Differential Roles of Positive and Negative Valence Systems in the Development of Post-Traumatic Stress Psychopathology

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Abstract

Negative and positive valence systems (NVS and PVS) pertain to processing of aversive and rewarding stimuli, respectively. Post-Traumatic Stress Disorder (PTSD) has been typically associated with abnormalities of the NVS, mostly related to heightened threat processing, yet more recent work also suggests deficits in PVS functionality in PTSD,

mainly in the form of reduced reward functioning. The current study examined the hypothesis that individuals' ability to recover from a potentially traumatic event relies on promoting reward-seeking behaviors (i.e., PVS) alongside diminished threat assessment (i.e., NVS), during the first year following trauma, a critical period for PTSD development or recovery. To do so, we longitudinally tracked behavioral and neural responses among 171 adult civilians with early post-traumatic stress symptoms at 1-, 6- and 14-months following trauma exposure (TP1, TP2, and TP3, respectively). At each time-point, participants played a naturalistic game encompassing dynamic provocation of risk-taking, punishments and rewards in an fMRI setting. Results showed that greater amygdala activation and functional connectivity with the lateral orbitofrontal cortex (lOFC) in response to punishments (i.e., hyperactive NVS) at TP1 were associated with more severe post-traumatic stress symptoms at both TP1 and TP3 (but not at TP2), and specifically with more hyperarousal and intrusion symptoms. On the other hand, decreased ventral striatum (VS) activity and functional connectivity with the ventromedial prefrontal cortex (vmPFC) in response to rewards (i.e., hypoactive PVS) at TP1 were associated with more severe post-traumatic stress symptoms at TP3 (but not at TP1 or TP2), and specifically with more avoidance symptoms. Explainable machine learning revealed the primacy of the PVS over the NVS at TP1 in predicting PTSD symptom development from TP1 to TP3. Behaviorally, fewer risky choices in the

task were associated with more severe symptoms at TP1, but not at TP2 or TP3. Finally, an integrative exploratory analysis revealed that reduction in risky choices in the task (from TP1 to TP2) moderated the relation between NVS hyperactivity at TP1 and symptom severity at TP3. Altogether, our results support the idea that trauma exposure might alter both NVS and PVS processing. While NVS presents early heightened saliency processing in the immediate aftermath of trauma, early PVS only affects the long-term outcome of traumatic stress. These insights inform possible mechanism-driven therapeutic strategies for PTSD, addressing not only negative but also positive valence processing.

Introduction

The concept of negative and positive valence systems (NVS and PVS, respectively) originated in psychology over a century ago, yet more recently was incorporated into the field of clinical neuroscience[1] and the Research Domain Criteria (RDoC)[2,3]. The NVS is responsible for responses to aversive situations or contexts, evoking negative feelings such as fear, anxiety, and loss, whereas the PVS is in charge of responses to positive motivational situations or contexts such as reward-seeking,

consummatory behavior, and reward learning. Valence estimation could be challenging in real-life as stimuli often evoke mixed or even conflicting emotions and consequence behaviors. Traumatic stress might hinder accurate valence estimations[4–6], as it increases vigilance and drains cognitive resources[7,8]. While this may serve survival in the immediate aftermath of stress, transition into reward-driven behavior over time, despite the presence of a heightened threat, is necessary for promoting stress resilience[9–13]. Indeed, chronic stress psychopathologies such as Post-Traumatic Stress Disorder (PTSD) are often characterized by a tendency to sacrifice potential rewards to avoid aversive encounters [14–17]. Here, we examine the idea that individuals' ability to recover from a potentially traumatic event relies on differential processing of the PVS and NVS by assessing neurobehavioral manifestations of these systems separately and together, in the early aftermath of trauma.

Substantial evidence links PTSD to abnormal NVS, consistently showing increased sensitivity to various negative stimuli (e.g. symptom provocation, fearful faces)[18,19] among PTSD patients, indicating elevated NVS, a phenomenon that may relate to the clinical symptoms of hyperarousal and intrusion (i.e., re-experiencing)[20–23]. Furthermore, studies using decision-making tasks demonstrated an association between PTSD and increased behavioral aversion to risk[24,25] and ambiguous losses[26], possibly reflecting the generalized (not only trauma-specific) oversensitivity of the NVS, often seen in PTSD patients. At the

neural level, the role of the NVS in PTSD has been repeatedly documented as abnormally heightened amygdala activation and hyperactive salience network (e.g., anterior insula, dorsal anterior cingulate cortex) in response to negative stimuli[20,27–29]. Furthermore, aberrant functional connectivity of the amygdala with the prefrontal cortex (PFC) in response to negative stimuli was observed in PTSD, specifically with the orbitofrontal cortex (OFC) in humans and the para-limbic cortex in animals, suggesting disrupted emotion regulatory capacity[30–33].

