Neuropsychology

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Online First Publication, July 28, 2014. http://dx.doi.org/10.1037/neu0000131

CITATION

Levy-Gigi, E., Szabo, C., Richter-Levin, G., & Kéri, S. (2014, July 28). Reduced Hippocampal Volume Is Associated With Overgeneralization of Negative Context in Individuals With PTSD. *Neuropsychology*. Advance online publication. http://dx.doi.org/10.1037/neu0000131

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0894-4105/14/$12.00 http://dx.doi.org/10.1037/neu0000131

Reduced Hippocampal Volume Is Associated With Overgeneralization of Negative Context in Individuals With PTSD

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Objective: Previous studies demonstrated reduced hippocampal volume in individuals with posttraumatic stress disorder (PTSD). However, the functional role the hippocampus plays in PTSD symptomatology is still unclear. The aim of the present study was to explore generalization learning and its connection to hippocampal volume in individuals with and without PTSD. Animal and human models argue that hippocampal deficit may result in failure to process contextual information. Therefore we predicted associations between reduced hippocampal volume and overgeneralization of context in individuals with PTSD. ***Method:*** We conducted MRI scans of bilateral hippocampal and amygdala formations as well as intracranial and total brain volumes. Generalization was measured using a novel-learning paradigm, which separately evaluates generalization of cue and context in conditions of negative and positive outcomes. ***Results:*** As expected, MRI scans indicated reduced hippocampal volume in PTSD compared to non-PTSD participants. Behavioral results revealed a selective deficit in context generalization learning in individuals with PTSD, $F(1, 43) = 8.27$, $p < .01$, $\eta_p^2 = .16$. Specifically, as predicted, while generalization of cue was spared in both groups, individuals with PTSD showed overgeneralization of negative context. Hence, they could not learn that a previously negative context is later associated with a positive outcome, $F(1, 43) = 7.33$, $p = .01$, $\eta_p^2 = .15$. Most importantly, overgeneralization of negative context significantly correlated with right and left hippocampal volume ($r = .61$, $p = .000$; $r = .5$, $p = .000$). Finally, bilateral hippocampal volume provided the strongest prediction of overgeneralization of negative context. ***Conclusions:*** Reduced hippocampal volume may account for the difficulty of individuals with PTSD to differentiate negative and novel conditions and hence may facilitate reexperiencing symptoms.

Keywords: generalization, context, hippocampus, structural brain imaging, PTSD

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A wide range of neuroimaging studies have demonstrated diminished medial temporal lobe (MTL) activation and/or reduced hippocampal volume in individuals with posttraumatic stress disorder (PTSD; e.g., Bremner, Vythilingam, & Vermetten, 2003; Kasai et al., 2008; Levy-Gigi, Szabo, Kelemen, & Kéri, 2013; Peres et al., 2011; for reviews and meta analyses, see Karl et al., 2006; Pitman et al., 2012; Shin & Liberzon, 2010; Smith, 2005; Woon, Sood, & Hedges, 2010). However, the relationship between structural abnormalities and the functional role the hippocampus plays in PTSD symptomatology is still unclear (for review see Woodward et al., 2009). The aim of the present study is to test whether individuals with PTSD display an overgeneralization of contextual information, and whether it is associated with reduced hippocampal volume. The results may help characterizing hippocampal-dependent learning deficits in PTSD and provide a possible explanation for its role in PTSD symptomology and etiology.

Animal and human models argue that hippocampal deficit may result in failure to process contextual information (e.g., Dickerson & Eichenbaum, 2010; Goosens, 2011; Moustafa et al., 2013; Rudy, Huff, & Matus-Amat, 2004). According to the item-in-context model, the perirhinal cortex is responsible for processing of objects, the parahippocampal cortex represents the context, while the hippocampus integrates the information from these sources. Therefore it is responsible for placing objects into their proper context (Davachi, 2006; Diana, Yonelinas, & Ranganath, 2012; Dickerson

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& Eichenbaum, 2010), and detecting novel changes in the relationship between objects and their surrounding context (Howard, Shankar, & Jagadisan, 2011). This suggests that people with a small or dysfunctional hippocampus may show a selective deficit in context generalization learning whereas failure to appropriately encode traumatic associations in their adequate context, results in a deficit to differentiate it from other novel conditions (Brewin, Gregory, Lipton, & Burgess, 2010; Hayes et al., 2011; Rudy, 2009).

In a recent study, we found that individuals with PTSD have a specific impairment in generalization learning (Levy-Gigi et al., 2012). However, it does not indicate whether it selectively affects generalization of contextual condition, and whether the impaired performance relates to reduced hippocampal volume. In order to test it, the current study applies MRI scans of bilateral hippocampal and amygdala formations as well as intracranial and total brain volumes in individuals with and without PTSD, together with a novel-learning paradigm.

The paradigm evaluates generalization learning by using a unique partial reversal design. In a common reversal-learning paradigm, participants acquire a stimulus–outcome association (S→Positive) and later learn to reverse it without any changes in the relevant stimulus dimension (S→Negative; Chudasama & Robbins, 2006). Such a paradigm does not take into account that stimulus dimensions regularly occur in a specific context (Mayes, MacDonald, Donlan, Pears, & Meudell, 1992; Murnane et al., 1999), and therefore, both the stimulus and its surrounding context may be relevant (Wickens, 1987). In our paradigm, participants learn stimulus–outcome associations (e.g., A hat on an orange background →Positive) and later view new associations, which require reversing the outcome of either the *cue* (A phone on an orange background →Negative) or the *context* (A hat on a gray background →Negative) of the acquired stimuli (see Figure 1). Such manipulation enables to detect selective impairments in reversing negative and positive outcomes of cue and context related information, which reflects overgeneralization of previously learned information.

