Neural Responsivity to Reward versus Punishment Shortly after Trauma Predicts Long-term Development of Post-Traumatic Stress Symptoms

Short Running Title: Biased Valence Processing Predicts PTSD Development

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Abstract

Background: Processing negative and positive valenced stimuli involve multiple brain regions including the amygdala and ventral striatum (VS). Post-Traumatic Stress Disorder (PTSD) is often associated with hyper-responsivity to negatively valenced, yet recent evidence also points to deficient positive valence functioning.

It is yet unclear what is the relative contribution of such opposing valence processing shortly after trauma to the development of chronic PTSD.

Methods: Neurobehavioral indicators of motivational positive vs. negative valence sensitivities were longitudinally assessed in 171 adults (87 females, age=34.19±11.47 years) at 1-, 6-, and 14-months following trauma exposure (TP1, TP2, TP3). Using a gambling fMRI paradigm, amygdala and VS functionality (activity and functional connectivity with the prefrontal cortex) in response to rewards vs. punishments were assessed with relation to PTSD severity at different time-points. The effect of valence processing was depicted behaviorally by the amount of risk taken to maximize reward.

Results: PTSD severity at TP1 was associated with greater neural functionality in the amygdala (but not the VS) towards punishments vs. rewards, and fewer risky choices. PTSD severity at TP3 was associated with decreased neural functionality in both the VS and amygdala towards rewards vs. punishments at TP1 (but not with risky behavior). Explainable machine learning revealed the primacy of VS biased processing, over the amygdala, in predicting PTSD severity at TP3.

Conclusions: These results highlight the importance of biased neural responsivity to positive relative to negative motivational outcomes in PTSD development. Novel therapeutic strategies early after trauma may thus target both valence fronts.

ClinicalTrials.gov: Neurobehavioral Moderators of Post-traumatic Disease Trajectories; https://clinicaltrials.gov/ct2/show/NCT03756545 ; NCT03756545.

Introduction

How do our brains determine whether something is good or bad? The concept of separate valence processing systems for negative and positive stimuli originated in psychology over a century ago, and was recently incorporated into the field of clinical neuroscience(1). These systems were further identified as two core dimensions of human behavior in the NIMH Research-Domain-Criteria (RDoC)(2,3). The negative valence system mediates responses to aversive situations or contexts, evoking negative feelings such as fear, anxiety, and loss, whereas the positive valence system mediates responses to positive motivational situations or contexts such as response to reward, consummatory behavior, and reward learning. Valence estimation could be challenging in real-life situations, as stimuli often evoke mixed or even conflicting emotions and consequence behaviors. Stress might further hinder accurate valence estimations(4–6), as it increases vigilance and drains cognitive resources(7,8). While such restrictions in the immediate aftermath of stressful events might be beneficial for survival, a transition into reward-driven behavior over time, despite the presence of a

heightened threat, is thought to be necessary for promoting stress resilience(9–14). Indeed, stress-related psychopathologies, most prominently Post-Traumatic Stress Disorder (PTSD), are often characterized by a tendency to sacrifice potential rewards in order to avoid aversive encounters(15–18).

On the one hand, this maladaptive behavioral pattern in PTSD could be the result of heightened responsivity to negative stimuli. To this end, substantial evidence links this chronic condition to over-sensitivity of the negative system, consistently showing increased response to various aversive or threatening stimuli among PTSD patients (e.g., symptom provocation, fearful faces)(19,20), potentially reflecting clinical symptoms of hyperarousal and intrusion (i.e., re-experiencing)(21–24). The role of the neural negative valence system in PTSD has been repeatedly documented as abnormally heightened salience network activation in response to a variety of negative valence stimuli, including hyperactivation of the amygdala, anterior insula, and dorsal anterior cingulate cortex (21,25–29). PTSD was also associated with an exaggerated response to negative motivational cues, such that more severe symptoms were associated with

both increased behavioral aversion to ambiguous losses(30) and increased amygdala activity during risky anticipation to punishment(31). Furthermore, aberrant amygdala's functional connectivity with the prefrontal cortex (PFC) to negative stimuli was also observed in PTSD, specifically with the orbitofrontal cortex (OFC)(32,33), suggesting disrupted emotion regulatory capacity.

On the other hand, more recent work suggests that PTSD might also involve blunted processing of positive valence stimuli, as indicated by deficient reward anticipation, decreased approach (reward-seeking) behavior, and diminished hedonic responses to rewarding outcomes(34,35). Reward processing is known to involve the meso-corticolimbic pathway, represented by dopamine projections from the ventral tegmental area (VTA) to the ventral striatum (VS), including the nucleus accumbens (NAcc), and further to ventromedial/orbital frontal brain structures(36,37). While decreased VS activation to positive stimuli was initially demonstrated in depressed individuals, mostly related to anhedonia symptoms(38,39), it was also recently reported in PTSD patients in response to monetary gains(40,41) and happy faces(42). Recent studies further pointed to

aberrant functional connectivity between the VS and ventromedial PFC (vmPFC) in PTSD, suggesting an altered function of the reward circuitry in this disorder(43,44).

Taken together, PTSD appears to be associated with biased neural valence processing, as indicated by hyper-responsivity to negative aversive stimuli and hypo-responsivity to positive rewarding stimuli. Nevertheless, the relative contribution of early negative and positive neural processing to the long-term development of post-traumatic psychopathology remains largely unknown, due to several substantial clinical and methodological challenges. First, only a small portion (around 20%) of individuals with early stress symptoms go on to develop chronic PTSD(45,46). Second, even within this group of PTSD patients, clinical phenotypes are largely heterogeneous(47,48), with different symptom manifestations (e.g., hyperarousal vs. avoidance) which might be related to different neurobehavioral processes (e.g., punishment vs. reward processing). Third, the typical cross-sectional designs used for PTSD research cannot infer on the immediate response to trauma, nor on any potential dynamics that may occur during the first year post-trauma, a critical period that determines who will

develop PTSD and who will recover from the initial acute stress response(49,50). Forth, while recent years depict an increase in longitudinal studies(28,51), the majority of them focused solely on the response to either negative or positive stimuli, thus cannot be used to infer on the unique role of each valence system or on their relative contribution to PTSD development over time.

To overcome these critical knowledge gaps, a large-scale prospective fMRI study of recent trauma survivors was conducted (see study protocol(52)). A sample of n=171 adult civilians were screened for early PTSD symptoms, suggestive of chronic PTSD risk(53,54), within 10-14 days following their release from a general hospital's emergency room (ER). Participants were longitudinally assessed at 1-, 6- and 14-months following exposure to traumatic life events (TP1, TP2, and TP3, respectively), as they underwent fMRI scan while playing an interactive naturalistic gambling game (termed 'Safe or Risky Domino Choice'; SRDC). To win the game, individuals had to make both "safe" and "risky" choices, reflecting the co-involvement of both positive and negative valence processing (e.g., how much I enjoy receiving a reward vs. how much I am afraid of or

threatened by receiving punishment). Their neural responses to positive vs. negative outcomes were assessed by the amygdala and VS functionality (i.e., activity and functional connectivity with the prefrontal cortex) in response to receiving rewards vs. receiving punishments.

