



Altered neural encoding of prediction errors in assault-related posttraumatic stress disorder



Marisa C. Ross^{a,*}, Jennifer K. Lenow^c, Clinton D. Kilts^d, Josh M. Cisler^{a,b}

^a Neuroscience Training Program, University of Wisconsin-Madison, United States

^b Department of Psychiatry, University of Wisconsin School of Medicine and Public Health, United States

^c Department of Psychology, New York University, United States

^d University of Arkansas for Medical Sciences, Department of Psychiatry, Brain Imaging Research Center, United States

A B S T R A C T

Posttraumatic stress disorder (PTSD) is widely associated with deficits in extinguishing learned fear responses, which relies on mechanisms of reinforcement learning (e.g., updating expectations based on prediction errors). However, the degree to which PTSD is associated with impairments in general reinforcement learning (i.e., outside of the context of fear stimuli) remains poorly understood. Here, we investigate brain and behavioral differences in general reinforcement learning between adult women with and without a current diagnosis of PTSD. 29 adult females (15 PTSD with exposure to assaultive violence, 14 controls) underwent a neutral reinforcement-learning task (i.e., two arm bandit task) during fMRI. We modeled participant behavior using different adaptations of the Rescorla-Wagner (RW) model and used Independent Component Analysis to identify timecourses for large-scale *a priori* brain networks. We found that an anticorrelated and risk sensitive RW model best fit participant behavior, with no differences in computational parameters between groups. Women in the PTSD group demonstrated significantly less neural encoding of prediction errors in both a ventral striatum/mPFC and anterior insula network compared to healthy controls. Weakened encoding of prediction errors in the ventral striatum/mPFC and anterior insula during a general reinforcement learning task, outside of the context of fear stimuli, suggests the possibility of a broader conceptualization of learning differences in PTSD than currently proposed in current neurocircuitry models of PTSD.

1. Introduction

Posttraumatic stress disorder (PTSD) is a psychological disorder characterized by hyperreactivity to threatening stimuli, avoidance behavior, and reexperiencing of a traumatic event (DSM-5). While trauma exposure is common, the lifetime prevalence of PTSD among adults is only about 10% (Kessler, 2000). The naturalistic course of PTSD symptom trajectories following trauma begins with elevated symptoms that naturally remit over time; conversely, in chronic PTSD the symptoms fail to remit naturally and patients continue exhibiting features of heightened fear responses (Steenkamp et al., 2012). Indeed, a hallmark characteristic of PTSD is the failure to learn to extinguish fear responding to trauma stimuli (Rothbaum and Davis, 2003). Experimental models aim to understand this phenotype through reinforcement learning (i.e., classical conditioning) paradigms (Lissek et al., 2014; Zeidan et al., 2012).

Reinforcement learning is a type of associative learning that involves forming predictive relationships between a cue (e.g., yellow

light) and an outcome (e.g., foot shock). Exposure therapy is a gold standard psychological treatment for PTSD and is presumed to work via the mechanisms of reinforcement learning (i.e., extinction) to help the patient form new, safe memories of a previously harmful stimulus (Foa, 2011; Rothbaum and Davis, 2003). Experimental models, specifically fear extinction models, rely on reinforcement learning paradigms to understand fear responses in patients with PTSD and anxiety disorders (Duits et al., 2015; Lissek et al., 2009; Milad et al., 2009). Many neurocircuitry models of PTSD specifically emphasize fear extinction as a key deficit in the disorder (Norrholm et al., 2011; Rauch et al., 2006). Further, there is ample evidence to suggest that individuals with histories of childhood abuse and PTSD demonstrate disrupted reinforcement learning and deficits in extinction of conditioned fear memories (Cisler et al., 2015; Pechtel and Pizzagalli, 2013; Peri et al., 2000). While it is relatively well established that individuals with PTSD demonstrate altered learning for fear-related stimuli, the degree to which the differences in fear learning and extinction in PTSD are due to a more general learning deficit rather than specific deficit related to

* Corresponding author.

E-mail address: mross9@wisc.edu (M.C. Ross).

threat-detection and fear learning is unclear.

The competing hypothesis that PTSD is characterized by general deficits in reinforcement learning mechanisms would predict that individuals with PTSD also show differences in learning associations with non-fear related stimuli. Though there is sufficient evidence of impaired performance by individuals with anxiety disorders (including PTSD) on cognitive tasks in the presence of threatening stimuli (Bishop et al., 2004; Cisler et al., 2011; McNally et al., 1990), evidence also exists for a broader conceptualization of learning differences in PTSD. A past study from our group showed that learning deficits may apply to social situations when women with PTSD demonstrated greater encoding of negative expected social outcomes in the medial prefrontal cortex (mPFC) and slower learning rates than controls in a simulated trust game (Cisler et al., 2015). In a similar study with adolescent girls, assault history was negatively correlated with activity in the anterior insula, indicating that girls with a history of assault differentially encode negative social outcomes (Lenow et al., 2014). Results for neurocognitive assessments in PTSD similarly suggest a broader conceptualization of learning differences. Several studies suggest lower IQ is associated with risk for PTSD (Breslau et al., 2013; Macklin et al., 1998; Saltzman et al., 2006; Vasterling et al., 1997) and verbal learning, sustained attention, and working memory are especially impaired in adults with PTSD (Scott et al., 2015; Vasterling et al., 2002). These results pointing to an overall cognitive deficit in individuals with PTSD lead to the prediction of a general reinforcement learning deficit in PTSD.

This study aims to test explicitly the hypothesis that PTSD is characterized by a broader deficit in learning of associations between stimuli outside of the context of fear-relevant stimuli by evaluating performance of women with PTSD and healthy controls on a neutral associative learning task. We used a network-level approach to examine the relationship between PTSD and reinforcement learning mechanisms. Several neural networks operate during learning, including the frontoparietal cognitive control network, which mediates a diverse set of executive functions (Niendam et al., 2012) and supports tasks with high processing demands (Cole and Schneider, 2007). An additional network, consisting of the mPFC and ventral striatum, is implicated in decision-making (Kable and Glimcher, 2009) and, along with the anterior insula, responds to feedback in the learning process (Stewart et al., 2014; van den Bos et al., 2012). The anterior insula network is also implicated in punishment-based learning and risk prediction (Palminteri et al., 2012; Preuschoff et al., 2008). Finally, the cingulate and pre-supplementary motor regions display coordinated neural activity that moderates action selection (Mueller et al., 2007) and action initiation (Srinivasan et al., 2013) during decision-making and learning tasks. We focus imaging analyses on these *a priori* large-scale networks to test the hypothesis that women with PTSD would demonstrate differential encoding of learning mechanisms during a neutral, non-threatening, and non-social reinforcement learning task.

