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Title: A Shift from Value- to Saliency- Neural Encoding of Subjective Value in Combat Veterans with PTSD during Decision Making under Uncertainty

Authors: Ruonan Jia[1,2], Lital Ruderman[2], Charles Gordon[3,4], Daniel Ehrlich[1], Mark Horvath[3,4], Serena Mirchandani[3,4], Clara DeFontes[3,4], John Krystal[3,4], Ilan Harpaz-Rotem[3,4], Ifat Levy[1,2,3]

1. Interdepartmental Neuroscience Program, Yale University; 2. Department of Comparative Medicine, Yale University; 3. National Center for PTSD, West Haven VA Medical Center; 4. Department of Psychiatry, Yale University

Abstract

Combat soldiers are vulnerable to Posttraumatic Stress Disorder (PTSD), following traumatic experiences in the battlefield. Studies have often used fear-related design to unravel the underlying neural deficits of learning and emotion regulation in PTSD patients. However, the role of individual uncertainty attitudes in the development of trauma-related psychopathology has hardly been examined, especially that uncertainty is highly related to the traumatic experiences from the battlefield. Through a monetary gambling paradigm inspired by behavioral economics, we explore the neural markers of PTSD symptoms of combat veterans in the realm of decision making, focusing on the subjective valuation of uncertain monetary gains and losses. We identify increased behavioral aversion to risky monetary gains and ambiguous monetary losses related to higher PTSD symptom severity. We find the key role of the emotional numbing cluster of PTSD symptoms in influencing the general activities of ventromedial prefrontal cortex (vmPFC) during valuation. We further suggest that a shift from value- to saliency- encoding pattern of subjective values across rewards and punishments in the valuation neural system, especially in ventral striatum, exist in combat veterans with PTSD, compared with trauma-exposed controls. Our results elucidate the increased neural sensitivity to highly salient rewards and punishments related to PTSD symptoms, and at the same time, point to the fundamental differences in brain regions involved in reward- and punishment- processing. We also identify

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potential resiliency neural mechanisms that could protect trauma-exposed individuals against developing PTSD symptoms.

Introduction

Following a traumatic experience, some individuals develop Posttraumatic Stress Disorder (PTSD) symptoms, which include core symptoms of re-experiencing the traumatic event, avoidance of trauma reminders, emotional numbing, and exaggerated arousal and reactivity. These symptoms can be highly debilitating and prevent patients from engaging in social interactions and work activities. While medications and psychotherapy are helpful for some individuals, many remain symptomatic following treatment (Foa, Keane, and Friedman 2000). A better understanding of the neural basis of PTSD is crucial, as it can inform new approaches to individualized treatment.

An important aspect of many traumatic experiences is the uncertainty surrounding actions and potential outcomes. Soldiers in combat, for example, are faced with highly uncertain life-threatening events that may result in serious injury of themselves or death of teammates. An individual's attitude towards uncertainty and the ability to handle uncertainty may therefore affect one's ability to cope with traumatic events. The notion of uncertainty has been incorporated in many fear-learning studies attempting to unravel the behavioral and neural mechanisms of PTSD (Brown et al. 2018; Homan et al. 2019). Participants in these studies encounter probabilistic deliveries of adverse outcomes (e.g. electric shocks), and their ability to predict these outcomes is measured (e.g. by their skin conductance responses). In a separate line of work, using a behavioral economic framework, our group has shown increased aversion to ambiguity (an uncertain situation where outcome probabilities are not known) in combat veterans with PTSD, choosing between potential monetary losses, compared to veterans with no PTSD (Ruderman et al. 2016). An intriguing possibility is that aversion to uncertainty, which is demonstrated in situations unrelated to the trauma, is also contributing to the exaggerated behavior in fear conditioning paradigms, and to the development and maintenance of PTSD symptoms.

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As uncertainty attitudes affect the subjective value of options, it is plausible that neural computations of subjective value are altered in the brains of individuals who developed PTSD following trauma exposure. A large network of brain regions has been implicated in valuation and decision making, including the ventromedial prefrontal cortex (vmPFC), anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), dorsolateral prefrontal cortex (dlPFC), ventral striatum, amygdala, and thalamus (Kable and Glimcher 2009; Gleichgerrcht et al. 2010). While the neural encoding of the subjective value of rewards has been extensively studied in the general population, it is still unclear how subjective values of punishments are represented in the brain. On the one hand, there is evidence for a unified valuation system, which encodes the values of both rewards and punishments (Tom et al. 2007; Fujiwara et al. 2009; Kahnt et al. 2014; Bartra, McGuire, and Kable 2013); on the other hand, there is evidence for different brain circuits processing outcomes from the two valence domains (O'Doherty et al. 2001; Yacubian et al. 2006; Kim et al. 2014; Monosov and Hikosaka 2012; Fiorillo 2013). Moreover, while we know that the subjective values of ambiguous gains are encoded in the valuation system (Levy et al. 2010; Zadelaar et al. 2019), we are not aware of any examination of the neural encoding of subjective value of ambiguous losses. Here we combined our simple economic task with functional MRI to examine the neural encoding of subjective value of ambiguous losses, and the alterations in this encoding in individuals exposed to trauma.

In this study, we use a gambling task in conjunction with fMRI and computational modeling to investigate the neural mechanisms underlying higher uncertainty aversion in combat veterans who developed PTSD following trauma exposure. We included combat veterans who did not develop PTSD symptoms as controls (trauma-exposed controls), thus were able not only to investigate psychopathology of PTSD but also resiliency factors against it. We find that veterans with PTSD encoded the subjective values of uncertain monetary outcomes in a U-shape manner (i.e. saliency-encoding), compared with trauma-exposed controls who encoded the subjective values monotonically (i.e. value-encoding). Our results suggest that this shift from value-encoding to saliency-encoding, especially of ambiguous monetary losses, could be a neural marker for PTSD symptom severity.

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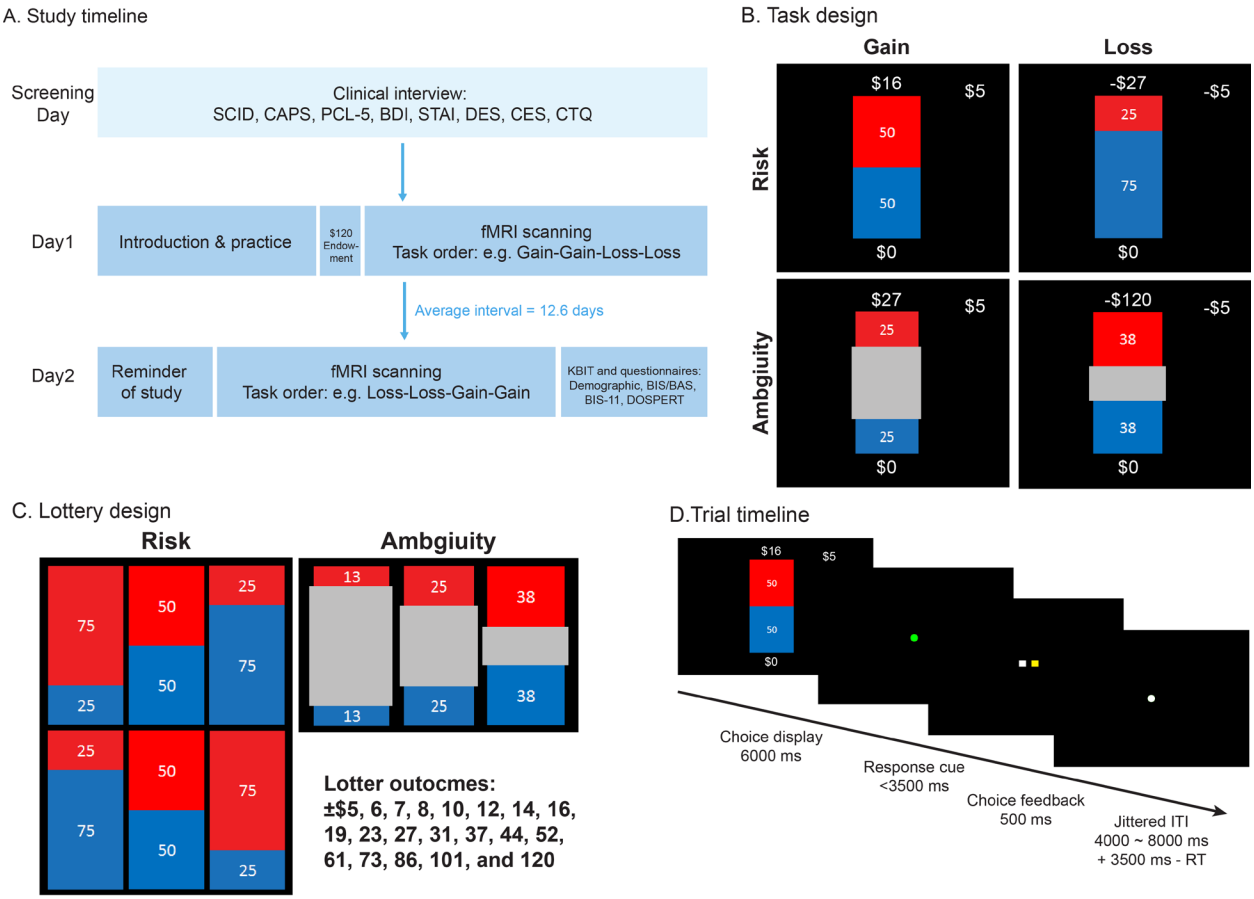
Results

In an fMRI experiment, combat veterans with current PTSD diagnosis and those who never developed PTSD completed a gambling task under four decision conditions on two separate days. Participants chose between a sure monetary outcome (either gaining or losing money) and an uncertain outcome (either risky or ambiguous, under gains or losses, Fig 1). We estimated the uncertainty attitudes of each participant through a behavioral model, and aimed to understand the influence of PTSD symptom severity on both the behavioral attitudes and the neural mechanisms of valuation.

Figure 1. Study design



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A: Timeline of the study. Participants went through a screening session and two scanning sessions on three different days. The screening session determined the eligibility of participants based on PTSD diagnosis, combat exposure, and exclusion of other neurological disorders. Eligible participants went through two days' fMRI scans of a decision making task. Labels of measures: SCID: Structured Clinical Interview for DSM-4, CAPS: Clinician Administered PTSD Scale, PCL5: , PTSD Checklist for DSM-5 , BDI: Beck Depression Inventory, STAI-1: State Anxiety, STAI-2: Trait Anxiety, DES: Dissociative Experiences Scale, CES: Combat Exposure Scale, CTQ: Childhood Trauma Questionnaire, KBIT: Kaufman Brief Intelligence Test, BIS/BAS: Behavioral Avoidance/Inhibition Scale, BIS-11: Barratt Impulsiveness Scale, DOSPERT: Doman-Specific Risk-Taking Scale. B: Task design: participants chose between a lottery and a sure outcome under four conditions: risky gains, ambiguous gains, risky losses, and ambiguous losses. Lotteries are shown as examples. C: Levels of risk (0.25, 0.5, and 0.75), ambiguity (0.74, 0.5, and 0.24), and monetary outcomes (20 monetary outcomes in either gains or losses) of the lottery. D: On each trial, participants had 6 seconds to view the options, and made a choice after a green response cue. They had a time limit of 3.5 seconds to register the choice, after which they would immediately see a confirmation with the yellow square representing the side they chose. The lottery was not played out during the scan to avoid learning. The inter-trial-interval (ITI) was jittered among 4, 6, and 8 seconds, and the remaining time during the response window (3.5 seconds – response time) would be added to the ITI.

Clinical symptom variation

Participants displayed a large range and variation of PTSD symptom severity (Fig 2A), assessed by the Clinician-Administered PTSD Scale (CAPS) (Blake et al. 1995). Veterans with PTSD showed higher total CAPS score compared to controls (PTSD, N = 23: *Mean* = 72.13, *SD* = 15.04; control, N = 34: *Mean* = 6.21, *SD* = 9.68; $t(34) = 18.58$, $p < 0.001$). PTSD symptoms as captured by the 5-factor model of CAPS (Harpaz-Rotem et al. 2014) were highly correlated with symptoms of depression, anxiety and dissociative experiences (Fig 2B, see Table 1 for descriptive statistics of all measures), suggesting comorbidity of

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these clinical symptoms in our participants. In order to fully account for the clinical symptoms' influence on participants' behavior and neural activity during the task, we conducted PCA on these clinical symptoms. Since the severity of psychopathology may be affected by experienced trauma, we also included measures of combat exposure (CES) and childhood trauma (CTQ) in the PCA. The first three components accounted for ~80% of the variance in those data (Fig 3A). Figure 3B presents the loading coefficients of these three components: the first component is affected by all clinical symptoms (PTSD, depression, anxiety, and dissociative experiences) and might reflect a general affective factor. This component is highly consistent with PTSD symptom severity (correlation with CAPS Spearman's ρ = 0.94, n = 55, $p < 0.001$), and PTSD diagnosis could be clearly classified using the first component (Fig 3C). The second component is mostly affected by re-experiencing, avoidance and anxious arousal symptoms of CAPS, and combat exposure severity, potentially representing a fear learning-updating deficit. The third component is mostly affected by trauma severity, reflecting combat exposure and childhood trauma. These components were not strongly correlated with PTSD symptom severity (n = 55, Component 2: correlation with CAPS Spearman's $\rho = 0.11$, $p = 0.43$; Component 3: correlation with CAPS Spearman's $\rho = 0.029$, $p = 0.84$).