This work examined the idea that individuals' recovery from traumatic stress relies on the differential and relative neural processing of negative vs. positive valenced stimuli in the early aftermath of trauma. The first aim was to establish a link between neural indicators of negative and positive valence processing and early PTSD symptom severity shortly after exposure (TP1). Based on previous findings(31,55), we hypothesized that more severe PTSD symptoms would be associated with increased response of the amygdala to punishments relative to rewards, decreased response of the VS to rewards relative to punishments, and altered functional connectivity of the VS and the amygdala with the PFC. The second aim was to reveal the contribution of early neural valence processing to the prediction of PTSD symptom development within the first year following trauma exposure. We hypothesized that increased amygdala activity and

connectivity with the PFC in response to punishments relative to rewards, as well as decreased VS activity and connectivity with the PFC in response to rewards relative to punishment at TP1, would be predictive of more severe PTSD symptoms at TP2 and TP3 (beyond initial symptom severity at TP1). By utilizing an explainable machine learning, the relative importance of neural processing of negative vs. positive valenced stimuli at TP1 to PTSD symptom severity at TP3 was further examined. The third and final aim of this work was to unveil the co-involvement of both negative and positive valence processing in PTSD symptomatology through risk-taking behavior. Based on previous work(31), we hypothesized that fewer risky choices at TP1 would be related to more severe symptoms at all three time-points.

Methods and Materials

Participants. The study group included 171 adult survivors of traumatic events who were admitted to a general hospital's ER. The most common trauma type among

participants was motor vehicle accidents (n=137, 80%), while other traumatic events included assaults, terror attacks, and more. Participants with head trauma or coma, incompatibility for MRI scan, history of substance abuse, current or past psychotic disorder, or chronic PTSD diagnosis pre-admission to ER, were excluded from the study. Survivors with a known medical condition that interfered with their ability to give informed consent or to cooperate with screening and/or treatment were similarly excluded. For additional information, see Table 1, supplementary methods, and study protocol(52).

Procedure. A member of the research team identified potential trauma-exposed individuals via the ER computerized medical records. Within 10–14 days of trauma exposure, approximately 4,000 potential participants were contacted by telephone for initial screening. Acute PTSD symptoms, indicative of the risk for PTSD development(53), were assessed using a modified dichotomous version of the PTSD Checklist (PCL) questionnaire(56). Those who met PTSD symptom criteria (except for the "1-month duration" criteria) and did not meet any of the exclusion criteria (see under Participants), were invited to participate in a face-to-face

clinical assessment and an fMRI scan, at one-month post-trauma (TP1). In addition to survivors who met PTSD diagnosis, clinical interviews were also conducted for a group of individuals with sub-threshold PTSD symptoms. Two identical follow-up meetings, including both clinical and neural assessments, were conducted at 6- and 14-months following trauma (TP2 and TP3, respectively).

Clinical Assessments. PTSD diagnosis and severity at each time-point were determined by a comprehensive clinical interview conducted by trained and certified clinical interviewers. A continuous measure of total symptom severity was obtained by summing individual items' scores of the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5)(57), the current gold standard for PTSD diagnosis. Total scores were further computed for each of the DSM-5 symptom clusters: intrusion (cluster-B), avoidance (cluster-C), negative alterations in cognition and mood (cluster-D), and hyperarousal (cluster-E).

Safe or Risky Domino Choice (SRDC) Game. Participants played a 2-player competitive gambling game for 14 minutes in the fMRI, in which they were required to make risky choices in order to win. The effectiveness of the SRDC to detect individuals' sensitivity to risk, punishment and reward was previously validated in both healthy and clinical populations(31,58–62). The focus was on the 'decision-making interval' for behavioral indexing (i.e., individual tendency to make risky vs. safe choices) and on the neural responses in the 'response to an outcome' interval (rewards vs. punishments). For more details, see Fig. 1 and supplementary methods.

Behavioral Analysis of the SRDC Game. To characterize individuals' behavioral choices during the game, a 'risky choice index' was defined as the ratio between the number of risky choices (e.g., choosing a non-matching chip) and the total number of choices made throughout the entire game (e.g., choosing either a matching or non-matching chip), multiplied by 100 (to obtain percentage). Game trials in which participants had no actual choice between safe and risky choices

were excluded (i.e., when there were only matching or only non-matching chips). This index represents a nonbiased choice when equal to 50% (exactly half of the choices were non-matching chips), a bias towards riskier behavior when greater than 50%, and a bias towards safer behavior (i.e., risk aversion and avoidance) when less than 50%.

$$risky\ choice\ index\ (\%) = \frac{\#\ non\ matching\ chips}{\#\ non\ matching\ chips + \#\ matching\ chips} * 100$$

fMRI Data Analysis. Preprocessing was conducted using FMRIPREP version 1.5.8(63), a Nipype based tool(64) (for full details, see 'fMRI Data Preprocessing' in the supplementary methods). First level neuroimaging analysis used a general linear model (GLM) implemented in Statistical Parametric Mapping software (SPM12), for each participant, including the different conditions of the SRDC game: "choose", "ready", "go", "picked-match", "picked-non-match", "show-match", "show-non-match", "no-show-match", "no-show-non-match". Individual statistical parametric maps were calculated for the a-priori defined contrast of receiving both rewarding outcomes vs. receiving both punishing outcomes and vice versa.

Based on previous findings using the SRDC paradigm(31,58–62), two main regions of interest (ROIs) were defined – the amygdala and VS - using the Human Brainnetome (HB) atlas(65) and California Institute of Technology 168 (CIT-168) atlas(66). The VS was composed of the ventral caudate (HB atlas, regions 219-220) and nucleus accumbens (CIT-168 atlas); The amygdala was composed of the medial and lateral amygdala (HB atlas, 211-214). MarsBaR ROI toolbox for SPM(67) was used to extract participants' contrast activations (average beta weight) separately from each ROI and for each hemisphere (left and right amygdala and VS). Examination of functional connectivity interactions was performed using generalized psychophysiological interaction (gPPI) as implemented in ROI-to-ROI analysis using CONN toolbox(68,69). This analysis was performed using the main a-priori ROIs as seed regions - right and left amygdala and VS - and a-priori selected PFC ROIs as target regions – right and left vmPFC (HB atlas, regions 41-42,47-48) and lateral OFC (lOFC) (HB atlas, regions 43-44,45-46,51-52). This selection was based on extensive literature pointing to involvement these regions

in processing both reward and punishment(70–74). For full details, see supplementary methods.

Statistical Analysis. IBM SPSS Statistics for Windows(75) and R(76) software were used for the statistical procedures. Participants with extreme scores of ±3 standard deviations from the mean were excluded from the analysis for all the neural variables. For all statistical tests, α=0.05 was used with either one-sided a-priori hypotheses or two-sided non-directional hypotheses. Benjamini–Hochberg False Discovery Rate (FDR) correction ($q<0.05$)(77) was calculated to control for multiple comparisons for each family of tests (e.g., neural activations, neural connectivity, PTSD symptom clusters). Concerning neural measures, our main a-priori hypotheses were regarding the relative responses of the amygdala and VS to rewards vs. punishments. Post-hoc exploratory analysis was further conducted for these ROIs in the contrasts of rewards (vs. baseline) and punishments (vs. baseline).

