Altered Neural and Behavioral Associability-Based Learning in Posttraumatic Stress Disorder

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ABSTRACT

Posttraumatic stress disorder (PTSD) is accompanied by marked alterations in cognition and behavior, particularly when negative, high-value information is present (Aupperle, Melrose, Stein, & Paulus, 2012; Hayes, Vanelzakker, & Shin, 2012) . However, the underlying processes are unclear; such alterations could result from differences in how this high value information is updated or in its effects on processing future information. To untangle the effects of different aspects of behavior, we used a computational psychiatry approach to disambiguate the roles of increased learning from previously surprising outcomes (i.e. associability; Li, Schiller, Schoenbaum, Phelps, & Daw, 2011) and from large value differences (i.e. prediction error; Montague, 1996; Schultz, Dayan, & Montague, 1997) in PTSD. Combat-deployed military veterans with varying levels of PTSD symptoms completed a learning task while undergoing fMRI; behavioral choices and neural activation were modeled using reinforcement learning. We found that associability-based loss learning at a neural and behavioral level increased with PTSD severity, particularly with hyperarousal symptoms, and that the interaction of PTSD severity and neural markers of associability based learning predicted behavior. In contrast, PTSD severity did not modulate prediction error neural signal or behavioral learning rate. These results suggest that increased associability-based learning underlies neurobehavioral alterations in PTSD.

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Introduction

Posttraumatic stress disorder (PTSD) is a debilitating psychiatric disorder characterized by sustained psychological and physiological responses to reminders of traumatic events. Symptoms of PTSD fall into four clusters: re-experiencing the traumatic event, avoidance of trauma reminders, blunted positive affect, and hyperarousal to threat (King, Leskin, King, & Weathers, 1998). Although great strides have been made toward understanding the pathophysiology of PTSD, particularly in terms of its neurobiological underpinnings (Aupperle et al., 2012; Hayes et al., 2012; Rauch, Shin, & Phelps, 2006) much is yet unclear about the disorder. Computational psychiatry, an approach combining quantitative specification of neural and behavioral processes with clinical investigation of mental illness (Lee, 2013; Montague, Dolan, Friston, & Dayan, 2012; Wang & Krystal, 2014), offers a powerful approach to provide more clarity into PTSD.

Altered learning and attentional processes are strongly connected to disrupted functioning in posttraumatic stress disorder. Neuropsychological studies of basic cognitive processes have found reduced performance in PTSD, particularly for attention, processing speed, and verbal learning (Qureshi et al., 2011; Scott et al., 2015). These effects are present when controlling for trauma exposure but may be modulated by overall cognitive capability and gender. Given the role of trauma-related reminders in impairment in PTSD, several studies have examined the additional effect of emotional and trauma-related stimuli during cognitive tasks. These studies have consistently found altered neural activation in a network involving anterior cingulate cortex, amygdala, ventromedial prefrontal cortex, insula, and lateral prefrontal regions (Brown & Morey, 2012; Hayes et al., 2012). However, behavioral results are more mixed, with some studies finding decreased functioning in the presence of distracting emotional and traumatic stimuli (Chemtob et al., 1999; Morey et al., 2009; Vythilingam et al., 2007) and others finding no effect (Blair et al., 2013). In addition, participants with PTSD show improved performance when attention to negative stimuli aids performance (Vythilingam et al., 2007). This facilitation versus interference effect is most obvious when examining a specific form of learning, fear conditioning and extinction. Participants with PTSD have increased responses during conditioning but show impairments during extinction (Fani et al., 2012; Milad et al., 2008; Norrholm et al., 2011; Orr et al., 2000; Peri, Ben-Shakhar, Orr, & Shalev, 2000). Studies of fear conditioning and extinction show diagnostic specificity; though other processes are disrupted in both PTSD and depression, which are highly comorbid (O'Donnell, Creamer, & Pattison, 2004; Zoellner, Pruitt, Farach, & Jun, 2013), altered fear learning appears to be unique to PTSD (Jovanovic et al., 2010).

Efforts to unify these findings have focused on the effects of salient or 'high value' stimuli, particularly negative stimuli, on functioning in PTSD over and above the effects of trauma exposure, gender, and comorbid depression (Aupperle et al., 2012; Hayes et al., 2012). These stimuli command additional cognitive resources in PTSD, facilitating performance when high-value negative information is useful and impairing performance when it is not. What aspect of value is responsible for this effect in PTSD is yet unclear; increased cognitive processing could occur when negative stimuli are unexpected, when they carry significant information, or both. Using a computational psychiatry approach to model different aspects of cognitive processes can disambiguate these influences.

Reinforcement learning (RL; Sutton & Barto, 1998), which models how organisms learn from positive and negative information, has helped to illustrate disrupted learning processes in several

mental illnesses (Montague et al., 2012; Stephan & Mathys, 2014). The basic premise of reinforcement learning is that learning occurs when the predicted value of a stimulus is different than the value received; this difference is called prediction error. If these values are equal, learning is not necessary. A portion of prediction error, determined by a quantitative parameter called learning rate, is used to update the predicted value for the next time the stimulus is encountered. Prediction error magnitude for reward corresponds to neural dopamine signaling from midbrain dopaminergic areas (Bayer & Glimcher, 2005), resulting in fMRI activation in ventral striatum (O'Doherty, Dayan, Friston, Critchley, & Dolan, 2003; Pagnoni, Zink, Montague, & Berns, 2002); this dopamine signal is necessary and sufficient for learning from reward (Steinberg et al., 2013). The neural circuitry involved in learning from negative outcomes is less clear, with studies showing reduced dopaminergic firing and lower activation in ventral striatum (Bayer & Glimcher, 2005; Brooks et al., 2010) as well increased activation in a circuit including amygdala, insula, thalamus, and habenula (Bromberg-Martin & Hikosaka, 2011; Li et al., 2011; Palminteri et al., 2012). One theory of loss learning posits separate roles for the ventral striatum and amygdala (Li et al., 2011), representing dissociable cognitive processes. In this model, prediction error is represented in ventral striatum while associability, or the surprisingness of the previous outcome associated with a stimulus, is represented in the amygdala as well as insula and ventrolateral prefrontal cortex. The greater the weight placed on associability, the more the learning rate and resulting value update is modulated by previous unexpected outcomes.

Reinforcement learning has successfully explained neural and behavioral differences in a variety of psychiatric disorders, including depression (Gradin et al., 2011; Kumar et al., 2008), schizophrenia (Collins, Brown, Gold, Waltz, & Frank, 2014; Gradin et al., 2011), and substance use (Chiu, Lohrenz, & Montague, 2008; Park et al., 2010). However, RL studies of posttraumatic stress disorder are limited. One behavioral study in military veterans with and without PTSD modeled the value of feedback during learning and found that participants with PTSD found a no-feedback outcome to be more positive relative to positive and negative feedback, but did not find any differences in other learning parameters (Myers et al., 2013).

The role of associability-based learning may be especially helpful for understanding disrupted cognitive processing in PTSD. First of all, the effect of high-value, negative stimuli on cognition in PTSD is similar to the role of associability in modulating learning. Both show modulatory effects of the value of stimuli on performance as well as valence-specific effects for negative information. Secondly, the brain networks involved in associability based learning and affected in posttraumatic stress disorder, including amygdala, insula, and lateral prefrontal cortex, have significant overlap. However, instead of altering associability, posttraumatic stress disorder may instead result in differences in updating the value of negative information, which would result in changes in learning rate instead of associability. The network involved in computing value and prediction error, including striatum and ventromedial prefrontal cortex (Garrison, Erdeniz, & Done, 2013), also shows disruptions in PTSD (Felmingham et al., 2014; Rauch et al., 2006). Distinguishing whether associability- or prediction error-based learning is disrupted in PTSD has important implications for understanding the neurobehavioral processes integral to the disorder and for informing treatment targets.