In a previous study that used a similar paradigm (Levy-Gigi, Kelemen, Gluck, & Kéri, 2011), we compared the performance of individuals with amnestic mild cognitive impairment (aMCI) with documented MTL atrophy and matched healthy controls. Both groups were equally able to acquire stimuli–outcome associations in the first phase of the task and successfully retrieve it in the second phase. However, individuals with damage to the MTL showed a selective context but not cue reversal-learning deficit, reflecting overgeneralization of contextual information. This impairment was independent of outcome valance and correlated with paired association learning task, which is a well-established neuropsychological marker of MTL dysfunctions in individuals with aMCI (Atienza et al., 2011; Hanseeuw et al., 2011; Talpos, Winters, Dias, Saksida, & Bussey, 2009; de Rover et al., 2011). The present study will help determining whether reduced hippocampal volume in PTSD is associated with similar inappropriate generalization of context.

Following the literature described above, we postulate that MRI scans will demonstrate a smaller hippocampal volume in individuals with PTSD compared to non-PTSD matched controls. In addition, we predict that both individuals with and without PTSD will equally be able to acquire and retain stimuli–outcome associations. However, individuals with PTSD will show a selective impairment in context reversal learning compared to individuals without PTSD, reflecting overgeneralization of context, but not cue related information. This impairment is expected to negatively correlate with bilateral hippocampal volume.

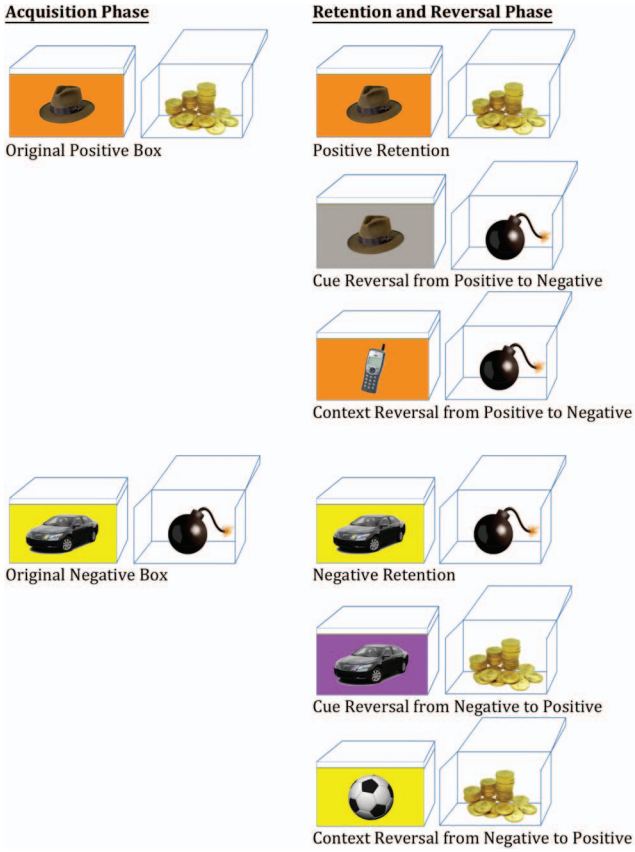

Figure 1. Example of acquisition, retention, and reversal trials in the two phases of the cue-context reversal paradigm. The color version of this figure appears in the online article only.

Method and Materials

Participants

Twenty-six individuals with PTSD and 22 individuals without PTSD participated in the study. Participants in both groups reported a single exposure to a traumatic event as defined by the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* criterion A (see Table 1 for a detailed description of the sample). Participants were referred by general practitioners, clinical psychologists, psychiatrists, and social workers, who was trained to recognize probable PTSD using the Primary Care PTSD Screen (Prins et al., 2003). In addition we published an ad in the local newspaper so volunteers could also contact our center directly by phone or email. Diagnosis of PTSD was established using the *Structured Clinical Interview for DSM-IV Clinician Version* and confirmed by two independent experts. Severity of symptoms was determined using the Clinician Administrated PTSD Scale

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Table 1
Demographic Characteristics of Individuals With and Without PTSD

	PTSD (N = 26)	Non-PTSD (N = 22)
Age (years)	35.46 (11.85)	38 (10.14)
Female/male	17/9	14/8
Education (years)	10.65 (2.25)	10.59 (2.08)
Medications* (N)	15/26	6/22
Type of trauma (N)	12/8/3/3	9/7/3/3
Environmental disaster/traffic/ crime/combat		
CAPS		
Reexperience	13.5 (4.55)	
Avoidance	21.88 (5.03)	
Arousal	23.19 (5.14)	

Note. PTSD = posttraumatic stress disorder; CAPS = Clinician-Administrated PTSD Scale.
* PTSD group: 8 received non-selective beta-blockers, 3 received selective serotonin reuptake inhibitors, 4 received other supplementary medications such as benzodiazepines; Non-PTSD group: 2 received selective serotonin reuptake inhibitors, 4 received other supplementary medications, such as benzodiazepine.