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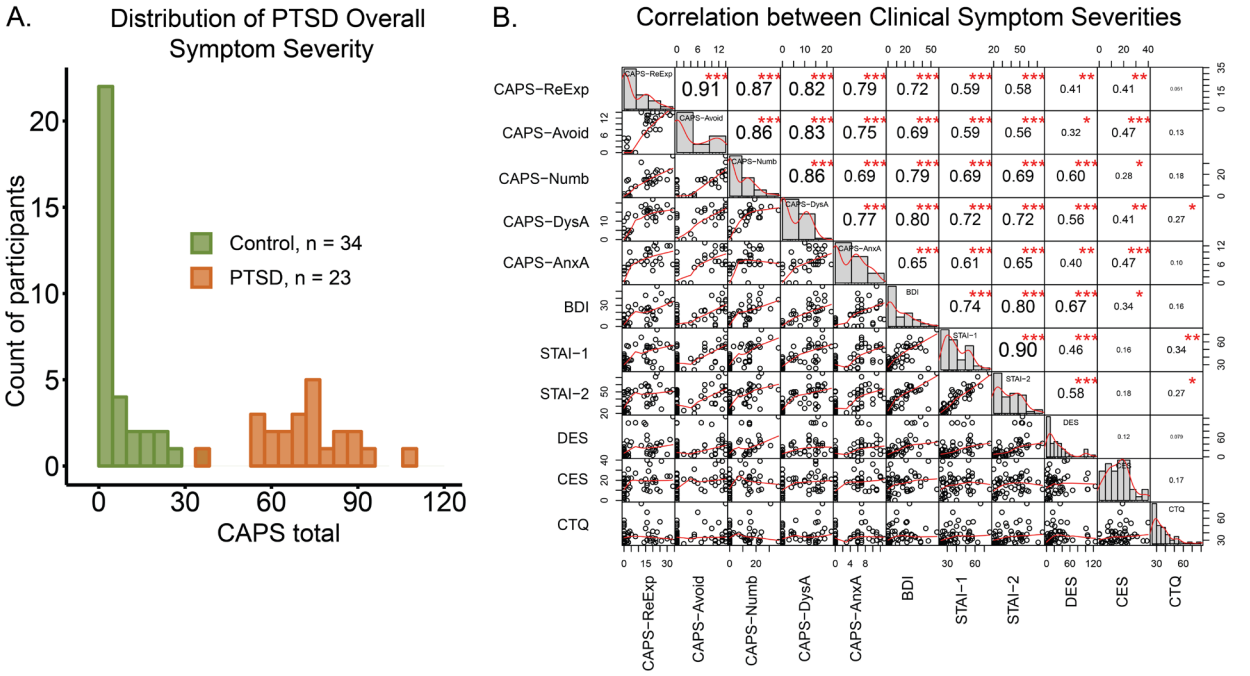
Figure 2. Symptom severities of participants.



A: Distribution of CAPS total score, colored by combat veterans with or without PTSD diagnosis. B: PTSD, depression and anxiety symptom severities were highly correlated. Numbers in the upper right panels indicate pair-wise Pearson correlation coefficients. Significance levels: ***, $p < 0.001$; **, $p < 0.01$; *, $p < 0.05$. Lower left panels show pair-wise scatter plots and smoothed curves using locally weighted polynomial regression. Panels in the diagonal show distributions and density curves for each measure. Labels of measures: CAPS-ReExp: re-experiencing, CAPS-Avoid: avoidance, CAPS-Numb: numbing, CAPS-DysA: dysphoric arousal, CAPS-AnxA: anxious arousal, BDI: Beck Depression Inventory, STAI-1: State Anxiety, STAI-2: Trait Anxiety, DES: Dissociative Experiences Scale, CES: Combat Exposure Scale, CTQ: Childhood Trauma Questionnaire.

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Table 1. Descriptive statistics of demographics and clinical measures of participants reported in the behavioral results.

	PTSD	**Control**
Number of participants	24	34
Age	34.70 (6.44)	39.17 (10.03)
Kaufman Brief Intelligence Test (KBIT)	105.63 (10.52)	111.59 (13.22)
Clinician Administered PTSD Scale (CAPS)-Total Score	72.13 (15.04)	6.21 (9.68)
CAPS-Re-experiencing	19.83 (6.79), n = 23	1.00 (1.86)
CAPS-Avoidance	10.65(3.41), n = 23	0.47 (1.38)
CAPS-Emotional Numbing	18.13 (6.61), n = 23	1.03 (3.03)
CAPS-Dysphoric Arousal	15.09 (3.15), n = 23	2.00 (3.65)
CAPS-Anxious Arousal	8.44 (2.56), n = 23	1.71 (2.87)
PTSD Checklist for DSM-5 (PCL-5)	41.54 (15.79)	10.88 (15.95)
Beck Depression Inventory (BDI)	26.11 (13.80)	5.50 (7.88)
State Anxiety (STAI-1)	47.92 (12.72)	32.62 (9.43)
Trait Anxiety (STAI-2)	47.32 (16.23)	31.33 (10.94)
Dissociative Experience Scale (DES)	44.04 (34.53)	17.31 (20.75), n = 33
Combat Exposure Scale (CES)	19.96 (9.06), n = 23	13.00 (8.57)
Childhood Trauma Questionnaire (CTQ)	39.04 (14.03), n = 23	34.43 (8.76)

Mean (standard deviation)

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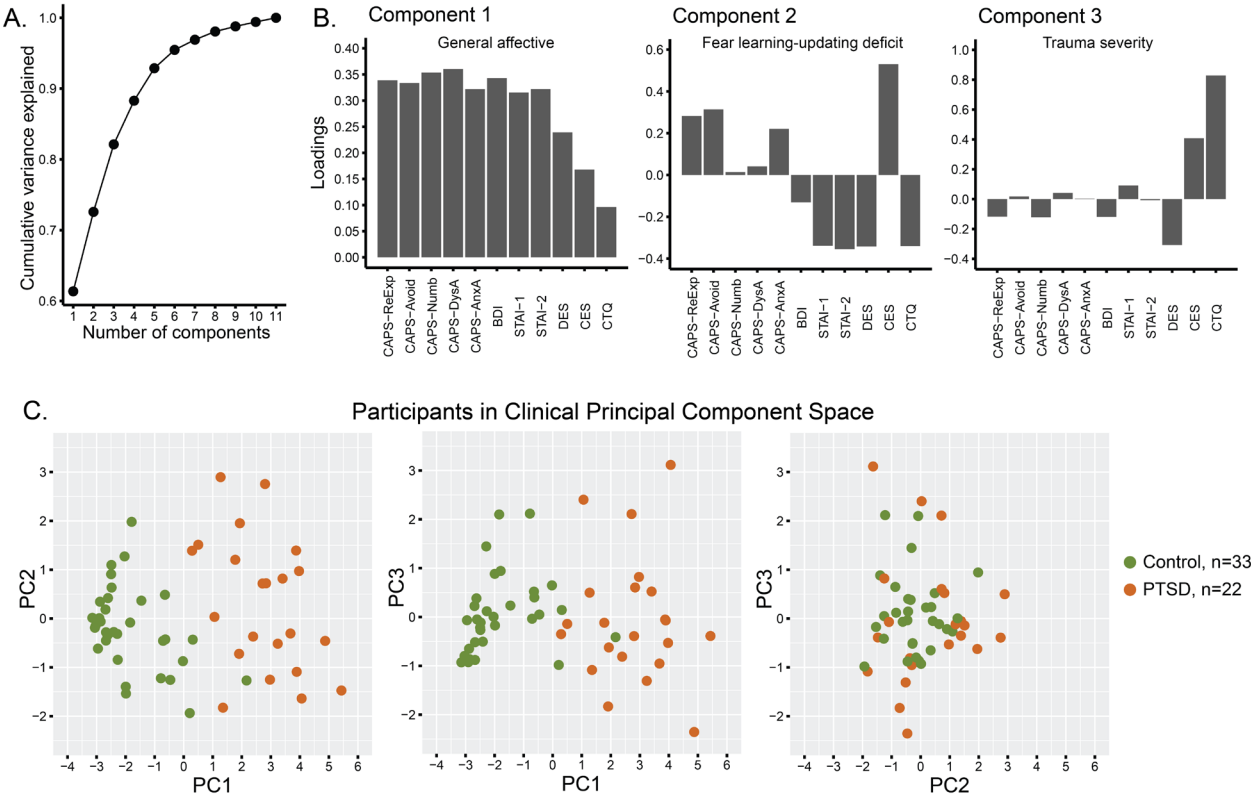
Figure 3. Principal component analysis (PCA) of clinical symptoms and trauma exposure measures.



A: Cumulative variance explained by all principal components. B: Loading coefficients of the first three principal components, representing general affective symptom, deficit in fear learning-updating, and trauma severity, respectively. Labels: CAPS-ReExp: re-experiencing, CAPS-Avoid: avoidance, CAPS-Numb: emotional numbing, CAPS-DysA: dysphoric arousal, CAPS-AnxA: anxious arousal, BDI: Beck Depression Inventory, STAI-1: State Anxiety, STAI-2: Trait Anxiety, DES: Dissociative Experiences Scale, CES: Combat Exposure Scale, CTQ: Childhood Trauma Questionnaire. C: Participants plotted in the two-dimensional spaces represented by pairs of the first three principal components, colored by PTSD diagnosis.

PTSD symptoms predict increased aversion to ambiguity in the loss domain, and increased risk aversion in the gain domain

For each participant, we estimated risk and ambiguity attitudes for gains and losses, using the combined data from both scanning sessions (see equations 1 and 2 in Model-based Risk and ambiguity attitudes

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estimation in the Methods section; see Supplementary Fig 1A for an example from one participant). We then investigated the associations between these attitudes and PTSD diagnosis status, as well as PTSD symptom severity. All attitudes were transformed such that negative numbers indicate aversion (to risk or ambiguity), and positive numbers indicate seeking. Based on the previous behavioral finding that PTSD symptom severity is associated with higher aversion to ambiguity in losses (Ruderman et al. 2016), we first investigated ambiguity attitudes. At the group level, participants were not significantly averse to ambiguity in the domain of losses (Fig 4A; PTSD: *Mean* = -0.25, $t(23) = -1.81$, $p = 0.11$; Control: *Mean* = 0.003, $t(33) = 0.040$, $p = 0.97$), and were significantly averse to ambiguity in the domain of gains (Fig 4A; PTSD: *Mean* = -0.35, $t(23) = -3.45$, $p < 0.01$; Control: *Mean* = -0.42, $t(33) = -7.27$, $p < 0.001$). However, a two-way ANOVA of ambiguity attitude with domain as the within-subject factor, and group as the between-subject factor showed a significant interaction between domain and group ($F(1,56) = 4.34$, $p < 0.05$, $\eta^2 = 0.0279$). Post-hoc comparisons showed that veterans with PTSD were marginally more averse to ambiguity under losses ($p = 0.081$), but not under gains ($p = 0.53$). A dimensional analysis (Fig 4B) of this symptom–behavior relationship, regardless of PTSD diagnosis, revealed a negative correlation between ambiguity attitudes in the loss domain and CAPS total score (Spearman's ρ with CAPS total score = -0.30, $p < 0.05$), indicating that higher symptom severity was related to higher aversion to ambiguity under losses. Since many control participants had a CAPS score of zero, we also repeated the analysis using PCL-5 scores instead of CAPS and overserved a similar effect (Supplementary Fig 1B, Pearson's r with PCL-5 = -0.31, $p < 0.05$).