More recent work suggests that PTSD might also involve abnormalities in the PVS, 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 mesocorticolimbic 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 demonstrated initially in depressed individuals mostly in relation to anhedonia[38,39], it was also 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 the ventromedial PFC (vmPFC) in PTSD, suggesting a compromised reward circuitry in this disorder[43,44].

Although both systems seem to have a role in PTSD, their relative contribution to the development of post-traumatic psychopathology remains largely unknown, due to several substantial clinical and methodological challenges. First, only a small portion (around 20%) of those with early stress symptoms go on to develop chronic PTSD[45,46]. Second, even within the group of PTSD patients, clinical phenotypes are heterogeneous[47,48], and different symptom manifestations (e.g. hyperarousal vs. avoidance) might be related to different neurobehavioral processes (e.g. NVS vs. PVS). Third, the typical cross-sectional designs used in PTSD research cannot infer 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[49,50]. While there is an increase in longitudinal studies of PTSD in recent years, most of them focused on either NVS or PVS and did not combine clinical, behavioral, and neural measurements altogether in trying to unravel the unique role of each system in the same person over time.

To overcome these challenges, we conducted a large-scale longitudinal fMRI study of recent trauma survivors (see study protocol[51]). A sample of n=171 adult civilians were screened for early PTSD symptoms, suggestive of chronic PTSD risk[52,53], within 10-14 days following their release from a general hospital's emergency room (ER). Participants were longitudinally tracked at 1-, 6- and 14-months

following trauma exposure (TP1, TP2, and TP3, respectively) as they underwent fMRI scanning while playing a naturalistic interactive gambling choice game encompassing safe or risky choices resulting in outcomes of reward (win) or punishment (loss). To depict the neural processing of the two valence systems, the NVS was represented by the amygdala's response to punishments vs. rewards, while the PVS was represented by VS response to rewards vs. punishments. This paradigm, termed here 'Safe or Risky Domino Choice' (SRDC), was previously shown to elicit VS response to rewarding outcomes and amygdala response to punishment outcomes[25,54–57]. More so, in order to win, individuals' behavior in the SRDC game must include both safe and risky choices (determined by the type of domino chip chosen and its subsequent exposure or not by the opponent), enabling a behavioral marker of the balance between the PVS and NVS activation.

Our first aim was to find neurobehavioral indicators of NVS and PVS abnormalities associated with post-traumatic symptom severity shortly after exposure (TP1). Based on previous findings[24–26,58], we hypothesized that more severe post-traumatic symptoms would be associated with greater response of the amygdala to punishment vs. reward, decreased response of the VS to reward vs. punishment, and altered functional connectivity of the VS and the amygdala with the PFC. In light of our previous finding with the SRDC game in soldiers[25], we expected that individuals with more severe symptoms at TP1 would take fewer risky-

choices in the game, reflecting combined abnormality of hyperactive NVS and hypoactive PVS. Our second aim was to reveal the relationship between early NVS and PVS abnormalities and post-traumatic stress symptom development (i.e., beyond initial severity) within the first year following trauma exposure (TP2 and TP3). We hypothesized that greater response (activity and connectivity) of the amygdala to punishment vs. reward, decreased response (activity and connectivity) of the VS to reward vs. punishment, and decreased risky choice behavior at TP1, would be predictive of more severe post-traumatic symptoms at TP2 and TP3. Specifically, we expected that individual differences in NVS activation (i.e., amygdala response to punishment vs. reward) would be associated with symptom clusters of hyperarousal and intrusion, whereas differences in PVS activation (i.e., VS response to reward vs. punishment) would be associated with avoidance symptoms.

Methods

Participants. The study group included adult survivors of potentially traumatic events who were admitted to Tel-Aviv Sourasky Medical Center's Emergency Room (ER). The most common trauma type among participants was motor vehicle accidents (n=137, 80%), while other traumatic events included assaults, terror attacks, drowning, mass casualty incidents, animal attacks, robbery, and electrocution. Exclusion