Predictor Importance Ranking. To examine the contribution of early neural activations (at TP1) and rank their importance for the prediction of PTSD symptom severity at the study's endpoint (TP3), Shapley Additive explanation (SHAP)(78), a state-of-the-art methodology in the field of explainable machine learning, was used. SHAP estimates "Shapely" values, which provide a surrogate for the individual additive contribution of each feature to the prediction. In other words, SHAP's rank order informs which feature values mostly influence the prediction, while accounting for the influence of all other feature values, and while controlling for the order in which features are added to the model(78). The official implementation of SHAP library for python was used here (https://github.com/slundberg/shap)(79). As in all other analyses, participant's age, gender, trauma type, and initial symptom severity were controlled for.

Results

Neural Responsivity to Reward Relative to Punishment and PTSD Symptom Severity Shortly after Trauma. Partial correlations were computed between neural indicators of valence processing and PTSD symptom severity (i.e., CAPS-5 total scores) at TP1, while controlling for participants' age, gender, and trauma type. As hypothesized, results revealed a significant positive correlation between amygdala's response to punishments vs. rewards and PTSD severity at TP1 (n=128;left-amygdala:r=0.155,p=0.043,p_{FDR}=0.043;right-amygdala:r=0.162,p=0.035,p_{FDR}=0.043; Fig. 2A). Further, increased amygdala-lOFC functional connectivity during punishments vs. rewards was also associated with more severe symptoms (n=124;right-amygdala-left-lOFC:r=0.254,p=0.005,p_{FDR}=0.041;Fig. 2C). Contrary to our expectation, VS activation to rewards vs. punishments was not significantly associated with PTSD symptom severity at one-month after trauma (n=131;left-VS:r=0.022,p=0.401,p_{FDR}=0.401;right-VS:r=0.048,p=0.297,p_{FDR}=0.401;Fig. 2B), nor did VS functional connectivity with the predetermined PFC regions (vmPFC or

lOFC) (n=122; for all comparisons:p_{FDR}>0.05). For further details and whole-brain results, see supplementary results, Table S1, Fig. S1 and Fig. S2.

Post-hoc exploratory analysis was conducted to further ascertain from which valence condition the neural effects at TP1 are arising (i.e., response to rewards alone and response to punishments alone). As can be seen in Table 2, PTSD severity at TP1 was significantly associated with bilateral amygdala's response to punishments vs. baseline (n=128;left-amygdala:r=0.193,p=0.032;right-amygdala:r=0.229, p=0.010), but not with its response to rewards vs. baseline (n=128;left-amygdala:r=0.036,p=0.690;right-amygdala:r=0.071,p=0.434). With regard to the VS, no significant association was found between PTSD severity and its activation to either rewards or punishments separately (for all: p>0.05, see Table 2).

Neural Responsivity to Reward Relative to Punishment Shortly after Trauma and PTSD Symptom Severity One-Year Later. Partial correlations were computed between neural indicators of valence processing at one-month post-trauma (TP1)

and PTSD severity at 6- and 14-months post-trauma (TP2 and TP3), while controlling for participants' age, gender, trauma type, and initial symptom severity (i.e., CAPS-5 total scores at TP1). In line with our hypothesis, both increased amygdala's activation to punishments relative to rewards, and decreased VS activation to rewards relative to punishments at TP1, were significantly predictive of more severe PTSD symptoms at TP3. Specifically, higher CAPS-5 total scores at TP3 were associated with greater left amygdala activation at TP1 (n=108,r=0.197,p=0.022;Fig.3A) and decreased right VS activation at TP1 (n=111,r=-0.235,p=0.007;Fig.3B). However, neither amygdala nor VS activations to rewards relative to punishments TP1 were associated with CAPS-5 total scores at TP2 (n=114;left-amygdala:r=-0.021,p=0.413;right-amygdala:r=-0.146,p=0.320;left-VS:r=0.065,p=0.249; right-VS:r=0.006,p=0.475). For whole-brain results, see supplementary materials.

Post-hoc exploratory analysis was conducted to further ascertain from which valence conditions the neural effects of TP1 activations and TP3 symptoms are arising. Results revealed that decreased activity of the right (but not left) VS in

response to rewards vs. baseline was significantly associated with more severe PTSD symptoms at TP3 (n=111,r=-0.220,p=0.022;Table 2). However, bilateral VS response to punishments vs. baseline at TP1 was not linked to PTSD severity at TP3 (n=111;left-VS:r=0.024,p=0.802;right-VS:r=0.022,p=0.818;Table 2). With regard to the amygdala, no significant association was found between PTSD severity at TP3 and its activation to either rewards or punishments separately at TP1 (for all: p>0.05;Table 2).

Exploratory analysis of the relation to specific symptom clusters revealed a trend towards a significant association between increased amygdala's activation to punishments vs. rewards TP1 and more severe hyperarousal ($r=0.176,p=0.037,p_{FDR}=0.074$) and intrusion symptoms at TP3 ($r=0.217,p=0.027,p_{FDR}=0.074$)(Fig.3A). Moreover, decreased VS activation to rewards vs. punishments at TP1 was significantly associated with more severe avoidance symptoms at TP3 ($r=-0.285,p=0.001,p_{FDR}=0.004$;Fig.3B).

Examining the predictive power of functional connectivity patterns of the neural components of the two valence systems at TP1 for predicting symptom

severity at TP3 revealed such a relationship only for the VS. Specifically, decreased VS-vmPFC connectivity during rewards vs. punishments at TP1 was associated with more severe PTSD symptoms at TP3 (n=108;right-VS–right-vmPFC:r=-0.292,p=0.003,p_{FDR}=0.036), indicating that individuals with decreased VS-vmPFC connectivity at TP1 developed more severe symptoms at TP3 (Fig. 3C). Amygdala's functional connectivity with the predetermined PFC regions (vmPFC or lOFC) during punishments vs. rewards at TP1 was not related to PTSD severity at TP3 (n=110;for all comparisons:p_{FDR}>0.05, see supplementary results).

Finally, to test the relative contribution of amygdala and VS functionality (activation and connectivity) at TP1 for PTSD symptom severity at TP3, a linear regression was performed using TP1 neural indices of valence processing that significantly predicted PTSD symptoms at TP3 (while controlling for participants' age, gender, trauma type, and initial symptom severity): left amygdala activation to punishments (Fig. 3A), right VS activation to rewards (Fig. 3B), and right VS–right vmPFC functional connectivity during rewards (Fig. 3C). As expected, all three

variables together at TP1 accounted for a significant amount of variance of CAPS-5 total scores at TP3 ($n=105, R^2=0.200, F_{3,101}=8.398, p<0.001$).

To identify the relative importance of each predictor compared to others, importance values were calculated using the SHAP analytic approach(78) (see Methods). In terms of absolute feature importance, VS-vmPFC connectivity during rewards vs. punishments at TP1 was the best predictor of PTSD symptoms at TP3, followed by VS activation to rewards vs. punishments, and amygdala's activation to punishments vs. rewards (Fig. 3D, lower panel). Notably, while the importance of VS functionality differed greatly between individuals (SHAP values ranging from -6 to +6), the amygdala had a small contribution in most participants (most SHAP values between -2 to +2), and a large contribution to only a minority (Fig. 3D, upper panel).