2. Methods

2.1. Participants and assessment

29 adult women, aged 20–53, were enrolled in the study following study approval from the local Institutional Review Board. The PTSD sample was comprised of 15 adult women and the control sample was comprised of 14 women (Table 1). Inclusion criteria for the PTSD group were a history of directly experienced assault exposure and a current diagnosis of PTSD; exclusion criteria were the presence of psychotic disorders, a primary substance use disorder, or internal metal. Control participants were included based on female sex and age and excluded based on a history of assault exposure, mental health disorder, internal metal, or major medical disorder.

Assaultive trauma histories were characterized using the trauma assessment section of the National Women's Survey and National

Survey of Adolescents (Kilpatrick et al., 2000, 2003; Resnick et al., 1993), a structured interview used in prior epidemiological studies of assault exposure and mental health functioning among adult women and adolescents. Specific assaultive events were assessed with behaviorally specific dichotomous questions and included sexual assault, physical assault, and specific severe abuse from a caregiver.

Psychological disorders were assessed with the Structured Clinical Interview for DSM-IV Disorders (SCID) (First et al., 2002) administered by a trained clinical interviewer and supervised by a licensed clinical psychologist. Participants additionally completed the Posttraumatic Stress Checklist-Civilian Version (Blanchard et al., 1996) and Beck Depression Inventory-II (Beck et al., 1996).

2.2. Behavioral tasks

2.2.1. Reinforcement learning task

Participants completed two versions of a two-arm bandit task during fMRI, a general learning task and a social learning task, with the order of the tasks counterbalanced. The focus of analyses in this manuscript is the non-social, general learning task (Fig. 1) and a previous manuscript described the results from the social task (Cisler et al., 2015). In this task, participants were presented with two houses and were told that their goal was to identify as many unlocked houses as they could. To motivate performance, participants were told that they would receive bonus monetary compensation based on the number of unlocked doors they find; however, all participants were paid the same compensation. There were three phases of each trial: decision, where participants viewed the house options and made a selection; interval, where participants awaited the outcome of their decision; and outcome, where participants viewed the outcome (locked or unlocked) of their decision. There were 100 total trials, divided into four epochs of 25 trials with different reward probabilities. For example, in the first epoch, the left house could be associated with a 0.75 probability of being unlocked and this could switch to a 0.4 probability in the next phase (Fig. S1). The participant's goal was to learn the structure of the changing probabilities in order to choose as many unlocked houses as possible to maximize monetary reward.

2.3. MRI acquisition and image preprocessing

MRI acquisition parameters and preprocessing are described in supplemental material.

2.4. Analyses

2.4.1. Reinforcement learning task analyses

We modeled participant behavior using a modified version of the Rescorla-Wagner (RW) reinforcement learning model (Rushworth and Behrens, 2008; Sutton and Barto, 1998). This simple and frequently used model takes the form of $V_{t+1} = V_t + \delta * \alpha$, where V refers to expected value of a chosen action, δ is a prediction error (PE; $outcome_t - V_t$), and α is a learning rate that ranges from 0–1. The expected value of a chosen action changes from trial to trial based upon δ , such that a positive δ (i.e., receiving more than expected) increases expected value and a negative δ (i.e., receiving less than expected) decreases expected value. The learning rate, α , controls the speed with which value expectations are updated, with higher learning rates leading to faster changes in expected value.

Following prior research (Behrens et al., 2007, 2008; Daw et al., 2006), we used the softmax function to transform value expectation into action probabilities through use of an exploration/exploitation parameter. To ensure best possible model fit, we tested four different RW-based models (Hauser et al., 2015) that manipulated whether the model was risk-sensitive (i.e., used a separate learning rate for positive and negative PEs) and whether the model updated the expected value of the unchosen option (i.e., anticorrelated updating of value expectation)

Table 1

Clinical and demographic characteristics of the sample. * Refers to days since menstruation among women who regularly menstruate; 5 PTSD women and 1 control woman either were not menstruating (e.g., menopause) or had irregular cycles (> 80 days since last menstruation).

Variable	PTSD (n = 15)	SD	Control (n = 14)	SD	p value group difference
	Mean (or frequency)		Mean (or frequency)		
Age	31.13	6.38	31.21	7.2	.49
Ethnicity	73.3% Caucasian	–	71% Caucasian	–	.36
	20% African-American		21% African-American		
	6.7% Other		7% Other		
Education	7% not graduate high school	–	0% not graduate high school		.60
	29% graduate high school or GED		14% graduate high school or GED		
	64% some college or more		86% some college or more		
Days since last menstruation*	13.5	7.14	12.5	12.4	.40
Current Job	40% unemployed	–	7% unemployed		.039
PCL score	59.1	17.3	20.01	3.6	< .01
BDI-II score	24.4	14.4	2.4	2.4	< .01
Number of total direct assaults	6.4	2.9	0	0	< .01
Number of physical assaults from non-caregiver	2.2	1.8	–	–	–
Number of physical assaults from caregiver	1.9	1.7	–	–	–
Number of sexual assaults	2.3	1.5	–	–	–
Current Major Depressive Disorder	47%	–	0	–	.01
Current Generalized Anxiety Disorder	60%	–	0	–	< .01
Current PTSD	100%	–	0	–	< .01
Current Marijuana Dependence	7%	–	0	–	.33
Current Alcohol Dependence	13%	–	0	–	.16

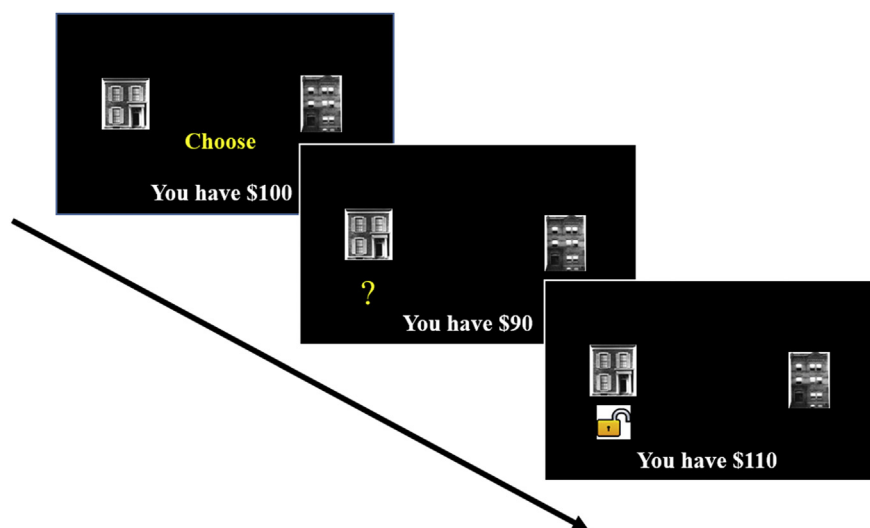


Fig. 1. fMRI Neutral Reinforcement-Learning Paradigm. Participants were shown two houses and told to choose the house they thought was most likely to be unlocked to invest \$10. If that house was unlocked, they received \$20 back; if it was locked, they lost the \$10. The task was 100 trials in which the alternating reward structure changed every 25 trials.