To accomplish this, we conducted a learning task along with fMRI in combat-deployed military veterans with and without posttraumatic stress disorder. We hypothesized that participants with PTSD would show either increased loss learning with prediction error, reflected in increased learning rate as well as increased activation in ventral striatum and ventromedial prefrontal cortex, or that they would show increased learning from unexpected negative outcomes, reflected in increased associability in loss as well as increased activation in amygdala, insula, and ventrolateral prefrontal cortex.

Methods

Participants
74 subjects served by the Houston, TX and Salem, VA Veterans Affairs medical centers were recruited through VA medical record searches, provider referrals, and community advertisements. All participants were US military veterans with combat deployments to Iraq or Afghanistan as part of Operation Iraqi Freedom or Operation Enduring Freedom. Additional inclusion criteria included: age 18 to 64, English speaking, corrected to normal vision, estimated IQ greater than 70, no contraindications to MRI scanning (e.g. implanted ferrous metal, claustrophobia), no loss of consciousness greater than 30 minutes, no current substance abuse or dependence (excluding nicotine dependence), no history of psychotic or bipolar disorders, and exposure to trauma satisfying criterion A1 of PTSD according to the DSM-IV (American Psychiatric Association, 2000). Participants with posttraumatic stress disorder could have comorbid depression or anxiety disorders, while non-PTSD control participants were required to be free from a history of mental illness.

An additional non-veteran reference cohort (n=23) was recruited from the Houston and southwest Virginia areas. Inclusion criteria were similar to the veteran cohort with the addition that participants were required to be free from a history of psychiatric disorders as well as trauma exposure. This cohort was not included in the full body of analyses but was used to construct regions of interest for the primary neuroimaging analyses. Experimental procedures for all participants were approved by the Institutional Review Boards of Baylor College of Medicine, the Salem VA medical center, or Virginia Tech.

Measures
For the veteran cohort, psychiatric diagnoses were assessed using the Structured Clinical Interview for DSM-IV (SCID; First, Spitzer, Gibbon, & Wiliams, 1996) and the Clinician Administered PTSD Scale (CAPS; Blake et al., 1995), administered by trained study staff. The CAPS interview provides a rating of severity (frequency + intensity) for each PTSD symptom. To meet diagnostic criteria for a symptom, participants had to have a severity rating of at least 3. Total PTSD severity was constructed from the summed severity score for all symptoms. Severity scores for four symptom clusters (King et al., 1998), measuring re-experiencing (CAPS questions B1-B5), avoidance (questions C6 and C7), numbing (questions C8-C12), and hyperarousal (questions D13-D17) symptoms were created to assess the effect of each symptom cluster. Participants also completed the Beck Depression Inventory (BDI; Steer, Ball, Ranieri, & Beck, 1999) measuring depressive symptoms; the Combat Exposure Scale (CES; Lund, Foy, Sipprelle, & Strachan, 1984), measuring combat trauma exposure; the Wechsler Test of Adult

Reading (WTAR; Wechsler, 2001), measuring approximate verbal IQ; and the Brief Traumatic Brain Injury Screen (Schwab, Brenner, Heidi, Lewis, & Scher, 2013) to assess for mild traumatic brain injury. In addition, participants completed a demographics questionnaire assessing age, gender, ethnicity, years of education, and medications taken.

The non-veteran cohort had psychiatric diagnoses assessed by the SCID (n=17) or the Mini International Neuropsychiatric Interview (MINI, Lecrubier et al., 1997; n=6). In addition, participants completed the WTAR to estimate IQ as well as a demographics questionnaire to assess age and gender. To be included in analyses, participants reported no trauma exposure that qualified for Criterion A1 for PTSD according to the DSM-IV and were matched to the veteran cohort on age, gender, and estimated IQ.

Procedures
Participants completed a probabilistic gain and loss learning task (adapted from Pessiglione, Seymour, Flandin, Dolan, & Frith, 2006) while undergoing fMRI scanning (Figure 1). For each trial, two abstract stimuli were shown. Participants selected one stimulus using a MRI-compatible button box (Current Designs, Inc.). The selected stimulus was highlighted for a jittered viewing time of 2-4 seconds, after which the outcome (monetary amount) was shown. Each block of trials had the same condition (gain or loss) for all outcomes. The outcomes were classified as 'better' or 'worse' based on whether the outcome was a larger gain/smaller loss ('better') or a smaller gain/larger loss ('worse'). For gain trials, the better outcome ranged from +70 to +80 cents, while the worse outcome ranged from +20 to +30 cents. For loss trials, the outcomes similarly ranged from -20 to -30 and -70 to -80 cents. For each block, one stimulus (better choice) had an 80% probability of leading to the better outcome, while the other stimulus (worse choice) had an 80% probability of leading to the worse outcome. Stimuli changed each block. Task difficulty was titrated to each individual participant's performance, such that the task alternated between gain and loss blocks of variable lengths until participants achieved at least 25 correct and 25 incorrect choices in each of the gain and loss conditions.

Before entering the scanner, participants viewed a series of slides with task instructions and were given the opportunity to ask questions. They were not provided information about the full structure of the task but were informed that "one picture is always better than the other". They completed a practice round and were shown an envelope containing their initial endowment ($10) and were informed they could keep any money they earned from that endowment at the end of the task.

Participants were scanned on a 3T Siemens Tim Trio MR scanner. Echoplanar images were collected in 34 4mm slices at a 30° hyperangulation from the AC-PC line (TR=2000 ms, TE=30 ms, flip angle= 90°, matrix= 64 x 64). A high-resolution (1 mm^3) anatomical MPRAGE T1 image was collected to aid in registration.

Analysis
Behavioral
Model free analyses assessed proportion of correct choices (i.e. better option chosen), total money earned, and proportion switch (vs. stay) choices by condition. To ensure participants were attending to the task and had behavior suitable for model fitting (Sokol-Hessner et al., 2009),

participants who switched options in either condition less than 10% of the time were excluded (n=19). Model free behavioral measures were correlated with total PTSD severity. To account for effects of depressive symptoms, combat exposure, age, and gender, covariates of BDI, CES, age, and gender were included.

To select the reinforcement learning model that best explained participants' data, models first were tested with separate versus combined learning rates and inverse temperatures for gain and loss conditions. Next, additional parameters of associability weight, reward sensitivity, and memory retention were tested and retained if they improved model fit. Model fit was assessed using maximum likelihood estimation of participants' data pooled within each diagnostic group. Models were compared using corrected Aikaike Information Criterion (AICc; Burnham & Anderson, 2002).

For the initial model with learning rate and inverse temperature, the expected value of the stimulus on the next trial was updated with the product of the learning rate (α) and prediction error (Figure 2). The probability of each choice was modeled with a softmax function incorporating inverse temperature (β). For models including associability weight, learning rate was modulated on a trial-by-trial basis by the associability value (κ; Li et al., 2011). This value in turn was updated on each trial based on the estimated associability weight (η) and the absolute value of the prediction from the previous trial. Associability values were initialized at 1 and updated for each stimulus separately. Models with reward sensitivity (ρ; Huys, Pizzagalli, Bogdan, & Dayan, 2013) included a multiplier on the value of the larger loss or gain and models with memory retention (γ; Dombrovski, Szanto, Clark, Reynolds, & Siegle, 2013; Schlagenhauf et al., 2013) included a multiplier (value update) on the value of the unchosen option.