Next, we examined risk attitudes. Both the PTSD and control groups exhibited risk aversion in the domain of gains (PTSD: *Mean* = -0.54, $t(23) = -13.34$, $p < 0.001$; Control: *Mean* = -0.28, $t(33) = -1.80$, $p < 0.001$). In the domain of losses, veterans with PTSD exhibited risk seeking (Fig 4C; PTSD: *Mean* = 0.34, $t(23) = 5.43$, $p < 0.001$), while combat controls exhibited marginal risk seeking (Control: *Mean* = 0.20, $t(33) = 1.82$, $p = 0.078$, FDR corrected for four comparisons). A two-way ANOVA of risk attitude with domain (gain or loss) as the within-subject factor, and group as the between-subject factor revealed a

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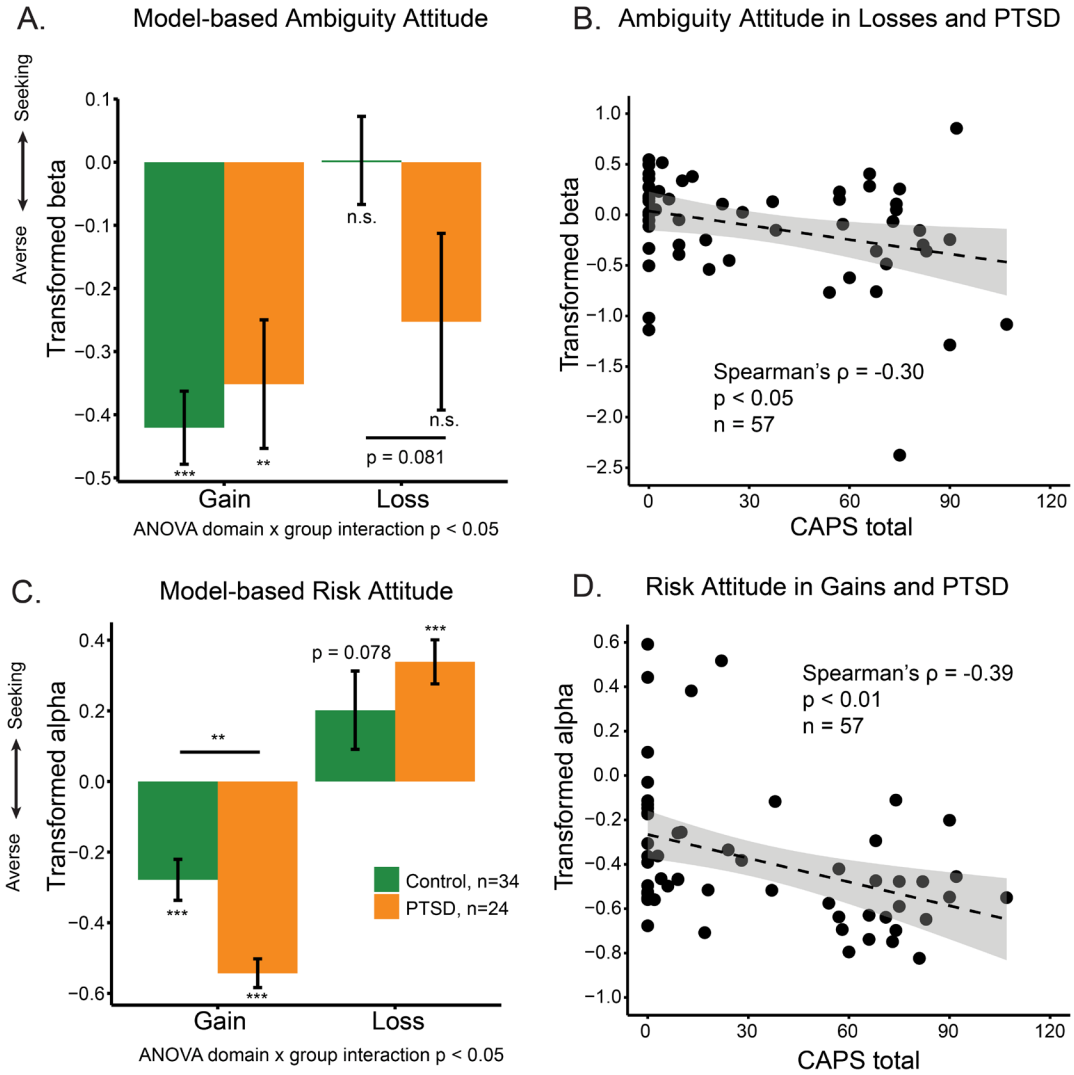
significant interaction between domain and group ($F(1,56) = 6.29$, $p < 0.05$, $\eta^2 = 0.0521$). Post-hoc comparisons showed that veterans with PTSD were more averse to risk under gains ($p < 0.01$), but not under losses ($p = 0.34$), compared with combat controls. Examining this relationship further with a dimensional approach (Fig 4 D and Supplementary Fig 1C), we observed a similar effect: PTSD symptom severity was negatively correlated with risk attitudes in the gain domain (Spearman's ρ with CAPS total = -0.39, $p < 0.01$; Pearson's r with PCL5 = -0.36, $p < 0.01$).

Figure 4. Uncertainty attitudes and PTSD symptom severity.



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A: Group comparison between veterans with PTSD and combat controls of ambiguity attitudes in gains and losses. B: PTSD symptom severity was negatively correlated with ambiguity attitude in losses. C: Group comparison between veterans with PTSD and combat controls of risk attitudes in gains and losses. D: PTSD symptom severity was negatively correlated with risk attitude in gains. In A and C, comparing each group's attitudes with zero were FDR-corrected across all four comparisons in each uncertainty type. Post-hoc comparisons between groups in A and C are FDR-corrected. Significance level: *, $p<0.05$; **, $p<0.01$; ***, $p<0.001$.

Because our participants showed high levels of comorbidity with other clinical symptoms, especially depression and anxiety (Fig 2B), we also examined the correlation between uncertainty attitudes and the first three principal components of all clinical measures. Principal component 1 (general affective symptom) was negatively correlated with risk attitude under gains (Pearson's $r = -0.35$, $p < 0.01$) and ambiguity attitude under losses (Pearson's $r = -0.29$, $p < 0.05$), consistent with the effect of the overall PTSD severity indicated by CAPS total. We did not find any relationship between uncertainty attitudes and the second (fear sensitivity) or the third (trauma severity) principal components. To control for differences in age, income, education and intelligence, we also looked at the relationship between PTSD symptoms and uncertainty attitudes accounting for these factors. We included PTSD severity (CAPS) together with age, income, education, and intelligence in a linear regression model to explain uncertainty attitudes. For risk attitude in the gain domain, only the effect of CAPS score was significant (see Methods: Model-based Risk and ambiguity attitudes estimation; multi-factor ANOVA by Generalized Linear Model: $F(1, 42) = 8.97$, $p < 0.01$), but not the four demographic factors. Similarly for ambiguity attitude in losses, CAPS (multi-factor ANOVA, $F(1, 42) = 5.54$, $p < 0.05$) was the only significant factor.

Because seven of the combat-control veterans in this study sample also participated in the previous behavioral study, we also repeated the analysis excluding these returning participants, to yield a completely independent dataset. The negative relationships between PTSD symptom severity and

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ambiguity attitude in losses (Spearman's ρ with CAPS total= -0.31, $p < 0.05$, $n = 50$), and between PTSD symptom severity and risk attitude in gains (Spearman's ρ = -0.42 with CAPS total, $p < 0.01$, $n = 50$) still hold in this independent sample (Supplementary Fig 2B, D).

We also assessed participants' risk-taking attitudes through the Domain-Specific Risk-Taking (DOSPERT) Scale self-report questionnaire, but none of the domains (Ethical, Financial, Health/Safety, Recreational, and Social) was correlated with PTSD symptoms severity measured by CAPS total. Among the other self-report measures, CAPS total was correlated with total score of Behavioral Inhibition Scale (BIS, Spearman's $\rho = 0.37$, $p < 0.01$, $n = 57$), and with total score of Barratt Impulsiveness Scale (BIS11, Spearman's $\rho = 0.47$, $p < 0.001$, $n = 57$).

PTSD symptom severity is related to diminished neural response to decision making under uncertainty, and emotional numbing plays the key role

To investigate the neural mechanism of the stronger aversion to uncertainty observed in veterans with PTSD, we first examined the general neural activity during decision making (see descriptive statistics of participants reported in the neural results in Table 2). Because the key process of our task is evaluating the subjective values of the uncertain and sure options, we looked at the neural activity during the 6-second period of options presentation on each trial. In a whole-brain analysis, we explored the relationship between PTSD symptom severity and the general neural activity during this valuation process. We found that activity in a vmPFC area was negatively correlated with CAPS total score ($p <$ 0.001, cluster-based corrected, Fig 5A), during the second session of the task .This negative relationship was not specific to a particular condition – rather, it was consistent across all four decision contexts (Figure 5B; Pearson's r(risky gains) = -0.50, r(ambiguous gains) = -0.51, r(risky losses) = -0.51, r(ambiguous losses) = -0.40). Interestingly, a linear regression of this region's activity on all five factors of the CAPS showed that only emotional numbing significantly contributed to this negative correlation (standardized regression coefficient, *Beta* = -0.72, $t = -2.32$, $p < 0.05$, Fig 5C). Age and intelligence

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(KBIT) did not significantly influence neural activity (standardized regression coefficient, Age: *Beta* = -0.14, t = -1.13, p = 0.26; intelligence: *Beta* = 0.044, t = 0.33, p = 0.75; Fig 5C). Variable selection using exhaustive search also indicated that including only the Emotional Numbing cluster out of all PTSD symptom clusters best explained the relationship between vmPFC neural activity and PTSD symptom severities (Fig 5D, BIC = 112.8; see details in fMRI GLM second-level analysis in the Methods section).

Table 2. Descriptive statistics of demographics and clinical measures of participants reported in the neural results.

	PTSD	**Control**
Number of participants	19	28
Age	35.59 (6.86)	38.62 (10.42)
Kaufman Brief Intelligence Test (KBIT)	104.16 (11.24)	112.97 (13.42)
Clinician Administered PTSD Scale (CAPS)-Total Score	71.42 (15.52)	5.55 (9.40)
CAPS-Re-experiencing	19.84 (7.41)	1.00 (1.95)
CAPS-Avoidance	10.21 (3.52)	0.38 (1.21)
CAPS-Emotional Numbing	17.95 (6.91)	0.72 (2.14)
CAPS-Dysphoric Arousal	14.89 (2.81)	1.79 (3.40)
CAPS-Anxious Arousal	8.53 (2.41)	1.66 (2.93)
PTSD Checklist for DSM-5 (PCL-5)	42.37 (15.46)	9.93 (15.99)
Beck Depression Inventory (BDI)	24.95 (13.40)	5.07 (8.08)
State Anxiety (STAI-1)	46.96 (11.41)	31.69 (8.69)
Trait Anxiety (STAI-2)	45.62 (16.07)	30.12 (10.32)
Dissociative Experience Scale (DES)	47.53 (36.50)	16.17 (20.61)
Combat Exposure Scale (CES)	21.06 (9.70), n = 18	13.14 (8.19)
Childhood Trauma Questionnaire (CTQ)	39.05 (15.53), n = 18	34.64 (9.25)

Mean (standard deviation)

For imaging analysis, 10 participants were excluded from those reported in the behavioral results because of fMRI data quality.

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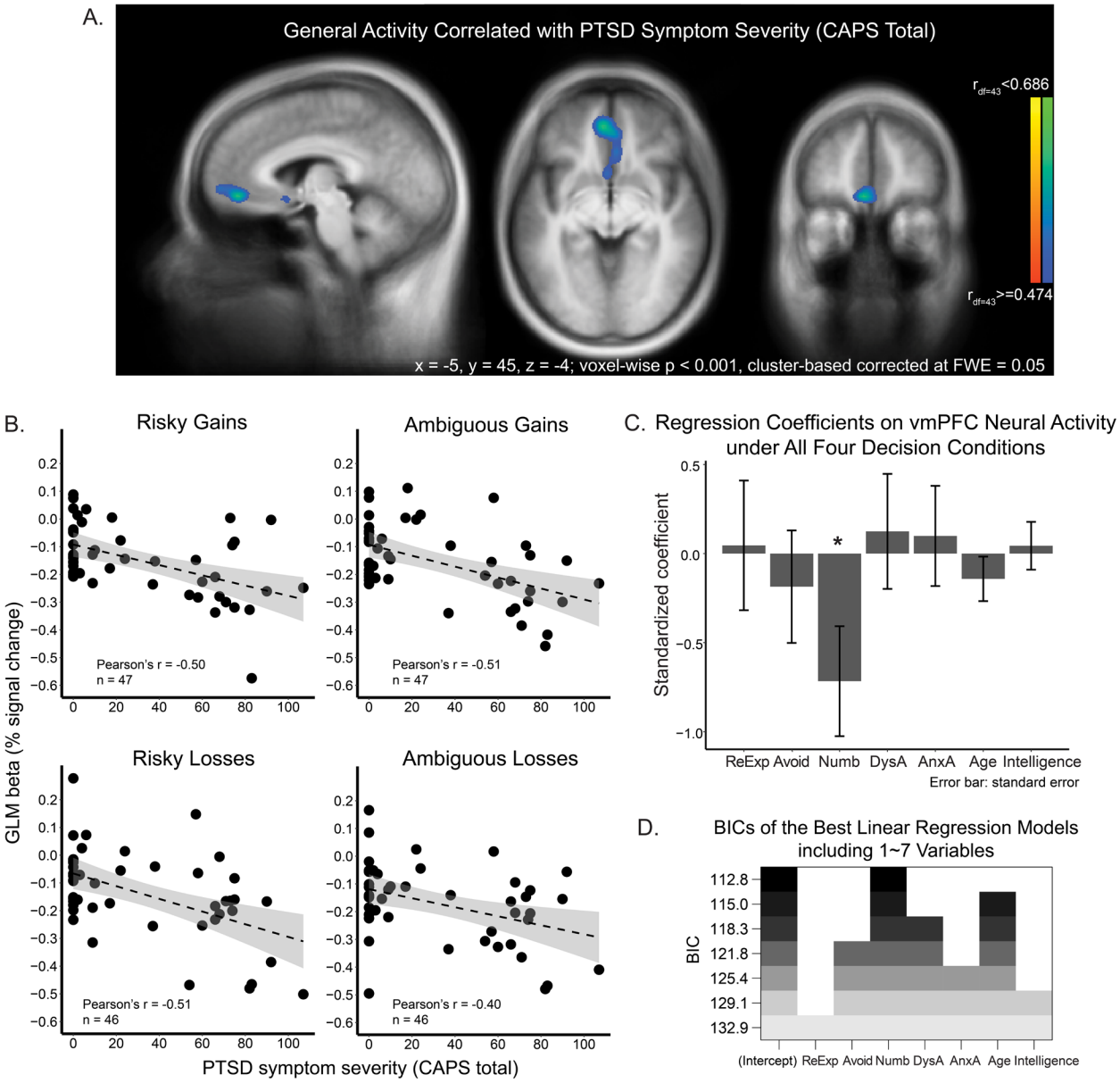
Figure 5. Reduced vmPFC activity during valuation is related to PTSD symptom severity