(Blake et al., 1995) administered by trained and regularly supervised clinical psychologists. Exclusion criteria included history of psychiatric or neurological disorders and current comorbid *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* mood disorders, psychotic disorders, and substance misuse. The study was done in accordance with the Declaration of Helsinki and received institutional ethics approval by the local ethics board. After a complete description of the experimental procedures, a signed informed consent was obtained from each participant.

Cue and Context Reversal Task

In this task participants view a series of boxes on a computer screen (see Figure 1). On each box there is a picture of a target cue (one of various objects, e.g., a hat) presented against a background context (different colors, e.g., orange; see Hockley, 2008; Isarida & Isarin, 2007; Lang et al., 2009; Macken, 2002; Rutherford, 2004; van Ast, Cornelisse, Meeter, Joëls, & Kindt, 2013 for studies that manipulated context in a similar way). When opened, each box is associated with a specific outcome (positive or negative). Participants receive the following instructions: "In this experiment, you will be shown various boxes. For each box you have the option to open it or to leave it closed. If you open a box you will either win or lose 25 points (Figure 2). If you do not open the box, you will not win or lose any points. Your job is to earn as many points as possible. Through trial and error you will learn to open the boxes that earn you points and not open the boxes that cost you points." After viewing the instructions, participants take part in a practice phase that demonstrates the task using two boxes; one associated with a positive outcome, and the other associated with a negative outcome. They see a closed box, with a picture of an object presented against a background color, and receive the following instructions: "Suppose you see a box and you want to open it. Click on Open, below." After opening the box, participants see gold inside of it (positive box) accompanied with a matching voice, a smiley face and a numeric indication that they earned 25 points. These points are added to the participants' total amount of points indicated at the side of the screen (see Figure 2). "Great job! There is gold inside." In the following screen, they see the same reward box with the following text: "Now suppose you see the same box again. You just learned there is gold inside. You should open it." After opening the box again, they see an open box with gold inside of it a smiley face and a numeric indication that they earned 25 points, and receive the following feedback: "Very good. You won gold." Later they see a screen with a new box that has a different object presented against a different background color on it. "Next, suppose you see another box and you want to open it. Click on Open, below." After opening the box, participants see an open box with a bomb inside of it (negative box) accompanied with a matching voice, a frown face and a numeric indication that they lost 25 points. "Oops, there is a bomb inside" In the following screen they see the same negative box, with the following text: "Now, suppose you see the same box again. You just learned that there is a bomb inside. You should decide not to open it." After choosing the "Do not open" option, participants receive the following feedback: "You were right not to open it. There is a bomb inside." The experiment starts at the end of the practice phase. We created new boxes for the experiment, different from those presented in the practice phase, using eight cue objects and eight distinctive context colors (for a schematic description see Table 2). Boxes were 4" × 3" size, presented on a 13" screen. The outcome of each box was counterbalanced across participants. The task has two phases: acquisition phase and retention and reversal phase. In the acquisition phase, participants learn by trial and error to predict the outcome of four different boxes (i.e., open the two positive boxes and skip the two negative boxes). Each box has a unique cue and context (i.e., a box with a hat on an orange background has gold inside while a box with a car on a yellow background has bomb inside). The acquisition phase contains a minimum of 40 trials. However, in order to ensure learning of the stimulus–outcome associations, participants have to reach a criterion of six consecutive correct responses before they move to the next retention and reversal phase. Participants who do not reach this criterion within 64 trials are automatically opt out from the experiment,

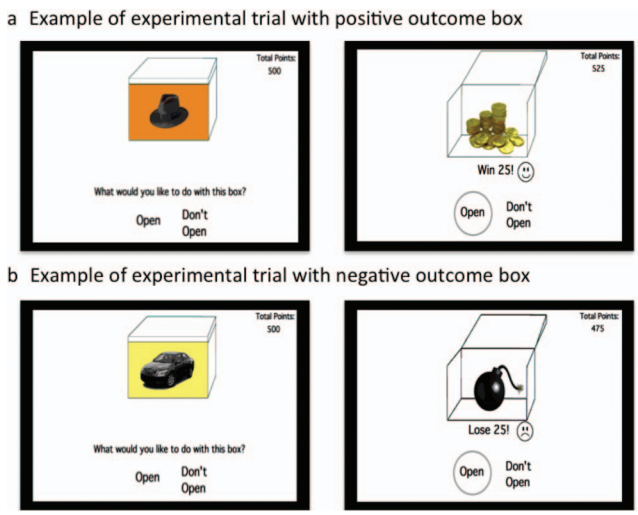

Figure 2. Example of experimental trials with different outcomes. The color version of this figure appears in the online article only.

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Table 2
Schematic Description of the Cue-Context Reversal Paradigm

Acquisition	Retention and reversal
A(1) → Positive	A(1) → Positive
	A(*5*) → Negative
	E(1) → Negative
B(2) → Positive	B(2) → Positive
	B(*6*) → Negative
	F(2) → Negative
C(3) → Negative	C(3) → Negative
	C(*7*) → Positive
	G(3) → Positive
D(4) → Negative	D(4) → Negative
	D(*8*) → Positive
	H(4) → Positive

Note. A–H represent 8 different cue stimuli (hat, phone, car, ball, television, chair, bird, and pot). 1–8 represent 8 different context stimuli (orange, grey, yellow, purple, green, pink, blue, and red). In both the acquisition and retention-reversal phases, each stimulus was presented 10 times. This constitutes a total of 40 acquisition trials, 40 retention trials, and 80 reversal trials.