in a factorial design. One cell was the basic RW model (described above) using a single alpha to update value expectations with PEs. Anticorrelated models updated the value expectation of the unchosen options in the opposite direction of the PE (Gläscher et al., 2010; Hauser et al., 2014). Risk sensitive models (Hauser et al., 2015; Niv et al., 2012) used a separate learning rate for positive and negative PEs and therefore had three free parameters while the not risk-sensitive models contained two free parameters. The anticorrelated and risk sensitive model updated the value of the unchosen option using the learning rate based on the sign of the PE.

The respective model's free parameters were fit by maximizing the sum of the log likelihood of action probabilities. We searched through continuous parameter space using Matlab's `fmincon` function, in which we constrained the searched parameter space for learning rates between 0 and 1 and for exploration/exploitation parameters between 0 and 10. Likelihood ratio tests were performed on aggregate log likelihoods for each model to determine which model best fit our participants' behavior (Daw et al., 2011; Li et al., 2011). The overall best-fitting model for the sample was used to define the value expectations and PEs for each participant using the sample mean of the alpha and

beta parameters, consistent with prior research (Daw et al., 2006; Daw, 2011). The resulting value expectation and PE values were carried forward to the fMRI analyses.

2.4.2. fMRI analyses

We chose to use Independent Component Analysis (ICA) to identify large-scale brain networks and their associated timecourses (Calhoun et al., 2009; McKeown et al., 1998). One free parameter that must be selected when conducting ICA is the number of components for which to solve (Calhoun et al., 2009). We selected 35 components, as this model order among these data provided a good balance between specificity without canonical components (e.g. default mode network) splitting into different sub-networks. 18 of the 35 components were deemed functional networks (versus artifact from head motion or CSF, etc.), and from these we selected the following *a priori* networks for further analysis: frontoparietal, cingulate and pre-SMA, bilateral insula, and a mPFC and ventral striatum network (Fig. 2).

2.4.3. Within-subject ICA network timecourse analyses

In order to determine task-related activation of component

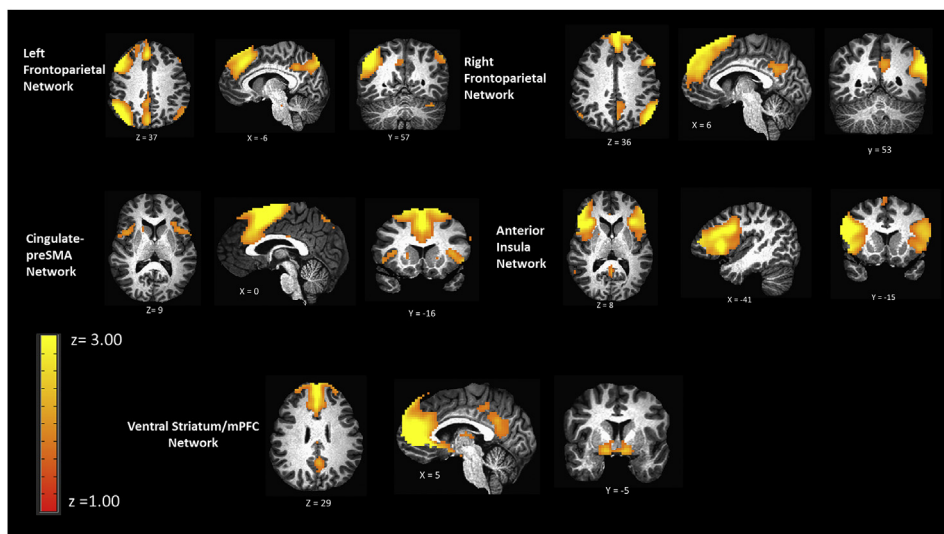


Fig. 2. Identified Component Networks of Interest. Our ICA algorithm identified 35 components. After selecting out 17 as noise, we inspected the remaining 18 networks and compared component activation between groups for our five *a priori* selected networks of interest. We ran our final analyses on the left and right frontoparietal networks (top), cingulate-preSMA and anterior insula networks (middle) and ventral striatum/mPFC (bottom). The maps indicate the degree to which each voxel contributes to the network of activation (colors represent z-scores), thresholded at $z = 1.0$. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

networks, we generated general linear models (GLMs) with individual subject-specific design matrices for each participant and using AFNI (3dREML; Cox, 1996) to generate the design matrices. The design matrix included the following regressors: outcome phase, outcome phase \times PE, anticipation phase (waiting for the outcome after making a decision), anticipation phase \times value expectation, decision phase, and decision phase \times value expectation. Using Matlab, we regressed the *a priori* ICA component timecourses onto this design matrix to estimate the beta coefficients for value expectation and PEs.

2.4.4. Between-subject ICA network timecourse analyses

We performed one-sample t-tests on the beta coefficients of each *a priori* component of interest to determine group-level patterns of component encoding of value expectation and PEs. Next, we used robust regression to compare first-level beta coefficients between groups, separately for value expectation and PEs, and covarying for age, ethnicity, and education level across the *a priori* networks of interest.

In additional follow-up analyses, we also tested scalar relationships between network component activation during PE and task performance (i.e., number of trial wins) as well as with PTSD and depression severity, comorbid diagnoses, and PTSD symptom clusters among the PTSD group.

2.4.5. Exploratory voxelwise analyses

We supplemented the network-level analyses provided by the ICA with a whole-brain voxelwise analysis. We performed one-sample t-tests and achieved a corrected $P < 0.05$ by identifying significant clusters of activation with a threshold of $|t|(28) = 3.408$ ($p < 0.001$) and a minimum of 19 contiguous voxels, using AFNI 3dFWHMx (Cox, 1996) to estimate the smoothness of these data and 3dClustSim to define the corrected cluster size given the amount of smoothing using a spatial autocorrelated function (Eklund et al., 2016).

3. Results

3.1. Reinforcement learning task

3.1.1. Model choice

The risk-sensitive, anticorrelated model slightly outperformed the other three models tested (Table 2). Additional comparisons of this model ensured internal validity such that the positive and negative alphas were different within the risk-sensitive anticorrelated model ($p = 0.0029$, $t(28) = 3.2574$).