criteria included head trauma or coma exceeding 30 minutes, incompatibility for MRI scanning, history of substance abuse, current or past psychotic disorder, or chronic PTSD diagnosis pre-admission to ER. Only trauma survivors without a known medical condition that interfered with their ability to give informed consent or to cooperate with screening and/or treatment were included. A total of 171 participants completed clinical and neuroimaging assessments within one-month following their traumatic incident (TP1). Of these, 39 individuals were excluded due to missing (n=16) or partial (n=5) functional scan while performing the SRDC game; poor quality of the functional scan (e.g., movements, artifacts, etc.) (n=6); missing or poor structural scan (n=5); missing or partial behavioral data of the paradigm (n=5); not understanding the instructions properly (n=1); and missing clinical data (n=1), for a final sample size of 132 individuals at TP1. Of these 132 participants, 115 and 112 participants completed clinical interviews at TP2 and TP3 (respectively). Participants' demographic and clinical characteristics across the three time-points (TP1, TP2, and TP3) are presented in Table 1. Of note, 6 individuals were excluded from the neural analysis at TP2 and 22 at TP3, due to missing/partial/poor quality of the functional scan, missing / poor quality structural scan, or missing/partial behavioral data of the SRDC game, for a final sample size of 109 and 90 individuals with valid neural data at TP2 and TP3.

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 n=4,000 potential participants were contacted by telephone for initial screening. Acute PTSD symptoms (indicative of the risk for PTSD development[52]) were assessed using a modified dichotomous version of the PTSD Checklist (PCL) questionnaire[59]. Out of 4,000 potential participants, only 600 met PTSD symptom criteria (except for the 1-month duration) based on the phone-screening interview. Participants who did not meet any of the exclusion criteria were invited to participate in both comprehensive face-to-face clinical assessment and an fMRI scan, within one-month post-trauma (TP1). We preferentially enrolled survivors who met PTSD diagnosis in the face-to-face clinical interview, but also enrolled some individuals with sub-threshold PTSD (n=35). Two identical follow-up meetings, including both clinical and neural assessments, were conducted at 6- and 14-months following trauma (TP2 and TP3, respectively). For more details, see Ben Zion et al. (2019).[51]

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)[60], 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).

fMRI Paradigm. During scanning, participants played a 2-player gambling game for 14 minutes (termed herby Safe or Risk Domino Choice game; SRDC), in which they were required to take risky choices to win (see Figure 1). The effectiveness of the SRDC to detect individuals' sensitivity to risk, punishment and reward was previously validated in both healthy and clinical populations[25,54–57,61]. Participants were told that their opponent is the experimenter who decides whether to expose their choice or not, thus their choices can increase their chances of winning. In fact, however, 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). The SRDC paradigm involved four intervals: decision-making (deciding which chip to choose), decision-execution (taking risky or safe chips), anticipation of an outcome (waiting passively for the opponent's decision to expose or not the player's choice), and response to an outcome (receiving a reward or punishment, defined by the chosen chip and opponent's decision). In this study, our focus was on the decision-making interval for behavioral indexing (i.e., individual tendency to take risky vs safe choices) and on

the neural responses to the outcome (rewards vs. punishments). At the beginning of each game, 12 random domino chips were assigned to the participant, while one domino "master" chip (constant throughout the game) appeared at the top left corner of the board. In each round of the game, players had to choose one chip and place it face down adjacent to the master chip. They then had to wait for the opponent's response (i.e., anticipation), to see whether the opponent challenges this choice by uncovering the chosen chip or not (i.e., outcome). Players were able to win this competitive game if they were able to successfully dispose of all 12 chips within 4 minutes. Each assigned chip either matched the master chip (had at least one of the master chip's numbers) or was non-matching. Since the master chip was constant throughout the game, it was only possible to win by choosing both matching and non-matching chips. In the game context, matching chips were considered ''safe'' moves since they were associated with rewards, while non-matching chips were considered ''risky'' moves since they were associated with punishments. Accordingly, based on players' choices, there were two possible anticipation periods, "risky anticipation" following a non-matching choice or "safe anticipation" following a matching choice. Based on players' choices and opponent's response, there were four possible consequences (outcomes) per game round: (1) Show of a non-matching chip (i.e., main punishment): the choice of a non-matching chip was exposed and the player was punished by receiving back the selected chip

plus 2 additional chips from the deck; (2) No-show of a non-matching chip (i.e., relative reward): the choice of a non-matching chip remained unexposed and only the selected chip was disposed of, so the player was relatively rewarded as he got away with a non-matching choice; (3) Show of a matching chip (i.e., main rewards): the choice of a matching chip was exposed and the player was rewarded by the disposal of the selected chip and one additional random chip from the game board; (4) No-show of a matching chip (i.e., relative punishment): the choice of a matching chip was not exposed and only the selected match chip was disposed of, so the player was relatively punished as he could have disposed of a non-matching chip instead. For more details, see supplementary methods.