without proceeding to the retention and reversal phase. Correct responses refer to conditions in which participants open positive boxes or leave negative boxes closed. Similarly, incorrect responses refer to conditions in which participants open negative boxes or leave positive boxes closed. A subsequent retention and reversal phase starts immediately after the acquisition phase without any signaled switch or delay. In this phase participants receive retention trials with the original boxes that keep the same learned outcome (e.g., a hat on an orange background has gold inside) in addition to two new types of boxes that share either the cue (e.g., a hat on a gray background) or the context (e.g., a phone on an orange background) with an original box (see Figure 1). The new boxes are associated with the opposite outcome relative to the original boxes (i.e., if the box with the hat on the orange background has gold inside, then the boxes with the hat on a gray background and a phone on the orange background will have bomb inside and vice versa). Therefore, in order to successfully learn these new associations participants need to reverse the association rule of either the original cue or the original context from positive to negative or from negative to positive. Boxes in this phase are presented in 10 blocks of 12 boxes each (two boxes from each of the following conditions: positive/negative retention, positive/negative cue reversal, positive/negative context reversal). Boxes in each block are presented in a random order. This sums up to a total of 120 trials, 20 trials per condition.

Brain Imaging

We used MRI and followed the FreeSurfer procedure for optimal volumetric measurements (Martinos Center for Biomedical Imaging, Boston, MA; version: v5.1.0, Dell XPS workstation) of the hippocampus, amygdala and intracranial volumes. We utilized multiecho FLASH sequence with a 1-mm^3 isotropic resolution (Siemens Trio 3T scanner; 256 × 256 matrix, 176 sagittal slices with a thickness of 1 mm, TR 2530 ms, TI 1100 ms, TE 1.64/3.5/5.36/7.22 ms, bandwidth 651 Hz, nonselective excitation at 71). Image processing included: removal of nonbrain tissue with a hybrid watershed/surface deformation technique, automated Talairach transformation, and segmentation of white and gray matter (Fischl et al., 2004; Ségonne et al., 2004; for methodological limitations, see Gronenschild et al., 2012). Measures of left and right hippocampus and amygdala formations were normalized according to the intracranial volume, which was measured with FreeSurfer (Whitwell, Crum, Watt, & Fox, 2001). Given that this normalization process minimizes within-group variability, we also analyzed uncorrected data with intracranial volume as a covariate.

Questionnaires and Cognitive Assessment

In order to control for potential confounds all participants completed the following questionnaires: Trauma and Life-Event Self-Report Inventory (Hovens, Bramsen, van der Ploeg, & Reuling, 2000) and Hamilton Depression Scale (Hamilton, 1980). In addition, we used the Wechsler Abbreviated Scale of Intelligence to measure estimated IQ levels (Pearson Education, Inc., 1999). Scales were administrated by trained psychologists. Table 3 depicts the comparison of PTSD and non-PTSD individuals on these measures. In accordance with previous reports in the literature (e.g., Levy-Gigi et al., 2012; Gilbertson et al., 2008), individuals with PTSD exhibited elevated levels of depression compared to trauma-exposed non-PTSD controls. There were no significant differences in IQ levels and history of childhood trauma between the two groups.

Data Analysis

We used SPSS (version 19) software (SPSS Inc., Chicago, IL, U.S.A.) to analyze the data. All data were checked for normality of distribution using Kolmogorov–Smirnov tests.

Results

Acquisition and Retention of Stimulus: Outcome Associations

We conducted a Group (PTSD vs. non-PTSD) × Acquisition (positive vs. negative stimuli) × Retention (positive vs. negative stimuli) mixed-model ANOVA on the percentage of correct responses. In this model, Group was the between-subjects factor, while Acquisition and Retention were the within-subjects factors. The results are depicted in Figure 3. As predicted the ANOVA revealed no significant main effects of Group, $F(1, 46) = .96$, $p = .33$, and no significant interactions of Acquisition × Group, $F(1, 46) = 1.12$, $p = .3$, or Retention × Group, $F(1, 46) = .97$, $p = .33$.

Table 3
Questionnaires and Cognitive Assessment (Means and Standard Deviations)

	PTSD ($N = 26$)	Non-PTSD ($N = 22$)
IQ scores	106.65 (9.25)	107.05 (9.13)
Hamilton Depression Scale	16.08* (8.37)	11.14* (5.44)
TLSI	5.96 (2.29)	5.5 (1.82)

Note. PTSD = posttraumatic stress disorder; TLSI = Trauma and Life-Event Self-Report Inventory.
* Indicates significant differences between means at the $p < .05$ based on Scheffe's post hoc paired comparisons.

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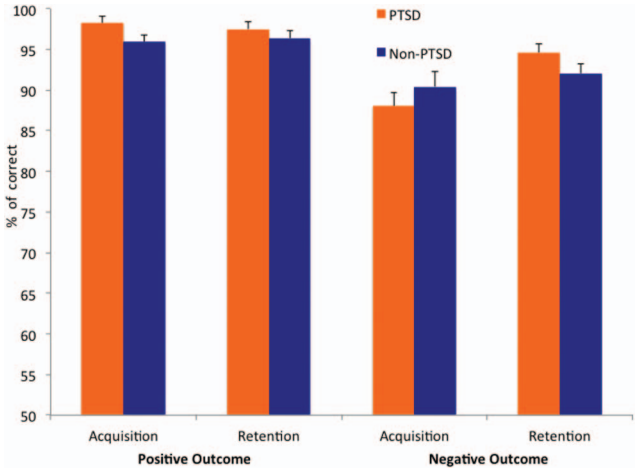

Figure 3. Percentage of correct responses to the four original boxes as a function of trials type (acquisition vs. retention), outcome (positive vs. negative), and experimental group (PTSD vs. non-PTSD). The color version of this figure appears in the online article only.