Table 2

Results of Model Comparisons for Learning Parameters. Model comparisons revealed that the risk-sensitive, anticorrelated model had a better model fit, both in aggregate log-likelihood and AIC, than the Rescorla-Wagner, risk-sensitive uncorrelated, and not risk-sensitive anticorrelated models in both groups. Likelihood ratios were summed across subjects to create an aggregate log-likelihood for each of the four models and this aggregate score was transformed using AIC to assess model fit. Models with a differing number of free parameters were also compared using a likelihood ratio test. Both the uncorrelated models and the anticorrelated models were significantly different from one another ($\chi_{29}^2 = 86.9$, $p < 0.0001$ and $\chi_{29}^2 = 191.3$, $p < 0.0001$ respectively). AIC = Akaike Information Criterion **Best model fit.

Model	Aggregate Log-Likelihood	AIC
Rescorla-Wagner	-1091.3	2186.6
Risk-sensitive, uncorrelated	-1047.9	2101.7
Not Risk-sensitive, anticorrelated	-1117.1	2238.1
Risk-sensitive, anticorrelated	-1021.4**	2048.8**

3.1.2. Between-group comparison of model fit

The learning model's average accuracy of predicting participants' choices was 0.730 (SD = 0.15), which is significantly better than chance ($ps < 0.001$). Model accuracy for the overall best-fitting model did not differ between groups ($ps > 0.14$). Group comparisons of modeling parameters were not significantly different (Table S1).

3.2. fMRI analysis

3.2.1. Networks identified with ICA

Of the 35 components obtained by the ICA, 17 were interpreted as artifacts and 18 were interpreted as meaningful neural network components. The *a priori* networks of interest were the left and right frontoparietal, cingulate-preSMA, anterior insula and ventral striatum/mPFC networks (Fig. 2). The remaining networks consisted of visual, somatosensory, motor, auditory, inferior frontal, mid-ventral insula, basal ganglia, and parahippocampal networks (Table S2).

3.2.2. Group differences in network activation during PE

We next compared network activation in response to the task parameters between groups. These analyses revealed significantly less engagement of the ventral striatum/mPFC ($p = 0.0172$, $t(24) = -2.5598$) and anterior insula ($p = 0.0061$, $t(24) = -3.0041$) networks during positive PE encoding in the PTSD group (see Table 3, Fig. 3). There were no other significant between-group differences in network activation.

Table 3

Brain regions differentially encoding the computational parameters of interest in a whole-brain between-group comparison. We used within group one-sample t-tests and between group robust regression to compared component networks' timecourse activity during the prediction error and value expectation stages of the task. Negative t-values within groups during prediction error indicate encoding of negative prediction errors, while positive t-values indicate encoding of positive prediction errors. Negative t-values for the group comparisons indicate a reduction in encoding of positive prediction errors for the PTSD group, while positive t-values indicate a reduction in encoding of negative prediction errors for the PTSD group.

Computation Parameter	Component	Group				PTSD vs. Control Group	
		Control		PTSD		t value	p value
		t value	p value	t value	p value		
Prediction Error	Left Frontoparietal	0.5925	0.5645	-1.4113	0.1786	-0.9417	0.3557
	Ventral Striatum/mPFC	4.4386	0.0008	0.8074	0.4320	-2.5598	0.0172
	Right Frontoparietal	2.0643	0.0613	-1.2934	0.2154	-2.0335	0.0532
	Cingulate-preSMA	-5.2975	0.0002	-5.9499	0.0000	-0.8027	0.4300
	Anterior Insula	3.1886	0.0078	-0.7367	0.4727	-3.0041	0.0061
Value Expectation	Left Frontoparietal	-5.8789	0.0001	-4.7517	0.0003	1.4720	0.1540
	Ventral Striatum/mPFC	2.0737	0.0603	0.8885	0.3883	-0.4274	0.6729
	Right Frontoparietal	0.1158	0.9097	0.4400	0.6662	-0.0761	0.9400
	Cingulate-preSMA	-4.4684	0.0008	-3.8329	0.0016	-0.2770	0.7841
	Anterior Insula	-4.1850	0.0013	-3.2164	0.0058	1.1816	0.2490

3.2.3. Network activation as a function of task parameters within each group

We next compared network engagement in the five networks of interest within groups (Table 3). In the control group during PE encoding, these analyses revealed significant encoding of positive PEs within the ventral striatum/mPFC ($p = 0.0008$, $t(12) = 4.4386$) and anterior insula ($p = 0.0078$, $t(12) = 3.1886$), and significant encoding of negative PEs in the cingulate-preSMA ($p = 0.0002$, $t(12) = -5.2975$). During value expectation in the control group, we also observed significant network activity in the left frontoparietal ($p = 0.0001$, $t(12) = -5.8789$), cingulate-preSMA ($p = 0.0008$, $t(12) = -4.4684$), and anterior insula ($p = 0.0013$, $t(12) = -4.1850$) networks. In the PTSD group, we identified significant encoding of negative PEs in the cingulate-preSMA network ($p < 0.0001$, $t(15) = -5.9499$), and significant encoding of value expectation in the left frontoparietal ($p = 0.0003$, $t(15) = -4.7517$), cingulate-preSMA ($p = 0.0016$, $t(15) = -3.8329$), and anterior insula ($p = 0.0058$, $t(15) = -3.2164$).

3.2.4. Network activation as a function of individual difference variables

Follow-up analyses of anterior insula and ventral striatum/mPFC networks failed to reveal any significant relationship between these networks' encoding of PEs and task performance (number of trial wins; $p = 0.9432$, $t(24) = -0.0720$; $p = 0.4886$, $t(24) = 0.7034$, respectively). We also tested for relationships with PTSD symptom clusters among the PTSD group specifically and did not observe any significant relationships with symptom severity (anterior insula $p = 0.8186$, $t(11) = 0.2349$; ventral striatum/mPFC $p = 0.8869$, $t(11) = 0.1456$) or individual symptom clusters (Table S3). We also did not observe any relationships with neural encoding of PEs and depression severity (BDI total score) or comorbid substance use disorders among the PTSD group

(Table S3).

3.2.5. Exploratory voxelwise analyses

One-sample t-tests for voxelwise comparisons revealed clusters of significant encoding of negative PEs in the premotor and dorsal anterior cingulate cortices in addition to encoding of positive PEs in the striatum and visual association areas (Fig. S2). Between-group voxelwise analyses failed to reveal any group differences in modeling parameter encoding following correction for multiple comparisons.

