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Individuals With Posttraumatic Stress Disorder Show a Selective Deficit in Generalization of Associative Learning

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Objective: Drawing on two different populations, Israeli police and Hungarian civilians, the present study assessed the ability of individuals with posttraumatic stress disorder (PTSD) to generalize previous learning to novel situations. Past neuroimaging studies have demonstrated diminished medial temporal lobe (MTL) activation and/or reduced hippocampal volume in individuals with PTSD. Our earlier computational models of cortico-hippocampal function and subsequent experimental tests of these models in MTL-impaired clinical populations argue that even mild hippocampal dysfunction may result in subtle impairments in generalization. Therefore, we predicted that individuals with PTSD would show impaired generalization. ***Method:*** We compared the performance of five groups from two countries, including 19 Israeli police with PTSD and 22 trauma-exposed police without PTSD, and 22 Hungarian civilians with PTSD, 25 trauma-exposed civilians without PTSD, and 25 individuals without PTSD unexposed to the same trauma. Participants were tested on a two-phase learning paradigm, the Acquired Equivalence Task, which measures the ability to generalize past learning to novel situations. ***Results:*** We found that both PTSD and non-PTSD participants were capable of learning the initial stimulus-outcome associations, $F(4, 108) = 1.79$, $p = .14$. However, as predicted, only individuals with PTSD showed a selective deficit in generalization of this learning to novel situations ($F(4, 108) = 8.35$, $p < .001$, Partial $\eta^2 = 0.26$). ***Conclusions:*** Individuals with PTSD show a selective impairment in generalization of past learning

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similar to other clinical populations with MTL/hippocampal dysfunction. This is consistent with an emerging view of PTSD as being not only an anxiety disorder but also a learning disorder.

Keywords: PTSD, learning, hippocampus, generalization

The present study tests whether individuals with posttraumatic stress disorder (PTSD) show a selective generalization impairment consistent with an emerging view of PTSD as being not only an anxiety disorder but also a learning disorder (Brewin et al., 2010; for review see Acheson et al., 2011). We first briefly review previous findings demonstrating reduced hippocampal volume in individuals with PTSD. Later we argue that according to previous computational and experimental studies of hippocampal function, people with PTSD may exhibit patterns of impaired generalization of learning. We test this prediction in two populations of individuals with PSTD (Israeli police and Hungarian civilians) using a two-phase associative-learning task in which participants are required to appropriately generalize past learning to novel situations.

Among other brain abnormalities, including hyperactivity of the amygdala, and hypoactivity of ventromedial prefrontal cortex (for review see Koenigs & Grafman, 2009), research has revealed that individuals with PTSD have reduced hippocampal volumes in comparison to healthy controls (e.g., Bremner et al., 2003; Gilbertson et al., 2002; Gurvits et al., 1996; Stein et al., 1997; Villarreal et al., 2002; Wignall et al., 2004; but see also Bonne et al., 2001 for opposite results; for meta-analyses see Karl et al., 2006; Smith, 2005; and Woon, 2010). However, while there is general agreement that small hippocampi are frequently found in people with PTSD, it is unclear how this structural deficit influences cognition (for review see Woodword et al., 2009).

Computational modeling theories argue that the hippocampus and surrounding medial temporal lobes (MTL) play a critical role in learning new stimulus-stimulus representations, especially those involved in encoding the relevant context within which learning took place (Gluck & Myers, 1993, 2001). This suggests that people with small or dysfunctional hippocampi may fail to appropriately encode the context in which a traumatic association was originally learned (see also Brewin et al., 2010, and Bisby et al., 2010 for similar impairment in recognition memory). As shown in several theoretical and experimental studies, this contextual-encoding deficit may then lead to subsequent inappropriate generalization of past learning to novel situations in the form of either over- or undergeneralization (Kéri et al., 2005; Myers et al., 2003).