The results indicate that both PTSD and non-PTSD individuals were equally able to learn and retain positive and negative stimulus–outcome associations.

Cue and Context Reversal Learning

We conducted a Group (PTSD vs. non-PTSD) × Reversal Type (cue vs. context) × Outcome (positive to negative vs. negative to positive) mixed-model ANOVA on the percentage of correct responses. In this model, Group was the between-subjects factor, while Reversal Type and Outcome were the within-subjects factor. In order to control for IQ, depression symptoms and childhood trauma we used these variables as covariates. The results are depicted in Figure 4. The ANOVA revealed a significant main effect of Group, $F(1, 43) = 4.95$, $p < .05$, $\eta_p^2 = .10$, but no significant main effects of Reversal Type or Outcome, Fs < 1, ps $> .4$. In addition, no significant main effects or interactions were found with any of the covariate variables. Finally and most importantly, we found a significant interaction between Group, Reversal Type, and Outcome, $F(1, 43) = 4.52$, $p < .05$, $\eta_p^2 = .10$. In order to reveal the source of this significant interaction, we conducted two mixed-model ANOVAs: one for conditions of Context Reversals and the other for conditions of Cue Reversals. In these analyses, Outcome (positive to negative vs. negative to positive) was the within-subjects factor and Group (PTSD vs. non-PTSD) was the between-subject factor. The results demonstrated a significant interaction between Group and Outcome in conditions of context, but not cue, reversal, $F(1, 43) = 8.27$, $p < .01$, $\eta_p^2 = .16$; $F(1, 43) = .09$, $p = .77$ for context and cue reversals, respectively. Pairwise comparisons with Bonferroni correction ($\alpha = .0125$) showed that relative to controls, individuals with PTSD were significantly impaired in reversing the outcome of negative context, $F(1, 43) = 7.33$, $p = .01$, $\eta_p^2 = .15$. There were no significant differences between the groups in reversing the outcome of positive context, $F(1, 43) = .01$, $p = .91$. Finally, groups did not differ in response time (ps $> .81$). These results indicate that individuals with PTSD have a selective impairment in learning of new associations in which a previously negative context becomes positive. This impairment reflects overgeneralization of negative context in this group. However, as can be seem in Figure 4, in the three other reversal conditions both PTSD and non-PTSD participants learned the new associations equally well. Hence, there was no overgeneralization of either negative cue and positive cue or context.

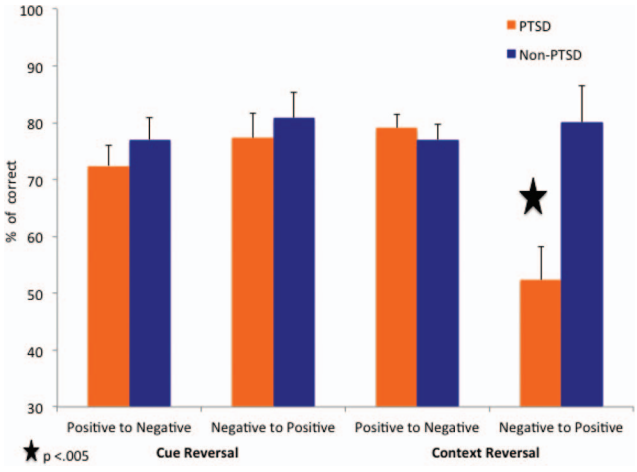

Figure 4. Percentage of correct responses in reversal trials as a function of reversal type (cue vs. context), outcome (positive to negative vs. negative to positive), and experimental group (PTSD vs. non-PTSD). The color version of this figure appears in the online article only.

Brain Imaging

A one-way ANOVA conducted on the normalized bilateral hippocampal volumes indicate volume reduction in individuals with PTSD relative to non-PTSD individuals: right hippocampal volume, $F(1, 46) = 8.56$, $p < .01$, $\eta_p^2 = .16$; left hippocampal volume, $F(1, 46) = 7.59$, $p < .01$, $\eta_p^2 = .14$). This effect was further confirmed with ANCOVA conducted on the uncorrected total hippocampal volume with intracranial volume as a covariate, $F(1, 45) = 8.17$, $p < .01$, $\eta_p^2 = .15$. There were no significant differences between PTSD and non-PTSD individuals in right and left amygdala volumes, intracranial volume, and total brain volume, Fs < 1.5; ps $> .2$ (see Table 4). Most importantly, we used absolute bilateral hippocampal volume in a partial correlation design to control for total brain volume (Doring et al., 2011; Whitwell et al., 2001) and found a significant positive correlation

Table 4
Absolute Hippocampal and Amygdala Volumes (Mm^3) and Intracranial and Total Brain Volumes ($Mm^3 \times 10^6$)

	PTSD ($N = 26$)	Non-PTSD ($N = 22$)
Left hippocampus	4604.35 (264.7)	4789.09 (184.26)
Right hippocampus	4626.35 (286.08)	4836.82 (193.89)
Left amygdala	1676.34 (105.34)	1636.36 (117.15)
Right amygdala	1724.62 (100.28)	1698.41 (117.02)
ICV	1.88 (.21)	1.89 (.28)
Total brain	1.41 (.21)	1.42 (.19)

Note. PTSD = posttraumatic stress disorder; ICV = intracranial volume.

