et al., 1994; Stein et al., 1999). However, a meta-analysis by Brewin and colleagues found a larger effect size for the decrement in verbal memory, compared to visual memory (Brewin et al., 2007). This was true for both immediate and delayed memory.

The strength of this dissociation is limited by the fact that few studies have administered comparable tests across material within the same population. In one study (Sozda et al., 2014), learning and memory performance was impaired on the Hopkins Verbal Learning Test (HVLT-R) but not on the Brief Visuospatial Memory Test (BVMT-R). This was more closely related to depression severity, however, and not to PTSD. In contrast, Jelinek et al. (2006) found that participants with PTSD showed a similar degree of impairment for both verbal and visual stimuli on the Picture Word Memory Test, which is even more similar in structure than the HVLT-R and the BVMT-R.

Working memory (WM) is a key aspect of efficient cognitive functioning that is often affected in PTSD (Scott et al., 2015). Is there any evidence of a dissociation between verbal and visual WM, especially in relation to symptom severity? Closer examination of this issue – including at the level of individual differences – could be informative in studies of treatment response to different psychotherapies (e.g., Haaland et al., 2016). The largest meta-analysis to date yielded a medium effect size ($d = -0.50$) for the combined construct of attention/working memory but did not differentiate between verbal and visual WM (Scott et al., 2015). Verbal WM is more commonly examined, typically using standardized tests such as digit span. Findings here are mixed, with impaired (Jenkins et al., 2000; Gilbertson et al., 2001; Vasterling et al., 2002; El-Hage et al., 2006; Tian et al., 2014; Stricker et al., 2015) and intact (Uddo et al., 1993; Zalewski et al., 1994; Neylan et al., 2004; Moores et al., 2008; Scheiner et al., 2014; Wrocklage et al., 2016) performance both reported.

In contrast to the literature on episodic memory, it is *visual* WM that might be more consistently impaired in PTSD (Uddo et al., 1993; Morey et al., 2009; Zhang et al., 2013;

Neipert et al., 2014; Olff et al., 2014), although sparing has been reported (Neylan et al., 2004). In studies that have assessed both verbal and visual WM, one found a visual deficit but verbal intact (Uddo et al., 1993), another found both intact (Neylan et al., 2004), a third reported that both were impaired (Falconer et al., 2008b). Besides the conflicting results in these studies, another issue is that the verbal and nonverbal WM tests were not closely matched in structure and format (Wilde et al., 2004). Missing from the literature are experiments that look for material-specific deficits in WM using identical task designs. The present study employed an item recognition WM task with words and visual patterns in separate blocks to address this question.

Our previous work demonstrated that PTSD patients showed a verbal working memory deficit when executive control functions were more heavily taxed (Honzel et al., 2014). That study examined WM for letters maintained across a delay that was either unfilled, or filled with a challenging flanker interference task. PTSD patients were slightly less accurate than controls on the unfilled (single task) version, but impaired to a disproportionate extent on the dual task version. Furthermore, the size of the event-related potential (ERP) old/new effect, a neural index of memory retrieval processes, was unaltered in the patients for the single task version but decreased for the dual task. Taken together, these results suggested that the WM impairment was linked to limitations in executive control resources (Honzel et al., 2014).

Another crucial executive control function is the ability to inhibit previously activated, but currently irrelevant, stimulus representations in WM (Nee et al., 2013). The capacity to overcome interference in WM could be relevant in the context of the re-experiencing symptoms of PTSD. Is the inability to discard or suppress intrusive memories related to poor interference control? Verwoerd et al. (2009) found a relationship between memory interference effects and the self-reported frequency of intrusive memories in a group of undergraduates. This finding provides a rationale for looking at the specific relationship between WM interference resolution and the re-experiencing symptom cluster. We did this by using a task that manipulated the presence or absence of interfering items. In this initial study, we focused on WM and interference control in PTSD using neutral material to provide a knowledge base for subsequent investigations of emotional and trauma-relevant material.

In the recent probes task (Monsell, 1978), the participant studies a set of items (e.g., letters) to maintain in working memory. After a brief delay, a probe stimulus is presented, and the participant indicates whether the probe was in the memory set by pressing a “yes” or “no” button (see Fig. 1). The recency of the probe item is manipulated, with half of the trials containing a recent probe (presented on the immediately preceding trial) and half a non-recent probe (not presented on the previous trial). Reaction times (RTs) are slower on “no” trials for the recent probe condition, when the subject must inhibit or suppress information that is no longer relevant, relative to RTs on non-recent “no” trials. This proactive interference (PI) effect is consistently large across studies (Jonides & Nee, 2006). To our knowledge, no studies have looked at subsequent trial PI effects in working memory for individuals with PTSD.

In the current experiment, we examined whether PTSD is associated with relatively worse verbal or visual WM, and with a greater PI effect. The participants were combat Veterans with PTSD and age-matched control Veterans. Our previous results indicated this patient population is impaired on some cognitive control tasks, with more errors of commission and more variable RTs in a Go/NoGo task (Swick et al., 2012, 2013). However, other cognitive control functions are preserved, including error monitoring and interference resolution in the flanker task (Swick et al., 2015). Here we predicted that the PTSD group: (1) would be likely to show lower WM accuracy overall (Scott et al., 2015); (2) would show more of an impairment in verbal than visual WM (Brewin et al., 2007), although the current literature is unclear on this point; and (3) would show greater PI, which may be related to the severity of re-experiencing symptoms (Verwoerd et al., 2009).

Materials and Methods

Participants

Participants were 31 Iraq and Afghanistan combat Veterans diagnosed with combat-related PTSD (30 male) and 30 age-matched control Veterans (28 male). The data from two participants with PTSD and one control were excluded for extreme values (see below), so the reported results include 29 in the PTSD group and 29 in the control group. PTSD diagnosis was based on the Clinician-Administered PTSD Scale (CAPS) or semi-structured clinical interview using DSM-IV criteria. The majority of individuals with PTSD were recruited from Mental Health, TBI, and PTSD specialty clinics. Nearly half of the Veterans without PTSD were recruited from other clinics (such as the Allergy clinic). We also placed advertisements and participated in Veterans' outreach activities to recruit individuals with and without PTSD. The groups did not differ significantly in age [$t(56) = 1.36$, $p=0.18$] but controls had more education [$t(56) = 3.58$, $p<0.001$]. Since this is a substantial difference, we include further analyses suggesting that years of education did not significantly influence the results, and also report on education-matched subgroups. See Table 1 for details on demographic data.