The present study assesses this hypothesis by using an Acquired Equivalence Task, in which prior training to treat two stimuli as equivalent increases the tendency to subsequently generalize rules regarding one stimulus to the other, even when those stimuli are superficially very different (Bonardi, Rey, Richmond, & Hall, 1993; Grice & Davis, 1960; Hall, Ray, & Bonardi, 1993; Myers et al., 2003). Specifically, this task has two phases: initial training and generalization. Although the initial training phase, which involves learning stimulus-outcome associations, does not depend on the MTL (Kéri et al., 2005; Myers et al., 2008; Myers et al., 2003), the latter generalization phase is thought to be MTL-dependent. For example, Myers and colleagues (2003) found spared stimulus-outcome associative learning but impaired ability to generalize in a sample of nondemented elderly with documented mild hippocampal atrophy. A similar pattern was demonstrated among different disorders that involve MTL dysfunction such as schizophrenia (Kéri et al., 2005; Shohamy et al., 2010) and mild Alzheimer's disease (Bódi et al., 2009). Finally, rats with hippocampal-region lesions have shown a selective impairment in the generalization phase (Coutureau et al., 2002). Human studies that applied different generalization tasks revealed similar results emphasizing the essential role of the hippocampus and related MTL regions in generalization (e.g., Levy-Gigi, Kelemen, Gluck, & Kéri, 2011; Myers et al., 2002). For example, Myers and colleagues (2002) have found that the ability to generalize rules to novel contexts is impaired in nondemented elderly with documented mild hippocampal atrophy. Later studies by Myers and colleagues showed that poor generalization predicted cognitive status two years later (Myers et al., 2008).

In the present study we used the Acquired Equivalence Task to examine whether generalization across contextual and task-demand changes will be impaired in PTSD. To that end, we compared the performance of PTSD and non-PTSD matched controls that were exposed to similar traumatic events. To control for possible effects of type of trauma and culture (Neria, Nandi, & Galea, 2008) we tested individuals from two different backgrounds. The first includes active-duty Israeli police who served as first responders to trauma in high-risk units (such as the Bomb Squad or Victims Identification Unit). The second includes Hungarian civilians who were exposed to a large environmental disaster in Hungary. We predicted that both PTSD and non-PTSD individuals would be able to learn stimulus-outcome associations equally well. However, individuals with PTSD should show a selective deficit when generalizing a set of learned rules to a novel context, much as had been seen previously among people with documented MTL dysfunction or atrophy. In addition, we predicted that similar results would be obtained in the Israeli and Hungarian groups and would not be affected by their different cultural backgrounds or type of trauma. Finally, we tested a fifth group of matched Hungarian civilians who were not exposed to the same traumatic event (i.e., non-PTSD nonexposed), to control for the effects of trauma exposure and other personal variables such as depression, anxiety, and inhibition. We predicted that their performance would not differ significantly from the performance of non-PTSD trauma-exposed individuals.

We used self-report questionnaires to measure state and trait anxiety, depression, and behavioral inhibition to detect possible differences between the experimental groups and to test whether such differences might account for variations in generalization performance. Anxiety relates to a tendency to perceive stressful situations as dangerous or threatening (Spielberger et al., 1983). Individuals with PTSD demonstrate higher levels of anxiety compared to non-PTSD controls (e.g., Casada & Roache, 2005, 2006; Orsillo et al., 1996). Behavioral inhibition is defined as a temperamental tendency to withdraw from or avoid novel situations

(Gladstone & Parker, 2005; Morgan, 2006). It was found that individuals who report avoidance symptoms or demonstrate avoidant behavior have a higher risk of developing PTSD (Gil & Caspi, 2006; North et al., 1999). Depression is commonly comorbid with PTSD. Individuals who were exposed to trauma are more likely to exhibit depression symptoms relative to those with no trauma history (e.g., Roberts, Damundu, Lomoro, & Sondorp, 2009). In addition, history of major depressive disorder was found to increase the risk for PTSD (Brewin, Andrews, & Valentine, 2000; Ozer et al., 2003). Finally, anxiety, behavioral inhibition and depressive symptoms are all strongly associated with PTSD symptom severity (Asmundson & Stapleton, 2008; Jurbergs & Long, 2009; Myers et al., 2012; Myers, VanMeenena, & Servatius, in press; Zatzick et al., 2006).

Method

Participants

We studied initial learning and generalization of participants in five groups from different backgrounds (see Table 1 for a detailed description of the sample). In Israel, we tested 19 individuals with PTSD and 22 trauma-exposed controls without PTSD. All participants were active-duty Israeli police who served as first responders in high-risk units such as the Bomb Squad or Victims Identification Unit and were exposed to similar traumatic events. Diagnosis of PTSD was established using the Mini-International Neuropsychiatric Interview (M.I.N.I.) PTSD module administered by a trained clinical psychologist (Sheehan et al., 1998).