3.2.6. Ruling out task order effects

Given that the order of the neutral task and social task was counterbalanced across participants, we performed additional analyses to test for any confounding effects of task order. There was no effect of task order or task order x group interaction on neural encoding of prediction errors in either the ventral striatum/mPFC network or anterior insula network ($t(22) = 0.510$, $p = 0.615$; anterior insula: $t(22) = -0.0155$, $p = 0.9878$, respectively), and the main effect of group remained significant in both cases. However, we did observe a significant interaction on the softmax exploration/exploitation parameter, such that control participants were more exploitative than PTSD participants when completing the neutral task first. Full results are provided in Supplemental Table S4.

4. Discussion

In this study, we investigated the relationship between PTSD and reinforcement learning during a neutral, non-threatening, and non-social task. While predominant models of PTSD emphasize differences in fear acquisition and extinction learning, which presumably rely upon mechanisms of reinforcement learning, it is thus far unclear whether

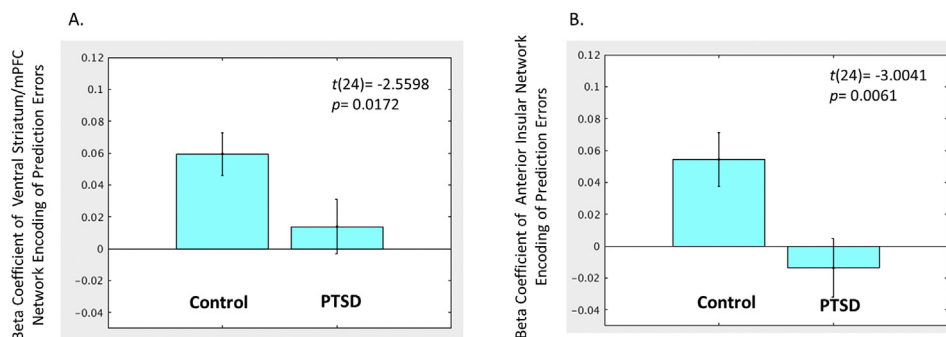


Fig. 3. Decrease in Component Activation in the Valuation and Anterior Insula Networks in the PTSD Group during Prediction Error. Between-group robust regression revealed a significant decrease in component activation during prediction error encoding of the task for the ventral striatum/mPFC (A) and anterior insula (B) networks for the PTSD group as compared to controls. This indicates a decreased ability for the PTSD group to encode prediction errors during reinforcement learning.

stimulus-association learning deficits extend beyond the domain of fear learning. Consistent with prior research, we found support for a risk-sensitive, anticorrelated RW-model as the best predictor of participant behavior on the neutral bandit task (Hauser et al., 2015; Niv et al., 2012). Our behavioral modeling revealed no overall differences between groups concerning number of trial wins or learning strategy, though there was some evidence that the PTSD group was less exploitative if they performed the neutral task first. Additionally, we observed weaker neural encoding of positive PEs in an anterior insula cortex network, and to a lesser degree in a ventral striatum/mPFC network, which supports the hypothesis of general neural differences in learning mechanisms in PTSD outside of fearful or social contexts. Prior to discussing these results in more detail, it is important to note the current small sample size and that inferences should accordingly be tempered.

Using Independent Component Analysis (ICA), we identified eighteen functional brain networks and focused on five *a priori* networks to compare PTSD and control groups. One identified network was a ventral striatum/mPFC network, comprised of the striatum, nucleus accumbens and medial prefrontal cortex. Whereas control women demonstrated robust positive PE encoding in this network, we saw no evidence for positive PE encoding by this network in the PTSD group. The ventral striatum/mPFC network, specifically the mPFC, has been shown to be important in reinforcement learning, as this network moderates goal-directed decision-making through encoding of a value signal in the vmPFC (Hare et al., 2009; Hiser and Koenigs, 2017) and allows the switch between planning and performance of motivated actions (Gläscher et al., 2012). Our observation of reduced encoding of positive PE in the ventral striatum/mPFC network provides neural evidence to support behavioral observations which indicate reduced reward expectancy (Hopper et al., 2008) and dampened motivation to pursue reward (Elman et al., 2005) in combat veterans with PTSD. A previous study from our group provides further support of neural impairment in response to value in PTSD, as we observed reduced encoding of expected social value in the pgACC, dmPFC, middle frontal gyri and temporoparietal junction in women with PTSD on a social learning task (Cisler et al., 2015). These observations, along with the finding that hypoactivation of the vmPFC is a robust correlate of PTSD (Etkin and Wager, 2007), indicate an impairment in encoding reward-related PEs in women with PTSD, irrespective of task context.

Similarly, among the control group, the anterior insula (AI) network robustly encoded positive PEs, whereas there was no evidence for AI positive PE encoding among the PTSD group. This observation is consistent with previous research from our group of lesser activation within the AI during trust violations on a social learning task for adolescent girls with a history of assault compared to healthy controls (Lenow et al., 2014). Beyond the general role of the insula in mediating attention as a key node of the salience network (Bressler and Menon, 2010), the insula has also been implicated in encoding risk and risk PEs (Preuschoff et al., 2008). The current result of weaker encoding of PEs in the AI among women with PTSD is interesting in light of prior research identifying hyperactive insula activity in PTSD (Hopper et al., 2007; Paulus and Stein, 2006). Given the canonical PTSD symptom of hypervigilance and the role of the insula in mediating attention as a key node of the salience network (Bressler and Menon, 2010), it might be expected that PTSD is associated with heightened AI encoding of PEs, regardless of the sign (i.e., positive versus negative PEs). However, the weaker encoding of positive PEs in the present context might better reflect the insula's role in learning (Doya, 2008; Preuschoff et al., 2008) rather than salience detection. As such, the results support an interesting dissociation in PTSD between insula hyper- vs hypoactivity depending on cognitive process. Further, negative PEs were encoded equally strongly in both groups in a component representing the dorsal anterior cingulate cortex and pre-SMA, suggesting that the PE encoding deficit we observe here in PTSD is specific to positive PE encoding during a neutral reinforcement-learning task.

The current results advance the hypothesis that PTSD is characterized by a broader deficit in mechanisms of reinforcement learning outside of the context of fear-relevant stimuli, likely through an impairment in neural encoding of positive PEs in the mPFC, ventral striatum and insula. This finding may have implications for understanding treatment response to therapies that utilize learning paradigms, such as exposure therapy. Exposure therapy is based on a fear extinction model, such that exposure to conditioned stimuli (i.e., trauma cues) in the absence of a negative outcome (i.e., PE) weakens the associative strength of the conditioned stimuli and results in less anticipatory anxiety. While prolonged exposure is one of the gold standard treatments for PTSD, remission rates are only ~55–60% (Foa et al., 1991, 1999). A reasonable hypothesis is that a general deficit in encoding of PEs might interfere with extinction learning, thus weakening the efficacy of exposure-based therapies. It is also possible that individual differences in PE encoding might predict response to exposure therapies, potentially serving as a marker for individuals who are able to benefit from exposure therapies and form new, safe associations. Additionally, a domain-general impairment in PE encoding in PTSD would presumably impact areas of functioning outside of fear extinction and exposure therapy domains, including social learning, reward learning, and neuroeconomic contexts and other learning domains that are dependent on PE encoding. Future research should continue to investigate mechanisms of learning in PTSD and their relationships to broader domains of functioning as well as treatment response.