Participants with a history of other psychological disorders, as based on review of clinical records, were excluded, with the exception of major depression in PTSD patients. None of the enrolled subjects reported significant substance abuse as assessed by a phone screen and in-person interview. Participants were questioned on the use, amount, and frequency of alcohol and recreational drugs. Additionally, participants were asked about whether they had ever been treated for alcohol abuse or drug dependence in the past. Those actively abusing alcohol (more than 3 drinks per night or 12 drinks per week) or cannabis (using more than 2–3 times per week) were excluded. In addition, those actively using cocaine, crystal methamphetamine, heroin, or other recreational substances, regardless of frequency or amount, were excluded. Among those with PTSD, 16 were taking prescribed psychotropic medications and 13 were not. There was no difference in performance between these subgroups (see Supplementary Material).

All of the Veterans with PTSD had been deployed to Iraq or Afghanistan, but only 15 control Veterans had been deployed. Importantly, 11 of these controls were exposed to combat in Iraq or Afghanistan. The PTSD group was an average of 4.1 years post-service and the combat-exposed controls 4.7 years post-service (not significantly different, p=.79). Separate analyses including controls with and without exposure to combat trauma are reported in the Supplementary Materials. In brief, error rates, material specificity, and PI effects were not significantly different between trauma-exposed and non-exposed controls, so we collapse across them in the text.

Twenty-one of the participants with PTSD reported a history consistent with mild TBI (mTBI); however, none reported a loss of consciousness (LOC) greater than 1–2 minutes or any other pre-existing neurological condition. A semi-structured clinical interview was conducted by a neurologist, and mTBI was diagnosed based on patient self-report of the following criteria from the VA/DoD Clinical Practice Guidelines – LOC 30 min or less or altered mental status (e.g., feeling dazed, disoriented, or confused), with post-traumatic amnesia less than 24 hrs (Management of Concussion/mTBI Working Group, 2009).

Three participants were extreme outliers (two patients, one control). The RTs for one patient were 5–10 standard deviations (SD) slower than the mean of the other patients, so this individual was excluded from further analysis. Two other participants were excluded for excessively high error rates. Error rates for one patient were 5.2 SD higher than the other patients for verbal, 3.0 SD higher for visual. Error rates for one control were 6.2 SD higher than the other controls for verbal, 3.9 SD higher for visual. Therefore, statistical results are reported for 29 patients and 29 controls.

The Institutional Review Board of the VA Northern California Health Care System approved the experimental protocol, and all participants gave informed consent prior to beginning the experiment. They were paid for transportation plus $20/hour for their participation.

Stimuli

Similar to the study of Badre and Wagner (2005), the verbal stimuli were 20 five letter abstract nouns (Fig. 2a). The words had a mean log frequency of 10.374 using the Hyperspace Analogue Language (HAL) frequency norms [1] from the online English Lexicon Project (ELP) Database (Balota et al., 2007), and mean concreteness rating of 313 from the MRC Psycholinguistic Database (Coltheart, 1981). An array of four words was presented in lower case in the study phase of each trial. In the test phase, a single probe stimulus was presented in upper case. The visual stimuli were 20 shapes and symbols from the MapInfo Cartographic, Bookshelf Symbol 7, and Marlett fonts (Fig. 2b). The visual study arrays were arranged in the same manner as the verbal arrays. The visual stimuli were similar in style to individual stimuli in the Brief Visuospatial Memory Test-Revised (BVMT-R; Benedict, 1997), a standardized test of visual memory often paired with the Hopkins Verbal Learning Test (HVLT-R; Brandt & Benedict, 2001). Performance was significantly worse for these visual patterns in the present study, relative to the abstract words, even though these patterns could be encoded using a verbal strategy. [2]

[1]The mean word frequency was 126 based on the Kučera and Francis (1967) norms, obtained from the ELP online database.
[2]In early pilot studies, performance on the verbal and visual tasks was better matched. Equating task difficulty has been a problem in comparing verbal vs. visual PI (e.g., Mecklinger et al., 2003; Badre & Wagner, 2005), with overall worse performance for visual stimuli. See Hartshorne (2008) for discussion.

Procedure

The experimental design was a modified version of the recent probes task (Thompson-Schill et al., 2002), with abstract words and visual patterns as the stimulus materials (instead of letters). Participants were required to judge whether a test probe was a member of a set of studied items. At the beginning of each trial, a "Get Ready" cue was presented for 1,000 msec. This was followed by a cross in the center of the screen. After 500 msec, the study set was presented: a visual display of four words or four visual patterns arranged above, below, to the left, and to the right of a central fixation cross (Fig. 1). The study set remained on the screen for 3,000 msec, followed by a 2,000-msec delay. Following this delay, the probe (i.e., a single word or pattern) appeared in the central location, and the subject was instructed to indicate whether that probe was a member of the current study set or not. Half of the trials presented probes that were members of the current set (positive trials, which required a "yes" response), and the other half presented probes that were not members of the current set (negative trials, which required a "no" response). For both positive and negative trial types, half contained probe items that were members of the previous study set (recent trials), and half contained probes that were not members of the previous two study sets (non-recent trials). For all trials, two of the four stimuli in the study set were repeated from the previous trial, so that repetition of items in the study set was not confounded with trial type. Verbal and visual stimuli were presented in separate, alternating blocks of 48 trials each. There was a total of four verbal blocks (n=192 trials) and four visual blocks (n=192 trials).

Questionnaires

All participants completed the PTSD Checklist, Military Version (PCL-M) for DSM-IV and the Beck Depression Inventory (BDI). The PCL-M is a 17-item self-report questionnaire that is used to establish the presence of PTSD symptoms in combat-exposed Veterans (Blanchard, et al., 1996). It has three symptom clusters: re-experiencing, avoidance/numbing, and hyperarousal. Symptoms are rated on a 1 to 5 scale. A total score of 50 is used as a cutoff for PTSD diagnosis in Veteran populations (Forbes et al., 2001). The BDI is one of the most commonly used self-report screens for major depressive disorder and has been validated with well-established psychometric properties (Beck et al., 1988). As expected, the two groups showed highly divergent scores on these questionnaires (Table 1), indicating greater levels of PTSD and depression symptoms in the patients. The PCL-M for one control was incomplete, so that individual was excluded from the correlational analyses involving PCL-M scores. The severity of self-reported depression symptoms was not correlated with WM performance measures (see Supplementary Material).