In Hungary, we tested 22 individuals with PTSD, 25 trauma-exposed controls without PTSD, and 25 individuals without PTSD who were not exposed to the same traumatic event as the two other groups. Participants from the first two Hungarian groups were exposed to a large environmental disaster in Hungary. On October 4, 2010, a dam containing a reservoir of sludge owned by an aluminum company ruptured and released hundreds of thousands of cubic meters of toxic red sludge, which inundated the towns of Kolontar, Devecser, and Somlovasarhely. Individuals comprising the trauma-exposed Hungarian groups lived on streets destroyed by the flood. We created a set of five trauma indicators for this event based on criteria previously used and validated as sufficient to define a traumatic event that may produce PTSD in similar disasters (Freedy, Resnick, & Kilpatrick, 1993; Freedy, Saladin, Kilpatrick, Resnick, & Saunders, 1994). In accordance with previous studies, exposure was defined by two or more of the following five indicators: (1) present during red-sludge flooding; (2) lack of adequate access to food, water, electricity, telephone, or clothing for a week or longer; (3) two or more disaster-related losses of furniture, sentimental possessions, automobile, pets, crops, trees, or garden; (4) displacement from home for one week or longer; and (5) loss of 200,000 Hungarian Forints ($1,000) or more that were not covered by insurance. A third group of Hungarian healthy controls, who were not exposed to the same traumatic event as the two other groups, was included and matched for age and level of education. The Hungarian participants were assessed with the Structured Clinical Interview for *Diagnostic and Statistical Manual for Mental Disorders-Fifth Edition* (*DSM–IV*) Axis I Disorders (SCID-CV) (First, Spitzer, Gibbon, & Williams, 1996).

Exclusion criteria for all participants were current or past diagnosis of an organic mental, schizophrenic, paranoid, bipolar, or other psychotic disorders; risk of suicidal/homicidal ideation; any substance dependence or abuse within the past 6 months; a history of concussion or other clinically significant head injury, including loss of consciousness for over 10 min; or a history of neurologic disorder such as epilepsy, multiple sclerosis, stroke, or encephalitis.

PTSD and non-PTSD participants from the same origin (Israel or Hungary) did not differ significantly in mean age and years of education (all p values $> .1$). However, participants in the Israeli sample were significantly older, $F(4, 108) = 6.98$, $p < .001$ and had a higher level of education, $F(4, 108) = 15.41$, $p < .001$ than participants in the Hungarian sample (see Table 1 for a detailed comparison between the groups).

Out of 41 individuals with PTSD who participated in this binational study, 22 reported taking antidepressant medications (18 received selective serotonin reuptake inhibitors (SSRIs) and 4 received tricyclic antidepressants), 18 were unmedicated and one participant refused to provide information regarding his therapy. None of the participants in the control groups ($n = 72$) reported receiving antidepressants or any other psychotherapeutic medication (see Table 1). The study was done in accordance with the Declaration of Helsinki and received institutional ethics approvals from Rutgers University, Szeged University, and the Israel Police. After a complete description of the

Table 1
Demographic Characteristics of the PTSD and Non-PTSD Groups

	Israel		Hungary		
	PTSD	Non-PTSD	PTSD	Non-PTSD exposed	Non-PTSD nonexposed
Number of participants	19	22	22	25	25
Men/women	16/3	21/1	12/10	14/11	13/12
Age (years)	44.53_{a} (5.39)	41.91_{a} (6.75)	32.5_{b} (9.5)	36.76_{b} (10.34)	$33.52_{a,b}$ (11.28)
Education (years)	14.53_{a} (1.58)	14.73_{a} (1.75)	10.86_{b} (3.1)	11_{b} (2.6)	10.52_{b} (3.12)
Antidepressant medications (number of participants)	9/18[a]	0/22	13/22	0/25	0/25

Note. Detailed description of the study's sample. Means with differing subscripts within rows are significantly different at the $p < .05$ based on Scheffé's post hoc paired comparisons.
[a] One participant refused to provide information.

experimental procedures, a signed informed consent was obtained from each participant.