While the current study has promising results for better understanding learning mechanisms of PTSD and informing future research on treatments for the disorder, it is not without its limitations. Firstly, our relatively small sample size of 29 presents potential challenges for reproducible effect sizes and did not include a trauma-exposed group without a PTSD diagnosis. Secondly, our sample was limited to biologically female participants so these observations cannot be generalized to men with PTSD. Finally, our PTSD group had significant comorbidity, which is representative of the clinical population but nonetheless the degree of comorbidity limits the specificity of our inferences.

Financial disclosures

All authors report no financial conflicts of interest.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.jpsychires.2018.05.008>.

References

- Beck, A.T., Steer, R.A., Brown, G.K., 1996. *Manual for the Beck Depression Inventory-ii*. Psychological Corporation, San Antonio, TX.
- Behrens, T.E.J., Hunt, L.T., Woolrich, M.W., Rushworth, M.F.S., 2008. Associative learning of social value. *Nature* 456, 245–249. <https://doi.org/10.1038/nature07538>.
- Behrens, T.E.J., Woolrich, M.W., Walton, M.E., Rushworth, M.F.S., 2007. Learning the value of information in an uncertain world. *Nat. Neurosci.* 10, 1214–1221. <https://doi.org/10.1038/nn1954>.
- Bishop, S.J., Duncan, J., Lawrence, A.D., 2004. State anxiety modulation of the amygdala response to unattended threat-related stimuli. *J. Neurosci.* 24, 10364–10368. <https://doi.org/10.1523/JNEUROSCI.2550-04.2004>.
- Blanchard, E.B., Jones-Alexander, J., Buckley, T.C., Forneris, C.A., 1996. Psychometric properties of the PTSD checklist (PCL). *Behav. Res. Ther.* 34, 669–673. [https://doi.org/10.1016/0005-7967\(96\)00033-2](https://doi.org/10.1016/0005-7967(96)00033-2).
- Breslau, N., Chen, Q., Luo, Z., 2013. The role of intelligence in posttraumatic stress disorder: does it vary by trauma severity? *PLoS One* 8, e65391. <https://doi.org/10.1371/journal.pone.0065391>.
- Bressler, S.L., Menon, V., 2010. Large-scale brain networks in cognition: emerging methods and principles. *Trends Cognit. Sci.* 14, 277–290. <https://doi.org/10.1016/j.tics.2010.04.004>.
- Calhoun, V.D., Liu, J., Adali, T., 2009. A review of group ICA for fMRI data and ICA for joint inference of imaging, genetic, and ERP data. *Neuroimage, Math. Brain Imag.* 45,