Statistical Analysis

The first two trials of each block were excluded, because they could not be classified according to trial history. Median RTs on correct trials and accuracy/error rates were entered into repeated measures ANOVAs with factors of Probe (positive, negative), Recency (recent, non-recent), Material (verbal, visual) and Group (PTSD, controls). The Probe × Recency interaction reflects the proactive interference (PI) effect: longer RTs and lower accuracy on recent negative trials compared to nonrecent negative trials. This specific metric, the PI difference score (recent negative – non-recent negative) was calculated separately for the verbal and visual tasks (for both RT and accuracy), and correlated with re-experiencing ratings using Spearman correlations.

Results

Reaction Times

PTSD patients and controls did not differ in their overall speed of responding [F(1,56)=0.08, p=.78, η_p^2 =.001]. Conversely, the main effects of Probe [F(1,56)=16.13, p=.0002, η_p^2 =.224], Recency [F(1,56)=107.73, p<.0001, η_p^2 =.658], and Material [F(1,56)=9.17, p=.004, η_p^2 =.141] were all significant. Participants were slower when the probe was not in the study set (i.e., on negative trials), when the probe had been presented recently (i.e., on recent trials), and when the probe was visual compared to verbal (Table 2). The effect of Recency was significant for negative probes [F(1,56)=188.19, p<.0001, η_p^2 =.771], but not for positive probes [F(1,56)=0.15, p=.70, η_p^2 =.003]. Importantly, the groups were comparably slowed on negative trials when the probe was recent, relative to when it was non-recent (Fig. 3). Thus, the expected Probe × Recency interaction [F(1,56)=199.25, p<.0001, η_p^2 =.781], which indexes PI, did not interact further with Group [F(1,56)=0.24, p=.63, η_p^2 =.004]. This finding suggests that previously relevant stimuli did not intrude into WM to a greater extent in the patients.

Errors

The PTSD patients made significantly more errors than controls, as revealed by the main effect of Group [F(1,56)=8.60, p=.005, η_p^2 =.133]. This decrement in WM accuracy was not significantly different for verbal and visual stimuli, however, as there was no interaction with Material [F(1,56)=1.34, p=.25, η_p^2 =.023] (Fig. 4, bottom). The main effects of Probe [F(1,56)=11.35, p=.0002, η_p^2 =.169], Recency [F(1,56)=25.94, p<.0001, η_p^2 =.317], and Material [F(1,56)=53.25, p<.0001, η_p^2 =.487] were all significant. Error rates were higher on positive trials (misses) compared to negative trials (false alarms), on recent compared to non-recent trials, and on visual compared to verbal trials (Table 2). Although participants with PTSD were less accurate overall, they did not show significantly greater interference. The Probe × Recency interaction [F(1,56)=79.90, p<.0001, η_p^2 =.588] did not interact further with Group [F(1,56)=2.02, p=.16, η_p^2 =.035]. The lack of an interaction with group suggests the PI effect was not significantly different in patients and controls.

Following up on the Probe × Recency interaction, participants were less accurate for negative probes on recent trials compared to non-recent [F(1,56)=109.17, p<.0001, η_p^2 =.661], but they were also *more* accurate for positive probes on recent trials [F(1,56)=6.59, p=.01, η_p^2 =.105]. In other words, the false alarm rate was higher on recent trials, while the rate of misses was lower – meaning that participants were more inclined to respond "yes" on recent trials.

Results are also reported for the signal detection theory measure of sensitivity (d'). Hit rates of 1 and false alarm rates of 0 were adjusted using the standard method of Macmillan and Kaplan (1985). Similar to the findings for accuracy, ANOVA for d' revealed that participants with PTSD showed worse performance than controls [F(1,56)=8.57, p=.005, η_p^2

=.133], with no differential deficit for verbal vs. visual stimuli [Material × Group: F(1,56)=0.006, p=.94, η_p^2 =.000] (Fig. 5). Results for bias (*C*) are presented in the Data Supplement.

Effects of Stimulus Material

As mentioned, participants were slower (1002 ms vs. 940 ms) and made more errors (11.5% vs. 5.2%) in blocks with visual stimuli, relative to verbal stimuli. For RTs, there was a modest Material × Group interaction [F(1,56)=6.21, p=.02, η_p^2 =.100], which reflected slower responses for visual vs. verbal stimuli in the controls (1019 vs. 906 ms), but not the participants with PTSD (984 vs. 973 ms). Finally, the proactive interference effect on negative trials (recent – non-recent) was greater for visual than verbal stimuli, both for RTs [F(1,56)=5.02, p=.03, η_p^2 =.082] (Fig. 4, top) and for errors [F(1,56)=7.45, p=.008, η_p^2 =.117] (Fig. 4, middle). Since further interactions between Material and other variables (Probe, Recency) are of secondary interest, these are described in the Supplementary Material.

Correlation Between Re-Experiencing Symptoms and Proactive Interference

To test the hypothesized relationship between PI and intrusive symptoms (Verwoerd et al., 2009), we examined the correlation between scores on the re-experiencing subscale of the PCL-M and proactive interference, using Spearman Rank Correlations (corrected at p<.005). There were no significant correlations between the severity of re-experiencing symptoms and the RT measure of PI for verbal (rho=−.088, p=.51) or visual stimuli (rho=−.217, p=.10). Nor were there correlations between re-experiencing scores and the error measure of PI for either verbal (rho=.004, p=.97) or visual stimuli (rho=.259, p=.05). Thus, the ability to overcome interference in WM was unrelated to symptom severity.

Bayesian Analysis

Since there were no significant differences between groups for proactive interference or the verbal/visual comparison (as hypothesized), we wanted to determine how confident we could be in these non-significant findings (Dienes, 2014). Therefore, we quantified the strength of evidence for the major results in Figs. 4 and 5 using Bayesian hypothesis tests. Bayes Factors (BF_{01}) were calculated using JASP statistical software version 0.7.5.5 (Love et al., 2015). We report the Scaled JZS Bayes Factors in Table 3, along with the mean values for error rates, RT interference, and error interference, separately for verbal and visual material. The alternate hypothesis (H_1) was that Controls < Patients in these cases. For d', the alternate hypothesis specified that Controls > Patients. $BF_{01} < 1$ indicates that the result is more likely to occur under H_1 than H_0 (the null hypothesis), and $BF_{01} > 1$ indicates the result is more likely under H_0 than H_1 (Wagenmakers et al., 2011). For example, BF_{01} =0.160 for errors in the visual WM task means that H_1 is 6.250 times more likely than H_0 (1/.160). This provides moderate (Love et al., 2015) or positive evidence (Wagenmakers, 2007) in favor of the hypothesized WM deficit in the patients. On the other hand, BF_{01} =9.467 for RT interference in the visual task means that H_0 is 9.467 times more likely than H_1, which provides positive evidence that the result is more likely to occur under the null hypothesis. The BF_{01} values for error interference, however, were both close to 1, which does not allow us to conclude beyond weak evidence either way.