A: A whole-brain analysis revealed that activity in vmPFC during valuation regardless of decision condition was negative correlated with CAPS total score. B: Visualization of this negative correlation between general activity during valuation and CAPS total score is presented separately in four decision conditions in this vmPFC ROI. C: Emotional numbing symptom severity drove this negative relationship, revealed by a linear regression model on the vmPFC activity including all clusters of the 5-factor model of CAPS. D: Variable selection using exhaustive search also indicated that emotional numbing was the key symptom driving this

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relationship. Each row of the graph shows the selected variables (shaded) for the best model with a given number of predictors. Rows are ranked and colored by BIC. The top row represents the best model, which includes only Emotional numbing as the predictor, among all possible combinations of predictors. Variable naming: ReExp: re-experiencing, Avoid: avoidance, Numb: emotional numbing, DysA: dysphoric arousal, AnxA: anxious arousal.

Neural encoding of subjective value of risky and ambiguous gains and losses

The association between vmPFC activity and PTSD symptom severity in our economic decision-making task is consistent with our hypothesis regarding the involvement of the valuation system in PTSD. We next turn to directly examine the neural correlates of valuation in the task. For each participant, we calculated the subjective value of the lottery presented on each trial based on the behavioral model (see equation 1 in Methods), using the participant-specific risk and ambiguity attitudes under gains and losses. We then included the subjective values (positive for gain lotteries, negative for loss lotteries) in the GLM, separately for each of the four decision conditions. Replicating previous results (Levy et al. 2010), a whole-brain analysis revealed a strong representation of subjective value of gains in medial brain regions, including vmPFC, ACC, PCC, and bilateral caudates (Fig 6A). Under losses, however, the picture was very different. Neural representations of subjective value were mostly found in lateral regions of the brain, including posterior parietal cortex (PPC), middle frontal cortex and cerebellum (Fig 6B; for complete list of regions for all four decision conditions, see Supplementary Table 1). These results suggest differences in basic mechanisms of neural encoding of the subjective value of rewards and punishments, and provide basis for further investigating the effect of PTSD symptoms on the neural encoding of value.

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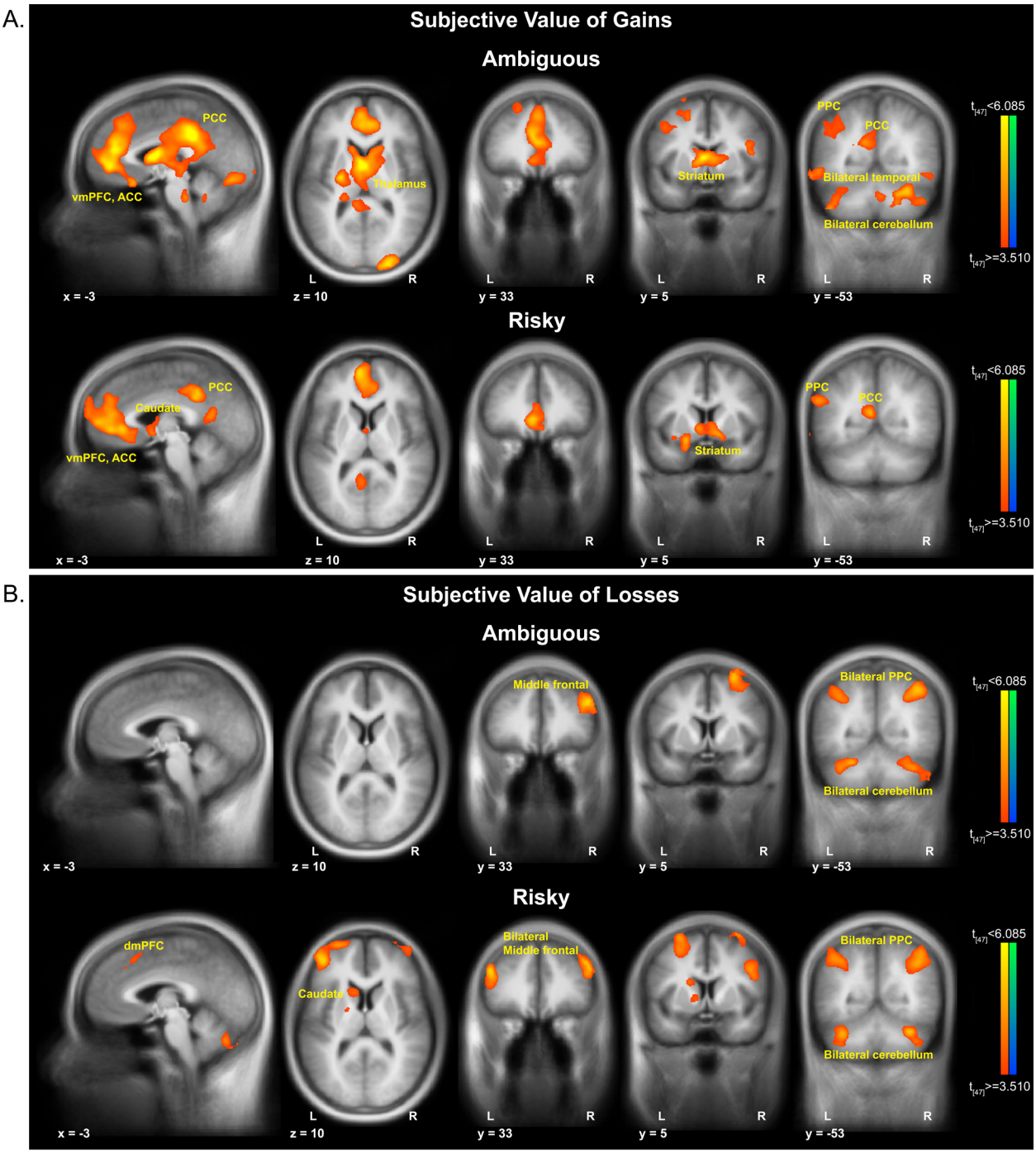
Figure 6. Neural representation of subjective value of gains and losses among all participants



All maps: voxel-wise p < 0.001, cluster-based corrected at FWE = 0.05

Whole-brain analyses revealed neural subjective-value signals of all veteran participants (n = 48, PTSD and control veterans combined), under domains of: A. gains, and B. losses. All maps were corrected using cluster-based method controlling family-wise error at 0.05, and thresholded at $p < 0.001$ at the voxel level.

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PTSD symptom severity is associated with altered neural encoding of subjective value of uncertain options

Since choices in the ambiguous-loss condition were related to PTSD symptoms both in a previous behavioral study (Ruderman et al. 2016) and in the current imaging study, we focused our analysis on this decision condition. First, we examined the encoding of subjective value in whole-brain analyses, separately in the PTSD and combat control groups. In controls (Fig 7A, right), activation patterns were similar to those observed in the combined group (Fig 6B), exhibiting positive correlation with subjective value (decreased activity for increased losses) in bilateral frontal, parietal, and cerebellar regions. Conversely, in veterans with PTSD, subjective value of ambiguous losses was represented in a negative manner (increased activity for increased losses) in bilateral temporal regions (Fig 7A left). Our behavioral data demonstrated an additional association between PTSD symptom severity and risk attitude in the gain domain. We therefore also examined the effect of PTSD on subjective-value encoding in this condition. Subjective value of risky gains was encoded positively in the brains of veterans with PTSD (increased activity for increased gains) in medial prefrontal cortex (mPFC), ACC, PCC, caudate and temporal regions, but was not strongly encoded in the brains of controls (Fig 7B). For completion, we also investigated the other two conditions: subjective values of ambiguous gains were represented in medial brain regions in both groups (supplementary Fig 3A); there was very little representation of subjective value of risky losses in either group (Supplementary Fig 3B; for a complete list of subjective-value-encoding regions from the whole-brain analysis, see Supplementary Table 2). Overall, these results demonstrate potential differences in the direction of loss-encoding, and in the magnitude of gain-encoding, between the two groups.

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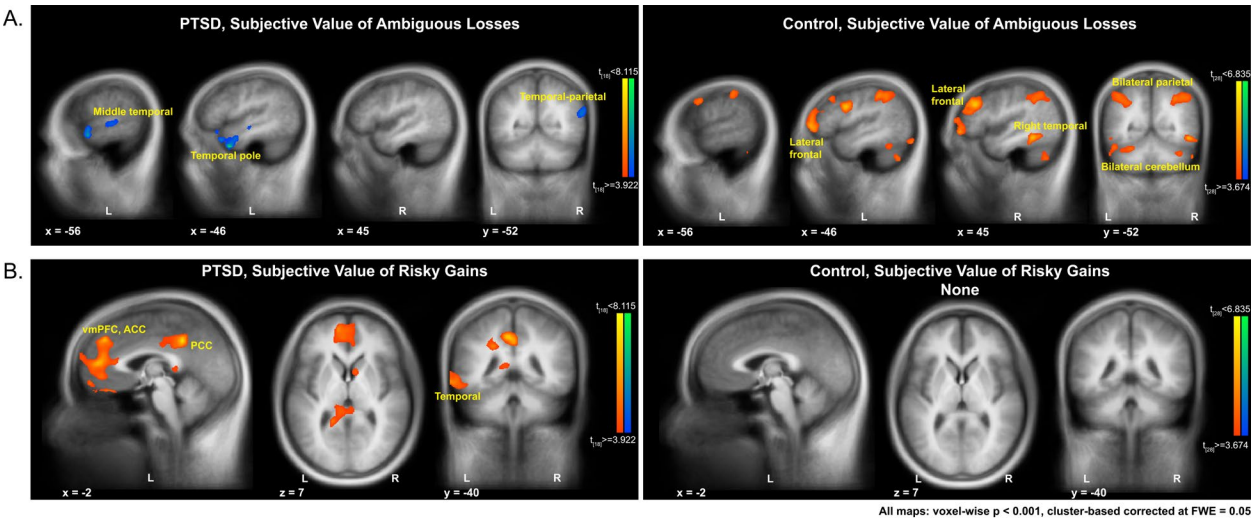
Figure 7. Neural representation of subjective value separately in PTSD and control



Neural representation of subjective value in veterans with PTSD (left) and combat controls (right), under A: ambiguous losses, and B: risky gains. All maps were corrected using cluster-based method controlling family-wise error at 0.05, and thresholded at $p < 0.001$ at the voxel level.