The Acquired Equivalence Task

This computer-based task (Myers et al., 2003; Myers, Hopkins et al., 2008) includes two phases: acquisition and generalization. In the acquisition phase, participants view three stimuli simultaneously (a face and two colored-fish) and are required to learn by trial-and-error which fish belongs with which face. For example, for some subjects, faces A and B might be associated with a red fish, and faces C and D with a green fish (see Figure 1 for a schematic illustration of the task and Table 2 for a complete summary of the task design). In this way, pairs of faces can be treated as "equivalent" based on their association with the same color fish. For example, even though faces A and B look quite different, each is associated with a red fish; therefore, participants may create a functional "equivalence" between them. Later in the acquisition phase, participants are exposed to new face–fish associations that include just one of the two faces studied previously (e.g., face A is now paired with a purple fish), in addition to the old face–fish associations. To complete the acquisition phase and move on to the generalization phase, participants must learn both the old and new face–fish associations to a criterion of 12 consecutive correct responses. The generalization phase started immediately after the acquisition phase without any signaled switch or delay.

In the generalization phase of the study, participants are tested on all the trained fish–face associations from the acquisition phase (retention trials) as well as novel fish–face trials, all without feedback. This phase tests whether participants show generalization, defined as the ability to use the same rules that were studied regarding one face (i.e., face A is associated with a purple fish) to the other functionally equivalent face (i.e., face B should be associated with a purple fish, too), even though this latter fish–face association had never been trained. In this phase, we refer to appropriate generalization as a "correct" response (i.e., associating face B with a purple fish) and impaired generalization (i.e., associating face B with a blue fish that was never presented before) as an "error."

Self-Report Questionnaires and Cognitive Assessment

All participants completed the following self-report questionnaires (translated to Hebrew or Hungarian): BDI-II (Beck Depression Inventory-II; Beck, Steer, Ball, & Ranieri, 1996), STAI (State–Trait Anxiety Inventory; Spielberger, Gorssuch, Lushene, Vagg, & Jacobs, 1983), PCL-C (PTSD Check-List-civilian version; Weathers et al., 1993), AMBI/RMBI (Adult Measure of Behavioral Inhibition/Retrospective Measure of Behavioral Inhibition; Gladstone & Parker, 2005) that were previously validated in their translated form. In addition, we used the scaled scores of the Block Design, a subtest of the Wechsler Adult Intelligence Scale IV (WAIS-IV) to compare the estimated IQ levels between groups from Israel and Hungary (Pearson Education, inc., 2008). Scores from this subtest have been found to be the best nonverbal predictor of full IQ scale scores in adults in older versions of the test (Spreen & Strauss, 1998).

Table 3 depicts the comparison of individuals from the five tested groups on the self-report questionnaires and IQ assessment. Overall, individuals with PTSD from both Israel and Hungary exhibited significantly higher levels of PTSD and depression symptoms, compared to the other three non-PTSD groups. Stress symptoms (both trait and state) were similar for all groups except-

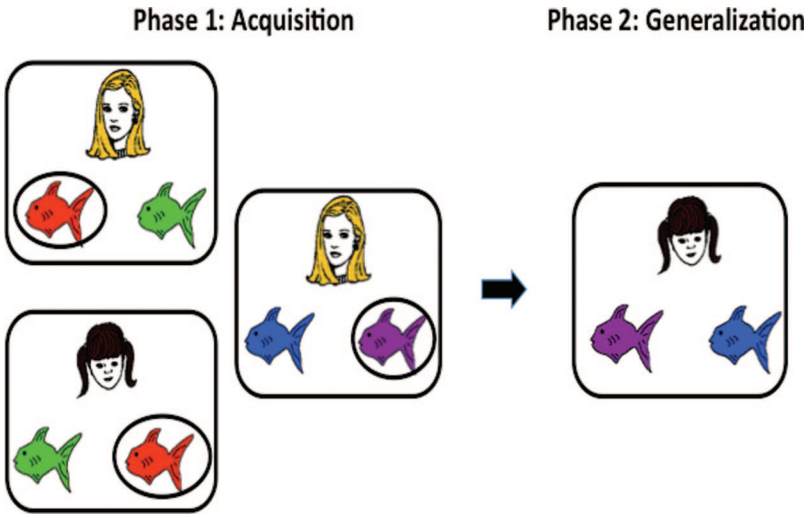

Figure 1. The Acquired Equivalence Task paradigm. In the first phase of acquisition, participants might learn, through trial and error with feedback, that the blonde girl with long hair and the brunette girl with ponytails both prefer the red fish over the green fish (actual features of the people are counterbalanced across subjects; see Table 1 for summary of the full experimental design). In the second phase of acquisition, participants would then learn that the blonde girl with long hair also prefers the purple fish over the blue fish. In the generalization phase, they would then be asked if the brunette girl with ponytail prefers the purple fish or the blue fish. Learning in this generalization phase is facilitated if the participants generalize the previously learned rule (both girls have same preferences) and infer from this that the brunette girl with ponytails also prefers the purple fish.