To quantify the strength of evidence against a Material × Group interaction for d', we ran a JZS Bayes Factor ANOVA (Love et al, 2015; Morey & Rouder, 2015; Rouder et al. 2012) with default prior scales. This revealed that the main effects model was preferred to the interaction model with BF_{01} of 3.643. The data provide positive evidence against the hypothesis that verbal WM is impaired to a greater extent than visual WM in the PTSD group.

Results from Bayesian Pearson correlation analyses provided positive evidence against a relationship between the severity of re-experiencing symptoms and PI (BF_{01} between 9.877 and 14.277), with the exception of re-experiencing and the error measure of PI for visual material, where evidence in favor of H_1 was weak (BF_{01} =0.745). We also tested for correlations between re-experiencing and error rate on the verbal WM blocks (BF_{01} =0.281) and the visual blocks (BF_{01} =0.255), and found positive evidence in favor of a relationship. This finding suggests that participants with more severe symptoms showed lower WM performance. The Fisher r-to-z transformation demonstrated that the correlations for verbal (.293) and visual stimuli (.299) were not significantly different from each other (p=0.98). Thus, while overall error rates were correlated with intrusion symptoms, interference control was not.

Effects of Education

To examine whether education level could have influenced the results, we omitted the seven PTSD patients with 12–13 years of education and the six controls with greater than 16 years. Mean education for the remaining 22 patients was well-matched to the 23 participants in this control subgroup (14.36 yrs vs. 14.61 yrs) [t(43) = 0.79, p=0.43]. The error rate was still higher in this group of patients [F(1,43)= 6.45, p=.01], and the Material × Group interaction effect was not significant [F(1,43)= 2.18, p=.15]. The PI effect was not significantly different for RT [F(1,43)= 1.30, p=.26] or for errors [F(1,43)= 1.08, p=.30].

We also looked for any relationship between years of education and performance measures in the entire population of 58 participants using Spearman Rank Correlations (corrected at p<.005). There were no significant correlations between years of education and error rate for verbal (rho=−.214, p=.11) or visual stimuli (rho=−.181, p=.17). Likewise, PI for errors did not show significant correlations for verbal (rho=−.111, p=.40) or visual stimuli (rho=−.180, p=.17). PI for reaction times showed *positive* correlations with education for verbal (rho=.289, p=.03) and visual stimuli (rho=.240, p=.07), although neither of these reached significance.

Discussion

Combat Veterans with PTSD showed less accurate performance on a recent probes working memory task, compared to a mixed group of combat-exposed and non-exposed control Veterans. The deficit in WM accuracy was independent of stimulus material, with a similar decrement on blocks with verbal or visual stimuli. Proactive interference from items previously presented, but no longer relevant, was not significantly different in those with PTSD and showed no relationship to the severity of re-experiencing symptoms. These findings suggest that PTSD is not associated with increased intrusion of irrelevant representations into WM when simple, non-emotional stimuli are used. The results also add to the neuropsychological literature indicating that executive components of WM can be dissociated from WM maintenance (Thompson-Schill et al., 2002; Kaller et al., 2014).

Verbal vs. Visual Working Memory

Contrary to our original prediction, there were no significant differences in the degree of WM impairment for verbal and visual material in the patients. One basis for this prediction was a meta-analysis of 27 studies of immediate and delayed memory for neutral stimuli in PTSD, which found greater impairments for verbal than visual stimuli (Brewin et al., 2007). The dual representation theory, a cognitive model of how traumatic experiences are represented in PTSD, posits that verbally accessible memories of trauma are separate from non-conscious representations of the trauma, which are nonverbal in nature (Brewin et al., 1996). The theory predicts that a weakness in verbal memory allows flashbacks, which are represented by the intact visual-spatial memory system, to continue unabated. Typically, the verbal memory system can inhibit involuntary intrusions of visual imagery, but PTSD may be associated with a poorly functioning verbal system, which becomes less effective at inhibition (Brewin et al., 2007).

Whether WM would behave in the same way was an open question, but dual representation theory does not make direct predictions for WM. In fact, our review of the literature suggested that *visual* WM is more consistently impaired in PTSD (which was initially unexpected). A major issue in these earlier studies, however, is the difference in task requirements across the verbal and visual assessments. Our experimental design allowed comparison of verbal and visual WM performance under identical task conditions. Although we tried to match performance across stimulus type, the visual stimuli were more difficult for both groups to remember. The geometric shapes and patterns were unfamiliar, in contrast to the abstract words that were used as stimuli. This discrepancy was similar to what was reported in previous studies (Mecklinger et al. 2003; Badre & Wagner, 2005; Hartshorne, 2008). Critically, however, the degree of impairment associated with PTSD was not statistically different for verbal and visual material, nor was there a differential correlation between error rates and re-experiencing scores.

The relationship between material-specific WM stores and clinical symptoms is an important area of research. Trauma memories retrieved from a long-term store are brought to conscious awareness and maintained in working memory. Baddeley's (2000) model predicts that separate WM systems would support the maintenance of verbal narratives and flashback-related visual imagery once retrieved from long-term memory (Baddeley & Andrade, 2000; Brewin, 2014). Study of an involuntary phenomenon is challenging, but laboratory tests can assess the modality-specific nature of intrusive memories once they are retrieved. A dual task experiment demonstrated the importance of visuospatial WM for the ability to generate trauma images (Lilley et al., 2009). Participants with PTSD were asked to recall trauma images while performing tasks recruiting verbal WM (counting), visuospatial WM (eye movements), or no task. Participants gave lower ratings on the vividness and emotionality of trauma images recalled during the visuospatial dual task than in the verbal or no-task conditions (Lilley et al., 2009). This suggests that the visual WM system is critical for supporting the elaborative processing of trauma images.

A large prospective study of active duty personnel found that soldiers with poor short-term visual memory (immediate recall) before deployment were more likely to have worse PTSD symptoms after deployment (Marx et al., 2009). Pre-deployment measures of immediate and delayed verbal memory did not show the same relationship to post-deployment symptom severity (with the caveat that the tasks were not matched across material). This finding was not predicted by dual representation theory, since poor verbal memory is considered a risk factor for the development of PTSD. Marx et al. (2009) did see a negative correlation between post-deployment verbal learning and PCL scores, in line with other cross-sectional studies. Thus, it's also possible that trauma exposure and subsequent post-traumatic stress can result in verbal learning and memory impairments (as reviewed in Brewin et al., 2007).