To confirm these group differences, we directly contrasted the neural representation of subjective value between veterans with PTSD and combat controls in a whole-brain analysis. Veterans with PTSD showed more negative subjective-value signals for ambiguous losses in left inferior frontal regions and bilateral occipital regions (Fig 8A.; for statistics of all regions, see Supplementary Table 3). We then used a leave-one-subject-out (LOSO) procedure to define regions around the inferior frontal gyrus (IFG) region and sampled activation in an unbiased manner (see Methods: Leave-one-subject-out (LOSO) procedure). The subjective-value signal of ambiguous losses in IFG was negatively correlated with PTSD symptom severity (Fig 8B; Spearman's $\rho = -0.35$, $p < 0.05$, $n = 48$), such that higher symptom severity was associated with more negative subjective-value signal. Veterans with PTSD showed more positive subjective-value signals for risky gains in right orbitofrontal cortex (OFC) in a whole-brain analysis (Fig 8C), and PTSD symptoms severity was positively correlated with subjective-value signal of risky gains in this OFC region (Fig 8D; Spearman's $\rho = 0.52$, $p < 0.001$, $n = 48$). For completion, we also looked at the

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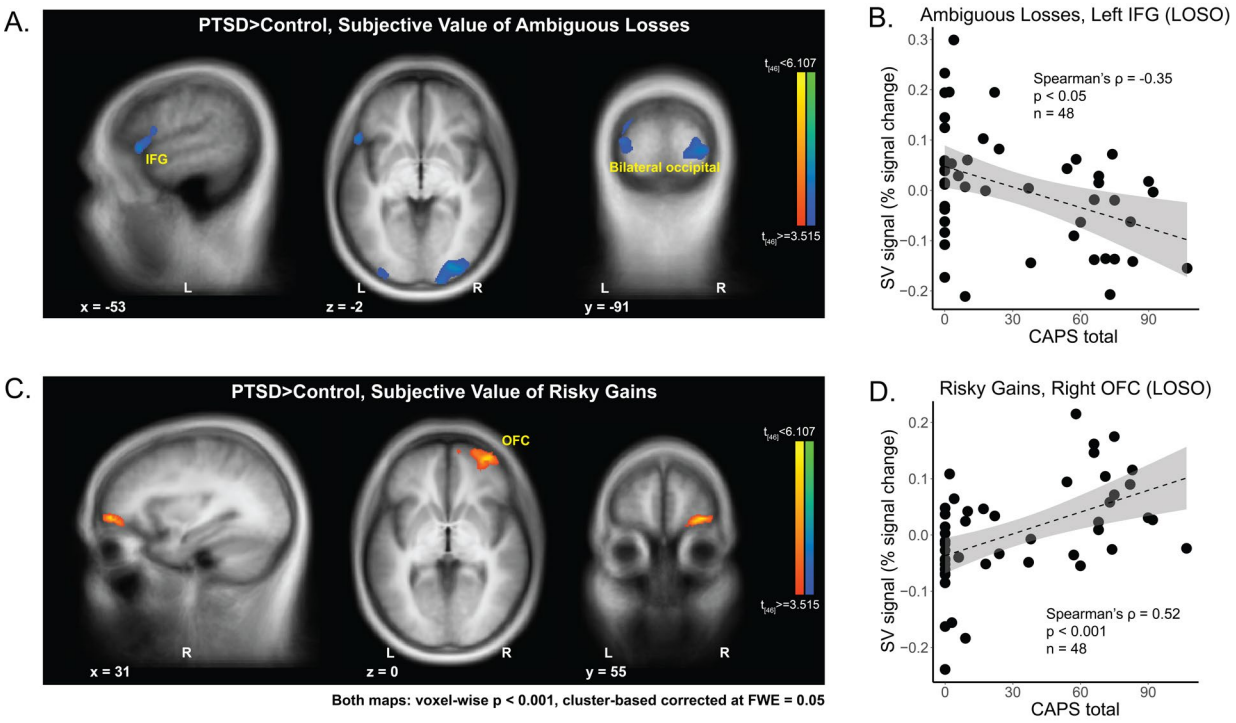
other two conditions. Veterans with PTSD showed more positive encoding of subjective value of ambiguous gains in the thalamus (Supplementary Fig 3C), and there was no group difference in the subjective-value encoding of risky losses.

Figure 8. Neural representation of subjective value directly contrasting PTSD and control



Whole-brain comparisons of neural subjective-value signals between veterans with PTSD and combat controls, under A: ambiguous losses, and C: risky gains. All maps were corrected using cluster-based method controlling family-wise error at 0.05, and thresholded at $p < 0.001$ at the voxel level. B: Neural subjective-value representation of ambiguous losses in the left IFG was negatively correlated with PTSD symptom severity. D: Neural subjective-value representation of risky gains in the right OFC was positively correlated with PTSD symptom severity. ROIs in B and D were defined by a leave-one-subject-out approach.

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To further probe group and individual differences in value encoding, we examined the subjective-value signals of each group in the classical value areas – the vmPFC and the ventral striatum – as defined in a meta-analysis by Bartra and colleagues (Bartra, McGuire, and Kable 2013). We again focused on the conditions of ambiguous losses and risky gains. In vmPFC, subjective-value signal of risky gain lotteries was positively correlated with PTSD symptom severity (Fig 9A, Spearman's ρ with CAPS = 0.31, $p < 0.05$). In ventral striatum, subjective-value signal of ambiguous loss lotteries was negatively correlated with PTSD symptom severity (Fig 9B, Spearman's ρ with CAPS = -0.35, $p < 0.05$). PTSD symptom severity was not significantly associated with the subjective-value signal of ambiguous losses in vmPFC (Fig 9A, Spearman's ρ with CAPS = -0.18, $p = 0.22$), or with the subjective-value signal of risky gains in ventral striatum (Fig 9B, Spearman's ρ with CAPS = 0.22, $p = 0.14$; see Supplementary Fig 4 A and B for correlations with PCL5). These relationships could also be revealed in the group comparison (Fig 9 C and D). The subjective-value signal of ambiguous losses was more negatively encoded in ventral striatum in veterans with PTSD compared with combat controls (Fig 9D, $t = -2.77$, $p < 0.01$). Conversely, the subjective-value signal of risky gains was marginally more positively encoded in vmPFC in veterans with PTSD than in combat controls (Fig 9C, $t = 1.97$, $p = 0.054$).

The relationships between subjective-value signals and PTSD symptom severity hold after controlling for age, income, education and intelligence. The subjective-value signal of ambiguous losses in ventral striatum was affected by CAPS (see Methods: fMRI GLM second-level analysis; multi-factor ANOVA by Generalized Linear Model, $F(1, 33) = 6.01$, $p < 0.05$), and not by the four demographic factors. The subjective-value signal of risky gain lotteries in vmPFC was marginally affected by CAPS (multi-factor ANOVA by Generalized Linear Model: $F(1, 33) = 3.53$, $p = 0.069$), and not by the four demographic factors.

Besides PTSD symptoms, we also examined potential relationships between subjective-value signals and other symptoms, as captured by the three principal components. In vmPFC, component 1 (general affective symptom) was positively correlated with encoding of subjective value of risky gains (Pearson's

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$r = 0.30$, $n = 47$, $p < 0.05$), consistent with the effect of PTSD symptom severity. Component 3 (trauma severity) was negatively correlated with encoding of subjective value of ambiguous losses (Pearson's $r = -0.29$, $n = 47$, $p < 0.05$), in the same direction as the correlation between subjective value of ambiguous losses and PTSD symptom severity. In ventral striatum, no correlation survived our statistical thresholds (see all correlations in Supplementary Fig 4C).

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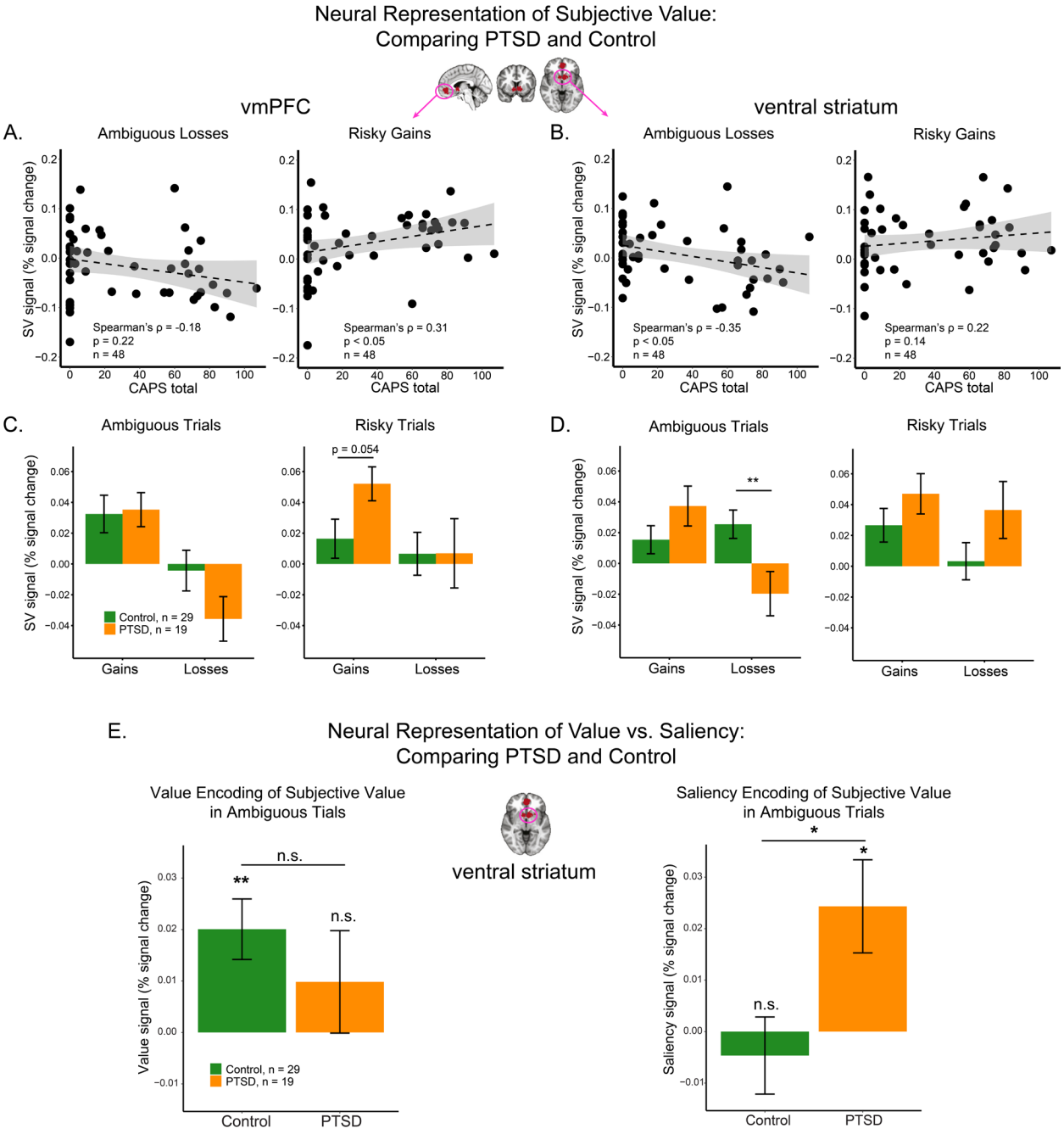
Figure 9. Neural subjective-value signals in external ROIs of vmPFC and ventral striatum were related to PTSD symptom severity



A: In vmPFC, correlation between subjective-value signals of ambiguous losses and risky gains and PTSD symptom severity (CAPS total). B: In ventral striatum, correlation between subjective-value signals of ambiguous losses and risky gains and PTSD symptom severity (CAPS total). C: In vmPFC, group comparison between veterans with PTSD and combat controls of neural subjective-value signals of four

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types of lotteries. D: In ventral striatum, group comparison between veterans with PTSD and combat controls of neural subjective-value signals of four types of lotteries. E: In ventral striatum, value-encoding of subjective values existed in combat controls but not in veterans with PTSD; saliency-encoding of subjective values existed in veterans with PTSD but not in combat controls. In panels C and D, comparisons are post-hoc FDR-corrected after ANOVA within each figure. In panel E, comparisons with zero for each PTSD and Control group were FDR-corrected across four comparisons in two figures. Significance level: *, $p<0.05$; **, $p<0.01$; ***, $p<0.001$.