Once the best fitting model was chosen, individual parameter values were estimated for each participant using Bayesian estimation (Daw, 2011; Wiecki, Poland, & Frank, 2014). As a first step, a prior distribution for all parameters was constructed using Markov Chain Monte Carlo estimation. Individual estimates were then conditioned on this prior. To simplify estimation, only each parameter of interest (learning rate or associability weight) and inverse temperature were allowed to vary for each set of individual estimates. Learning rate and associability were then correlated with total PTSD severity. To account for effects of depressive symptoms, combat exposure, age, and gender, covariates of BDI, CES, age, and gender were included. Separate follow-up analyses excluded participants on psychotropic medication (n=15) and with potential mild traumatic brain injury (mTBI; n=8) and assessed the effect of each symptom cluster and each hyperarousal symptom in place of total PTSD severity.

Imaging
Imaging analyses were conducted using SPM8 for fMRI (Wellcome Trust Centre for Neuroimaging, http://www.fil.ion.ucl.ac.uk/spm/software/spm8). Preprocessing consisted of: slice timing correction, realignment to the first functional scan, coregistration to the participant's structural image, normalization to the MNI template, and smoothing to ensure Gaussianity (6mm FWHM). Participants with motion greater than 3mm or 0.5 radians in any direction were excluded (n=4). Functional images were visually inspected for signal drop out in ventral areas, including ventromedial prefrontal cortex and amygdala, and were excluded if significant signal

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loss was present (n=3). An additional two participants were excluded due to technical issues with their imaging data.

Subject-level analyses used trial-by-trial regressors for prediction error and associability calculated from participants' individual parameter estimates. Analyses of prediction error used prediction error as a paramedic modulator at the time of outcome, while associability analyses used associability value as the parametric modulator at outcome. Both analyses used probability of selection (computed by the softmax function) as a parametric modulator at time of stimulus presentation. Additional regressors of no interest included button press, block number, and six motion regressors. Data were high pass filtered with a cutoff of 128 seconds.

To assess the impact of PTSD symptoms on neural prediction error and associability, total CAPS score was entered at the group level along with covariates of BDI, CES, age, and gender. If total CAPS score showed a significant relationship, additional analyses used the four CAPS symptom cluster scores to understand the contribution of each symptom cluster. Follow-up analyses excluded participants on psychotropic medication and with mTBI. Group level analyses were set to a significance level of $p<.05$ false discovery rate (FDR) corrected for the whole brain, masked inclusively by a gray matter mask. For analyses with no CAPS effects surviving a whole brain significance threshold, regions of interest (ROIs) were constructed based on activations from the non-veteran cohort. Group-level activations for prediction error and associability were thresholded at $p<.005$ uncorrected with a cluster extent ≥ 20 voxels. Activation clusters were binarized as masks and used to create ROIs. The first eigenvariate of the beta values in each ROI was extracted for the veteran group. Values were read into R statistical software (version 3.1.0; R Foundation for Statistical Computing, http://www.R-project.org) and regressed against total CAPS scores along with covariates of BDI, CES, age, and gender. To verify intact prediction error signaling, ROIs in the striatum were used in one-way t-tests to determine if mean activation for the veteran cohort was significantly different from zero.

To confirm the relationship of associability-related brain activation and PTSD severity with behavior, anatomically defined ROIs of amygdala and anterior insula, as well as a comparison ROI of ventral striatum, were created (amygdala from centromedial and laterobasal subregions from the Jühlich atlas, Amunts et al., 2005; anterior insula from portion of insula anterior to y=10 from the AAL atlas, Tzourio-Mazoyer et al., 2002; and ventral striatum from the IBASPM atlas as part of the WFU PickAtlas, Maldjian, Laurienti, & Burdette, 2004; Maldjian, Laurienti, Kraft, & Burdette, 2003). In addition, a functional mask was created based on the group level effect of PTSD severity on associability, thresholded at $p<.05$ FDR corrected and binarized. The first eigenvariate of the beta values of associability- and prediction error-related activation was extracted from these ROIs. The interaction of these values with PTSD severity was entered into a mixed effects logistic regression model to predict the likelihood of switching behavior for each trial, controlling for the previous three trials' outcomes and for the nesting of trials within subjects. Likelihood ratio tests compared this model to a model without the interaction of PTSD severity and neural activation to assess if this interaction added significant explanatory power to the model. Follow-up analyses examined the role of symptom cluster severity in place of total PTSD severity as well as the role of each hyperarousal symptom cluster. To determine if prediction-error related activity affected switching behavior independent of PTSD, models with

and without the main effect of prediction error-related brain activity (both with no interaction with PTSD severity) were compared.

Results
Behavioral
45 participants were included in analyses. Basic clinical and demographic information is reported in Table 1 for included participants. Included and excluded participants did not differ on any demographic measures (age, gender, estimated IQ, household income level, proportion nonwhite, proportion with greater than high school education) or on PTSD severity or proportion with a PTSD diagnosis (all ps> .05). Reflecting the adaptive nature of the task, model free behavioral performance was not affected by total PTSD severity. Participants increased performance from chance on the first trial to near 80% correct after ~15 trials (Figure 3), indicating that participants learned the task but did not reach 100% accuracy.

The best fitting behavioral model included separate learning rates and inverse temperatures for gain and loss, an additional associability weight parameter, and reward sensitivity and memory retention parameters (see Table 2 for model fit comparisons). Trials binned by predicted performance according to the model showed good accordance with participants' actual choices (Figure 4). The proportion of choices correctly predicted by the model did not vary with PTSD severity (r_{44}=.05, p>.1). All combat-exposed control veterans showed no associability effect during gain learning; two of these participants showed no modulation by associability for loss learning as well. As a result, associability was only investigated for loss learning. The two participants lacking loss associability learning were excluded for neural analyses involving loss associability as well (resulting in n=43 for these analyses).

A regression of PTSD severity along with covariates of depression, combat exposure, age, and gender found an effect of PTSD severity on loss associability (t_{39}=3.616, p<.005) but not loss learning rate (t_{39}=-.313, p>.5; Figure 5). Gain learning rate also showed differences by diagnostic group (t_{44}=-3.407, p<.005) and PTSD severity (t_{39}=2.656, p<.05). Similarly, individual estimates of loss associability weight differed by group (t_{44}=-8.367, p<.001), while loss learning rate did not differ (t_{44}=1.346,p>.1). Excluding participants on psychotropic medications or with mTBI did not significantly alter results. As associability weights showed significant departures from normality based on Q-Q plots, these values were rank-transformed prior to analysis.