In sum, the present study is the first to test verbal and visual WM using identical task requirements in participants with PTSD. Therefore, the lack of a material-specific deficit in WM cannot be due to differences in task demands. Different results might be obtained if the stimuli were combat-related words and scenes of combat. The neutral stimuli used in the present experiment are not related to the types of intrusions that cause significant distress in PTSD. The trauma-relevance of the material could be a critical element for finding the verbal/visual dissociation, a question that could be addressed in future experiments.

The general finding of less accurate WM performance in the PTSD patients agrees with many previous studies that used verbal (Jenkins et al., 2000; Gilbertson et al., 2001; Vasterling et al., 2002; El-Hage et al., 2006; Falconer et al., 2008b; Tian et al., 2014; Newsome et al., 2015) and visual (Jenkins et al., 2000; Gilbertson et al., 2001; Vasterling et al., 2002; El-Hage et al., 2006; Falconer et al., 2008b; Tian et al., 2014) stimuli. Nevertheless, the cross-sectional nature of these studies precludes assumptions about the direction of causality. Pre-existing weaknesses in cognitive function may increase the risk of PTSD (DiGangi et al., 2013), rather than post-traumatic symptoms causing the cognitive deficits. On the other hand, a recent prospective study (n=230) suggested that pre-deployment cognitive function was not associated with post-deployment traumatic stress symptoms (Dretsch et al., 2016). Additional research is needed, but it could be that the connection between PTSD and cognitive function is a two way street.

Proactive Interference

The patients' relatively preserved ability to inhibit irrelevant stimuli in WM may be surprising in the context of Verwoerd et al. (2009), who found a correlation between PI and intrusive memories, but that study used a different task to measure proactive interference. The AB-AC-AB task involves learning lists of 12 cue-target word pairs (list AB, then list AC) and is more akin to an episodic memory task. Memory intrusions occur over a delay, when reverting back to the original AB pairing, not immediately. In contrast, the recent probes WM task measures PI on a trial by trial basis, and may not assess the same construct. Indeed, there was no relationship between the severity of re-experiencing symptoms and intrusions of stimuli from the previous trial in the current study.

The recent probes task has been identified as an optimal measure of interference control in WM and is thought to have good construct validity (Barch et al., 2009). Neuroimaging studies have suggested the importance of the left inferior frontal gyrus (especially Brodmann area 45) in overcoming PI in this task (Jonides et al., 1998; Postle et al., 2004; Jonides & Nee, 2006). Support for the *necessity* of this region was provided by a patient with extensive left BA 45 damage, who showed a four-fold increase in PI (Thompson-Schill et al., 2002). In contrast, PI was unaltered in frontal patients with lesions sparing left BA 45 (Thompson-Schill et al., 2002). Those patients were less accurate in the task, which is similar to the pattern shown by the present participants with PTSD. A high capacity to resist PI has been associated with higher WM accuracy in the recent probes task in controls (e.g., Mecklinger et al., 2003). However, evidence that patient groups can show dissociations in these two measures suggests the maintenance and cognitive control elements of WM can be separated in this task.

Why was WM interference resolution relatively unimpaired in participants with PTSD? What is different about proactive interference in this WM task compared to interference caused by performing a secondary task (El-Hage et al., 2006; Honzel et al., 2014)? Nee et al. (2013) identified four different executive components of working memory. Along with shifting and updating, these components included “intrusion resistance” (internal distraction from irrelevant memory representations), which was relatively spared in the present study, and “distractor resistance” (external distraction from other stimuli), which was impaired in the dual task experiment (Honzel et al., 2014). The need to overcome intrusion on recent negative trials may arise from the conflict between the high familiarity of a stimulus presented on *n-1* and *n* trials, and the lack of a contextual code indicating that it matches the study set on the current trial (Jonides & Nee, 2006). This increases the selection demands necessary to resolve this interference, whether at the level of contextual retrieval or response selection, to inhibit the intrusion of task-irrelevant thoughts into WM. Selection demands may be tapped further if negative material must be inhibited, particularly in the PTSD group.

In contrast to PI, which is typically not subject to strategic control (Bunge et al., 2001), another body of work has examined more deliberate forms of control over the contents of memory. These studies use designs such as the directed forgetting (DF) task (Hauswald & Kissler, 2008) and the Think/NoThink (TNT) task (Anderson & Green, 2001). In both cases, cues are given during the encoding phase (for DF) or during a specific TNT phase to remember some items but to forget others. A subsequent memory test asks participants to recall or recognize not only the “remember” items, but also the “forget” or “no-think” items. The DF effect is measured by lower memory for F than for R items, and the TNT effect is indicated by worse memory for no-think vs. think items. Participants with PTSD showed reduced DF effects for neutral scenes (Zwissler et al., 2012) and for neutral and positive words (McNally et al., 1998), but not for trauma-related words (McNally et al., 1998). On the other hand, a recent study using the TNT task showed that retrieval suppression for negative scenes was impaired in PTSD patients (Catarino et al., 2015). Trauma-related scenes were not presented in that study.

Distractor resistance is the ability to ignore or filter out extraneous stimuli to protect the contents of WM. Resistance to external distractors may be difficult for PTSD patents, since they were disrupted by task-irrelevant items during visual search to a greater extent than controls (Esterman et al., 2013). Extending this line of research with neutral stimuli to include comparisons of trauma-related vs. neutral distractors is an important future direction. For example, PTSD patients showed greater impairments in WM for neutral verbal (Schweizer & Dalgleish, 2011) and visual stimuli (Zhang et al., 2013; Schweizer & Dalgleish, 2016; cf. Morey et al., 2009) when trauma-related distractors appeared during the retention interval (relative to neutral distractors).

Previous studies in Iraq and Afghanistan Veterans with PTSD revealed impaired performance on tasks that require the inhibition of inappropriate motor responses (Swick et al., 2012; DeGutis et al., 2015). This replicable response inhibition deficit has been seen in other PTSD populations (Vasterling et al., 1998; Falconer et al., 2008a; Wu et al., 2010) and stands in contrast to the present results. This is not entirely surprising from a perspective that considers the diversity of executive control functions, since motor inhibition and PI are dissociable in factor analysis (Miyake et al., 2000; Friedman & Miyake, 2004). Inhibitory control may play a specific role in establishing and maintaining PTSD symptoms (Aupperle et al., 2012), and it is important to distinguish between facets that are impaired and those that are spared.