A shift from value-encoding to saliency-encoding of ambiguous losses in PTSD

Our results so far point to differences in the mechanisms of subjective-value encoding between veterans with PTSD and combat controls. This difference is most notable for ambiguous losses: in combat controls, ambiguous losses were encoded in a positive manner (decreased activity for increased losses) consistent with a monotonic representation of value. Conversely, in the brains of veterans with PTSD, losses were encoded negatively (increased activity for increased losses), consistent with a U-shaped saliency-encoding mechanism (Fig 10). This difference in representation was particularly striking in the ventral striatum (Fig 9D). To directly confirm this group difference, however, we need to examine gains and losses on the same scale. To this end, we constructed two GLMs, one with a single predictor for the value of ambiguous gains and losses, and the other with a single predictor for the saliency of the same gains and losses. Subjective values of the lotteries were used for the value predictor, and saliency was computed as the absolute value of these subjective values (Fig 9E; see Methods: fMRI GLM first-level analysis). While the ventral striatum in controls significantly encoded value (one-sample t test GLM beta compared with 0, $t(28) = 3.4$, $p < 0.01$), but not saliency ($t(28) = -0.62$, $p = 0.54$), the opposite pattern was observed in veterans with PTSD: activity in the same brain area in the PTSD group encoded saliency ($t(18) = 2.7$, $p < 0.05$), but not value (($t(18) = 0.99$, $p = 0.45$; all p values were FDR corrected for four

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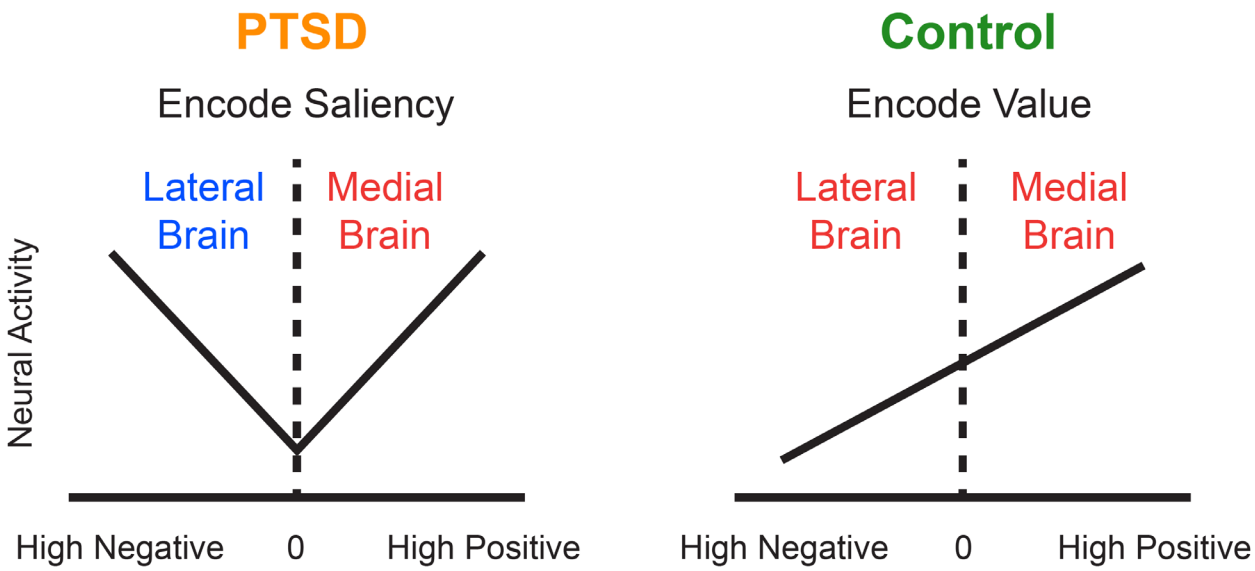
comparisons). Furthermore, the saliency-encoding patterns were significantly different between veterans with PTSD and combat controls (two-sample t test: $t(39.3) = -2.5$, $p < 0.05$).

Figure 10. A shift from value- to saliency- encoding of subjective value in veterans with PTSD, compared with controls



Summary of the relationship between PTSD symptom severity and subjective-value encoding, focusing on the differences between shapes of encoding across gains and losses.

PTSD symptom severity variation was explained better by neural activities than behavioral uncertainty attitudes

Finally, we explored whether PTSD symptom variation could be better explained by neural activities or behavioral uncertainty attitudes, or combining them both. We constructed three linear models to predict PTSD symptom severity indicated by CAPS total score, using (1) only general neural activities under four decision conditions in vmPFC area defined in Fig 5, (2) only behavioral uncertainty attitudes under four decision conditions, (3) both general neural activities and behavioral uncertainty attitudes under four decision conditions, all controlling for age and intelligence (KBIT) (see details in Using behavioral and neural variation to predict PTSD symptom variation of the Methods section). The model including only

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neural measures best explained the variation of PTSD symptom severity, indicated by BIC (BIC(neural model) = 132.8, BIC(behavioral model) = 154.7, BIC(full model) = 143.8, Supplementary Fig 5A).

Discussion

In this study, we explored the neural basis of valuing uncertain monetary rewards and punishments, in veterans exposed to combat trauma with a wide range of PTSD symptoms. Behaviorally, symptom severity was associated with increased aversion to ambiguous losses, and increased aversion to risky gains. These two conditions were also the ones in which PTSD symptom severity influenced the neural representations of subjective value. Two main effects were observed: first, while ambiguous losses were encoded in a positive manner in the brains of controls, individuals with PTSD showed, on average, negative encoding of ambiguous losses in several brain areas (Fig 8A, Fig 7A, Fig 9D), consistent with a saliency representation. Second, increased PTSD symptoms were associated with stronger representation of subjective value of risky gains in value-related areas, including the vmPFC, PCC and OFC. In fact, the average activation pattern for subjective value of risky gains in the PTSD group (Fig. 7B left) was very similar to activation patterns observed in the general population (Levy et al. 2010; Bartra, McGuire, and Kable 2013), whereas controls did not show strong value-encoding signals (Fig 7B right). An intriguing possibility is that the altered processing of ambiguous losses is a marker for vulnerability to PTSD, whereas the altered processing of risky gains is a marker of resiliency to PTSD. Future research, and in particular longitudinal studies that compare individuals exposed to trauma to those who never experienced trauma, are needed to explore this possibility.

Using behavioral economics to identify markers of psychopathology

Our results add to a growing body of research, demonstrating the utility of behavioral economics in studying psychopathology (Paulus and Yu 2012; Pushkarskaya et al. 2015; Buckholtz et al. 2017; Konova et al. 2019). Replicating the previous behavioral study (Ruderman et al. 2016), we confirmed the

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association between higher PTSD symptom severity and greater ambiguity aversion in losses, in an independent combat veteran sample. We also identified greater aversion to risk in gains in veterans with PTSD, likely due to a task design with increased range and variance of monetary outcomes, that provides higher sensitivity for capturing true uncertainty attitudes. Our neural measure allowed us to also quantify individual and group differences in neural sensitivity to rewards and punishments. Previous studies have shown alterations in the neural processing of aversive outcomes in individuals with PTSD, in various brain areas, including several medial and lateral prefrontal regions. Many of these studies, however, used fear and trauma-related stimuli (Hayes, Hayes, and Mikedis 2012). Here we show that activation in the same brain areas is affected by PTSD symptoms even in an economic decision task, completely unrelated to the trauma. This raises the possibility of developing treatment methods in the domain of decision making under uncertainty, which does not require the patients to be reminded of traumatic experiences. Several previous studies have also reported altered reward processing in PTSD (Nawijn et al. 2015), including reduced expectation of uncertain monetary outcomes (Hopper et al. 2008; May and Wisco 2019) and decreased differentiation between monetary gains and losses in the striatum (Elman et al. 2009). Our experimental approach allowed us to estimate individual uncertainty attitudes during active decision making under four unique contexts. We applied a well-established computational model to infer these behavioral individual differences from the observed choice behavior, rather than estimate them through self-reports, and use the individual differences in the analysis of the neural data. Interestingly, participants' self-reported risk-taking on the DOSPERT questionnaire was not strongly correlated with their PTSD symptom severity, suggesting that our method for estimating uncertainty attitudes through a behavioral task is likely more sensitive for capturing subtle differences associated with clinical symptoms.

Neural processing of rewards and punishments is influenced by PTSD symptom

By including both monetary gains and losses in the task design, our results illuminate the basic mechanisms of neural processing of rewards and punishments in two ways. First, our data suggest that neural processing of positive and negative outcomes may be realized through two distinct circuits in our sample of combat veterans, regardless of clinical symptoms. While rewards are processed primarily in

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medial parts of the brain, punishments are processed in lateral regions. This medial-lateral segregation and, more generally, the separate neural representation of rewards and punishments have been reported in previous fMRI studies (O'Doherty et al. 2001; Yacubian et al. 2006; Kim et al. 2014). Single unit recordings from non-human primates also indicate different populations of vmPFC neurons (Monosov and Hikosaka 2012) and dopaminergic neurons (Fiorillo 2013) responding to primary appetitive and aversive outcomes. Other studies, however, reported overlap between representations of gains and losses, supporting the common currency hypothesis (Tom et al. 2007; Fujiwara et al. 2009; Kahnt et al. 2014). Some of the discrepancies between the findings may stem from differences in task design. In particular, simultaneous processing of gains and losses, for example when considering mixed lotteries (Tom et al 2007), may lead to overlapping representations of gains and losses, whereas presentation of gains and losses in separate blocks, like in our design, may unravel differences in their neural representation. The separate involvement of medial and lateral brain regions in the valuation of gains and losses also points to an intriguing link to the default mode network which includes the mPFC and PCC, and the executive function network which includes the dlPFC and PPC. Also referred to as the task-negative and task-positive networks, these two networks are thought to be involved in the self-referential thinking and executive control processes respectively, as well as in reward processing (Lesage and Stein 2016). One hypothesis is that attention is shifted inward and outward in response to valuation of rewards and punishments respectively. Research has also shown the relationship between PTSD symptom severity and decreased default mode network strength (Akiki et al. 2018), providing evidence of further influence of PTSD on the involvement of these networks in neural processing of rewards and punishments.

Second, we identified a shift from value-encoding to saliency-encoding in the brains of individuals who developed PTSD following trauma exposure (Fig 10). This shift could potentially imply an attention or arousal signal, that leads to avoidance of aversive outcomes like uncertain monetary gains or losses. Several previous studies examined the neural processing of value and saliency and revealed both distinct and overlapping regions for each type of encoding. Value signals were found in ventral striatum, parietal

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cortex, OFC, rostral ACC, and saliency signals were found in ventral striatum, rostral ACC, dorsal ACC, anterior insula by both univariate and multivariate analyses (O'Doherty et al. 2001; Yacubian et al. 2006; Tom et al. 2007; Fujiwara et al. 2009; Litt et al. 2011; Kim et al. 2014; Kahnt et al. 2014; Zhang et al. 2017). To our knowledge, our results are the first to recognize the influence of psychiatric symptoms on the value/saliency-encoding pattern. PTSD is highly comorbid with symptoms of depression and anxiety, and our clinical PCA results also suggest that general affective symptoms likely influence these processes (Supplementary Fig 4). Additionally, we found that trauma symptoms are also related to neural representation of subjective value, but only of ambiguous loss lotteries in vmPFC. Although we did not find the effect of trauma symptom in the domain of risky gains and in ventral striatum, this raised the possibility that trauma exposure has additional influence on sensitivity to monetary outcomes when they are aversive. Future research could investigate more generally how trauma exposure, as well as the transdiagnostic concepts of depression and anxiety, could additionally influence the neural processing of aversive stimuli.

One concern in our investigation of neural representation of value is that the range of subjective values is lower in the group of veterans of PTSD because of their higher aversion to uncertainty, which could influence the sensitivity of the neural response to value differences. It should be noted, however, that our main conclusion is based on a difference in the direction of correlation (negative vs. positive), rather than a difference in the magnitude of slope of the correlation (Fig 7A, 8A, and 9D). This represents a substantial difference in the shape of subjective-value encoding and would not be affected by group difference in the range of subjective values.

Investigating the influence of trauma-related psychopathology beyond fear

Previous studies of PTSD often focused on the neural processing of fear and trauma, and identified both functional and structural abnormalities in amygdala, hippocampus, and vmPFC (Hayes, Hayes, and Mikedis 2012; Admon, Milad, and Hendler 2013; Wolf and Herringa 2015; Rabellino et al. 2016; Homan

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et al. 2019). Other studies have looked into more general cognitive processes and found blunted neural activation to monetary rewards (Sailer et al. 2008; Elman et al. 2009). In our study using a more nuanced computational approach, PTSD symptoms were associated with increased neural sensitivity to rewards and altered direction of sensitivity to punishments. While the sensitivity to rewards may seem at odds with the previous studies, it should be noted that in those studies reward signals were defined as the difference in activation to gains and losses. A weaker contrast in individuals with PTSD could stem from a weaker reward signal, but also from a stronger punishment signal, consistent with a U-shaped saliency representation, as we report here, which essentially indicates that both highly salient positive and negative outcomes elicit similar magnitude of neural activation. With this being said, in the reward domain, we do find evidence of surprisingly stronger value sensitivity in PTSD (Fig 7 and 8C), and interpret the lack of sensitivity to reward in combat controls as a potential resiliency marker to PTSD symptoms. This result is in the opposite direction of Sailer and colleagues' finding of lower gain-related activation in PTSD. Many potential factors could contribute to this discrepancy, such as female participants, non-trauma-exposed controls, mixed types of trauma, and different task paradigm in Sailer and colleagues' study, which opens up many interesting future directions of investigating neural sensitivity to reward in PTSD. Among all these factors, investigating the specific effect of combat trauma is particularly interesting, as uncertainty incorporated in our study (while not in Sailer and colleagues') is a central component of the battlefield experience. Furthermore, the resiliency marker in combat controls indicated by our data points to the uniqueness of combat veterans who did not develop PTSD symptoms. Further evidence from non-combat-exposed healthy controls should be combined to fully elucidate the existence of such resiliency marker.