Imaging
Loss associability showed significant modulation by PTSD symptom severity at an FDR-corrected whole brain significance level, including amygdala, insula, and lateral frontal regions (Figure 6, Table 3) as well as activation independent of PTSD symptom severity and other confounds (Figure 7). The hyperarousal symptom cluster also showed significant brain activity corresponding with loss associability in similar areas (Table 4). Of the hyperarousal symptoms, hypervigilance and exaggerated startle showed the strongest relationship with associability, followed by sleep problems and concentration; irritability did not have a significant relationship with associability. Other symptom clusters did not have significant whole-brain corrected results with associability. Relationships with PTSD severity in anatomical amygdala and anterior insula ROIs showed a significant effect of total symptom severity and hyperarousal in both amygdala

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and insula; avoidance also showed a significant relationship with amygdala activation (Figure 8). Excluding participants on psychotropic medications or with mTBI did not meaningfully alter results. For prediction error, total PTSD severity did not have a significant relationship in either gain or loss at a whole brain level.

To further investigate whether altered prediction error signaling was present with PTSD severity, activation masks from the non-veteran reference group were created (Figure 9). No ROIs (of 21) showed a relationship with PTSD severity for gain PE, while for loss PE one ROI (out of 13) encompassing anterior cingulate cortex was significant before correcting for multiple comparisons (t_{36}=-2.271, p<.05); none survived multiple comparison correction. Striatal ROIs showed significant activation with prediction error in both gain and loss independent of PTSD symptoms (gain: t_{44}=2.484; p<.05; loss: t_{44}= 2.477, p<.05), confirming intact PE-related signal in the veteran cohort.

To connect the interaction of neural associability activation and PTSD severity with model free behavior, logistic regression models predicting trial-by-trial switching behavior as a result of the interaction of neural activation with associability or prediction error and PTSD severity on behavior were conducted. Regression models with the interaction of neural associability and PTSD severity revealed a trend towards increased model fit when predicting switching behavior for the insula (χ^2_1=3.0, p<.1). When excluding participants with mTBI, this interaction became significant (χ^2_1=4.6, p<.05). A regression with the hyperarousal symptom cluster showed significant model fit improvement when including the interaction of PTSD severity with neural associability for insula (χ^2_1=8.2, p<.01) and amygdala (χ^2_1=4.6, p<.05), but not ventral striatum (χ^2_1=3.8, p>.05), in predicting switching behavior (Figure 10). For amygdala and insula interactions with individual hyperarousal symptoms, sleep problems (amygdala: χ^2_1=6.8, p<.05; insula: χ^2_1=8.2, p<.01), irritability (amygdala: χ^2_1=8.2, p<.01; insula: χ^2_1=4.6, p<.05), and exaggerated startle (amygdala: χ^2_1=8.2, p<.01; insula: χ^2_1=5.6, p<.05) significantly predicted switching behavior. No other PTSD symptom cluster showed a relationship with switching behavior (ps>.05) in the full sample. Excluding participants with mTBI resulted in a significant interaction of numbing symptoms and ventral striatum activation to associability (χ^2_1=4.4, p<.05). The functional mask did not predict switching in interaction with total PTSD severity or any symptom cluster (ps>.1). For prediction error related activation, none of the ROIs showed a significant improvement in model fit when adding an interaction with PTSD severity (ps>.1). However, a model without the main effect of prediction error-related activity in the ventral striatum was a significantly worse fit (χ^2_1=51.6, p<.001), showing that prediction error activity in the brain affected switching behavior independent of PTSD symptoms.

Conclusion

Previous research has implicated altered learning and attentional processes in posttraumatic stress disorder. Specifically, high value negative information in the environment may command additional cognitive resources in posttraumatic stress disorder, affecting performance and functioning. However, the specific nature of this dysfunction was unclear. In the current study, we found significantly increased associability-based loss learning, but unchanged loss prediction error and learning rate, behaviorally and neurally in combat-deployed military veterans as a function of PTSD severity. This effect was the strongest for the hyperarousal symptom cluster,

and was significantly related to switching behavior. These results point towards preferential allocation of cognitive resources towards previously unexpected information in PTSD, which is guided by a network of brain areas including amygdala, insula, and lateral prefrontal cortex.

These results add to the growing literature illustrating altered neurobiological and cognitive function in PTSD. Initial research on disrupted functioning in PTSD focused on the role of trauma-specific information on processing. This work found disruptions in memory and attention in the presence of traumatic distractors (Chemtob et al., 1999; McNally, Kaspi, Riemann, & Zeitlin, 1990). However, further work found effects of PTSD for negative stimuli in general and disruptions extending beyond trials where trauma reminders were presented (Morey et al., 2009; Vythilingam et al., 2007). These results suggested that PTSD is characterized by altered processing of negative information. However, such findings do not diminish the role of trauma reminders as especially disruptive for people with PTSD. In associability-based learning, trauma-related information is likely processed as especially salient, while other information is downweighted.

The hyperarousal symptom cluster showed the strongest relationship with associability-based learning. This cluster consists of symptoms of hypervigilance, irritability, insomnia, concentration problems, and exaggerated startle (American Psychiatric Association, 2000; King et al., 1998). Longitudinal studies have highlighted the role of hyperarousal symptoms in the development and maintenance of PTSD; increased hyperarousal symptoms predict increases in other PTSD symptom clusters as well as a more chronic course of illness (Marshall, Schell, Glynn, & Shetty, 2006; Schell, Marshall, & Jaycox, 2004). Impaired safety signal learning, a cardinal finding of PTSD, is specifically related to hyperarousal symptoms as well (Jovanovic et al., 2010). The relationship of increased associability-based learning with hyperarousal may underlie these effects.

In contrast to associability, which was increased at both behavioral and neural levels, learning rate and prediction error were not affected during loss learning by PTSD. Participants showed intact prediction error signaling in the ventral striatum, which had a significant effect on switching behavior independent of PTSD severity. Unlike associability, however, PTSD severity did not interact with prediction error signaling. Therefore, the effects of PTSD were specifically related to modulation of learning from previously unexpected outcomes in negative contexts, and not to learning from value differences themselves. This distinction suggests that previous findings of altered performance in the presence of high-value stimuli are due to increased associability-based learning rather than altered learning rate.

Beyond its use in monetary gain and loss learning paradigms, as in the current study, associability has also been used to study fear conditioning (Boll, Gamer, Gluth, Finsterbusch, & Büchel, 2013; Li et al., 2011). Studies on acquisition of fear in PTSD have been mixed; few have found specific alterations in acquisition of responses to conditioned stimuli (Lissek et al., 2005). Rather, the most consistent differences between people with and without PTSD are in extinction and extinction retention of previously conditioned stimuli (Milad et al., 2008, 2009; Norrholm et al., 2011). Reduced extinction learning may seem to be at odds with our finding of increased learning from previously unexpected outcomes. However, in extinction learning one consistent outcome (no conditioned stimulus) is presented for every trial. In associability-based learning,

when a stimulus is repeatedly paired with an outcome, the associability value decreases, which in turn reduces learning. Therefore, the role of associability-based learning during fear extinction is not to increase learning from previously surprising outcomes but to decrease learning from predictable outcomes, reducing the effectiveness of extinction. Indeed, gradual extinction where some conditioned stimuli remain paired with the unconditioned stimulus leads to more successful fear extinction retention (Gershman, Jones, Norman, Monfils, & Niv, 2013).

During gain learning, PTSD did have a relationship with learning rate but not prediction error. Previous studies on reward learning and processing of positive stimuli in PTSD have been equivocal; most used small sample sizes and did not account for trauma exposure (Nawijn et al., 2015). Some studies suggest that PTSD is related to diminished effort to obtain reward (Casada & Roache, 2005; Elman et al., 2009), while others found greater reward seeking behavior in connection with experiential avoidance (Contractor, Elhai, Ractliffe, & Forbes, 2013; Pickett, Bardeen, & Orcutt, 2011). The latter set of findings is similar to our results showing accelerated reward learning with PTSD severity. In addition, other learning mechanisms may play a role in anhedonic symptoms of PTSD, or subgroups of patients with and without disrupted reward learning may exist. For example, gender may moderate reward processing in PTSD (Nawijn et al., 2015); as our sample was primarily male, this effect could not be investigated in the current study.