The question most relevant to the current work is whether presentation of negatively valenced or trauma-related stimuli in the recent probes task would lead to increased intrusions of the aversive items. Although both retrieval suppression and PI can be considered forms of intrusion resistance (Nee et al., 2013), the cognitive and neural mechanisms underlying these processes appear to be different. For instance, neuroimaging studies have emphasized the importance of right dorsolateral prefrontal cortex for retrieval suppression in the TNT task (Anderson et al., 2004; Depue et al., 2007), but left BA 45 for overcoming proactive interference in the recent probes task (Jonides & Nee, 2006). Future neuroimaging and EEG experiments can administer these tasks to the same group of participants with PTSD. The results could be informative about the types of intrusive cognitions and flashbacks experienced by these patients.

Limitations

One limitation is that the present study reported null findings for two of the hypothesized effects. Nonetheless, Bayes factors indicated that the evidence in favor of H_0 was more likely than H_1 in both cases. Thus, our current results suggest that PTSD is not associated with differential impairments in verbal and visual working memory when using identical task parameters. There was also positive evidence in favor of the null hypothesis for the RT measure of PI, which is more robust that the error measure of PI (Barch et al., 2009). A complicating factor is that the evidence against (in the case of verbal stimuli) or for (visual stimuli) a group difference for the error measure of PI was weak (Table 3). However, neither PI measure was correlated with re-experiencing scores, which tentatively suggests that this process of interference control is not related to the frequency or severity of intrusion symptoms.

Another potential issue is that the controls and patients were not matched for years of education. Control Veterans can typically return to school after deployment if this is a personal goal, but the burden of PTSD can prevent many Veterans from furthering their education. In this light, the overall deficit in WM accuracy should be interpreted with caution. However, analyses with subgroups of patients and controls matched in education found results similar to the main analyses. Furthermore, education level was not significantly correlated with any performance measure in this study. We also note the Bayesian evidence in favor of a comparable RT interference effect in controls and patients, despite the discrepancy in education.

We could not decisively dissociate the potential effects of mTBI from those of PTSD due to small sample sizes, but informal analyses suggested no effect of mTBI on error rates or PI (Supplementary Material). In line with these tentative findings, other investigations in OEF/OIF Veterans suggest that cognitive deficits are associated with PTSD symptom severity, but not with a history of blast-related mTBI (Neipert et al., 2014; Verfallie et al., 2014; Storzbach et al., 2015). These results also agree with our earlier studies that found no additive effect of mTBI on inhibitory control impairments in this PTSD population (Swick et al., 2012, 2013).

Other limitations could be addressed in future investigations. Only a subset of the Veteran controls was exposed to trauma, which does not allow us to clearly disentangle the effects of combat experiences from the effects of PTSD symptoms. This shortcoming is mitigated by the lack of correlation between PI performance measures and re-experiencing symptoms, and the lack of significant differences between combat-exposed and non-exposed controls. [3] Another drawback is the relatively small size of the groups under study here, which limits the strength of evidence in favor of the null effect. Nonetheless, well-conducted studies with small sample sizes can still contribute to future meta-analyses of working memory. A final limitation is that we don't know whether the results from this military population would generalize to civilian PTSD.

Conclusions

The present study is the first (to our knowledge) to examine the effects of PTSD on verbal and visual WM using identical task conditions. Participants with PTSD made more errors on a recent probes WM task than controls, and this impairment in performance was independent of stimulus material. Proactive interference from items previously presented, but no longer relevant, was not significantly different in participants with PTSD, and showed no relationship to the severity of re-experiencing symptoms. Thus, the findings demonstrated that PTSD is not associated with increased intrusions of irrelevant representations into WM when simple, non-emotional stimuli are used. Future studies that use trauma-related stimuli may provide insight into the flashbacks and intrusive thoughts that plague those with PTSD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

[3]One potential limitation of the PCL – Military Version is that the non-combat controls could have undocumented civilian PTSD that was not captured by this instrument. However, we find this possibility unlikely. The controls did not report incidents or symptoms consistent with PTSD in screening interviews. Furthermore, a subset of controls completed the Life Events Checklist as part of another study. Reports of exposure to civilian trauma were not accompanied by elevated PCL-5 scores.

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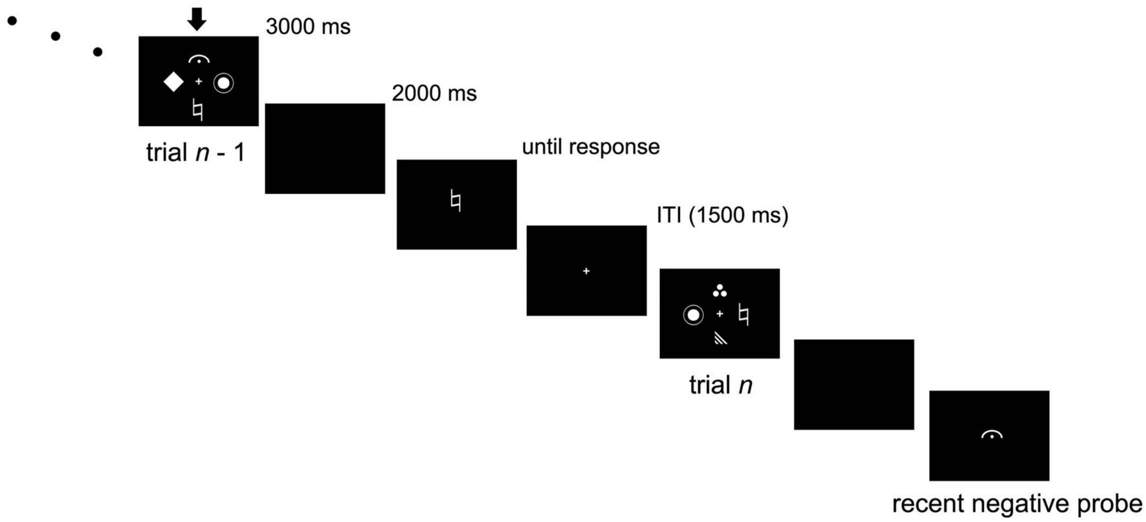

Fig. 1.

Schematic of the trial sequence in the visual blocks of the recent probes working memory task. The arrow indicates the single stimulus (out of four) on trial $n-1$ that will appear again as a probe in the next trial (trial n). In this example, the probe is a recent negative from trial $n-1$ that requires a "no" response in trial n. ITI =inter-trial interval. *Note*: stimuli are not to scale.