In line with the NIMH RDoC, we did not exclude veterans with history of substance abuse, to allow for a diverse representative sample of trauma exposed symptomatology. We controlled for substance abuse by conducting urine test and breathalyzer for anyone with substance abuse history or if we suspected any intoxication, and excluded those with positive results. The severity for substance abuse history in our

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sample was low and did not vary too much as measured by the Addiction Severity Index (ASI-alcohol: median = 0.089, range = [0, 1.47]; ASI-drug: median = 0, range = [0, 0.092]). Future research could better control for substance abuse history and medication, and potentially look into the pharmacological effect involving the dopamine and serotonin systems, which are crucial for value-based decision making (Castrellon et al. 2019; Macoveanu 2014).

It should also be noted that our study could not establish causal relationship between decision making under uncertainty and the development of PTSD symptoms. Heightened aversion to uncertainty could possibly predispose individuals to developing PTSD symptoms, and on the other hand, acquiring PTSD symptoms could result in altered uncertainty attitudes. There is some evidence, however, that risk attitude is correlated with relatively stable biomarkers including structural volume of right posterior parietal cortex (Gilaie-Dotan et al. 2014), structural and functional connectivity of the amygdala (Jung et al Neuron 2018) and genetic variations (Zyphur et al. 2009). These pieces of evidence might indicate that risk attitude is a personal trait, raising the possibility of its predisposing effect on the development of PTSD symptoms. Less evidence exists for biomarkers of ambiguity attitude, although there is some evidence for a genetic association among females (Chew, Ebstein, and Zhong 2012). Further longitudinal studies comparing veterans pre- and post- military service may disentangle the role of pre-existing uncertainty attitudes on the development of PTSD from the subsequent impact of PTSD symptomatology on uncertainty attitudes.

Decision making under risk and ambiguity has also been studied in relation with other psychiatric disorders, including higher ambiguity aversion and choice inconsistency in individuals with Obsessive Compulsive Disorder (Pushkarskaya et al. 2015), and decreased ambiguity aversion in individuals with antisocial personality disorder (Buckholtz et al. 2017). Interestingly, a recent longitudinal study demonstrated transient increased in tolerance to ambiguity before relapses in opioid users undergoing treatment (Konova et al. 2019). Overall, these efforts to study psychiatric disorders using behavioral

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economics approaches could collectively lead to both early identification of behavioral and biological factors at risk for symptom development, and more effective treatment.

Methods

Participants

68 male veterans (ages: 23.6-74.6; mean ± standard deviation: 39.4 ± 11.5), who had been deployed and exposed to combat, were recruited. Participants either had current diagnosis of PTSD at the time of the study or were never diagnosed with PTSD (controls). Due to the small proportion of female combat veterans (15% of female in Army 2019, Department of Defense), we only included male participants. PTSD diagnosis was based on the Clinician Administered PTSD Scale for DSM-4 (CAPS) (Blake et al. 1995). Data from 10 participants were excluded due to a large number of missing responses or low correct response rate in catch trials in the main task (see Task design and Manipulation check), resulting in 58 participants (ages: 23.6-67.0; mean ± standard deviation: 37.3 ± 8.9) whose behavioral data are reported. Imaging data from 10 additional participants were excluded due to excessive movement in the scanner, or because their data were collected using different scanning parameters (5 participants), resulting in 48 participants (ages: 23.6-67.0; mean ± standard deviation: 37.4 ± 9.2), whose neural results are reported. Full characteristics of the sample included in the analysis are reported in Table 1. Seven participants also took part in a previous behavioral study (Ruderman et al. 2016) using a similar paradigm, and these participants are included in both behavioral and imaging analysis. It should be pointed out that two of these participants were diagnosed as PTSD in the previous behavioral study but were grouped into combat controls who never developed PTSD in this imaging study. This discrepancy could be due to the inaccuracy of subjective report at the time of the behavioral study, or of the imaging study, and could not be resolved. It adds the noise to our analysis either in the behavioral results or in the current imaging study. Behavioral results excluding these seven recurring participants were also reported in Supplementary Fig 2.

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The study was approved by the Yale University Human Investigating Committee and the Human Subjects Subcommittee of the VA Connecticut Healthcare System, and compliance with all relevant ethical regulations was ensured throughout the study. All participants gave informed consent and were compensated with $100 for their participation, plus a variable bonus ($0-$240) based on choices they made in the task (see Experimental design).

Experimental design

The study is composed of three separate visits on three different days (Fig 1A). On the first day (Screening Day), recruited participants went through clinical interviews for screening. After decided as eligible for the study, participants went through two study sessions, and in each session went through an fMRI scan of a decision making task under uncertainty. The task engaged participants in making decisions between a sure monetary outcome and an uncertain monetary outcome with either known (risky) or unknown (ambiguous) outcome probability, in scenarios of both gaining and losing money (Fig 1B, see details in Task design below). On each trial, participants viewed the two options side-by-side, and made a choice after a fixed duration of 6 seconds for evaluation (Fig 1D). To prevent learning, chosen option was not played out during the scan, and one randomly selected trial was realized only at the end of the experiment. The task designs were identical for the scans on Day1 and Day2, and we separated them into two days mainly due to the need to limit the scanning time during each visit. Participants were introduced to the task at the beginning on the first scanning day (Day1) and were reminded of the study on the second scanning day (Day2). Extra non-clinical tests of intelligence and questionnaires were collected at the end of Day2.

Clinical assessment and exclusion criteria

Participants were recruited through flyers and were screened by clinicians at West Haven Veterans Affairs hospital. Participants went through the Structured Clinical Interview for DSM-4 (SCID) (First et al. 1997) and the Clinician Administered PTSD Scale (CAPS) (Blake et al. 1995), on which the PTSD diagnosis was mainly based. Other than CAPS, we also collected the following measurements in the screening session:

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PTSD Checklist for DSM-5 (PCL-5) (Weathers et al. 2013), Beck's Depression Inventory (BDI) (Beck et al. 1961), State-Trait Anxiety Inventory (STAI) (Spielberger and Gorsuch 1983), Dissociative Experiences Scale (DES) (E. M. Bernstein and Putnam 1986), Combat Exposure Scale (CES) (Keane et al. 1989), and Childhood Trauma Questionnaire (CTQ) (D. P. Bernstein et al. 2003). Participants with the following conditions were excluded after screening: psychosis, bipolar disorder, traumatic brain injury, neurologic disorder, learning disability, and ADHD. We did not exclude veterans with history of substance abuse, to allow for a diverse representative sample of trauma exposed symptomatology. However, we conducted urine test and breathalyzer for anyone with substance abuse history or if we suspected any intoxication, and excluded those with positive results. Participants also completed other questionnaires including demographic information, Behavioral Avoidance/Inhibition (BIS/BAS) Scales (Carver and White 1994), the Barratt Impulsiveness Scale (BIS-11) (Patton, Stanford, and Barratt 1995), and Doman-Specific Risk-Taking (DOSPERT) Scale (Blais and Weber 2006). Kaufman Brief Intelligence Test (KBIT) (Kaufman 1990) was also administered after scanning as a measure of non-verbal intelligence.

Decision making under risk and ambiguity

Task design

The experimental design was based on a previous neuroimaging study (Grubb et al 2016) and similar to the design of a previous behavioral study in combat veterans (Ruderman et al 2016).

The experiment consisted of choices about risky and ambiguous gains and losses. On gain trials, participants made choices between a fixed monetary gain ($5) and a lottery with chance of a monetary gain but also chance of no gain at all ($0) (Fig. 1B, left). Lottery outcome probability was represented by an image of a rectangle with blue and red areas. On each trial, one color was associated with a monetary gain, and the other color was associated with the null outcome ($0). The size of each colored area represented the probability of getting the outcome associated with it. In half of the trials, outcome probability was fully known (25%, 50% or 75%; 'Risk', Fig. 1C left). In the other half of the trials, probability was only partially

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known. This was achieved by covering the middle part of the colored image with a grey bar ('Ambiguity', Fig. 1C right). On different trials the bar covered 24%, 50% or 74% of the image, creating three levels of ambiguity. For example, the lower left example in Fig 1B represents a lottery with a chance between 25% and 75% of winning $27. Each of the risk and ambiguity levels corresponded to an actual physical bag with a total number of 100 red and blue chips inside. For risky bags (corresponding to the risk level images), the exact numbers of red and blue chips were the same of the numbers shown on the images. For ambiguous bags (corresponding to the ambiguity level images), the exact numbers of red and blue chips were within the range shown on the image. Participants were shown these bags during study introduction and were informed that the risk and ambiguity images they saw during the task corresponded to these bags. The bags would be used to actualize participants' choice, and they were free to inspect the contents of the bags after finishing the study. The potential monetary gain of the lottery varied within a wide range ($5, 6, 7, 8, 10, 12, 14, 16, 19, 23, 27, 31, 37, 44, 52, 61, 73, 86, 101, and 120). The non-zero monetary outcome was randomly related to red or blue, so the color was not related to whether the outcome was preferable.

Loss trials were similar to gain trials, except that participants chose between losing $5 for sure, and playing a lottery with chance of losing money, but also chance of not losing any money ($0) (Fig 1B, right). Same as gain trials, half of the loss lotteries were risky and half of them were ambiguous, and the outcome probability was presented in the same way. The potential monetary loss of the lottery varied within the same range but of negative monetary outcomes (–$5, 6, 7, 8, 10, 12, 14, 16, 19, 23, 27, 31, 37, 44, 52, 61, 73, 86, 101, and 120).

Fig 1D illustrates the timing of each trial. Participants had 6 seconds to look at the options and consider their decision. A green circle then appeared in the middle of the screen, cueing participants to make a choice within 3.5 seconds. If they did not register a response, the response would be counted as missing. A feedback image of two side-by-side squares was shown for 0.5 second immediately following the button press to confirm the choice, with the yellow square indicating the side participants chose. The feedback was followed by a jittered inter-trial-interval of a white circle, the duration of which was among 4, 6, among 8

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seconds plus the remainder of the response time limit (3.5s – reaction time). To avoid learning, chosen lotteries were not played during the scan. In both the gain and the loss domains, all risk and ambiguity levels were paired with all amount levels, resulting in 120 unique gain trials ((3 + 3) × 20) and 120 unique loss trials. Each trial type was presented once. All trials were grouped into 8 blocks of 30 trials each. Each block contained either only gain trials or loss trials, but risky and ambiguous trials were mixed in a random order. This resulted in 4 gain blocks and 4 loss blocks. Due to the length of the experiment, these blocks were divided into two scanning sessions on two separate days. The interval between two scanning sessions was on average 12.6 days.

Manipulation check

To verify that participants understood the task, and that they aimed to maximize earnings and minimize losses, we included 12 trials in which the potential lottery outcome was identical to the certain amount (±$5). In these trials, one option is clearly better than the other (e.g. a certain gain of $5 should be preferred over a 50% chance of gaining $5). Data from participants who chose the inferior option on more than 50% of these trials were excluded.

Task administration

On the Day1, participants were introduced to the task, and were required to correctly respond to several questions to make sure they understand the task and the lottery presentation. They also practiced 16 trials before the actual task. After the introduction, each participant was endowed with $120 (the maximal possible loss), and then went through two gain and two loss blocks, whose order was counterbalanced across participants (either Gain-Gain-Loss-Loss or Loss-Loss-Gain-Gain). Each block contained 30 trials together with an additional trial in the beginning (a choice between +/-$5 and a lottery offering +/-$4) to capture the initial burst of activity. The added one trial was excluded from analysis.

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On the Day1, participants were first reminded of the task, and then went through another four blocks of the choices (two gain and two loss), in an opposite order to what they had on Day2. Following the scanning, one trial out of the 240 trials (including both gains and losses) was randomly selected and realized. If the participant chose the sure option, $5 were added to or subtracted from the $120 endowment. If the participant chose the lottery, she would play the lottery by pulling a chip out of the physical bag corresponding to the lottery image, and the outcome related to the color of the pulled-out chip would be added to or subtracted from the $120. At the end of the second session, KBIT, demographic questionnaires, BIS/BAS, and BIS-11 were collected.

MRI scans

MRI data were collected with two scanners (due to scanner upgrade) at the Yale Magnetic Resonance Research Center: Siemens 3T Trio (37 participants, 29 reported in imaging results) and 3T Prisma (31 participants, 19 reported in imaging results), using a 32-channel receiver array head coil. High resolution structural images were acquired by Magnetization-Prepared Rapid Gradient-Echo (MPRAGE) imaging (TR = 2.5 s, TE = 2.77 ms, TI = 1100 ms, flip angle = 7°, 176 sagittal slices, voxel size = 1 × 1 × 1 mm, 256 × 256 matrix in a 256 mm field-of- view, or FOV). Functional MRI scans were acquired while the participants were performing the choice task, using a multi-band Echo-planar Imaging (EPI) sequence (TR= 1000 ms, TE= 30ms, flip angle=60°, voxel size = 2 × 2× 2 mm, 60 2 mm-thick slices, in-plane resolution = 2 × 2 mm, FOV= 220mm).