Behavioral Analysis of the Paradigm. 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 throughout the entire game (e.g., choosing either a matching or non-matching chip), multiplied by 100 (to obtain percentage). Rounds 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 on the screen). Previous work using the SRDC game in healthy individuals showed an average risky choice index of 50% across individuals[54]. We thus assume here that a balanced PVS/NVS processing is needed to achieve an index of 50%, while

an index greater than 50% represents a bias towards more risky behavior, and less than 50% represents a bias towards safer behavior (i.e. risk aversion and avoidance tendencies).

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

fMRI Data Acquisition. Whole-brain functional and anatomical images were acquired using a 3.0 Tesla Siemens MRI system (MAGNETOM Prisma, Germany) with a 20-channel head coil at Tel-Aviv Sourasky Medical Center. Functional images were acquired in an interleaved order (anterior to posterior), using a T2*-weighted gradient-echo planar imaging pulse sequence (TR/TE=2000/28ms, flip angle= 90°, voxel size 2.2×2.2×2.2mm, FOV=220×220mm, slice thickness=3mm, 36 slices per volume). A T1-weighted three-dimensional anatomical image was also collected, using a magnetization prepared rapid gradient echo (MPRAGE) sequence (TR/TE=2400/2.29ms, flip angle = 8°, voxel size 0.7 × 0.7 × 0.7 mm, FOV = 224 × 224 mm), enabling optimal localization of the functional effects.

fMRI Data Analysis. Preprocessing was conducted using FMRIPREP version 1.5.8[62], a Nipype based tool[63]. The preprocessing procedures included spatial realignment of the echo planar imaging volumes, co-registration with the structural image, segmentation, normalization, and spatial smoothing (for full details, see supplementary methods). The

preprocessed imaging data was further analyzed using Statistical Parametric Mapping 12 (SPM12). The size of the effect for each condition for each participant was computed by a general linear model (GLM), which included the different conditions of the game: "choose", "ready", "go", "picked match", "picked non-match", "show match", "show non-match", "no show match" and "no show non-match". Individual statistical parametric maps were calculated for the a-priori defined contrasts of interest of "rewards vs. punishments" (receiving both rewarding outcomes > receiving both punishing outcomes) and "punishments vs. rewards" (receiving both punishing outcomes > receiving both rewarding outcomes). This was done for all participants at each time-point separately (n=132 at TP1, n=109 at TP2, and n=90 at TP3).

ROI analysis. Based on previous findings using the same paradigm[25,54-57,61], two main regions of interest (ROIs) were defined using the Human Brainnetome atlas (developed by Fan and colleagues[64]) and California Institute of Technology 168 (CIT-168) atlas (developed by Pauli and colleagues[65]). In the condition of rewards vs. punishments, the focus was on the left and right ventral striatum (VS), composed of the ventral caudate from the Human Brainnetome atlas (regions 219-220) and the nucleus accumbens from the CIT-168 atlas. In the opposite condition of punishments vs. rewards, the focus was on the left and right amygdala, composed of the medial (regions 211-212) and lateral amygdala (regions 213-214) from the Human Brainnetome atlas. MarsBaR region of interest

toolbox for SPM[66] was used to extract participants' contrast activations (average beta weight) from each ROI separately for each time point. Analyses were performed separately for each hemisphere (left and right amygdala, left and right VS). For more details regarding whole-brain and ROI analyses, see supplementary methods.

Functional Connectivity Analysis. Examination of how the brain region interacts in a task-dependent manner was performed using generalized psychophysiological interaction (gPPI) as implemented in CONN toolbox[67,68] (for full details, see supplementary methods). ROI to ROI analysis was performed using the two main a-priori ROIs, amygdala and VS, as seed regions and two prefrontal a-priori ROIs, ventromedial prefrontal cortex (vmPFC) and lateral orbitofrontal cortex (lOFC), as target regions. These regions were chosen based on previous literature reporting medial- medial-lateral segregation in the human prefrontal cortex, indicating that rewards are processed in the medial part of the PFC, while punishments are processed in the OFC[69–73]. The two target regions were anatomically defined by the Human Brainnetome atlas[64]: The vmPFC was composed of regions 41–42, 47–48, whereas the lOFC was composed of regions 43–44, 45–46, 51–52. For more details, see supplementary methods.

Statistical Analysis. IBM SPSS Statistics for Windows[74] and R[75] software were both used for the statistical procedures. Participants with extreme

scores of ±3 standard deviations from the mean in the relevant variables were defined as outliers and excluded from the analysis. For all statistical tests, $\alpha=0.05$ was used with either one-sided a-priori hypotheses or two-sided non-directional hypotheses (according to the a-priori hypotheses outlined at the end of the introduction section). Benjamini-Hochberg False Discovery Rate (FDR) correction ($q<0.05$)[76] was calculated to control for multiple comparisons.