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between right and left hippocampal volumes and the ability to reverse the outcome of negative context in the whole sample (r = .61, p = .000; r = .5, p = .000 for right and left hippocampal volumes, respectively; Figures 5, 6). This correlation is not driven from the variance in the control group and remains significant when we test individuals with PTSD separately (r = .57, $p < .005$, for both right and left hippocampal volumes). These findings indicate that a smaller hippocampal volume is associated with increased overgeneralization of negative context. Finally, to examine which variables best predicts overgeneralization of negative context in the whole sample we conducted a stepwise regression with right and left hippocampal and amygdala volumes as the predictor variables and overgeneralization of negative context as the dependent variable. The model was adjusted for intracranial volume, total brain volume, IQ levels, depression symptoms and childhood trauma that were entered together in one separate step. The results showed that intracranial volume, total brain volume, IQ levels, depression symptoms and childhood trauma do not account for significant variance in overgeneralization of negative context, $F(5, 42) = .89$, p = .5. As expected, right and left hippocampal volumes provided the strongest prediction of performance and account for significant variance in overgeneralization of negative context, $F(1, 41) = 22.98$, p = .000, ΔR^2 = 33%; $F(1, 40) = 10.1$, p = .003, ΔR^2 = 12%, for right and left hippocampal volumes, respectively.

Effects of Medication

Participants in the current study were either unmedicated (PTSD, N = 11; non-PTSD, N = 14) or on different medications (PTSD, N = 15; non-PTSD, N = 6; See Table 1 for a detailed description of the medications). As a preliminary assessment of the effect of medications on generalization in PTSD, we conducted a two-way ANOVA with Medication Status (unmedicated vs. medicated) and Group (PTSD vs. non-PTSD) as between-subjects variables and Negative Context Reversal as the dependent variable. We found no significant main effect of Medication Status, $F(1, 44) = .93$, p = .34, nor interaction between Group and Medication Status, $F(1, 44) = .03$, p = .85. The results in this small sample suggest that although several participants from both groups consume psychotropic medications, the observed overgeneralization of negative context in this sample is not a function of medication status. These results are in line with a previous study, which showed no association between medication status and generalization learning (Levy-Gigi et al., 2012). However, further studies with greater statistical power are needed to address this issue definitively.

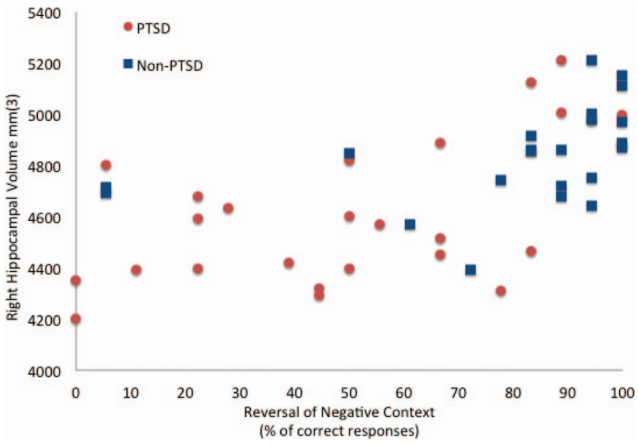

Figure 5. Significant correlation between reversal of negative context and right hippocampal volume in PTSD and non-PTSD participants. The color version of this figure appears in the online article only.

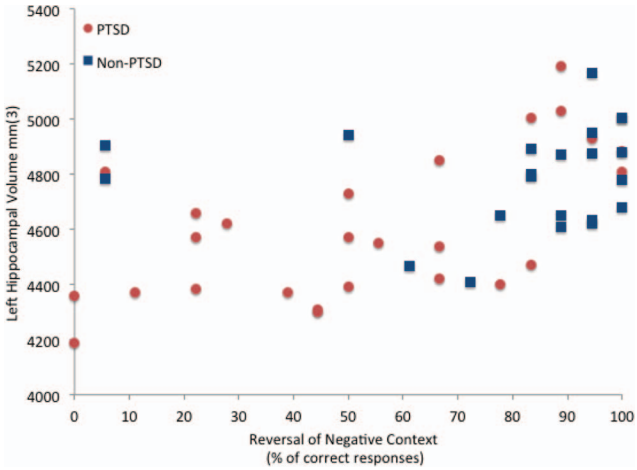

Figure 6. Significant correlation between reversal of negative context and left hippocampal volume in PTSD and non-PTSD participants. The color version of this figure appears in the online article only.

Discussion

In the present study, we compared the performance of individuals with and without PTSD on a novel cue-context reversal paradigm and tested its correlation with structural imaging of right and left hippocampal volumes in order to better understand the functional role of the hippocampus in PTSD etiology and symptomology. As predicted, we found that both PTSD and non-PTSD individuals were equally able to learn and retain positive and negative stimulus–outcome associations. In addition, aligned with previous findings (Levy-Gigi et al., 2011), both groups displayed spared cue reversal learning; they were able to learn that an object, which was first associated with positive or negative outcome, is associated with the opposite outcome when presented later in a different context (e.g., a hat on an orange background is positive, while a hat on a gray background is negative, and vice versa). However, only individuals with PTSD showed a selective deficit in reversing the outcome of negative, but not positive, context; after they learned that a specific context is associated with a negative outcome (e.g., a car on a yellow background is negative) they could not learn that it predicts positive outcome when presented later with a new object (e.g., a football on a yellow background is positive). The results reflect overgeneralization of negative context in individuals with PTSD and are consistent with other findings in the literature (Brown et al., 2013; Levy-Gigi & Kéri, 2012). Potential explanations for the intact reversal of positive context in PTSD relate to the functional role of the hippocampus and will be discussed in the next section.