(a) Verbal Stimuli

CAUSE	MIGHT
CLAIM	MONTH
COUNT	PEACE
DREAM	PROOF
FAITH	SENSE
FORCE	SKILL
GRACE	SPEED
GUESS	THEME
HASTE	TREND
MERCY	TRUTH

(b) Visual Stimuli

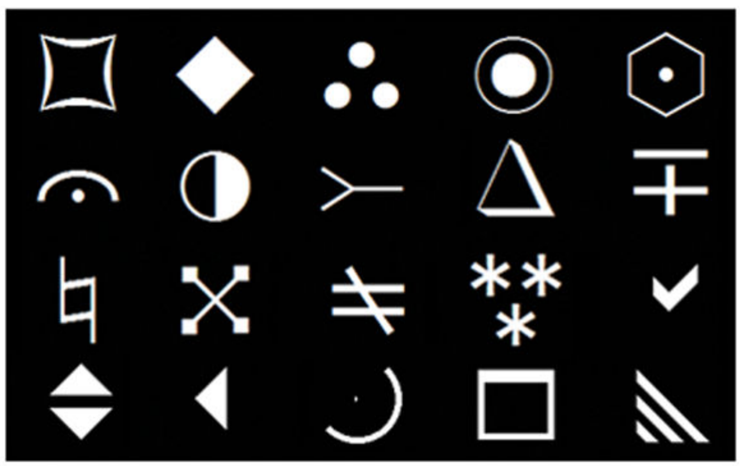

Fig. 2.
Stimuli used in the experiment. **(a)** List of abstract words. **(b)** Illustration showing visual patterns.

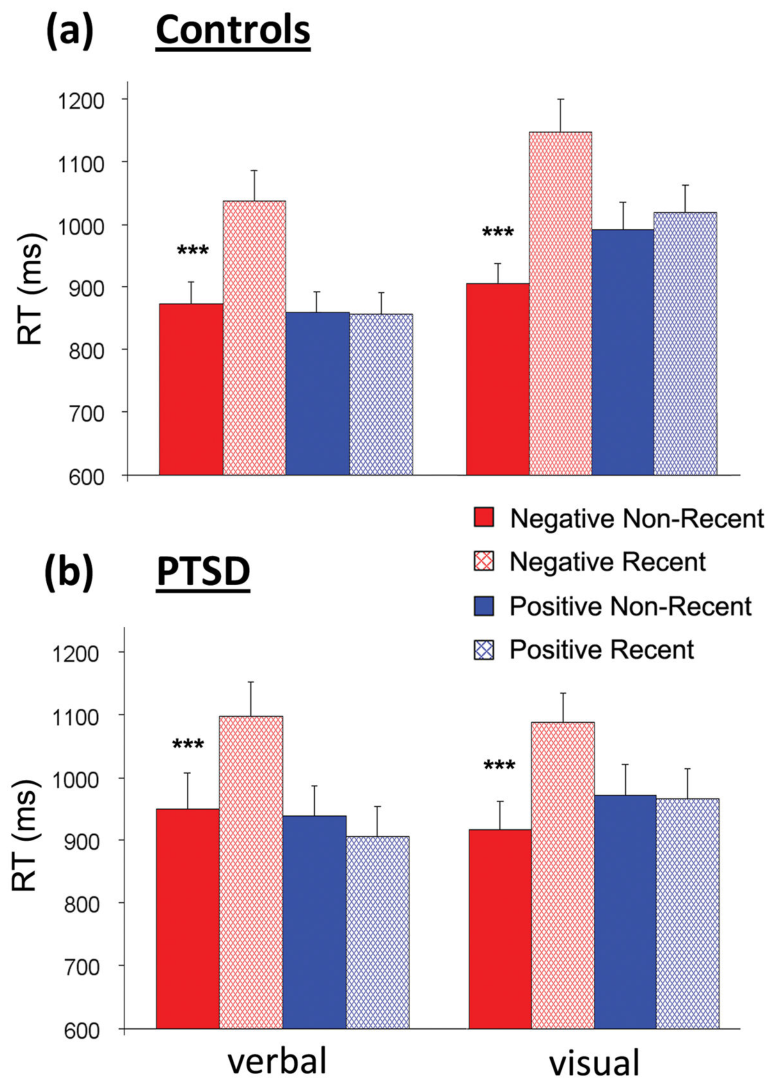

Fig. 3.

Group means of individual subjects' median reaction times (RT) for negative probes (in red) and positive probes (in blue) for **(a)** Controls and **(b)** participants with PTSD. Nonrecent trials are shown in solid bars, recent trials in lighter patterned bars. The proactive interference (PI) effect is the significant slowing for recent negative vs. nonrecent negative probes. For positive probes, there is no significant difference between recent and nonrecent trials. Error bars are standard errors. *** p<.0001

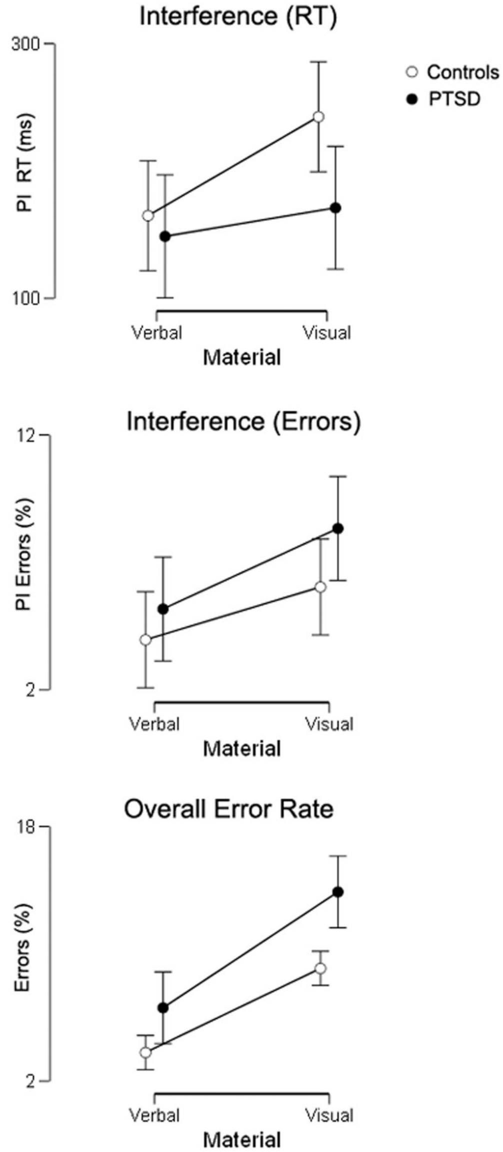

Fig. 4.