- S163–S172. <https://doi.org/10.1016/j.neuroimage.2008.10.057>.
- Cisler, J.M., Bush, K., Scott Steele, J., Lenow, J.K., Smitherman, S., Kilts, C.D., 2015. Brain and behavioral evidence for altered social learning mechanisms among women with assault-related posttraumatic stress disorder. *J. Psychiatr. Res.* 63, 75–83. <https://doi.org/10.1016/j.jpsychires.2015.02.014>.
- Cisler, J.M., Wolitzky-Taylor, K.B., Adams, T.G., Babson, K.A., Badour, C.L., Willems, J.L., 2011. The emotional Stroop task and posttraumatic stress disorder: a meta-analysis. *Clin. Psychol. Rev.* 31, 817–828. <https://doi.org/10.1016/j.cpr.2011.03.007>.
- Cole, M.W., Schneider, W., 2007. The cognitive control network: integrated cortical regions with dissociable functions. *Neuroimage* 37, 343–360. <https://doi.org/10.1016/j.neuroimage.2007.03.071>.
- Cox, R.W., 1996. AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. *Comput. Biomed. Res. Int. J* 29, 162–173.
- Daw, N.D., 2011. Trial-by-trial data analysis using computational models. *Decis. Mak. Affect Learn. Atten. Perform.* XXIII. <https://doi.org/10.1093/acprof:oso/9780199600434.003.0001>.
- Daw, N.D., Gershman, S.J., Seymour, B., Dayan, P., Dolan, R.J., 2011. Model-based influences on humans' choices and striatal prediction errors. *Neuron* 69, 1204–1215.
- Daw, N.D., O'Doherty, J.P., Dayan, P., Seymour, B., Dolan, R.J., 2006. Cortical substrates for exploratory decisions in humans. *Nature* 441, 876–879. <https://doi.org/10.1038/nature04766>.
- Doya, K., 2008. Modulators of decision making. *Nat. Neurosci.* 11, 410–416.
- Duits, P., Cath, D.C., Lissek, S., Hox, J.J., Hamm, A.O., Engelhard, I.M., van den Hout, M.A., Baas, J.M.P., 2015. Updated meta-analysis of classical fear conditioning in the anxiety disorders. *Depress. Anxiety* 32, 239–253. <https://doi.org/10.1002/da.22353>.
- Eklund, A., Nichols, T.E., Knutsson, H., 2016. Cluster failure: why fMRI inferences for spatial extent have inflated false-positive rates. *Proc. Natl. Acad. Sci.* 113, 7900–7905. <https://doi.org/10.1073/pnas.1602413113>.
- Elman, I., Ariely, D., Mazar, N., Aharon, I., Lasko, N.B., Macklin, M.L., Orr, S.P., Lukas, S.E., Pitman, R.K., 2005. Probing reward function in post-traumatic stress disorder with beautiful facial images. *Psychiatr. Res.* 135, 179–183. <https://doi.org/10.1016/j.psychres.2005.04.002>.
- Etkin, A., Wager, T.D., 2007. Functional neuroimaging of anxiety: a meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. *Am. J. Psychiatr.* 164, 1476–1488. <https://doi.org/10.1176/appi.ajp.2007.07030504>.
- First, M.B., Spitzer, R.L., Gibbon, M., Williams, J.B.W., 2002. Structured Clinical Interview for DSM-IV-tr Axis I Disorders, Research Version, Non-patient Edition. (SCID-I/NP). Biometrics Research. New York State Psychiatric Institute, New York.
- Foa, E.B., 2011. Prolonged exposure therapy: past, present, and future. *Depress. Anxiety* 28, 1043–1047. <https://doi.org/10.1002/da.20907>.
- Foa, E.B., Dancu, C.V., Hembree, E.A., Jaycox, L.H., Meadows, E.A., Street, G.P., 1999. A comparison of exposure therapy, stress inoculation training, and their combination for reducing posttraumatic stress disorder in female assault victims. *J. Consult. Clin. Psychol.* 67, 194–200.
- Foa, E.B., Rothbaum, B.O., Riggs, D.S., Murdock, T.B., 1991. Treatment of posttraumatic stress disorder in rape victims: a comparison between cognitive-behavioral procedures and counseling. *J. Consult. Clin. Psychol.* 59, 715–723.
- Gläscher, J., Adolphs, R., Damasio, H., Bechara, A., Rudrauf, D., Calamia, M., Paul, L.K., Tranel, D., 2012. Lesion mapping of cognitive control and value-based decision making in the prefrontal cortex. *Proc. Natl. Acad. Sci.* 109, 14681–14686.
- Gläscher, J., Daw, N., Dayan, P., O'Doherty, J.P., 2010. States versus rewards: dissociable neural prediction error signals underlying model-based and model-free reinforcement learning. *Neuron* 66, 585–595. <https://doi.org/10.1016/j.neuron.2010.04.016>.
- Hare, T.A., Camerer, C.F., Rangel, A., 2009. Self-control in decision-making involves modulation of the vmPFC valuation system. *Science* 324, 646–648. <https://doi.org/10.1126/science.1168450>.
- Hauser, T.U., Iannaccone, R., Ball, J., Mathys, C., Brandeis, D., Walitza, S., Brem, S., 2014. Role of the medial prefrontal cortex in impaired decision making in juvenile attention-deficit/hyperactivity disorder. *JAMA Psychiatr.* 71, 1165–1173. <https://doi.org/10.1001/jamapsychiatry.2014.1093>.
- Hauser, T.U., Iannaccone, R., Walitza, S., Brandeis, D., Brem, S., 2015. Cognitive flexibility in adolescence: neural and behavioral mechanisms of reward prediction error processing in adaptive decision making during development. *Neuroimage* 104, 347–354. <https://doi.org/10.1016/j.neuroimage.2014.09.018>.
- Hiser, J., Koenigs, M., 2017. The multifaceted role of the ventromedial prefrontal cortex in emotion, decision making, social cognition, and psychopathology. *Biol. Psychiatr.* <https://doi.org/10.1016/j.biopsych.2017.10.030>.
- Hopper, J.W., Frewen, P.A., van der Kolk, B.A., Lanius, R.A., 2007. Neural correlates of reexperiencing, avoidance, and dissociation in PTSD: symptom dimensions and emotion dysregulation in responses to script-driven trauma imagery. *J. Trauma Stress* 20, 713–725. <https://doi.org/10.1002/jts.20284>.
- Hopper, J.W., Pitman, R.K., Su, Z., Heyman, G.M., Lasko, N.B., Macklin, M.L., Orr, S.P., Lukas, S.E., Elman, I., 2008. Probing reward function in posttraumatic stress disorder: expectancy and satisfaction with monetary gains and losses. *J. Psychiatr. Res.* 42, 802–807. <https://doi.org/10.1016/j.jpsychires.2007.10.008>.
- Kable, J.W., Glimcher, P.W., 2009. The neurobiology of decision: consensus and controversies. *Neuron* 63, 733–745. <https://doi.org/10.1016/j.neuron.2009.09.003>.
- Kessler, R.C., 2000. Posttraumatic stress disorder: the burden to the individual and to society. *J. Clin. Psychiatr.* 61, 4–12.
- Kilpatrick, D.G., Acierno, R., Saunders, B., Resnick, H.S., Best, C.L., Schnurr, P.P., 2000. Risk factors for adolescent substance abuse and dependence: data from a national sample. *J. Consult. Clin. Psychol.* 68, 19–30.
- Kilpatrick, D.G., Ruggiero, K.J., Acierno, R., Saunders, B.E., Resnick, H.S., Best, C.L., 2003. Violence and risk of PTSD, major depression, substance abuse/dependence, and comorbidity: results from the National Survey of Adolescents. *J. Consult. Clin. Psychol.* 71, 692–700. <https://doi.org/10.1037/0022-006X.71.4.692>.
- Lenow, J.K., Scott Steele, J., Smitherman, S., Kilts, C.D., Cisler, J.M., 2014. Attenuated behavioral and brain responses to trust violations among assaulted adolescent girls. *Psychiatry Res. Neuroimaging* 223, 1–8. <https://doi.org/10.1016/j.pscychres.2014.04.005>.
- Li, J., Schiller, D., Schoenbaum, G., Phelps, E.A., Daw, N.D., 2011. Differential roles of human striatum and amygdala in associative learning. *Nat. Neurosci.* 14, 1250–1252. <https://doi.org/10.1038/nn.2904>.