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The Role of the Hippocampus in Context Generalization Learning

In accordance with past findings, MRI scans demonstrated smaller bilateral hippocampal volume in individuals with PTSD relative to those with no PTSD (e.g., Bremner et al., 2003; Levy-Gigi et al., 2013; for meta-analyses see Karl et al., 2006; Smith, 2005; Woon et al., 2010). Most importantly, as expected, right and left hippocampal volume was positively correlated with the ability to reverse the outcome of negative context. Hence, reduced bilateral hippocampal volume was associated with overgeneralization of negative context. Moreover, bilateral hippocampal volume served as the sole predictor of overgeneralization of negative context, accounting for 45% in performance variance above and beyond effects of IQ, depression symptoms and childhood trauma. The results strengthen our assertion regarding the relationship between structural abnormalities and context related impairment in PTSD (see also Hayes et al., 2011; Hennig-Fast et al., 2009). This is also in line with other studies conducted in our labs (Levy-Gigi & Richter-Levin, 2014), which show that firefighters with repeated exposure to trauma and probable hippocampal volume reduction demonstrate similar impairment. Finally, the results of the present study are consistent with other neuroimaging findings regarding structural abnormalities in PTSD. These studies have shown that hippocampal reductions in this population are more specific to the cornuammonis 3 (CA3)/dentate gyrus (DG) subfields (Wang et al., 2010), which involve integration of contextual information (Colgin, Moser, & Moser, 2008; Kesner, 2007). Although the methodology of the present study does not allow differentiating between hippocampal subfields, our results support deficit in integration of contextual information. Specifically, it may suggest that individuals with PTSD who have reduced hippocampal volume may fail to appropriately encode traumatic associations in its adequate context and, therefore, may experience difficulty to differentiate it from other novel conditions. Such impairment may facilitate reexperiencing symptoms and therefore contributes to PTSD etiology and symptomology.

As opposed to our previous findings, which demonstrated valance-independent impairment in context reversal learning among individuals with aMCI who have documented hippocampal deficit (Levy-Gigi et al., 2011), participants with PTSD displayed intact ability to reverse the outcome of positive context, showing no evidence for overgeneralization of positive context. Hence, similar to non-PTSD individuals, they were able to learn that a context, which was first associated with a positive outcome, is associated with a negative outcome when presented later with a new object (e.g., a hat on an orange background is positive while a phone on an orange background is negative). One way to explain these results is by claiming that hippocampal related deficits in PTSD are more specific. Support for such a claim can be found in other hippocampal-related theories of PTSD, which are focused exclusively on aversive conditions (Acheson, Gresack, & Risbrough, 2012; Brewin et al., 2010; Rudy, 2009; Rudy et al., 2004). Rudy (2009) and colleagues (2004) suggest that aversive events can be represented in the brain in one of two forms: elemental or conjunctive. In the elemental form elements present at the same time as the aversive event are encoded individually and become independently associated with it. In the conjunctive form, all the elements, which were present in the environment, are encoded as a whole, and therefore, a conditioned response would occur only in the presence of the full representation. In the cue-context reversal paradigm, a conjunctive representation may help to perceive each box at the reversal phase as a new unconditioned stimulus although it shares similar features with other conditioned stimulus and prevent inappropriate generalization. Animal studies have shown that the hippocampus is necessary for retrieval of conjunctive, but not elemental, associations in aversive conditions (Barrientos, O'Reilly, & Rudy, 2002; Iordanova, Burnett, Aggleton, Good, & Honey, 2009; Rudy et al., 2002; Rudy & Matus-Amat, 2005). Therefore, reduced hippocampal volume in participants with PTSD may result in predominance of elemental representation strategy and hence may explain overgeneralization of negative context.

Alternatively, it can be claimed that the hippocampus–amygdala connectivity in PTSD facilitates learning in conditions of negative feedback (LaBar & Cabeza, 2006) and therefore may compensate for possible deficits in generalization learning. Neuroimaging studies observed enhanced amygdala response in threatening and aversive contextual conditions (Büchel, Dolan, Armony, & Friston, 1999; Phelps et al., 2001; Smith, Henson, Dolan, & Rugg, 2004, 2006; Stevens et al., 2013). Brohawn, Offringa, Pfaff, Hughes, and Shin (2010) have shown that individuals with PTSD display even greater amygdala activation when viewing negative images compared to non-PTSD matched controls (see also Bryant et al., 2008; Bourne, Mackay, & Holmes, 2013). Behavioral studies revealed that individuals with PTSD have an advantage in processing aversive stimuli (Kleim, Ehring, & Ehlers, 2012; Vythilingam et al., 2007) and exhibit attention bias toward threat (Fani et al., 2012; Wald et al., 2013). Together these findings may explain how, despite overgeneralization of negative context, individuals with PTSD show no evidence for overgeneralization when a previously positive context becomes negative. Future fMRI research, which assesses hippocampus–amygdala connectivity in PTSD in conditions of positive and negative context generalization, is needed in order to clarify this point.