Behavioral Indicators of the Co-involvement of Negative and Positive Valence Processing Shortly after Trauma. Partial correlations were computed between 'risky choice index' at TP1 (see Methods) and CAPS-5 total scores at all three time-

points, while controlling for participants' age, gender, trauma type, and initial symptom severity. In line with our hypothesis, greater PTSD symptom severity shortly after exposure was associated with a decreased tendency to make risky choices in the SDRC game (n=132,r=-0.185,p=0.018;Fig.4). In an exploratory analysis, this behavioral tendency towards safe behavior was found to be particularly associated with more severe avoidance (r=-0.244,p=0.003,p_{FDR}=0.012) and intrusive symptoms (r=-0.212,p=0.016,p_{FDR}=0.032;Fig.4). Contrary to our hypothesis, no significant correlations emerged between risky choice index at TP1 and CAPS-5 total scores at TP2 (n=115,r=-0.039,p=0.341) or TP3 (n=112,r=-0.073,p=0.226).

Discussion

The longitudinal design of this fMRI study, along with the use of a naturalistic gambling task in a large cohort of recent trauma survivors, enabled the

investigation of the relationships between neurobehavioral components of valence processing and PTSD symptom development during the first critical year following trauma. While increased amygdala's functionality towards punishments vs. rewards shortly after trauma (TP1) was associated with more severe PTSD symptoms both at the same time-point and over a year later (TP1 and TP3), lower VS functionality towards rewards vs. punishments shortly after trauma (TP1) was associated with more severe symptoms only a year later (TP3). These results highlight the importance of early biased neural responsivity to positive relative to negative outcomes, in two key areas of the mesolimbic system, to long-term development of PTSD symptoms.

Consistent with the vast literature on the amygdala's hyper-responsivity to negative stimuli in PTSD(21,25–27,80–82), its increased activity to punishments vs. rewards was found to be associated with more severe symptoms at TP1. This association was mainly driven by the amygdala's increased response to punishments, rather than its decreased response to rewards. Additionally, functional connectivity between the amygdala and the lOFC in response to

rewards over punishments was associated with more symptoms at TP1. The OFC modulates the amygdala's activity during volitional suppression of negative emotion and in the presence of threatening stimuli(83–86) and is known to be involved in the processing of negative outcomes that signal a need for behavioral change(74,87). Along this line, disturbed amygdala-frontal functional connectivity was observed in PTSD patients in response to negative stimuli(88,89), but also in individuals suffering from other affective psychopathologies(90–94), suggesting that it might not be disorder-specific. While the current study design cannot disentangle causes from consequences of traumatic stress, the causal role of the amygdala in predisposed stress vulnerability was implicated in previous prospective studies(31,95).

In line with the second hypothesis, diminished responses of both VS and amygdala to reward relative to punishment at TP1 were associated with more severe symptoms at TP3, beyond initial severity. These results allude to similar findings in healthy soldiers(31), showing that increased PTSD-related symptoms post-exposure to stressful military experiences corresponded to increased

amygdala response to risk (pre- and post-exposure) and decreased NAcc/VS response to reward (only post-exposure). Both studies are in line with a putative casual model of PTSD development(95), suggesting that while hyperactive amygdala to negative outcomes may represent a predisposing risk factor for PTSD development, diminished VS activity to positive rewarding outcomes might only be acquired after trauma exposure.

Focusing on functional connectivity patterns, decreased VS-vmPFC connectivity at TP1 was found to be associated with more severe symptoms at TP3. Both regions are prominent nodes of the reward circuit, involved in value computations and decision-making processes(96,97). Human neuroimaging studies have repeatedly demonstrated coincident activation and functional connectivity between the VS and vmPFC during reward processing(98,99). Animal studies further demonstrated that the vmPFC modulates VS activity(100–102), and damage to the vmPFC is associated with diminished VS response to reward(103). This VS-vmPFC connectivity was found here to be the most important feature in predicting PTSD symptom development. It was previously shown to contribute to

the natural time course of positive mood(104) and the positive feeling of self-esteem(105). These findings point to an early role of VS functionality in post-traumatic stress psychopathology, corresponding to theoretical accounts on the importance of the positive valence system in promoting stress recovery, by broadening attention and building cognitive and social resources(106,107).

Post-hoc analysis revealed that the association between amygdala's sensitivity at TP1 and PTSD severity at TP3 was not mainly driven by its increased response to punishments as might be expected, but more so by its reduced response to rewards (even though both were not statistically significant). In the VS, as expected, the association with PTSD severity at TP3 was significantly driven by its reduced response to rewards, rather than its increased response to punishments, at TP1. Taken together, it is possible that decreased reward processing after trauma, in both the amygdala and VS, might serve as a risk factor for PTSD development. Given the lack of sufficient insights into how trauma affects the reward system(35), results from this study and future research may advance more targeted and effective treatments for PTSD.

Importantly, amygdala and VS activations at TP1 did not significantly predict PTSD symptom severity at TP2. This null result might be explained by the dynamic clinical manifestations during the first year following trauma exposure, with substantial inter-individual variability(108–111). An intermediary point of 6-months post-trauma (TP2) might be too early to capture the tangible chronic PTSD subtype, whereas 14-months (TP3) may portray a more stable representation of the chronic disorder, as it was shown to predict over 90% of the expected recovery from PTSD(112,113). A similar trend of null results at six-months post-trauma was also observed in previous work on the same dataset, examining neuroanatomical risk factors for PTSD(114).

Consistent with our final hypothesis, decreased risk-taking behavior in the SRDC game was associated with increased PTSD symptom severity, only at TP1. This is a replication of previous findings in soldiers exposed to military stress(31). The reduced likelihood to achieve rewards, particularly in light of potential punishments, suggests that the negative component might had a higher weight than the rewarding one in the decision-making process. In other words, it may

represent a combination of increased threat sensitivity (i.e., hyperactive negative valence processing) and reduced hedonic reward responsivity (i.e., hypoactive positive valence processing) among individuals with elevated PTSD symptoms in the early aftermath of trauma. This is also in line with reports of increased behavioral aversion to both risky monetary gains and ambiguous monetary losses in chronic PTSD patients(30,115), and corresponds to the idea that trauma exposure might alter the homeostatic balance in motivational behavior towards decreased approach and increased avoidance, possibly leading to development of the chronic disorder(16). Beyond general PTSD severity, risk-taking behavior was specifically correlated with both intrusion (also associated with the amygdala's response) and avoidance symptoms (also associated with the VS response), supporting a possible complementary functionality of both negative and positive valence systems.