Table 2
Acquired Equivalence Task Paradigm

Acquisition			Generalization
Face A → Fish 1	Face A → Fish 1	Face A → Fish 1	
	Face B → Fish 1	Face B → Fish 1	
Face C → Fish 2	Face C → Fish 2	Face C → Fish 2	
	Face D → Fish 2	Face D → Fish 2	
		Face A → Fish 3	Face B → Fish 3?
		Face C → Fish 4	Face D → Fish 4?

ing that: the Hungarian non-Exposed group showed significantly less symptoms on both measures, and the Hungarian non-PTSD group showed an intermediate level of trait related symptoms. Finally, individuals with PTSD showed higher levels of retrospective behavioral inhibition (both Israeli and Hungarian groups) and adult behavioral inhibition (only Hungarian group), compared to both non-PTSD from Israel and non-Exposed individuals from Hungary (see Table 3). Estimated IQ scores as measured by Block Design (WAIS-IV) scaled scores did not differ across groups.

Results

Phase 1: Acquisition of Associations Between Stimuli

We conducted a one-way ANOVA with group (PTSD-Israel, non-PTSD Israel, PTSD-Hungary, non-PTSD Hungary, and non-exposed Hungary) as the independent variable and the number of incorrect responses in the acquisition phase as the dependent variable. The ANOVA revealed no significant effect of group on performance, $F(4, 108) = 1.79$, $p = .14$, indicating that all groups were equally able to acquire new information in the first phase of training (see Figure 2).

Phase 2: Generalization to New Pairs

We conducted a mixed-design ANOVA, with group (PTSD-Israel, non-PTSD Israel, PTSD-Hungary, non-PTSD Hungary, and non-exposed Hungary) as a between-subjects variable and learning type (retention vs. generalization) as a within-subject variable. As seen in Figure 3, the ANOVA revealed a significant main effect of group ($F(4, 108) = 9.33$, $p < .001$, Partial $\eta^2 = 0.26$), learning type ($F(1, 108) = 32.46$, $p < .001$, Partial $\eta^2 = 0.23$), and most importantly, a significant interaction between group and learning type ($F(4, 108) = 8.35$, $p < .001$, Partial $\eta^2 = 0.26$).

We conducted post hoc F tests with Bonferroni correction ($\alpha = .025$) and found that while there were no significant differences in retention between the groups, $F(4, 112) = 1.64$, $p = .17$, there were significant differences in generalization, $F(4, 112) = 11.62$, $p < .0001$. Scheffé post hoc tests revealed that the two PTSD groups had a significantly higher percentage of generalization errors compared to the three non-PTSD groups. There were no significant differences in generalization between groups with the same diagnosis (PTSD or non-PTSD).

Finally, follow-up pairwise comparisons with Bonferroni correction ($\alpha = .01$) showed that there were no significant differences between retention and generalization in the non-PTSD groups (non-PTSD group, Israel: $t(21) = -.20$, $p = .84$; non-PTSD group, Hungary: $t(24) = -1.08$, $p = .29$; nonexposed group, Hungary: $t(24) = -1.37$, $p = .18$) However, in the PTSD groups the percentage of generalization errors was significantly higher than the percentage of retention errors (Israeli PTSD group: $t(18) = -3.10$, $p < .01$, $\eta^2 = 0.35$; Hungarian PTSD group: $t(21) = -4.52$, $p < .001$, $\eta^2 = 0.49$).

The balanced distribution of gender in the Hungarian group (39 men; 33 women) allowed us to test whether men and women performed differently on the generalization phase. The result revealed that there were no differences in generalization performance as a function of gender, $t(70) = 0.24$, $p = .81$.