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), we used SHAP (Shapley Additive exPlanation)[77], a state-of-the-art methodology in the field of explainable machine learning. 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 influence the prediction the most while accounting for the influence of all other feature values and controlling for the order in which features are added to the model[77].

Results

Neurobehavioral indicators of PVS and NVS for PTSD severity shortly after trauma

To find the neural indicators of the PVS and NVS associated with PTSD symptom severity shortly after exposure (TP1), partial correlations were computed between neural indices (mean activations of the VS and amygdala to rewards vs. punishments, as well as their connectivity patterns), and PTSD symptom severity (i.e., CAPS-5 total scores), while controlling for participants' age, gender, and trauma type (i.e., covariates). Results revealed a significant positive correlation between the amygdala's responses to punishments (vs. rewards) and symptom severity at TP1 *($n=128$; left amygdala: $r=0.155$, $p=0.043$, $p_{FDR}=0.043$; right amygdala: $r=0.162$, $p=0.035$, $p_{FDR}=0.043$)*, indicating that individuals with more severe symptoms showed greater amygdala activation (Fig. 2a). In contrast to our expectation, VS activation in the contrast of rewards vs. punishments was not significantly associated with symptom severity at TP1 *($n=131$; left VS: $r=0.022$, $p=0.401$; right VS: $r=0.048$, $p=0.297$)* (Fig. 2b). When examining functional connectivity patterns with predetermined PFC regions, we found that stronger amygdala-lOFC connectivity in the contrast of punishments vs. rewards was associated with more severe symptoms *($n=124$; right amygdala – left lOFC: $r=0.254$, $p=0.005$, $q_{-FDR}<0.05$*), indicating that greater connectivity was associated with greater symptom severity at TP1 (Fig. 3c). VS functional connectivity with the PFC in the contrast of rewards vs.

punishments was not related to total symptom severity (n=122, $q_{FDR}>0.05$). For whole-brain results, please refer to supplementary results, supplementary table 1, and supplementary figure 1.

To assess the relation between risky choice index, a behavioral measure reflecting balance/imbalance between the PVS and NVS, and PTSD symptom severity, we used both independent t-test between individuals with and without PTSD, and a partial correlation between the behavior and symptoms while controlling for participants' age, gender, and trauma type. At the group level, a two-sample independent t-test revealed a significant difference in risky choice index between 'PTSD' (n=97, dark gray) and 'non-PTSD' (n=35, light gray) groups *(t=2.833, p=0.006)* (Fig. 3a). While individuals who did not qualify for PTSD diagnosis showed an average choice of 50/50 between risky and safe choices *(M=49.69%, SE=2.00%)*, those with PTSD at TP1 displayed a significantly decreased risky choice index *(M=42.73%, SE=1.40%)* with a bias towards safer behavior. Notably, similar differences were observed between the groups when examining risky choice index following rewards *(t=3.466, p=0.001)* and following punishments *(t=2.828, p=0.005)*, separately. Specifically, while non-PTSD individuals (n=35) showed balanced behavior both after receiving rewards *(M=50.39%, SE=2.53%)* and punishments *(M=52.09%, SD=2.77%),* those with PTSD at TP1 (n=97) took significantly fewer risks after receiving rewards *(M=39.32%, SE=1.96%)* and punishments *(M=43.04%, SD=1.64%).* At the individual

level, a negative correlation was found between risky choice index and CAPS-5 total scores at TP1 *(n=132, r=-0.185, p=0.018),* indicating that individuals with more severe post-traumatic stress symptoms made less risky choices in the SDRC game (Fig. 3b). This behavioral tendency towards safe behavior was particularly associated with more severe avoidance (CAPS-5 cluster C) *(r=-0.244, p=0.003, p_{FDR}=0.012)* and intrusive symptoms (CAPS-5 cluster B) *(r=-0.212, p=0.016, p_{FDR}=0.032)*, but not with other symptom clusters (Fig. 3b).

Neural abnormalities of PVS and NVS predict first-year PTSD development

To assess the relationship between early neural PVS and NVS abnormalities (TP1) and PTSD symptom development within the first year following trauma exposure (TP2 and TP3), partial correlations were computed between neural indices at TP1 and PTSD symptom severity at TP2 and TP3, while controlling for participants' age, gender, trauma type, and initial symptom severity (CAPS-5 total scores at TP1). In line with our hypothesis, both hyperactive NVS (i.e., amygdala's activation to punishment) and hypoactive PVS (i.e., VS activation to reward) at TP1 were significantly predictive of more severe PTSD symptoms at TP3. Specifically, greater left amygdala activation at TP1 was associated with higher CAPS-5 total scores at TP3 *(n=108; r=0.197, p=0.022)* (see Fig. 4a); and decreased right VS activation at TP1 was associated with higher CAPS-5 total scores at TP3 (*n=111, r=-0.235, p=0.007)* (see Fig. 4b).