- Lissek, S., Bradford, D.E., Alvarez, R.P., Burton, P., Espensen-Sturges, T., Reynolds, R.C., Grillon, C., 2014. Neural substrates of classically conditioned fear-generalization in humans: a parametric fMRI study. *Soc. Cognit. Affect Neurosci.* 9, 1134–1142. <https://doi.org/10.1093/scan/nst096>.
- Lissek, S., Rabin, S., Heller, R.E., Lukenbaugh, D., Geraci, M., Pine, D.S., Grillon, C., 2009. Overgeneralization of conditioned fear as a pathogenic marker of panic disorder. *Am. J. Psychiatr.* 167, 47–55.
- Macklin, M.L., Metzger, L.J., Litz, B.T., McNally, R.J., Lasko, N.B., Orr, S.P., Pitman, R.K., 1998. Lower precombat intelligence is a risk factor for posttraumatic stress disorder. *J. Consult. Clin. Psychol.* 66, 323–326.
- McKeown, M.J., Jung, T.-P., Makeig, S., Brown, G., Kindermann, S.S., Lee, T.-W., Sejnowski, T.J., 1998. Spatially independent activity patterns in functional MRI data during the Stroop color-naming task. *Proc. Natl. Acad. Sci. U. S. A* 95, 803–810.
- McNally, R.J., Kaspi, S.P., Riemann, B.C., Zeitlin, S.B., 1990. Selective processing of threat cues in posttraumatic stress disorder. *J. Abnorm. Psychol.* 99, 398–402.
- Milad, M.R., Pitman, R.K., Ellis, C.B., Gold, A.L., Shin, L.M., Lasko, N.B., Zeidan, M.A., Handwerker, K., Orr, S.P., Rauch, S.L., 2009. Neurobiological basis of failure to recall extinction memory in posttraumatic stress disorder. *Biol. Psychiatr.* 66, 1075–1082. <https://doi.org/10.1016/j.biopsych.2009.06.026>.
- Mueller, V.A., Brass, M., Waszak, F., Prinz, W., 2007. The role of the preSMA and the rostral cingulate zone in internally selected actions. *Neuroimage* 37, 1354–1361. <https://doi.org/10.1016/j.neuroimage.2007.06.018>.
- Niendam, T.A., Laird, A.R., Ray, K.L., Dean, Y.M., Glahn, D.C., Carter, C.S., 2012. Meta-analytic evidence for a superordinate cognitive control network subserving diverse executive functions. *Cognit. Affect Behav. Neurosci.* 12, 241–268. <https://doi.org/10.3758/s13415-011-0083-5>.
- Niv, Y., Edlund, J.A., Dayan, P., O'Doherty, J.P., 2012. Neural prediction errors reveal a risk-sensitive reinforcement-learning process in the human brain. *J. Neurosci.* 32, 551–562. <https://doi.org/10.1523/JNEUROSCI.5498-10.2012>.
- Norrholm, S.D., Jovanovic, T., Olin, I.W., Sands, L.A., Karapanou, I., Bradley, B., Ressler, K.J., 2011. Fear extinction in traumatized civilians with posttraumatic stress disorder: relation to symptom severity. *Biol. Psychiatr.* 69, 556–563. <https://doi.org/10.1016/j.biopsych.2010.09.013>.
- Palminteri, S., Justo, D., Jauffret, C., Pavlicek, B., Dauta, A., Delmaire, C., Czernecki, V., Karachi, C., Capelle, L., Durr, A., Pessiglione, M., 2012. Critical roles for anterior insula and dorsal striatum in punishment-based avoidance learning. *Neuron* 76, 998–1009. <https://doi.org/10.1016/j.neuron.2012.10.017>.
- Paulus, M.P., Stein, M.B., 2006. An insular view of anxiety. *Biol. Psychiatr.* 60, 383–387.
- Pechtel, P., Pizzagalli, D.A., 2013. Disrupted reinforcement learning and maladaptive behavior in women with a history of childhood sexual abuse: a high-density event-related potential study. *JAMA Psychiatr.* 70 (499). <https://doi.org/10.1001/jamapsychiatry.2013.728>.
- Peri, T., Ben-Shakhar, G., Orr, S.P., Shalev, A.Y., 2000. Psychophysiological assessment of aversive conditioning in posttraumatic stress disorder. *Biol. Psychiatr.* 47, 512–519.
- Preuschhoff, K., Quartz, S.R., Bossaerts, P., 2008. Human insula activation reflects risk prediction errors as well as risk. *J. Neurosci.* 28, 2745–2752.
- Rauch, S.L., Shin, L.M., Phelps, E.A., 2006. Neurocircuitry models of posttraumatic stress disorder and extinction: human neuroimaging research—past, present, and future. *Biol. Psychiatr.* 60, 376–382. <https://doi.org/10.1016/j.biopsych.2006.06.004>.
- Resnick, H.S., Kilpatrick, D.G., Dansky, B.S., Saunders, B.E., Best, C.L., 1993. Prevalence of civilian trauma and posttraumatic stress disorder in a representative national sample of women. *J. Consult. Clin. Psychol.* 61, 984.
- Rothbaum, B.O., Davis, M., 2003. Applying learning principles to the treatment of post-trauma reactions. *Ann. N. Y. Acad. Sci.* 1008, 112–121. <https://doi.org/10.1196/annals.1301.012>.
- Rushworth, M.F.S., Behrens, T.E.J., 2008. Choice, uncertainty and value in prefrontal and cingulate cortex. *Nat. Neurosci.* 11, 389–397. <https://doi.org/10.1038/nn2066>.
- Saltzman, K.M., Weems, C.F., Carrion, V.G., 2006. IQ and posttraumatic stress symptoms in children exposed to interpersonal violence. *Child Psychiatr. Hum. Dev.* 36, 261–272. <https://doi.org/10.1007/s10578-005-0002-5>.
- Scott, J.C., Matt, G.E., Wrocklage, K.M., Crnich, C., Jordan, J., Southwick, S.M., Krystal, J.H., Schweinsburg, B.C., 2015. A quantitative meta-analysis of neurocognitive functioning in posttraumatic stress disorder. *Psychol. Bull.* 141, 105–140. <https://doi.org/10.1037/a0038039>.
- Srinivasan, L., Asaad, W.F., Ginat, D.T., Gale, J.T., Dougherty, D.D., Williams, Z.M., Sejnowski, T.J., Eskandar, E.N., 2013. Action initiation in the human dorsal anterior cingulate cortex. *PLoS One* 8, e55247. <https://doi.org/10.1371/journal.pone.0055247>.
- Steenkamp, M.M., Dickstein, B.D., Salters-Pedneault, K., Hofmann, S.G., Litz, B.T., 2012. Trajectories of PTSD symptoms following sexual assault: is resilience the modal outcome? *J. Trauma Stress* 25, 469–474.
- Stewart, J.L., Connolly, C.G., May, A.C., Tapert, S.F., Wittmann, M., Paulus, M.P., 2014. Striatum and insula dysfunction during reinforcement learning differentiates abstinent and relapsed methamphetamine dependent individuals. *Addict. Abingdon Engl* 109, 460–471. <https://doi.org/10.1111/add.12403>.
- Sutton, R.S., Barto, A.G., 1998. *Learning: an Introduction*. MIT Press, Cambridge, MA.
- van den Bos, W., Cohen, M.X., Kahnt, T., Crone, E.A., 2012. Striatum-medial prefrontal cortex connectivity predicts developmental changes in reinforcement learning. *Cerebr. Cortex* 22, 1247–1255. <https://doi.org/10.1093/cercor/bhr198>.

- Vasterling, J.J., Brailey, K., Constans, J.I., Borges, A., Sutker, P.B., 1997. Assessment of intellectual resources in gulf war veterans: relationship to PTSD. *Assessment* 4, 51–59.
- Vasterling, J.J., Duke, L.M., Brailey, K., Constans, J.I., Allain, A.N., Sutker, P.B., 2002. Attention, learning, and memory performances and intellectual resources in Vietnam veterans: PTSD and no disorder comparisons. *Neuropsychology* 16, 5–14. <https://doi.org/10.1037//0894-4105.16.1.5>.

- Zeidan, M.A., Lebron-Milad, K., Thompson-Hollands, J., Im, J.J.Y., Dougherty, D.D., Holt, D.J., Orr, S.P., Milad, M.R., 2012. Test-retest reliability during fear acquisition and fear extinction in humans. *CNS Neurosci. Ther.* 18, 313–317. <https://doi.org/10.1111/j.1755-5949.2011.00238.x>.