Table 3
Comparison of Individuals From the Five Groups on the Self-Report Questionnaires and IQ Assessment

	PTSD Israel	Non-PTSD Israel	PTSD Hungary	Non-PTSD exposed Hungary	Non-PTSD Non-exposed Hungary	F	p
PCL-C	58.21_{a} (8.31)	$28.41_{b,c}$ (14.58)	59.45_{a} (8.34)	31.88_{b} (8)	21.44_{c} (4.77)	80.67	<.0001
BDI-II	24.53_{a} (11.17)	8.36_{b} (7.85)	24.41_{a} (10.39)	10.32_{b} (4.22)	6.96_{b} (3.46)	27.97	<.0001
STAI-Trait	50.21_{a} (4.85)	$46.59_{a,b}$ (4)	49.14_{a} (5.31)	43.48_{b} (8.01)	30.36_{c} (6.58)	41.76	<.0001
STAI-State	49.63_{a} (5.89)	48.14_{a} (6.23)	49_{a} (5.75)	48.72_{a} (9.15)	29.76_{b} (7.9)	34.06	<.0001
AMBI	$19.37_{a,b}$ (8.55)	12_{b} (7)	20.82_{a} (8.75)	$17.04_{a,b}$ (9.63)	11.96_{b} (7.69)	5.36	<.005
RMBI	14.68_{a} (5.22)	8.68_{b} (3.15)	14.32_{a} (5.37)	$11.32_{a,b}$ (4.91)	8.68_{b} (5.73)	7.46	<.0001
Estimated IQ	10.68_{a} (1.73)	11.55_{a} (2.34)	9.95_{a} (1.76)	11.08_{a} (2.2)	11.36_{a} (2.02)	2.14	>.05

Note. Comparison of individuals from the five tested groups on the self-report questionnaires and IQ assessment. Data are means and standard deviations, compared with one-way ANOVAs. All dfs = (4,108). BDI-II (Beck Depression Inventory-II), STAI (State-Trait Anxiety Inventory), PCL-C (PTSD Check-List-civilian version), AMBI/RMBI (Adult Measure of Behavioral Inhibition/Retrospective Measure of Behavioral Inhibition), Estimated IQ as measured by the Wechsler Adult Intelligence Scale- WAIS-IV subtest-Block Design. Means with differing subscripts within rows are significantly different at the $p < .05$ based on Scheffé's post hoc paired comparisons.

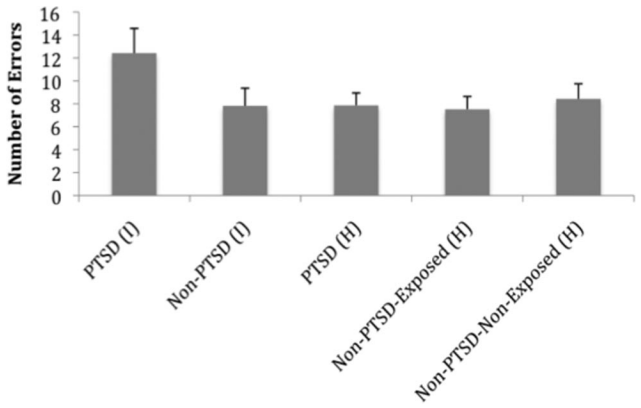

Figure 2. Acquisition among the five participants' groups. Performance on the acquisition phase: PTSD and non-PTSD participants learn associations between two stimuli equally well. I = Israel; H = Hungary.

We used the median number of errors to divide the participants into two groups according to their performance on the generalization phase. Chi-square test reveals that the number of PTSD participants in the first group (lower than the median) is significantly higher than the number of non-PTSD participants. While the number of non-PTSD participants in the second group (higher than the median) is significantly higher compared with the number of non-PTSD participants ($\chi^2(1) = 16.3$, $p < .0001$). The distribution of error scores for non-PTSD participants is relatively small ($M = 1.4$, $SD = 2.06$), whereas that for PTSD participants is much wider ($M = 5.2$, $SD = 3.99$).

To summarize, our results indicate that individuals with PTSD are significantly impaired (as compared with healthy controls) when asked to apply their previous learning to new situations, and this impairment is consistent across both the Israeli and Hungarian samples despite considerable differences in cultural background and type of trauma to which they were exposed.

To examine which variables best predict generalization, we conducted a stepwise regression with PCL-C, BDI-II, STAI, AMBI/RMBI, and Block Design as the predictor variables and generalization as the dependent variable. We found that the strongest predictor for performance were the PTSD symptoms as measured by the PCL-C ($r = .53$). This one factor model accounts for significant variance in generalization of learning, $F(6, 106) = 6.71$, $p = .001$. Other factors did not contribute significantly to accounting for additional variance in generalization learning (all $p > .05$).