Individuals with hyperactive NVS or hypoactive PVS early after trauma (TP1) were thus prone to develop more severe symptoms a year later (TP3).

Testing specific symptom clusters, greater amygdala activation to punishments at TP1 was associated with more severe hyperarousal *($r=0.176$, $p=0.037$, $p_{FDR}=0.074$)* and intrusion *($r=0.217$, $p=0.027$, $p_{FDR}=0.074$)* at TP3 (Fig. 4a), whereas decreased VS activation to rewards at TP1 was linked to more avoidance at TP3 *($r=-0.285$, $p=0.001$, $p_{FDR}=0.004$)* (Fig. 4b). Of note, neither amygdala activation to punishments nor the VS activation to rewards at TP1 were significantly 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: $r=0.006$, $p=0.475$)*, nor with any specific CAPS-5 symptom clusters.

Examining the power of functional connectivity patterns of the PVS and NVS at TP1 for predicting PTSD at TP3 revealed such a relation only for the PVS. Specifically, decreased VS-vmPFC connectivity during rewards vs. punishments at TP1 was associated with more severe post-traumatic stress symptoms at TP3 *($n=108$, right VS – right vmPFC: $r=-0.292$, $p=0.003$, $q_{-FDR}<0.05$)*, indicating that individuals with less VS-vmPFC connectivity at TP1 developed more severe PTSD symptoms at TP3 (see Fig. 4c). Amygdala functional connectivity with the lOFC in the contrast of

punishments vs. rewards at TP1 was not related to PTSD symptom severity at TP3 (n=110, $q_{-FDR}>0.05$).

To assess the relation between risky choice index and PTSD symptom severity, we used both independent t-test between individuals with and without PTSD, and a partial correlation between behavior and symptoms while controlling for participants' age, gender, trauma type, and initial symptom severity. At the group level, no significant difference was found between PTSD and non-PTSD groups at TP2 *($t=0.760$, $p=0.449$)* or TP3 *($t=1.120$, $p=0.265$)*. Similarly, at the behavioral level, no significant correlations were found between risky choice index at TP1 and PTSD symptoms at TP2 *($n=115$, $r=-0.039$, $p=0.341$)* or TP3 *($n=112$, $r=-0.073$, $p=0.226$)*.

Finally, we tested the relative contribution of amygdala and VS functionality (activation and connectivity) at TP1 for PTSD symptom severity per CAPS-5 scores at TP3, using linear regression with the baseline neurobehavioral indices of PVS and NVS from TP1, which significantly predicted post-traumatic stress symptoms at TP3: left amygdala activation to punishments vs. rewards (Fig. 4a), right VS activation to rewards vs. punishments (Fig. 4b), and right VS-right vmPFC functional connectivity during rewards vs. punishments (Fig. 4c). 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 these three

neural predictors, we calculated importance values using the SHAP[77] analytic approach (see Predictor Importance Ranking in Methods). In terms of absolute feature importance, PVS abnormalities showed greater importance compared to NVS abnormalities. VS-vmPFC connectivity during rewards vs. punishments at TP1 was the best predictor of subsequent CAPS scores at TP3, followed by the right VS average response to rewards vs. punishments at TP1, and lastly the left amygdala's response to punishments vs. rewards at TP1 (Fig. 4d, right panel). Notably, when comparing the variances of VS activity and connectivity to amygdala activity, it seems that while the importance/contribution of the VS differed greatly between individuals (SHAP values ranging from -6 to +6), the amygdala had a small contribution in most participants (SHAP values between -2 to +2), and a large contribution to only a minority (Fig. 4d, left panel).

Integrative modeling of brain, behavior and PTSD development

In light of the null finding of the relationship between risky choice index at TP1 and PTSD symptoms at TP2 or TP3, we further explored the possibility that behavioral change in risky choice in the SRDC game (TP2-TP1 or TP3-TP1) moderates the relation between early NVS or PVS activity (at TP1) and post-traumatic stress symptom severity at the study's endpoint (TP3). Moderation effects were tested with PROCESS macro for SPSS[78,79] using hierarchical multiple regression analysis with centered

variables and a centered interaction term. Specifically, 8 moderation models were tested, including 4 different neural activations (left and right amygdala and VS at TP1) and 2 different behavioral measures (change in risky choice index from TP1 to TP2, and from TP1 to TP3).