Nevertheless, this study has several limitations. First, the neural model of specific brain responses to reward relative to punishment is a schematization of positive and negative valence processing, involving multiple brain areas and

networks and different interactions between them(1,116,117). Future studies may shed additional light on these processes by using network perspectives or data-driven whole-brain approaches(118). Second, the two predetermined neural regions (amygdala and VS) were shown to respond to both positive and negative outcomes separately (119–122). Nevertheless, this work focused on their relative responses to positive vs. negative valenced stimuli, with additional exploratory analysis of the separate responses to each valence by itself. Finally, positive and negative valence processing in this study were both examined in the context of motivation, decision-making, and risk-taking behavior. Thus, these findings are limited to neural valence processing of motivational values (i.e., rewards and punishments) and might not be generalizable to other positive and negative stimuli (e.g., passive viewing of happy and sad faces).

In conclusion, this study provides insights on the differential roles of positive relative to negative valence processing in the early development of post-traumatic stress psychopathology. While PTSD research to date has mostly focused on the hyperactive negative valence system (e.g., fear, threat), our

findings suggest that it is the relative contribution of both valence systems that predict long-term PTSD, and highlight the importance of deficient VS activity and connectivity in response to rewards relative to punishments as risk factors for PTSD development at the first critical year after trauma. As the neurobehavioral mechanisms of the human response to positive and negative valence are intrinsically linked, novel therapeutic strategies for PTSD should benefit from addressing symptoms while considering both valence systems fronts(123).

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Tables

	TP1 (n=132)		TP2 (n=115)		TP3 (n=112)	
Measure	*M*	*SD*	*M*	*SD*	*M*	*SD*
Age	33.52	11.01	33.73	11.08	33.56	11.27
Gender (F:M)	63:69	-	55:60	-	56:56	-
CAPS-5 Total	24.91	11.68	14.97	10.89	10.69	10.10
% MVA's	89% (n=117)		88% (n=101)		88% (n=99)	
% PTSD	74% (n=97)		35% (n=40)		24% (n=27)	

Table 1. Participants' Demographic and Clinical Characteristics. Main characteristics of the participants included in the final analyses across all three time-points. Means and standard deviations of participants' age, gender (Female: Male), and PTSD severity (CAPS-5 total scores), at 1-, 6- and 14-months post-trauma (TP1, TP2, and TP3). Additionally, the percentage of motor-vehicle accidents of individuals diagnosed with PTSD (%MVA's, %PTSD) are reported for each time-point separately.

Task Contrast	Rewards vs. Baseline		Punishments vs. Baseline	
Activation at TP1	L Amy	R Amy	L Amy	R Amy

PTSD Symptom Severity at TP1	r=0.036 p=0.690	r=0.071 p=0.434	r=0.193 p=0.032*	r=0.229 p=0.010*
PTSD Symptom Severity at TP3	r=-0.148 p=0.134	r=-0.071 p=0.474	r=0.059 p=0.552	r=0.010 p=0.924
Activation at TP1	**L VS**	**R VS**	**L VS**	**R VS**
PTSD Symptom Severity at TP1	r=0.106 p=0.232	r=0.093 p=0.298	r=0.103 p=0.248	r=0.066 p=0.458
PTSD Symptom Severity at TP3	r=-0.171 p=0.078	r=-0.220 p=0.022*	r=0.024 p=0.802	r=0.022 p=0.818

Table 2. Neural Indicators of Positive and Negative Valence Processing in Response to the Different Task Contrasts Associated with PTSD Symptom Severity.

Pearson correlation coefficients (r) and statistical significance (p) between PTSD symptom severity (CAPS-5 total scores) at 1-month (TP1) and 14-months (TP3) after trauma and TP1 neural activations of the a-priori regions of interest (ROIs) in response to rewards vs. baseline and punishments vs. baseline. The top part of the table relates to left and right amygdala (Amy) activation at TP1, whereas the bottom part relates to left and right ventral striatum (VS) activation at TP1. *Significant correlations ($p<0.05$, two-sided, uncorrected) are marked with light gray background.

Figures Titles and Legends

Figure 1. Safe or Risky Domino Choice (SRDC) Paradigm. While participants were told that the opponent is the experimenter and that their choices can increase their chances of winning, the computer randomly generated the opponent's responses in a predetermined pattern to allow a balanced design (exposing the player's choices 50% of the time). Each round of the game is composed of four intervals. First, participants choose which chip to play next (i.e., decision-making), either a matching choice (e.g., a chip with at least one of the master chip's numbers) or a non-matching choice. Next, they move the cursor to the chosen chip and place it facing down adjacent to the master chip (i.e., decision execution). Participants then wait for the opponent's response (i.e., anticipation of an outcome) to see whether the opponent challenges their choice by uncovering the chosen chip or not (i.e., response to an outcome). Participants' choices and opponents' responses are interactively determined by the flow of the game round after round, creating a natural progression of a game situation that lasts 4 min or until the player wins the game by disposing of all his chips. Each player played consecutively for 14 min (approximately 3-4 game rounds).

Figure 2. Neural Responsivity to Reward Relative to Punishment and PTSD Symptom Severity Shortly after Trauma. A. Partial regression scatter plots depicting the relation between CAPS-5 total scores at TP1 (y-axis) and neural activations (mean beta values) of the left and right amygdala in response to punishments vs. rewards (x-axis). The anatomical amygdala ROI which was used for this analysis is presented on a coronal view of the brain (in red). Each dot represents one subject. B. Partial regression scatter plots depicting the relation between CAPS-5 total scores at TP1 (y-axis) and neural activations (mean beta values) of the left and right ventral striatum (VS) in response to rewards vs. punishments (a-axis). The anatomical VS ROI which was used for this analysis is presented on a coronal view of the brain (in green). Each dot represents one subject. C. Partial regression scatter plots depicting the relation between CAPS-5 total scores at TP1 (y-axis) and functional connectivity (mean beta values) between the right amygdala and the left lateral orbitofrontal cortex (lOFC) in response to punishments vs. rewards at TP1 (x-axis). The anatomical ROIs which were used for

this analysis, right amygdala (red) and left lateral OFC (violet), are presented on an axial view of the brain. Each asterisk represents one subject. For all panels (A,B,C) - values on all axes are unstandardized residuals, after controlling for age, gender and trauma type (covariates).

Figure 3. Neural Responsivity to Reward Relative to Punishment Shortly after Trauma and PTSD Symptom Severity One-Year Later. **A.** Partial regression scatter plot depicting the relation between CAPS-5 total scores at TP3 (y-axis) and neural activations (mean beta values) of the left amygdala in response to punishments vs. rewards at TP1 (x-axis). Each dot represents one subject. On the left, the bar plot presents correlations between left amygdala activation and all four PTSD symptom clusters at TP3 according to CAPS-5: intrusion (B), avoidance (C), negative alterations in cognition and mood (D), and hyperarousal symptoms (E). Pearson correlation coefficients (r) are presented above each bar. *p-FDR<0.05. **B.** Partial regression scatter plot depicting the relation between CAPS-5 total scores at TP3 (y-axis) and neural activations (mean beta values) of the right ventral

striatum (VS) in response to rewards vs. punishments at TP1 (x-axis). Each dot represents one subject. On the left the bar plot presents correlations between right VS activation and all CAPS-5 PTSD symptom clusters at TP1 (see above). Pearson correlation coefficients (r) are presented above each bar. *p-FDR<0.05. C. Partial regression scatter plot depicting the relation between CAPS-5 total scores at TP3 (y-axis) and functional connectivity (mean beta values) between the right VS and the right ventromedial prefrontal cortex (vmPFC) in response to rewards vs. punishments at TP1 (x-axis). The corresponding predefined anatomical ROIs, right VS (green) and right vmPFC (yellow), are presented next to the plot. For panels A,B,C – values on all axes are unstandardized residuals, after controlling for age, gender ,trauma type, and initial symptom severity (covariates). D. Top panel - absolute feature importance as calculated by Shapley Additive explanation (SHAP), pointing to the importance of the neural features at TP1 in predicting CAPS-5 total scores at TP3. Larger SHAP values indicate higher importance of the feature to discriminate between individuals with different symptom severity (CAPS-5 total scores). For every individual from the n=105 included in our sample,

a dot represents the attribution value for each feature from low (blue) to high (red). **Bottom panel -** SHAP importance summary dot plot displaying features that influenced the linear regression model predictions of PTSD symptom severity (CAPS-5 total scores) at TP3. Features are first sorted by their global impact (y-axis).