Effects of Medication

PTSD participants in the current study were either unmedicated ($n = 18$) or on different antidepressant medications ($n = 22$). As a preliminary assessment of the effect of medications on generalization in PTSD, we conducted a mixed-design ANOVA with medication status as a between-subjects variable (unmedicated vs. medicated) and learning type (retention vs. generalization) as a within-subject variable. Both groups had normal distributions. We found that there was no significant interaction between medication status and learning $F(1, 38) = 1.97$, $p = .17$. The results in this small sample, however, suggest that the generalization deficit among PTSD participants is not a function of medication status, but further studies with greater statistical power are needed to definitively address this issue.

Discussion

To test a possible role of the hippocampus in generalization of associative learning we compared the performance of individuals with PTSD and non-PTSD matched controls from different cultural backgrounds and different types of trauma. As predicted, the performance of individuals with PTSD was found to be similar to that of populations with MTL atrophy or deficit. Both PTSD and non-PTSD participants were able to learn stimuli-outcome associations in phase 1; however, only individuals with PTSD showed a selective deficit in generalization in phase 2. The results support our claim regarding inappropriate generalization processes in PTSD and are consistent with a recent study showing overgeneralization of autobiographical memories among individuals with PTSD (Brown et al., 2012).

In accordance with previous reports in the literature (e.g., Gilbertson et al., 2008), individuals with PTSD showed significantly higher levels of PTSD symptoms in addition to elevated levels of depression. However, only PTSD symptoms were found to be a strong predictor for poorer generalization; measures of depression, anxiety, inhibition, and IQ did not significantly explain additional variance in generalization scores.

There were no significant differences between the Israeli and Hungarian participants in both the initial training and generalization, suggesting impaired generalization associated with PTSD is not affected by different cultural backgrounds (Israel vs. Hungary) or type of trauma (combat vs. civilian-related trauma). These results were obtained even though different instruments, both based on *DSM–IV* criteria, were used to establish the PTSD diagnosis in Israel and Hungary.

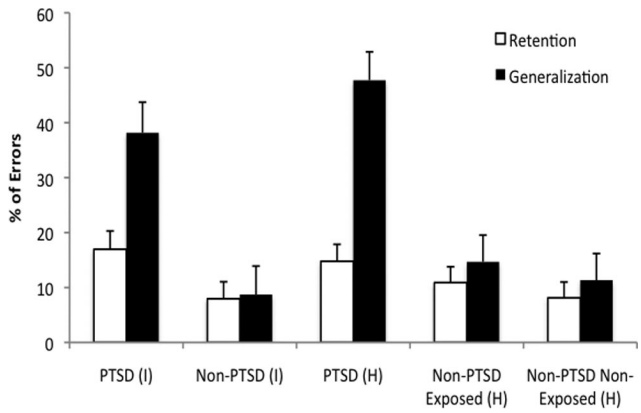

Figure 3. Retention versus generalization among the five participants' groups. Performance on the retention and generalization phases: PTSD participants from Israel and Hungary are significantly impaired when applying rules that were learned in one context, to a different new context. Non-PTSD participants have intact generalization learning. I = Israel; H = Hungary.

Open Questions and Future Directions Regarding Generalization in PTSD

Interestingly, when examining individual performance during the generalization phase, while most PTSD participants performed at a chance level, some individuals showed an opposite-generalization strategy (errors $> = 80\%$, $N = 10$). Thus, instead of guessing or using the appropriate criterion to solve the task, some individuals with PTSD seem to be using an alternative and opposite generalization rule. Comparisons between PTSD participants using different strategies (i.e., correct generalization, chance, and opposite generalization) revealed no significant differences in terms of performance on other phases of the tasks (initial training and retention), self-report questionnaires, or IQ assessment. Further research is needed to better describe and further understand the reasons that lead to this opposite-generalization strategy.

In our model, hippocampal deficit results in inappropriate generalization of past learning to novel situations and may take the form of either over- or undergeneralization. It is possible that the form of the impairment depends on the stimulus valance. As we showed in the current study in which we used neutrally valenced stimuli, individuals with PTSD fail to generalize past learning to novel situations. However, in case of stimuli with a negative valence and strong arousal it is possible that they may show overgeneralization, reflecting a tendency to generalize fear responses to stimuli outside the trauma context. Future studies may wish to compare these two conditions.