The current study does have limitations that should be noted. Although alterations in posttraumatic stress disorder are presumed to be largely independent of the type of trauma, certain aspects, such as gender, the chronicity of trauma exposure, and age at trauma exposure, can affect the presentation of PTSD (Chung & Breslau, 2008; Hetzel-Riggin & Roby, 2013). As previously noted, our sample was composed primarily of males whose index trauma was military combat exposure in adulthood. Therefore, our results should be tested in other groups that vary in gender and type of trauma exposure. Additionally, our study is cross-sectional and cannot provide causal information about associability-based learning and posttraumatic stress disorder. Studies examining associability-based learning prior to trauma exposure can show whether associability-based learning leads to increased PTSD symptoms or vice versa.

Clinically, these results have several important applications. Effective treatments for PTSD include exposure-based psychotherapies (Foa & Kozak, 1986; Resick & Schnicke, 1992) and selective serotonin reuptake inhibitors (SSRIs; Marshall, Beebe, Oldham, & Zaninelli, 2001). Configuring exposures and cognitive reappraisal techniques to diminish associability-based learning may further improve psychotherapeutic approaches. As serotonin may be involved in learning from negative outcomes (Daw, Kakade, & Dayan, 2002) and since SSRIs modulate activity in amygdala, insula, ventrolateral prefrontal cortex, and other areas involved in associability-based learning (Brühl, Jäncke, & Herwig, 2011; McCabe, Mishor, Cowen, & Harmer, 2010; Pringle, McCabe, Cowen, & Harmer, 2013), SSRIs may reduce symptoms through reducing associability-based learning. Specifically testing this relationship is needed, however. Additionally, altered associability-based learning in PTSD could be directly targeted through cognitive bias modification treatment (Fani et al., 2012; Kuckertz et al., 2014; Schmidt, Richey, Buckner, & Timpano, 2009) to improve symptoms.

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Table 1
Demographic and clinical characteristics

Measure	All veterans	PTSD	Combat-exposed Controls	PTSD vs. Control Comparison
PTSD Severity (CAPS)[a]	39.89 ± 4.72	64.65 ± 4.27	12.76 ± 2.86	t_{42}=-9.13; p<.001
Depressive Symptoms (BDI)[a]	15.95 ± 2.00	24.09 ± 2.59	7.05 ± 1.52	t_{42}=-5.54; p<.001
Combat Exposure (CES)[a]	18.10 ± 1.50	21.81 ± 1.45	14.38 ± 2.40	t_{40}=-2.65; p<.05
Estimated IQ (WTAR)[a]	109.77 ± 1.39	106.17 ± 1.68	113.71 ± 1.95	t_{42}=2.94; p<.01
Psychotropic medication use[b]	15 (34.1%)	14 (60.9%)	1 (4.8%)	χ^2=12.98; p<.001
Age[a]	33.39 ± 1.23	31.57 ± 1.14	35.38 ± 2.22	t_{42}=1.57; p>.1
Gender (female)[b]	4 (9.1%)	2 (9.5%)	2 (8.7%)	χ^2<.001, p=1

[a]mean ± SE   [b]number (%)

Table 2
Model fit comparisons

Group	Combat-exposed controls		PTSD		Combined	
	Model	AICc	Model	AICc	Model	AICc
Best fit	G	2194.344	I	2422.796	I	4618.184
	I	2195.388	H	2424.709	G	4622.021
	H	2197.634	G	2427.677	H	4622.343
	E	2200.071	E	2437.325	E	4637.396
	F	2284.006	F	2538.654	F	4822.659
	C	2314.038	C	2545.087	C	4859.126
	D	2325.109	D	2578.159	D	4903.268
	B	2347.767	B	2579.006	B	4926.772
	A	2461.918	A	2732.245	A	5194.163
Worst fit	chance	3201.343	chance	3483.758	chance	5194.163

Model A: combined learning rate and inverse temperature across gain and loss
Model B: separate learning rate and inverse temperature between gain and loss
Model C: Model B + associability
Model D: Model B + reward sensitivity
Model E: Model B + memory retention
Model F: Model B + associability and reward sensitivity
Model G: Model B + associability and memory retention
Model H: Model B + reward sensitivity and memory retention
Model I: Model B + associability, reward sensitivity, and memory retention
Chance: assumes random responding

Table 3

fMRI activation clusters for loss associability correlation with PTSD severity (total CAPS score)

Region	Peak MNI coordinate	Peak T value	Cluster size
Right supplementary motor area	-2 -4 50	5.6664	46997
Left middle occipital gyrus	*-40 -84 12*	*5.57*	
Left superior temporal gyrus	*-66 -18 2*	*5.40*	
Left postcentral gyrus	*-46 -12 48*	*5.20*	
Right superior temporal gyrus	*46 -20 -6*	*5.19*	
Right supramarginal gyrus	*54 -46 24*	*5.06*	
Right middle temporal sulcus	*48 -20 -10*	*4.93*	
Left precuneus	*-16 -74 46*	*4.92*	
Left inferior temporal	*-48 -26 -26*	*4.91*	
Left cerebellum	*-10 -54 -22*	*4.88*	
Right cerebellum	*20 -44 -22*	*4.84*	
Left insula	*-34 -22 18*	*4.83*	
Right precuneus	*10 -46 60*	*4.71*	
Right fusiform gyrus	*40 -34 -22*	*4.70*	
Right superior temporal gyrus	*48 -50 12*	*4.69*	
Right middle temporal sulcus	*50 -16 -12*	*4.68*	
Left medial frontal gyrus	-8 42 30	3.7521	503
Anterior cingulate cortex	*-6 36 -2*	*3.41*	
Right middle frontal gyrus	40 14 24	3.7132	164
Right middle frontal gyrus	28 42 40	3.0387	212
Anterior cingulate cortex	12 44 6	3.0206	115
Left lingual gyrus	-18 -80 -8	2.7274	48
Right cerebellum	42 -78 -26	2.5874	20
Left inferior parietal lobule	-44 -60 46	2.4978	38
Left frontal orbital gyrus	-2 40 -30	2.4953	26
Right inferior frontal gyrus	44 40 2	2.4477	11
Anterior cingulate cortex	8 28 20	2.4288	7
Left brainstem	-6 -34 -40	2.3643	5
Right middle frontal gyrus	32 46 22	2.362	9
Left cerebellum	-52 -52 -42	2.326	14
Right cerebellum	18 –70 -48	2.3055	5
Left cerebellum	-8 -64 -8	2.2914	7
Right inferior occipital gyrus	44 -80 -10	2.2579	5
Right superior temporal gyrus	34 6 -28	2.196	5

Note: Italicized peaks are local maxima > 4mm apart.