Analysis

Analysis of clinical symptoms and trauma-related measures

We used the 5-factor model of PTSD (Harpaz-Rotem et al. 2014) to assess multidimensional PTSD symptoms, including re-experiencing, avoidance, emotional numbing, dysphoric arousal, and anxious arousal. We calculated both the overall symptom severity, and the 5 factors' symptom severities by

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breaking down the questionnaire items. To account for comorbidities, we conducted principal component analysis (PCA) on all clinical and trauma-exposure measurements, including the 5 factors of CAPS, Beck's Depression Inventory (BDI), state and trait anxiety indexes separately from State-Trait Anxiety Inventory (STAI), Dissociative Experiences Scale (DES), Combat Exposure Scale (CES), and Childhood Trauma Questionnaire (CTQ).

Model-based Risk and ambiguity attitudes estimation

We fitted each participant's choice data into a behavioral economics model that was used in previous studies (Levy et al. 2010; Ruderman et al. 2016). The model fitting was conducted separately for gain and loss choices. The model separates the decision process into two steps: valuation and choice. In the valuation step, the subjective value (SV) of each option is modelled by equation (1),

$$SV = \left[P - \beta\left(\frac{A}{2}\right)\right] \times V^{\alpha} \quad (1)$$

where P is the outcome probability (0.25, 0.50, or 0.75 for risky lotteries, 0.5 for ambiguous lotteries, and 1 for the certain option); A is the ambiguity level (0.24, 0.5, or 0.74 for ambiguous lotteries; 0 for risky lotteries and the certain amount); V is the non-zero outcome magnitude of the lottery or the amount of money of the certain option. For choices in the loss domain, amounts are entered with a positive sign. Risk attitude was modeled by discounting the objective outcome magnitude by a participant-specific parameter, α. In the gain domain, a participant is risk averse when $\alpha < 1$, and is risk seeking when $\alpha > 1$. Because we fitted the choice data in the loss domain using positive outcome magnitudes, the participant is risk averse when $\alpha > 1$, and is risk seeking when $\alpha < 1$. Ambiguity attitude was modeled by discounting the lottery probability linearly by the ambiguity level, weighted by a second participant-specific parameter, β. A participant is averse to ambiguity when $\beta > 0$, and is ambiguity seeking when $\beta < 0$ in the gain domain. In the loss domain, participant is averse to ambiguity when $\beta < 0$, and ambiguity seeking when $\beta > 0$.

The choice process is modeled by a standard soft-max function (equation 2),

$$P_{\mathrm{V}} = \frac{1}{1+e^{\gamma(SV_{\mathrm{L}} - SV_{\mathrm{C}})}} \quad (2)$$

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where P_V is the probability of choosing the lottery option, SV_C and SV_L are the subjective values of the certain option and the lottery respectively, calculated by equation (1); γ is a participant-specific noise parameter.

The model-fitting was conducted in MATLAB (R2018b) through maximum likelihood. We primarily used Matlab function fminunc to minimize the negative log-likelihood function, and switched to using fminsearch if it failed to converge. Under our task design, we could detect risk parameters (α) in the range of [0.0905, 7.6036], and ambiguity parameters β in the range of [-4.0303, 4.1667]. These constraints were calculated based on the range of uncertainty levels and monetary magnitudes in our task design, same as the procedure used in previous studies (Ruderman 2017). The lower boundary of α was determined by equating the subjective value of the best lottery (75% chance of $120) with the subjective value of the certain option ($5), using equation (1). Similarly, to determine the upper boundary of α, we equated the subjective values of the worst lottery (25% chance of $6) and the certain option ($5). Because the choices of ambiguous lotteries also depend on the risk attitude α, the boundary values of β also depend on α. So we simply calculated all possible β's by equating the subjective values of each ambiguous lottery and the certain option ($5), using the boundary values of α. The boundary values of β were then determined by the minimum and maximum of all calculated β's. Even without constraining α and β during the modeling fitting procedure, the fitted results of all participants included in behavioral and imaging analysis were within this range. We fitted each participant's choices combining data from two sessions and obtained four attitudes: risk attitudes for gains and losses, ambiguity attitudes for gains and losses. For consistency, we transformed all attitudes in the following way such that negative values indicate aversion and positive values indicate seeking: risky gains: α – 1, risky losses: 1 – α, ambiguous gains: - β, ambiguous losses: β. Since participants performed the task on two separate sessions, we also fitted each session's choice data separately. These fitted parameters from separate sessions were used to calculate trial-wise subjective

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values of the lotteries for GLM neural analysis, because they could capture the subjective values more accurately for searching neural activity change induced by variations of subjective values.

We then analyzed the fitted risk and ambiguity attitudes both in group comparisons between veterans with PTSD and combat controls, and through a dimensional approach by looking at their correlation with clinical symptoms and other continuous measurements. We also took into account of the potential influence of demographic factors (age, income, education and intelligence) on uncertainty attitudes, by conducting multi-factor ANOVAs through Generalized Linear Model:

Uncertainty attitude in one decision condition (e.g. Risk attitude in gains) ~ CAPS total + age + income (categorical) + education (categorical) + intelligence

In the data we collected, age and intelligence were continuous variables, income was a categorical variable with 10 possible levels, and education was a categorical variable with 6 possible levels. All continuous variables were standardized before fitting the linear model.

MRI data preprocessing

Preprocessing of MRI data were conducted in BrainVoyager (Version 20.2.0.3065). Anatomical images were normalized to the standard brain template in the Talairach space for each participant. Steps of preprocessing of functional data included motion correction, slice scan time correction (cubic spline interpolation), temporal filtering (high-pass frequency-space filter with cut-off cycle of 3), spatial smoothing (Gaussian filter with 8mm full-width at half-maximum), co-registration with high-resolution standardized anatomical data, and normalization to the Talairach space. Scan data with movement of over 2 mm in any direction were excluded from analysis.

fMRI GLM first-level analysis

Analysis of fMRI data were conducted in Neuroelf (Version 1.0) through MATLAB (Version R2018b) for the purpose of fitting generalized linear models (GLM), extracting regions-of-interest (ROI) data, and

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visualizing brain statistical maps. Further statistical analysis and visualization were conducted in R (Version 3.5.1) (R Core Team 2018) with packages ez (Lawrence 2013), psych (Revelle 2018), nlme (Pinheiro et al. 2013), emmeans (Russell 2018), ggplot2 (Wickham 2016), and PerformanceAnalytics (Peterson and Carl 2019). We investigated the neural response under different decision conditions through fitting pre-processed functional signals with generalized linear models (GLM). The pre-processed fMRI signal time course was first converted to percent signal change within each scanning block, and activity of each voxel was modeled by GLM predictors convolved with a standard double-gamma hemodynamic response function.

In the first GLM, we looked at the general activity during decision making by including four binary predictors for all four decision conditions: ambiguous gains, risky gains, ambiguous losses, and risky losses. Each binary predictor was modeled as a box-car function, with the duration of choice display (6TR). We modeled choice response of all trials by another binary predictor with the duration of 1TR at the time of button press, and missing responses were not modeled. We also included nuisance predictors of 6 motion correction parameters (translation and rotation in the x, y, and z directions) in the GLM to account for influence of head motions on the neural activity.

In a second GLM, we modeled the neural response to the variation of trial-wise subjective value of the lottery by including the subjective value as a parametric modulator for each of the four decision condition binary predictors. Subjective value of the lottery in each trial was calculated uniquely for each participant by equation (1) (See section Model-based risk and ambiguity attitudes estimation), by taking the fitted α and β for each participant under each domain of either gains and losses. Because we fitted the choice data in the loss domain by inputting the positive outcome value, we flipped the sign of the calculated subjective value back in the loss domain. We calculated the subjective values taking α's and β's fitted from the two sessions separately, because it would make the estimate of neural response to subjective value variation more accurate. Subjective values were normalized within each scanning block before GLM fitting, so that the estimated effect reflected each participant's neural response to the variation of

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subjective value, rather than to its absolute magnitude. Predictor of choice response and nuisance predictors of motion correction was included in the same way as above in this GLM.

In the third and the fourth GLMs, we aimed to further investigate the shape of neural representation of subjective values. In both GLMs, we compared gains and losses on the same scale, and only separated trials by uncertainty types. Thus, we included two binary predictors, ambiguous trials and risky trials, in both GLMs, and modeled them as box-car functions with a duration of choice display (6TR). In the third GLM, we included the subjective value itself as a parametric modulator to accompany each binary predictor, to look at the monotonical value-encoding of subjective values. In the third GLM, we included the absolute value of subjective value as a parametric modulator to accompany each binary predictor, to look at the U-shaped saliency-encoding of subjective values. The predictor of choice response and nuisance predictors of motion correctly were included in the same way as above in these two GLMs.

fMRI GLM second-level analysis

After individual GLM fitting, random-effect group analysis was conducted to test whether the mean effect of interest was significantly different from zero across participants, or significantly different between groups by contrasting veterans with PTSD and combat controls. We also took a dimensional approach to test whether the predictor effects were related to PTSD and other clinical symptom severities. The tests were conducted both in a whole-brain search and in ROIs.

In whole-brain analyses, all statistical maps were thresholded at $p < 0.001$ per voxel, and corrected for multiple comparisons using cluster-extent correction methods through Alphasim by AFNI (Cox 1996) to control family-wise error (FWE) rate at 0.05.

In ROI analyses investigating the general neural activity during decision making based on the first GLM, we chose the region in vmPFC whose activity showed negative correlation with CAPS total in the whole-brain analysis. We further investigated which factor of the PTSD symptoms drove this negative

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relationship, by fitting a linear model including all five symptoms based on the CAPS measurements together with age and intelligence:

$$\text{Averaged GLM beta over all four decision conditions} \sim \text{re-experiencing} + \text{avoidance} + \text{emotional numbing} + \text{dysphoric arousal} + \text{anxious arousal} + \text{age} + \text{intelligence}$$

We then conducted variables subset selection to identify which symptom cluster(s) best influenced vmPFC neural activity, using exhaustive search through the package "leaps" (Lumley and Miller 2009) in R. We compared regression models including all possible combination of variables for each given number of predictors of this linear model (ranging from including only one predictor to including all seven predictors), and selected the best model with the lowest Bayesian Information Criterion (BIC). The best linear model identified by this exhaustive approach could identify both the best number of symptom clusters to include, as well as which symptom cluster(s).

In ROI analyses investigating subjective value representation based on the second, third and fourth GLMs, we chose two brain regions, vmPFC and ventral striatum, based on the meta-analysis by Bartra et al. (Bartra, McGuire, and Kable 2013), which showed value encoding of different categories of rewards. To control for the potential influence of demographic factors on neural activity, we conducted multi-factor ANOVAs through Generalized Linear Model that included the PTSD symptom and demographic factors to explain neural subjective value signal, similar to the behavioral analysis of uncertainty attitudes:

$$\text{Neural subjective value signal of a type of lottery (e.g. risk gain lottery)} \sim \text{CAPS total} + \text{age} + \text{income (categorical)} + \text{education (categorical)} + \text{intelligence}$$

All continuous variables were standardized before fitting the linear models.

Leave-one-subject-out (LOSO) procedure

After identifying regions from the whole-brain analysis from our data, in which the neural representation of subjective values was influenced by PTSD symptom severity, we took a leave-one-subject-out (LOSO)

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approach to define these ROIs in an un-biased way for each participant. For each left-out participant, we defined a ROI from a whole-brain analysis using data from all other participants, so this ROI definition was not influenced at all by the left-out participants. We then sampled neural signals of the left-out participant's data from this ROI. We repeated the process for all participants.

Using behavioral and neural measures to predict PTSD symptom variation

After identifying vmPFC in a whole-brain analysis as the area showing negative correlation between its activity and PTSD symptom severity, we want to investigate whether symptom variation could be better explained by behavioral uncertainty attitudes or by neural activity during decision making. We sampled fitted GLM betas of each decision condition (ambiguous losses, risky losses, ambiguous gains, and risky gains) based on the first GLM explained above from this vmPFC area. We then constructed a linear model using general neural activity in four decision conditions to explain PTSD symptom severity indicated by CAPS total:

Neural model: CAPS total ~ neural activity under risky gains + neural activity under ambiguous gains + neural activity under risky losses+ neural activity under ambiguous losses + age + intelligence

Similarly, we constructed a linear model using behavioral uncertainty attitudes in four decision conditions to explain PTSD symptom severity:

Behavioral model: CAPS total ~ risk attitude in gains + ambiguity attitude in gains + risk attitude in losses + ambiguity attitude in losses + age + intelligence

We also constructed a full model including both neural and behavioral measures:

Full model: CAPS total ~ risk attitude in gains + ambiguity attitude in gains + risk attitude in losses + ambiguity attitude in losses + neural activity under risky gains + neural activity under ambiguous gains + neural activity under risky losses+ neural activity under ambiguous losses + age + intelligence

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All variables were standardized before fitting the linear model. All models included age and intelligence to control for these two demographic factors. We compared these three model by BIC.

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