Of these 8 moderation models tested, only one was statistically significant after correcting for multiple comparisons ($q_{-FDR}<0.05$) (see Fig. 5a). This regression model consisted of left amygdala activation to punishments vs. rewards at TP1, change in risky choice index from TP1 to TP2, and the interaction between them, together with four covariates (age, gender, trauma type, and initial symptom severity), accounted for a significant amount of variance in symptom severity at TP3 ($n=90$; $R^2=0.400$, $F_{7,82}=7.805$, $p<0.001$). A significant interaction (moderation) effect was detected between amygdala activation at TP1 and risk-taking behavior (change from TP1 to TP2) in predicting CAPS-5 total scores at TP3 ($b=-1.074$, $t_{82}=-3.311$, $p=0.001$, $p_{FDR}=0.011$) (see supplementary table 2). This significant interaction was further probed by testing the conditional effects of the left amygdala activation at different values of the behavioral change in risky choice index (Mean-1SD, Mean, Mean+1SD) (see Fig. 5b). For individuals who demonstrated a shift towards less risky choices over time (negative change in TP2-TP1 risky choice index, blue line), the amygdala's activation to punishments at TP1 was associated with more symptoms at TP3 ($t=3.754$, $p=0.003$). However, for those with no major change (green line) or with a shift

towards more risky behavior from TP1 to TP (red line), the relation between amygdala activation at TP1 and CAPS-5 total scores at TP3 was not significant *($p>0.05$)* (Fig. 5b).

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 a comprehensive multi-parametric assessment of the relationships between the two valence systems' functionality and the development of PTSD. The NVS was represented by the amygdala's response to punishments vs. rewards, whereas the PVS was represented by the VS response to rewards vs. punishments. Our results demonstrate the differential contribution of the valence systems in the early manifestation of post-traumatic psychopathology (TP1), as well as in predicting the development of symptom severity (beyond initial symptoms) over the first year following traumatic exposure (TP3). At TP1, we found a leading contribution of the NVS neural processing to post-traumatic stress symptom severity (Fig. 2). While heightened processing in NVS (shown as hyperactive amygdala in response to punishment and its connectivity with the lOFC) was associated with more severe PTSD, diminished processing of PVS (as indicated by VS activity to reward and its connectivity with the vmPFC) was not associated with early symptoms.

Behaviorally, individuals with more severe symptoms at TP1 showed less risky choices (Fig.3), possibly reflecting an imbalance between NVS and PVS. Neural activation of the two valence systems at TP1 showed an opposite association with the development of post-traumatic stress symptoms at TP3 (beyond initial symptom severity) (Fig. 4). Hyperactive NVS and hypoactive PVS at TP1 were thus both associated with more severe symptoms at TP3. In a combined regression model aiming to predict symptom severity at TP3, early PVS neural abnormalities at TP1 were more important to the prediction model compared to early NVS abnormalities (Fig. 4d). Although we did not find risky-choice behavior at TP1 to be predictive of PTSD symptoms at TP3, an exploratory moderation analysis revealed that individuals with both early NVS (and not PVS) abnormality (TP1) and a reduction in risky choice behavior (from TP1 to TP2) were prone to develop more severe PTSD symptoms at TP3 (Fig. 5).

Contribution of NVS and PVS to early PTSD manifestations

The large cohort of symptomatic individuals in this study (n=132) provided the opportunity to examine the variability in neurobehavioral measures of PVS and NVS in relation to post-traumatic stress symptom severity as early as one-month after trauma (TP1). Consistent with the vast literature on increased amygdala response to negative stimuli in PTSD[20,27–29,80,81], hyperactive amygdala to punishments during the SRDC

game was associated with increased general post-traumatic stress symptom severity. Furthermore, increased amygdala-OFC functional connectivity while receiving punishments was also linked to greater PTSD severity. The OFC has a known role in the modulation of the amygdala[82,83] during volitional suppression of negative emotion[84] and in the presence of threatening stimuli[85], and its connectivity with the amygdala is involved in processing negative outcomes that signal a need for a behavioral change[72,73]. Indeed, disturbed fronto-amygdalar connectivity was previously observed in patients with PTSD[86,87] and other anxiety disorders[88,89], but this might not be specific as it was also found in depression[90,91] and bipolar disorders[92]. Although the current study cannot confidently disentangle causes from consequences of traumatic stress, the causal role of the NVS was implicated in previous prospective studies, showing for example that hyperactive amygdala in soldiers prior to exposure to stressful military experience was associated with more PTSD symptoms post-exposure[25,93].