Figure 4. Behavioral Indicators of the Co-involvement of Negative and Positive Valence Processing Shortly after Trauma. On the right, partial regression plot depicting the relationship between individuals' risky choice index at TP1 (%, x-axis) and their total CAPS-5 scores (y-axis) at TP1, while controlling for age, gender, and trauma type (covariates). On the left, a bar plot presenting the correlations between 'risky choice index' and all four PTSD symptom clusters at TP1 according to CAPS-5 (B, C, D, E). Pearson correlation coefficients (r) are presented above each bar. *p-FDR<0.05.

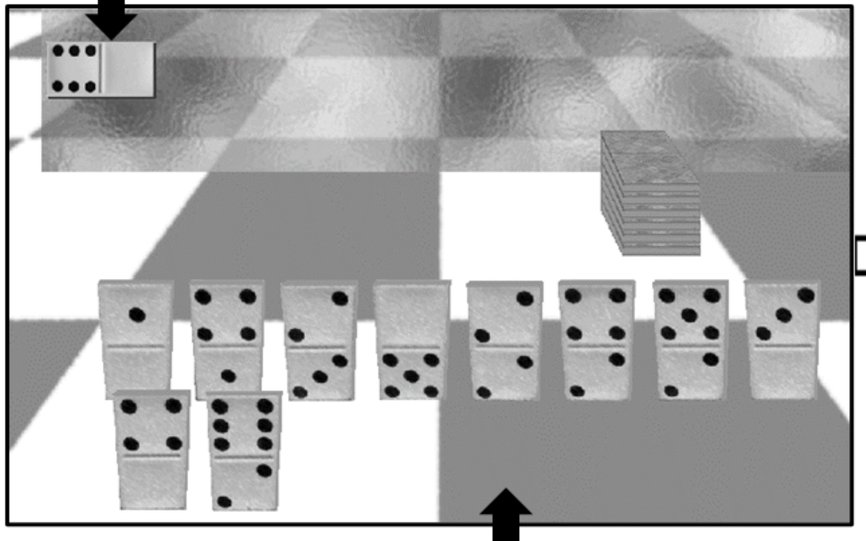
Decision-Making (4s)	Decision-Execution (≤12s)	Anticipation of an Outcome (4.5±1.5s)	Response to Outcome (4.5±1.5s)

Choose

Ready

Go

Master Chip



Player's Chips

Match Choice

Non-Match Choice

?

Anticipation of an Outcome

Show

No-Show

Show

No-Show

Main Reward
Player disposes of chip played and one more

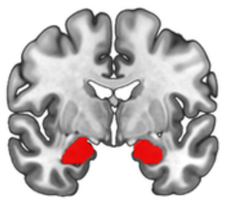
Relative Punishment
Player disposes of chip played

Main Punishment
Player receives chip played and two more

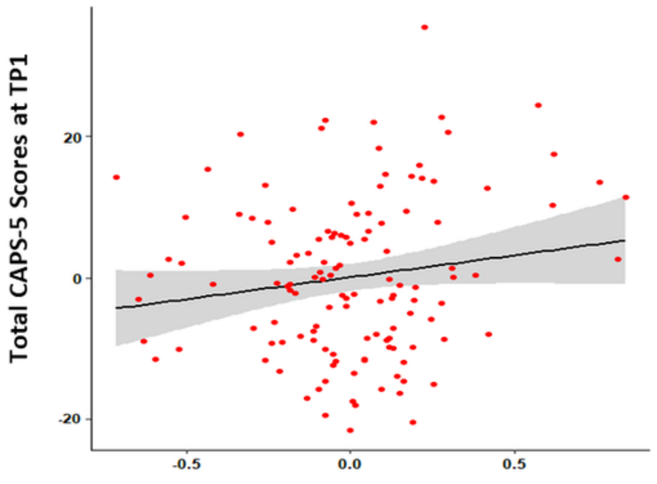
Relative Reward
Player disposes of chip played