Table 4

fMRI activation clusters for loss associability correlation with hyperarousal symptom severity (CAPS cluster D score)

Region	Peak MNI coordinate	Peak T value	Cluster size
Left postcentral gyrus	-46 -12 48	6.9913	72689
Right supplementary motor area	2 -4 50	6.55	
Right insula	34 18 8	5.92	
Left superior temporal gyrus	-52 2 4	5.85	
Right medial frontal gyrus	8 -14 56	5.84	
Left middle occipital gyrus	-40 -78 12	5.75	
Right superior temporal gyrus	56 -14 -2	5.71	
Left middle frontal gyrus	-32 38 30	5.64	
Right insula	36 14 6	5.60	
Precuneus	10 -48 58	5.59	
Right middle temporal gyrus	56 -10 -6	5.54	
Right middle temporal gyrus	54 -12 -10	5.37	
Posterior cingulate cortex	-10 -24 38	5.32	
Left superior temporal gyrus	-64 -20 0	5.29	
Middle cingulate cortex	8 12 36	5.28	
Right middle frontal gyrus	28 4 52	5.24	
Right brainstem	0 -22 -36	2.6533	21
Left cerebellum	-32 -60 -50	2.5739	21
Right cerebellum	28 -88 -30	2.3747	34
Right inferior frontal gyrus	10 42 -18	2.2	6
Right superior frontal gyrus	6 58 -22	2.1688	9
Left inferior frontal gyrus	-48 30 -12	2.1432	7
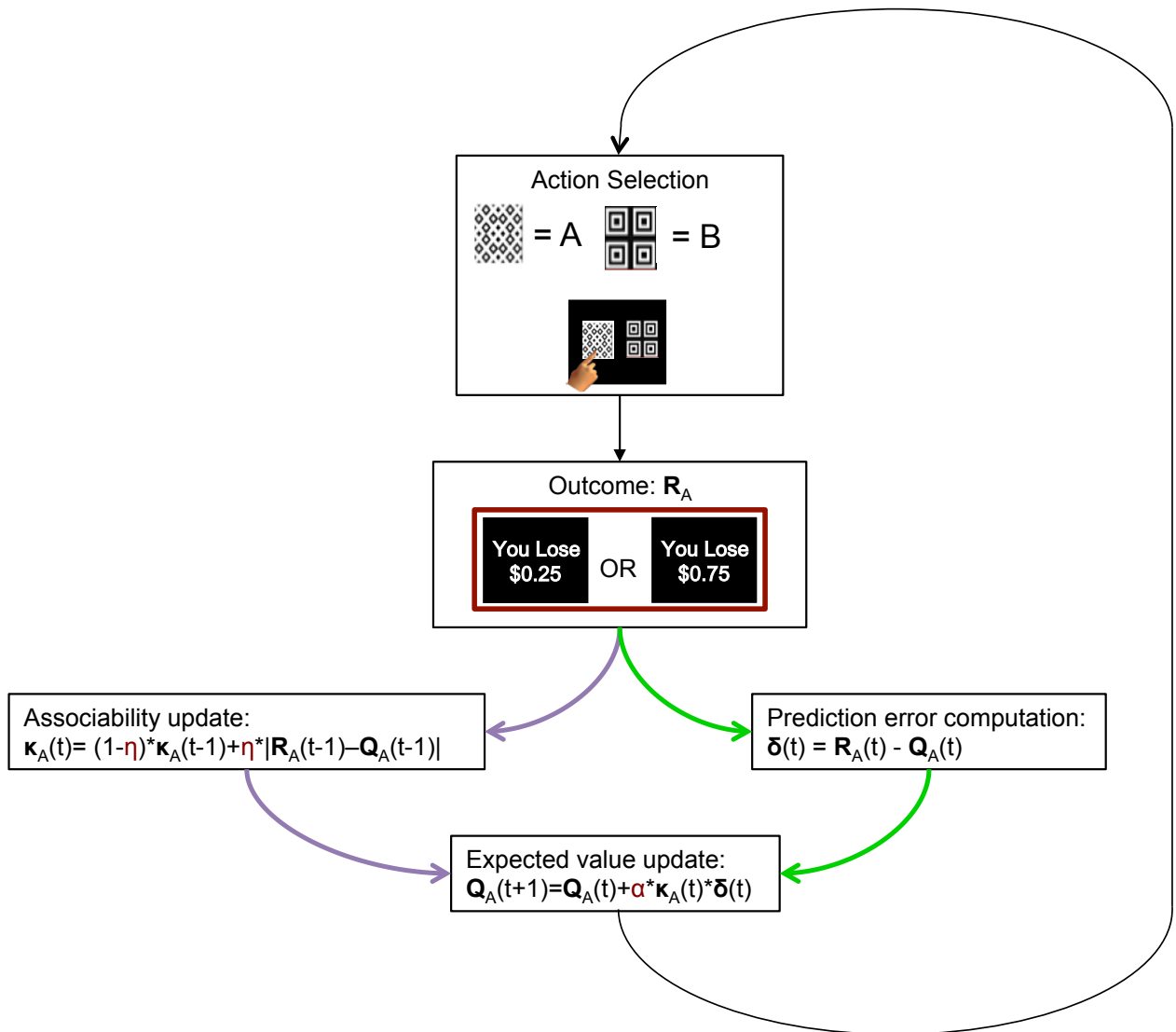
Figure 1. Overview of task and behavioral model. Purple lines indicate how prediction error changes value updates through associability and green line indicates how prediction error changes value updates directly. Note that associability values are affected by outcome and expected value of previous trial.

A $Q_A(t + 1) = Q_A(t) + \alpha[R_A(t) - Q_A(t)]$

B $P_A(t + 1) = \dfrac{e^{\beta Q_A(t+1)}}{e^{\beta Q_A(t+1)} + e^{\beta Q_B(t+1)}}$

C $\kappa_A(t + 1) = (1 - \eta)\kappa_A(t) + \eta|R_A(t) - Q_A(t)|$

D   If $R_A(t) > .5$ OR $R_A(t) < -.5$:

$R_A(t) = \rho R_A(t)$

If $-.5 < R_A(t) < .5$:

$R_A(t) = R_A(t)$

E $Q_B(t + 1) = \gamma Q_B(t)$

Figure 2. Overview of model parameters. Meaning of variables used are A: chosen option, B: unchosen option, Q: expected value, R: outcome, P: probability of choice, t: trial number. 2A: Learning rate. 2B: Inverse temperature. 2C: Associability weight. 2D: Reward sensitivity. 2E. Memory retention.
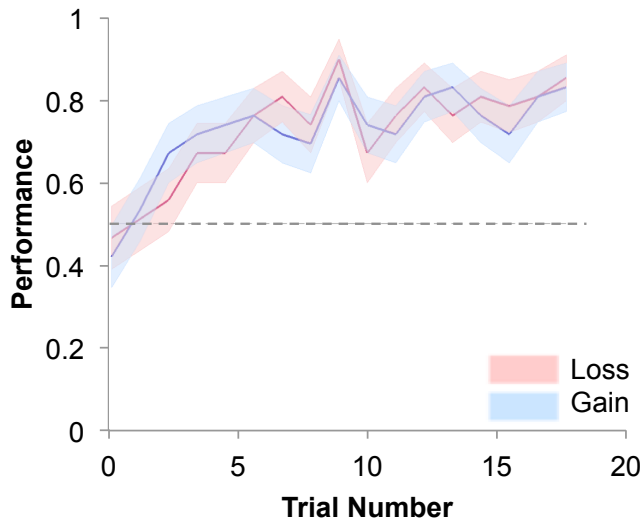
Figure 3. Performance over time for first block per condition (mean ± SE; gray dotted line is chance).
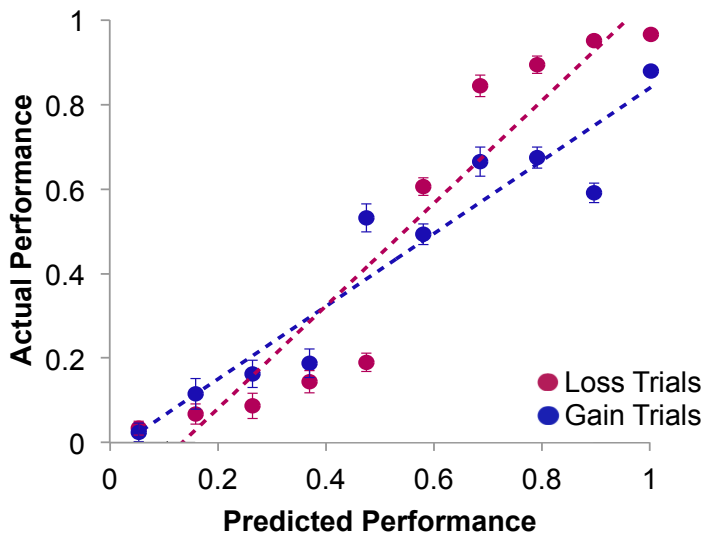
Figure 4. Performance predicted by behavioral model versus actual performance (line is best fit line per condition; error bars are SE)
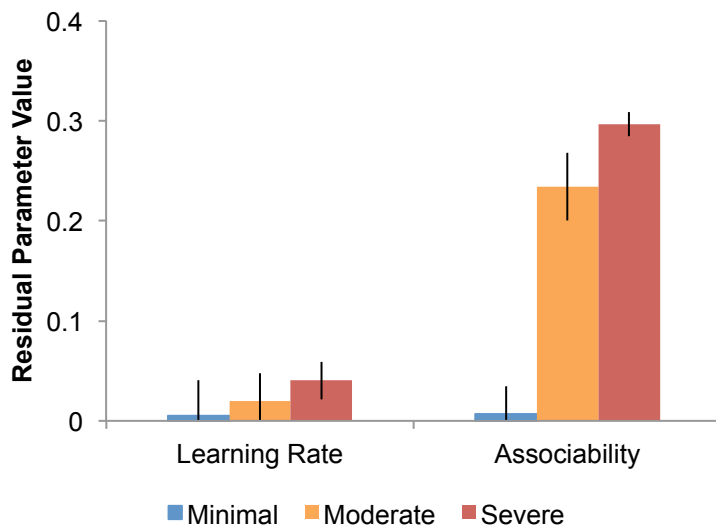
Figure 5. Loss associability parameter increases with PTSD severity while loss learning rate does not (residual parameter values after controlling for depression, combat exposure, age, and gender; minimal: CAPS score of 0-29, moderate: 30-59, severe: 60+).
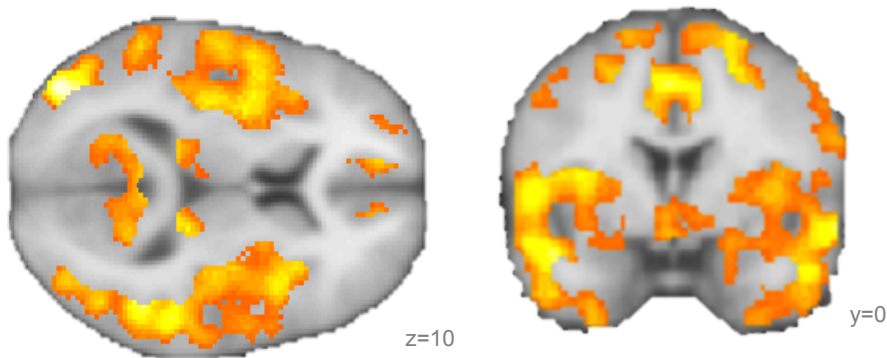
Figure 6. Significant correlations of trial-by trial associability activation with PTSD severity (p<.05 whole brain false discovery rate corrected).

$$Q_A(t+1) = Q_A(t) + \alpha * \kappa_A(t) * \delta(t)$$
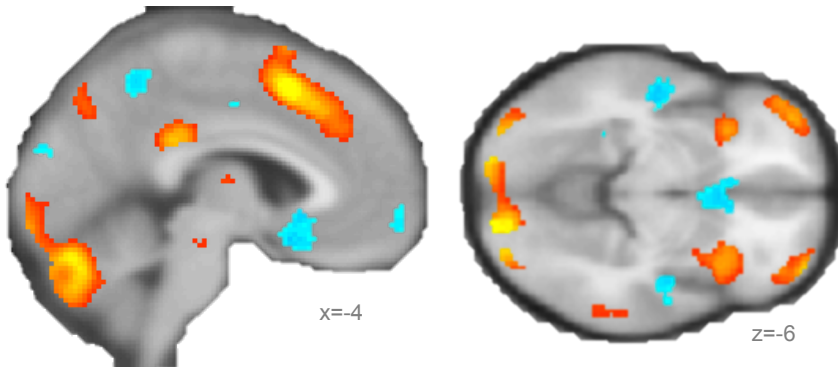
Figure 7. Associability signaling (constant term independent of covariates; veteran cohort, p<.05 false discovery rate corrected).
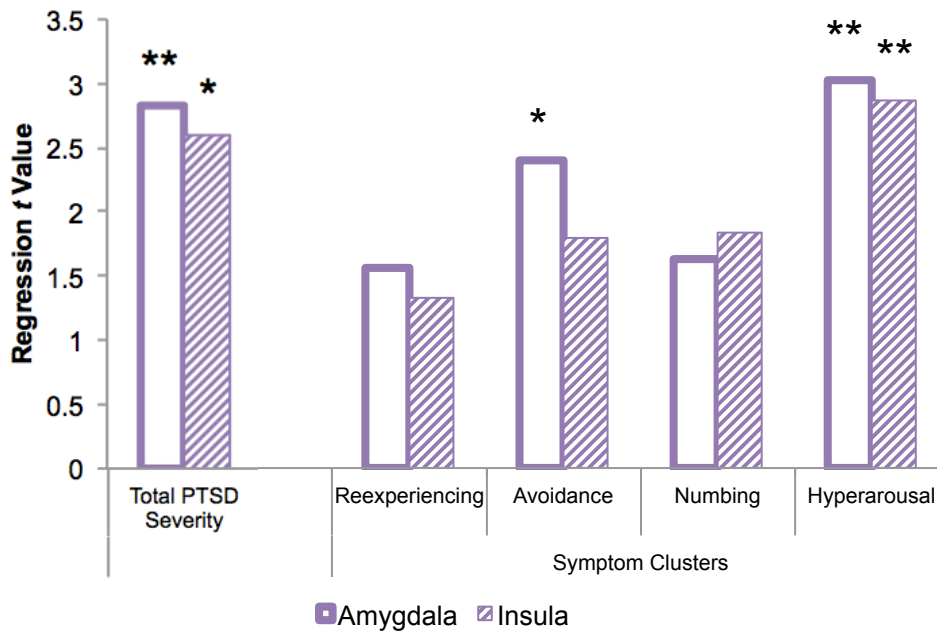
Figure 8: Neural correlates of PTSD severity with associability in amygdala and insula are specific to hyperarousal and avoidance symptom clusters (regression controlling for depression, combat exposure, age, and gender).
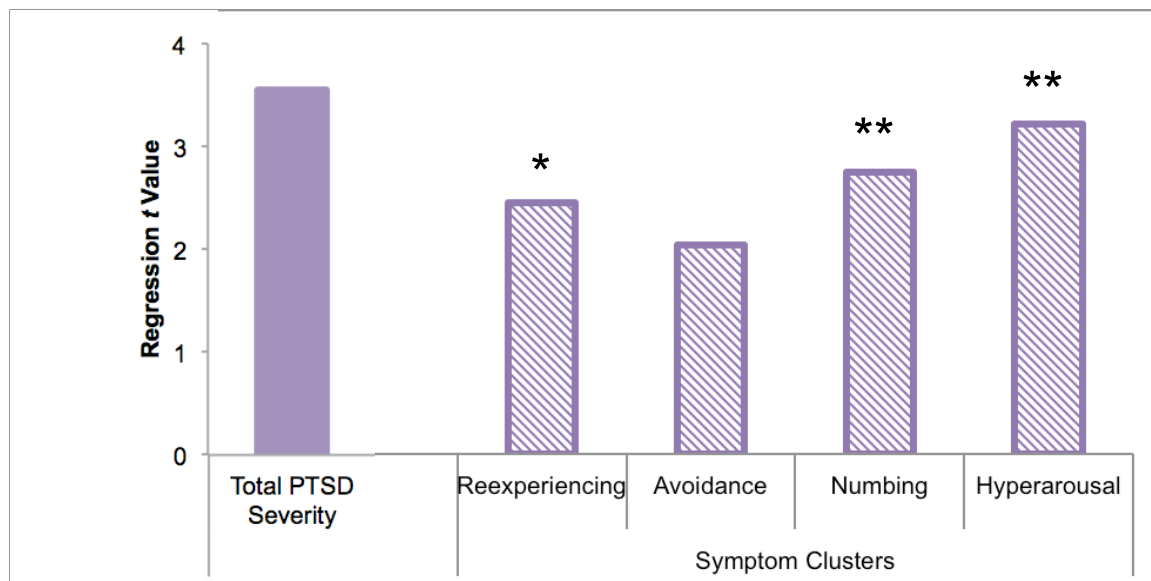
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Figure 9. Re...h associability-related activation in... functional m...hip with total PTSD severity (regression controlling for depression, combat exposure, age, and gender).