Potential Relevance to Prospective Prediction of Therapy Efficacy

Overgeneralization of negative context may account for the development and maintenance of PTSD symptoms and therefore is relevant in treating PTSD. One of the most common treatments for PTSD is cognitive behavioral therapy (CBT). CBT aims to modify maladaptive cognitions and behaviors in order to help patients master their anxiety (Foa, 2000, 2009). It also may be viewed as a form of learning, which targets to improve generalization learning by preventing overgeneralization of fear responses and delimiting them to an appropriate context (Butler, Chapman, Forman, & Beck, 2006; Kar, 2011; Nacasch et al., 2011). Because CBT and the cue-context reversal paradigm are both based on similar learning principles, it is possible that therapy, which aims to improve learning skills, may also improve performance on our task. Such assumption is also in line with other studies suggesting that PTSD-related effects on hippocampal volume are reversible once PTSD symptoms remit and the patient recovers (Apfel et al., 2011; Levy-Gigi et al., 2013; Wild & Gur, 2008).

Accordingly, the cue-context reversal paradigm has the potential to become a tool for therapists who wish to assess the effectiveness

of treatment and the recovery process in PTSD patients. Such assessment is especially important due to the significant individual differences in CBT efficacy (Mendes et al., 2008; Otte, 2011; Seidler & Wagner, 2006; Shalev et al., 2012) and may help avoiding loss of resources by allowing early detection of patients who do not respond to the therapy. However, future work is needed to evaluate performance on our task and treatment responsiveness at different benchmarks along the therapy process.

Potential Relevance to Prospective Prediction of Risk for PTSD

Several studies propose that reduced hippocampus volume is a preexisting vulnerability factor for PTSD. Gilbertson and colleagues (2002, 2007) have demonstrated that not only combat veterans with PTSD have a smaller-than- average hippocampal volume, but also their unexposed, non-PTSD identical twins. These results suggest that people with a smaller hippocampus may be at a higher risk to develop PTSD. Because there is a significant correlation between performance in the cue-context reversal paradigm and bilateral hippocampal volume, the task has the potential to form the basis for developing a set of effective tools for rapid, inexpensive and convenient measure of risk for developing PTSD. However, future prospective research is needed in order to further validate the predictive value of this task. This can be done both by testing people before exposure to traumatic events (e.g., soldiers in high risk units at the training stage) or shortly after exposure to a traumatic event (patients in emergency rooms) and assessing correlations between performance on the cue-context reversal paradigm and future PTSD.

Limitations

A possible limitation of the current study may relate to the nature of the cue-context reversal paradigm. The basic assumption in this and other similar paradigms (e.g., Fellows & Farah, 2003; Foerde & Shohamy, 2011; Rogers, Andrews, Grasby, Brooks, & Robbins, 2000) is that the participants are rational learners. However, it is possible that decision makers have expectancies and concepts (i.e., inner values and representations) on acts, outcomes, and contingencies (Tversky, Kahneman, & Choice, 1981). Therefore, decisions are often guided by biases and heuristics rather than stimulus-response mechanisms. Accordingly, it may be claimed that factors such as expectations, risk taking, and loss aversion would affect the performance on the cue-context reversal paradigm. If this were the case we would expect to see a robust effect of negative or positive outcome. For example, participants who avoid risk would struggle to learn negative boxes. However, note that these participants would not be able to reach the learning criterion (six consecutive correct responses) and would automatically opt out from the experiment. Moreover, even if one claims that these tendencies are more likely to affect behavior in conditions of generalization, it seems that the results of the current study do not support it. Specifically, because these tendencies represent inner values and expectations, it is not necessarily relates to PTSD, and would be expected in both PTSD and non-PTSD participants. Finally, even if such tendencies are specific to individuals with PTSD, and affects only conditions of generalization, the results of the present study show an exclusive deficit in conditions of negative context (but not cue) generalization learning. Therefore it suggests a much more specific impairment which is not necessarily relates to general tendencies and expectancies. However, future study may aim to test possible interactions between tendencies such as loss aversion, generalization learning, and PTSD in order to further clarify these points (see Schechtman, Laufer, & Paz, 2010 for a similar approach).

Additional limitation that must be taken into consideration when interpreting our results is that, although the cue-context reversal paradigm was designed to detect hippocampal related deficits, it is an oversimplification to imply that performance on a given task can be identified with the functioning of a specific brain region. In addition, the results reflect only structural mechanisms in PTSD. In order to further understand the role of the hippocampus in PTSD, it is important to test the interactions between the hippocampus and other brain regions such as the amygdala during task performance. This is especially important in order to better understand why overgeneralization of context in PTSD individuals is limited to negative conditions. Finally, the results in this small sample suggest that overgeneralization of negative context among PTSD participants is not a function of medication status; however, these are only preliminary results. Further studies with greater statistical power are needed to address this issue definitively.

Conclusions

In conclusion, our results demonstrate a strong association between overgeneralization of negative context and bilateral hippocampal volume and contribute to the understanding of the hippocampus role in PTSD etiology and symptomology. It also suggests that the cue-context reversal paradigm may provide inexpensive and rapid screening for mild deficits in hippocampal function and form the basis for developing a set of effective tools that may help in diagnosing and evaluating PTSD and treatment efficacy.

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Received November 19, 2013
Revision received June 16, 2014
Accepted June 27, 2014 ■

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