Open Questions and Future Directions Regarding Role of Medications

Several studies have found that treatment with medications such as SSRIs (i.e., paroxetine and sertraline) and anticonvulsants that modulate glutamatergic transmission (i.e., phenytoin), resulted in increased hippocampal volume and diminished PTSD symptoms among PTSD patients (Bossini et al., 2007; Bremner et al., 2005; Vermetten et al., 2003). In addition, two studies have found that treatment also improved hippocampal-dependent memory performance (Bremner, 2006; Vermetten et al., 2003; see also Bremner, 2005). The present study could not optimally address potential medication effects because of the wide range of medications that were used, the relatively small sample size. A recent review (Lanius et al., 2010) showed that most commonly prescribed medications do not affect task performance among individuals with PTSD. However, this meta-analysis included many different tasks and did not focus on hippocampal-dependent skills. Future studies with larger enrollment will be needed to address more directly the role of medications in mediating changes in cognitive functioning among those with PTSD.

The Need for Future Imaging Studies

Results of the present study are consistent with those from studies showing generalization impairment in animals with MTL lesion (Coutureau et al., 2002) and in humans across multiple disorders involving MTL dysfunction (Bódi et al., 2009; Kéri et al., 2005; Myers et al., 2008; Myers et al., 2003). One limitation of the present study is the lack of neuroimaging assessment of MTL and related areas. A future study that includes MRI screening would allow testing of the correlations between performance on the Acquired Equivalence Task and measures of hippocampus volume.

Potential Relevance to Prospective Prediction of Therapy Efficacy

The possible role played by the MTL and related areas in the generalization of associative learning in PTSD supports an innovative perspective that views PTSD, not only an anxiety and stress disorder, but also as a learning disorder (e.g., Brewin et al., 2010; for review see Acheson et al., 2011) whereby individuals form inappropriate representations of context. The etiology of PTSD might then be explained by suggesting that individuals with small or dysfunctional hippocampi may fail to appropriately encode the context in which a traumatic association was originally learned. This could lead to inappropriate generalization of past learning to the wrong contexts, especially the wrong time and place, which may facilitate the development or persistence of PTSD.

This view provides a challenge to certain behavioral therapeutic methods, such as cognitive–behavioral therapies that rely on the application of learning to new contexts, and might explain the inconsistent findings regarding the effectiveness of such therapies in treating PTSD (e.g., Mendes, Mello, Ventura, Passarela, & Mari, 2008; Seidler & Wagner, 2006; Shalev et al., 2012; Spence et al., 2011). If a PTSD patient undergoing cognitive–behavioral therapy has difficulty generalizing learning to new contexts, he or she could fail to generalize learning that occurs during therapy to the contexts of daily life. Thus, PTSD patients' ability to generalize new learning, as measured by the Acquired Equivalence Task, may predict treatment responsiveness. Future work is needed to test the possibility that performance on the Acquired Equivalence Task can predict which individuals may benefit most from cognitive–behavioral treatment.

Potential Relevance to Prospective Prediction of Risk for PTSD

Understanding the role of the hippocampus and related MTL areas in PTSD is also important because of the possible implications it has on evaluating risk for PTSD and developing ways to prevent it. Gilbertson and colleagues (2002) have demonstrated that not only do combat veterans with PTSD have a smaller-than-average hippocampal volume, but so do their noncombat-exposed, non-PTSD identical twins. This finding raises the possibility that smaller hippocampal size is a pretrauma risk factor for the development of PTSD. By way of comparison, Gilbertson and colleagues have shown that other markers of PTSD, including reductions in frontal lobe volume and heightened heart rate acceleration in response to loud tones, do not appear in the individuals' nonexposed twins (Kasai et al., 2008; Orr et al., 2003). Thus, variation in hippocampal size is probably a preexisting risk factor for developing PTSD and is not simply the consequence of exposure to stress. The role of a small hippocampus in increased risk for PTSD may include either or both of (1) increasing the risk of inappropriate traumatic responses at a later time and place, and/or (2) decreasing efficacy of behavioral and cognitive therapies; future study that uses structural magnetic resonance imaging scans

before and after treatment is required to better assess the contribution of each of these factors.

The present study's demonstration of the Acquired Equivalence Task as a potential measure of hippocampal deficit among individuals with PTSD is a first step toward a more comprehensive prospective study that would assess correlations between hippocampal volume, measured from structural magnetic resonance imaging, and performance on this and other learning-transfer tasks. If a generalization deficit is found to be present before exposure to a traumatic event in those people who subsequently develop PTSD, the Acquired Equivalence Task may provide an inexpensive, rapid, and automated screening for mild deficits in hippocampal-function that may represent an elevated risk for developing PTSD.

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