Graphs highlighting the effects of Group and Material on working memory performance. Top: Proactive interference (PI) for reaction time (RT) in milliseconds (ms), i.e. the difference in RT on recent negative vs. nonrecent negative trials. Middle: PI for percent errors, the difference between error rates on recent negative vs. nonrecent negative trials. Bottom: Overall error rates during verbal and visual blocks, collapsed across Recency and Probe Type. Error bars are 95% confidence intervals. See text for details.

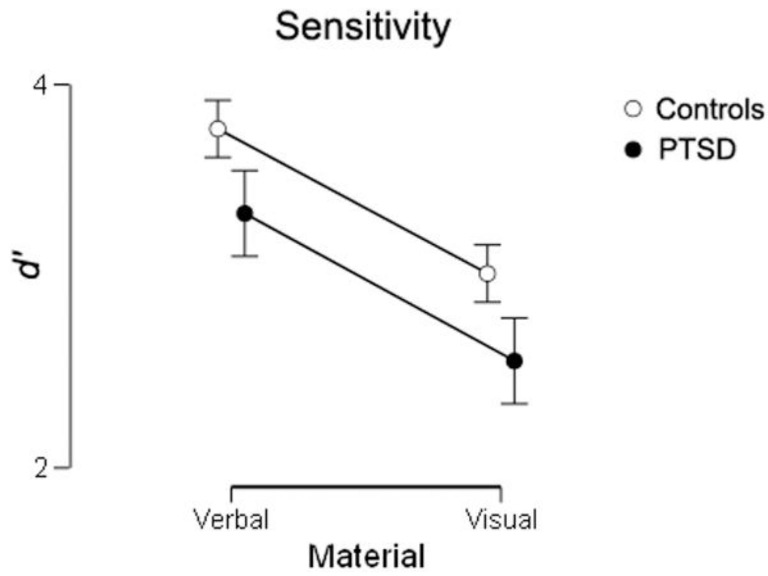

Fig. 5.
Graph highlighting the effects of Group and Material on signal detection theory measures. Sensitivity (d') clearly indicates that controls are better able to detect the "signal" (previously studied stimuli) than participants with PTSD, who show no evidence of a material-specific deficit (despite a large overall discrepancy between verbal and visual stimuli).

Table 1

Demographic information and symptom severity scores for Controls and participants with PTSD.

	Controls (n=29)	PTSD (n=29)
Age (yrs)	36.7 (8.8)	33.8 (7.6) n.s
Education (yrs)	15.3 (1.9)	13.9 (1.0) ***
Handedness	24 R, 5 L	26 R, 2 L, 1 amb
Combat-exposed	11	29
PCL-M	25.5 (8.3)	55.5 (14.3) ***
• re-experiencing	8.2 (1.7)	15.9 (5.0) ***
• avoidance/numb	10.3 (4.0)	21.6 (6.7) ***
• hyperarousal	8.6 (3.0′)	18.1 (4.5) ***
BDI	6.1 (5.1)	21.7 (11.3) ***

Note: The means (standard deviations) are given for age, education, PCL-M, and BDI.

n.s. = not significantly different from controls;

*** significantly different from controls at p<.001.

R = right, L = left; amb = ambidextrous; PCL-M = PTSD checklist, military version; BDI = Beck Depression Inventory.

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Table 2

Behavioral Performance in the Recent Probes Task. Means of individual subjects' median reaction times (top) and error rates (bottom) are shown for Controls and participants with PTSD. On Positive trials, the probe was present in the study set and on Negative trials, it was absent. Proactive interference is measured by the difference between recent and nonrecent Negative.

Verbal				
RT	**Positive**		**Negative**	
(ms)	**nonrecent**	**recent**	**nonrecent**	**recent**
Controls	859 (179)	857 (183)	872 (196)	1037 (264)
PTSD	939 (257)	907 (249)	949 (309)	1098 (331)
Visual				
Controls	994 (236)	1022 (245)	909 (170)	1151 (283)
PTSD	970 (261)	965 (249)	915 (229)	1086 (249)

Verbal				
Errors	**Positive**		**Negative**	
(%)	**nonrecent**	**recent**	**nonrecent**	**recent**
Controls	3.31 (3.85)	2.59 (3.64)	2.67 (2.92)	6.63 (5.77)
PTSD	8.41 (9.12)	6.97 (8.63)	2.95 (3.50)	8.12 (5.69)
Visual				
Controls	13.60 (9.50)	11.76 (7.90)	2.47 (2.68)	8.50 (6.57)
PTSD	19.04 (16.34)	16.68 (16.61)	5.75 (6.29)	14.08 (9.53)

Note: The means (standard deviations) are in milliseconds for RT (reaction time) and in percentages for error rate.

Table 4

Behavioral performance measures for Verbal (top) and Visual (bottom) blocks for Controls and participants with PTSD. The Bayes Factor (BF_{01}) indicates the strength of evidence for or against the null hypothesis (Wagenmakers, 2007).

Verbal	**Controlsmean (SD)**	**PTSDmean (SD)**	**BF_{01}**
PI RT	165 (108)	149 (114)	5.378
PI Error	3.96 (4.54)	5.17 (6.22)	1.787
Error Rate	3.80 (4.45)	6.61 (4.61)	0.092
Sensitivity (d')	3.77 (.62)	3.33 (.57)	0.075
Visual			
PI RT	243 (161)	171 (138)	9.467
PI Error	6.03 (5.02)	8.33 (6.49)	0.800
Error Rate	9.08 (8.22)	13.88 (9.21)	0.160
Sensitivity (d')	3.01 (.67)	2.56 (.84)	0.227

Note: SD = standard deviation; PI RT = proactive interference (recent negative – nonrecent negative) for reaction time (in milliseconds); PI error = proactive interference for percent errors. $BF_{01} > 1$ indicates that the result is more likely to occur under the null hypothesis (H_0) than the alternate hypothesis (H_1). $BF_{01} < 1$ indicates the result is more likely under H_1 than H_0. Descriptively speaking, $BF_{01} > 3$ has been seen as “moderate” (Love et al., 2015) or “positive” (Wagenmakers, 2007) or “substantial” (Jeffreys, 1961) evidence in favor of H_0.