A

Y=4

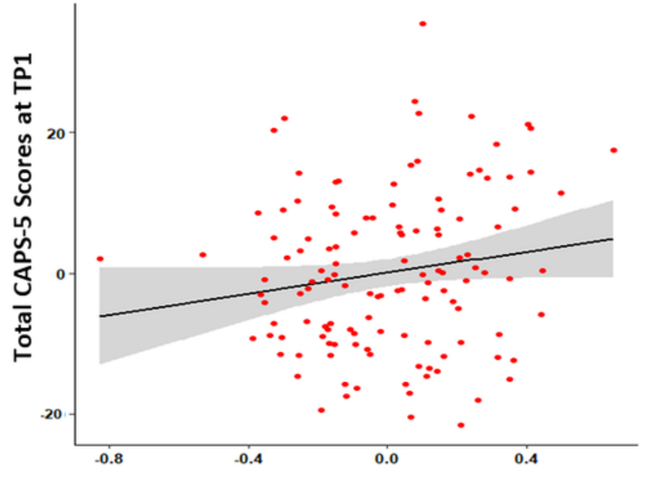


n=128, r=-0.156, p=0.042



Left Amygdala Activation at TP1
Punishments > Rewards

n=128, r=-0.162, p=0.035

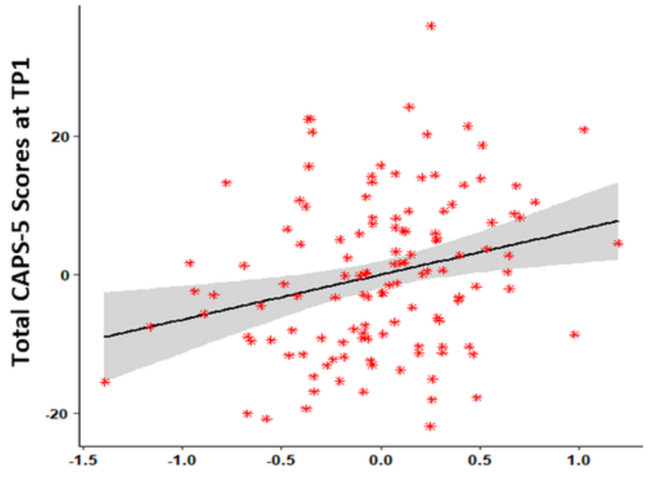


Right Amygdala Activation at TP1
Punishments > Rewards

C

Z=111

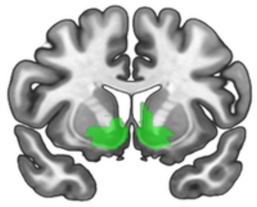
n=124, r=0.254, p=0.005



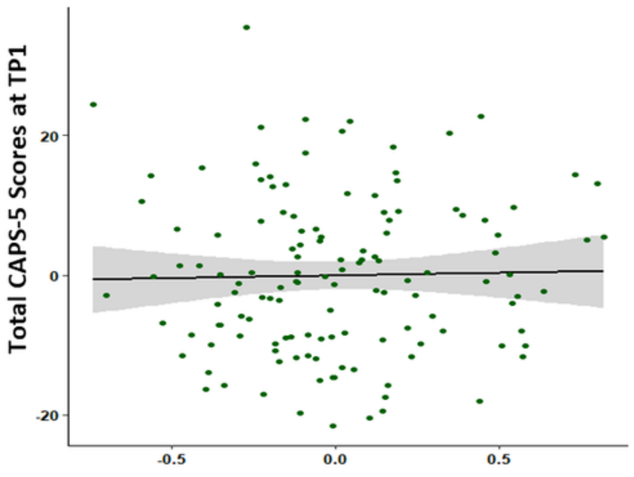
Right Amygdala – Left Lateral OFC at TP1
Punishments > Rewards