$$Q_A(t+1)=Q_A(t)+\alpha*\kappa_A(t)*\delta(t)$$

x=0

y=6
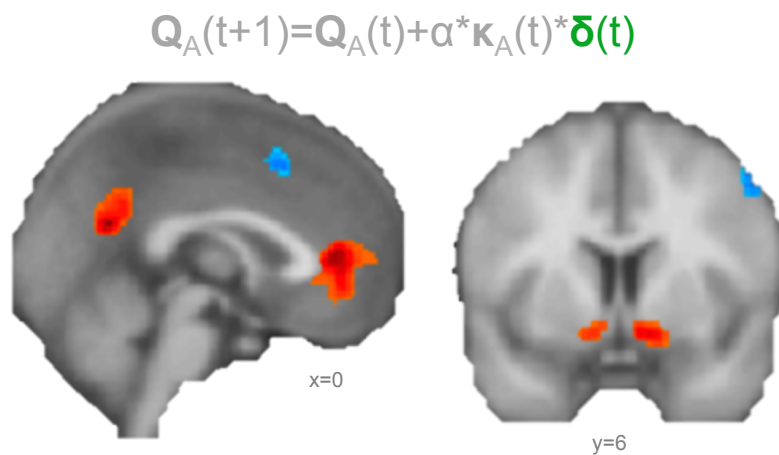
Figure 10. Prediction error signaling (reference cohort, p<.005 & k≥20 uncorrected).
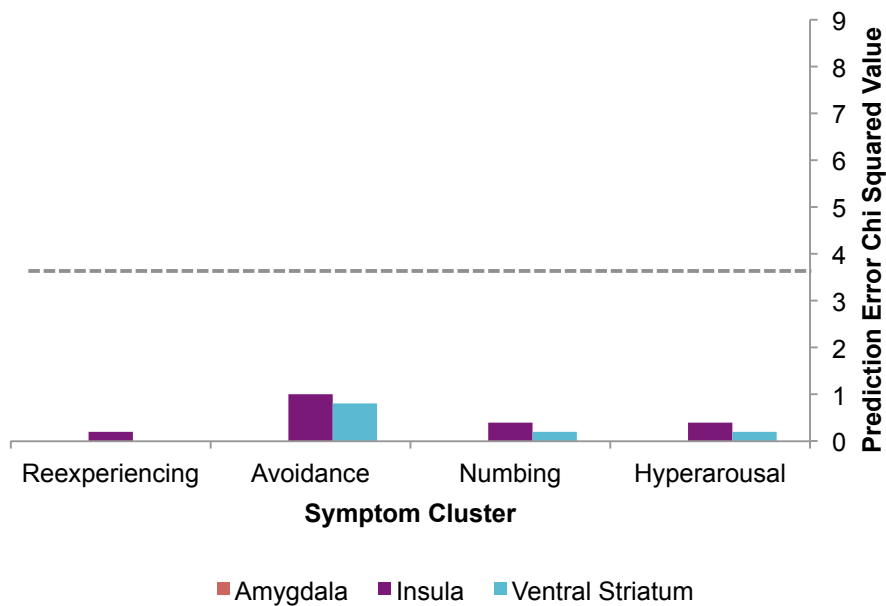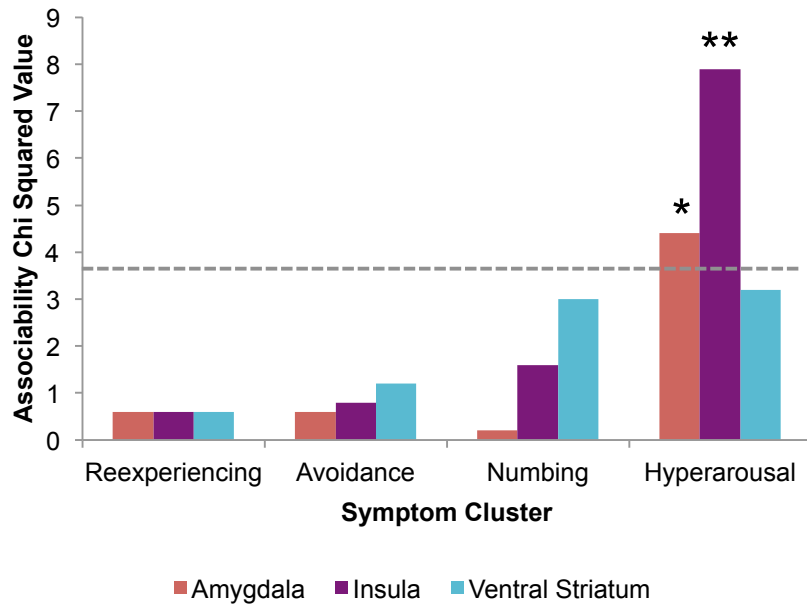
Figure 11. Effect on switching behavior of interaction of neural activation to associability is specific to hyperarousal compared to other PTSD symptom clusters (top panel; likelihood ratio test assessing significantly improved model fit with addition of interaction term) and is not related to the interaction of neural activation to prediction error for any symptom cluster (bottom panel).