B

Y=6

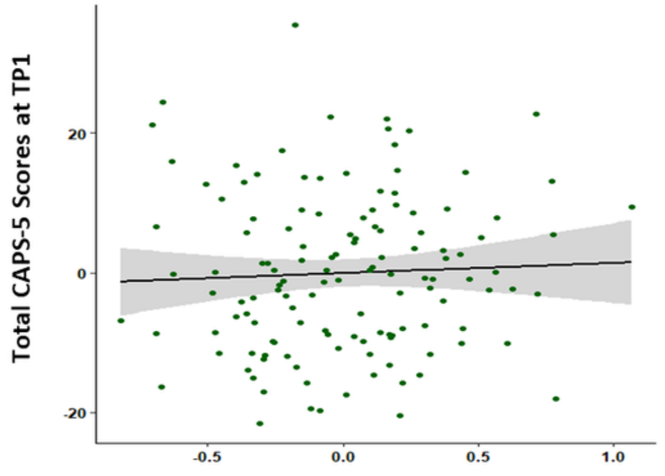


n=131, r=0.022, p=0.401

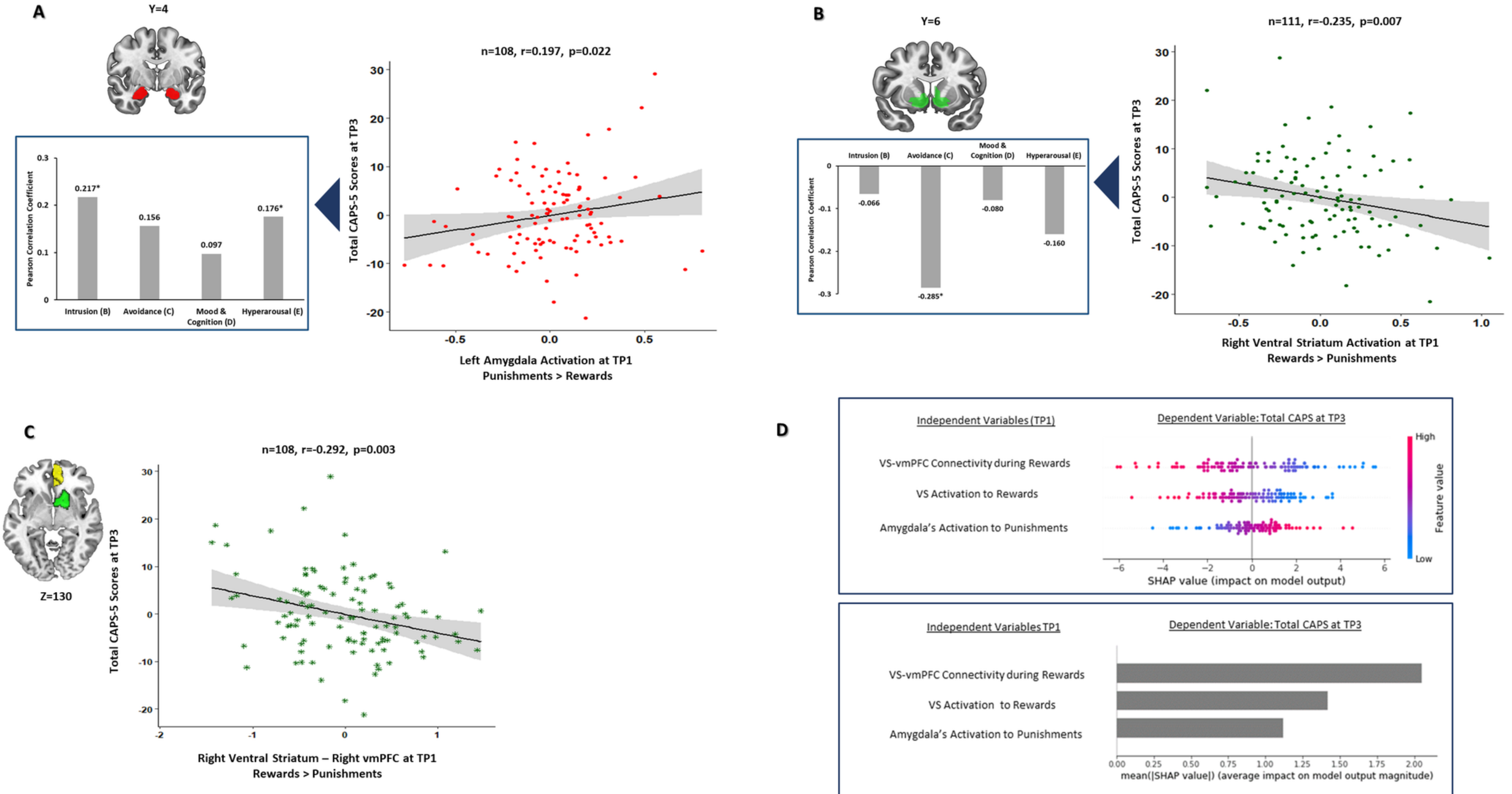


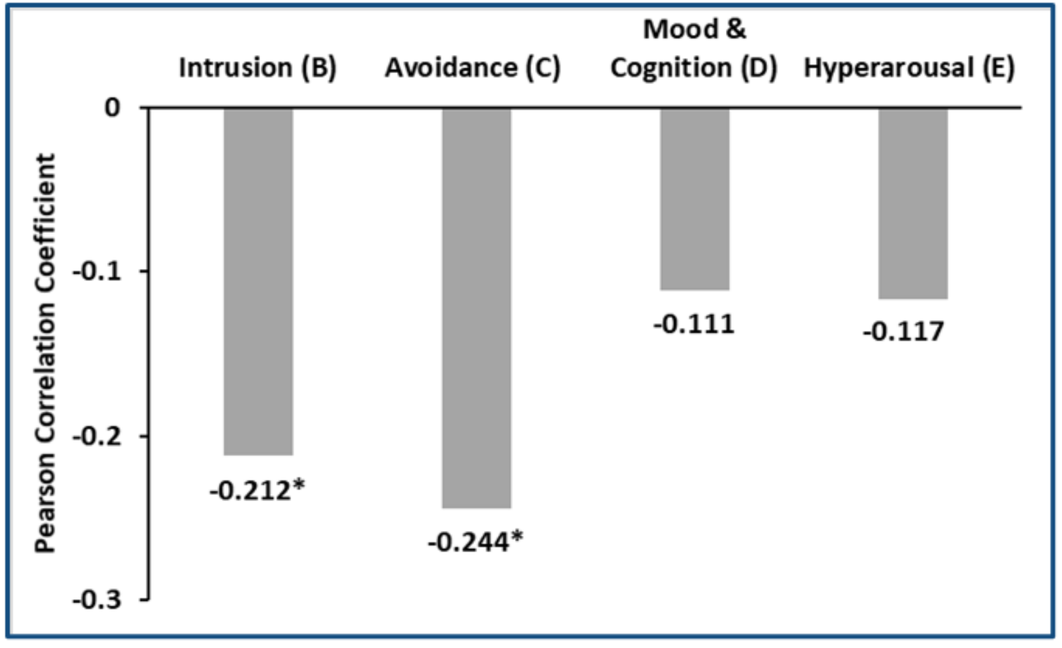
Left Ventral Striatum Activation at TP1
Rewards > Punishments

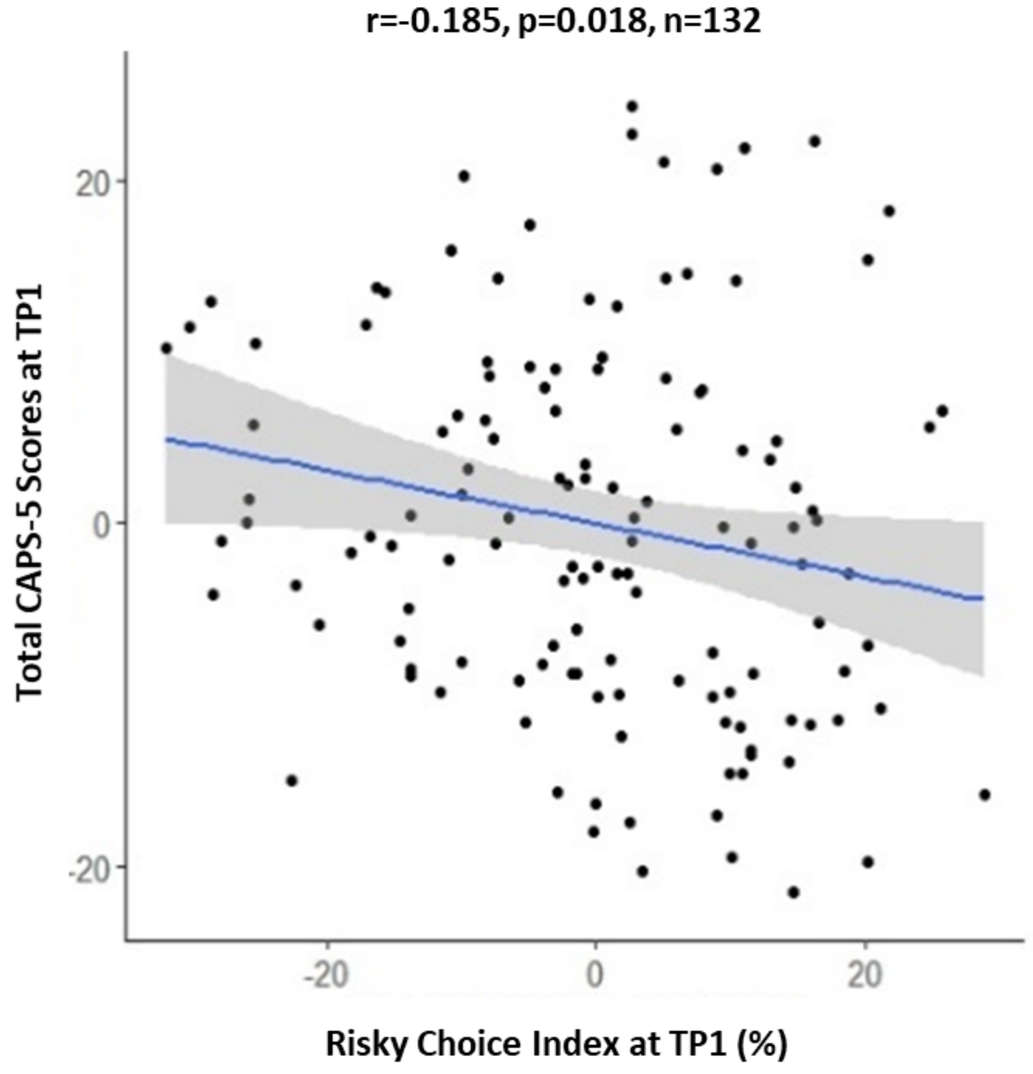
n=131, r=0.048, p=0.297



Right Ventral Striatum Activation at TP1
Rewards > Punishments


A
Y=4
Pearson Correlation Coefficient
0.217*
0.156
0.097
0.176*
Intrusion (B)
Avoidance (C)
Mood & Cognition (D)
Hyperarousal (E)
n=108, r=0.197, p=0.022
Total CAPS-5 Scores at TP3
Left Amygdala Activation at TP1
Punishments > Rewards
B
Y=6
Intrusion (B)
Avoidance (C)
Mood & Cognition (D)
Hyperarousal (E)
-0.066
-0.285*
-0.080
-0.160
n=111, r=-0.235, p=0.007
Total CAPS-5 Scores at TP3
Right Ventral Striatum Activation at TP1
Rewards > Punishments
C
Z=130
n=108, r=-0.292, p=0.003
Total CAPS-5 Scores at TP3
Right Ventral Striatum – Right vmPFC at TP1
Rewards > Punishments
D
Independent Variables (TP1)
Dependent Variable: Total CAPS at TP3
VS-vmPFC Connectivity during Rewards
VS Activation to Rewards
Amygdala's Activation to Punishments
High
Feature value
Low
SHAP value (impact on model output)
Independent Variables TP1
Dependent Variable: Total CAPS at TP3
VS-vmPFC Connectivity during Rewards
VS Activation to Rewards
Amygdala's Activation to Punishments
mean(|SHAP value|) (average impact on model output magnitude)


Intrusion (B)
Avoidance (C)
Mood & Cognition (D)
Hyperarousal (E)
Pearson Correlation Coefficient
0
-0.1
-0.2
-0.3
-0.212*
-0.244*
-0.111
-0.117


r=-0.185, p=0.018, n=132
Total CAPS-5 Scores at TP1
20
0
-20
-20
0
20
Risky Choice Index at TP1 (%)