Decreased risk-taking during the game (less than 50%) was also associated with more severe PTSD symptoms at TP1. This safer than risky choice tendency was apparent after both reward and punishment outcomes, suggesting an outcome independent behavior at an early stage. This supports the specific association with avoidance symptoms. It is interesting to note that trauma-exposed individuals who did not meet PTSD diagnostic criteria (n=35) at TP1 demonstrated risk taking-behavior

of around 50% throughout the whole game (half safe and half risky choices), similar to previous studies in healthy individuals using the same SRDC game[54–57,61]. This adaptive flexible behavior was optimal for wining the SRDC paradigm, as the computer randomly generated the opponent's responses, exposing the player's choices 50% of the time (see fMRI Paradigm under Methods). In contrast, individuals diagnosed with PTSD at TP1 (n=97) showed significantly less risk-taking across the game and thus reduced their chance of winning in the end. We suspect that this behavioral abnormality might reflect an imbalance between the valence systems, combining increased threat from negative outcomes (heightened NVS) and reluctance to take risks in order to achieve rewards which might not elicit a great enough hedonic response (diminished PVS). Such imbalance is in line with previous work in chronic PTSD patients reporting increased behavioral aversion to risky monetary gains and ambiguous monetary losses[24,26]. This further corresponds to the idea of Stein & Paulus (2009)[15] that trauma exposure might alter the homeostatic balance in motivation behavior towards less approach and more avoidance, which in turn might lead to the development of chronic PTSD. To elucidate the exact mechanism that underlies this behavioral abnormality, future studies should compare more formal behavioral indices of reinforcement learning and reward-seeking and valuation.

Early NVS and PVS neural abnormalities predict PTSD first year development

Using a longitudinal design, we were able to demonstrate that neural responsivity of NVS and PVS components shortly after trauma predicted post-traumatic stress symptom severity at more than one year following the traumatic event. Specifically, increased amygdala response to punishment and decreased VS response to reward at TP1 were associated with more severe symptoms at TP3 (beyond initial symptom severity) (Figure 2). These opposite effects of the NVS and PVS allude to a similar finding by Admon et al. (2013)[25] in a-priori healthy soldiers, in which increased PTSD-related symptoms after-exposure to stressful military experience corresponded to increased amygdala response to risk, both pre- and post-exposure, and to decreased VS response to reward, only post-exposure. Likewise, the amygdala's response to punishment at TP1 here was related to PTSD symptoms both at TP1 and TP3, whereas VS response to reward at TP1 was not associated with symptoms at the same time-point, but was predictive of subsequent symptoms at TP3. Both studies, in line with a suggested casual model of PTSD development[93], suggest that while heightened NVS neural activity represents a predisposing risk factor for this disorder, diminished PVS neural activity may contribute to long-term consequence following the trauma. Furthermore, decreased VS-vmPFC connectivity at TP1 was associated with more severe symptoms at TP3. The VS and vmPFC are two prominent

nodes of the reward circuit, involved in value computations and decision-making processes[94,95]. Human neuroimaging studies have repeatedly demonstrated coincident activation and functional connectivity between these regions[96,97], with animal studies further showing that the vmPFC modulates VS activity[98–100]. Intriguingly, Pujara et al. (2016)[101] reported that vmPFC damage was associated with decreased VS volume and diminished response to reward, further supporting a causal role of the vmPFC for reward processing via the VS. Of particular interest is the relationship found between decreased PVS activation at TP1 to avoidance symptoms at TP3 (beyond total severity). Recent animal studies suggested that dopaminergic neurons in the VS regulate approach-avoidance behavior under goal-conflict situations[102,103]. Comparably in humans, VS activity measured by fMRI discriminated between personality tendencies for approach or avoidance under naturalistic high goal-conflict situations[104].

Looking at the brain's reward system in the context of resilience, PVS activation was shown to mitigate subsequent stress responses to a wide range of stressors in animals and humans[12,13,105,106]. It has been suggested that recruitment of positivity accelerated recovery shortly after stress, by assisting the return to homeostasis[12,13,105–108]. This implies that PVS processing may interrupt the development of stress-related psychopathology, even in the presence of heightened NVS[109]. One mechanism for such an effect has been recently suggested by a

longitudinal study showing that trauma exposure impacted prospective relationships between markers of the reward circuitry function and affective symptom trajectories[110]. Specifically, trauma exposure moderated the prospective relationships between VS and amygdala activations to reward prediction error and hypo/mania severity trajectory[110]. Yet, the association of this interaction to PTSD severity following trauma is unclear.

Altogether it seems that post-traumatic psychopathology might involve neural deficits in the NVS, PVS, or both, which might underlie abnormalities in different key processes, reflected in different clinical phenotypes of this disorder. Utilizing explainable machine learning, we found that VS activity and connectivity in response to rewards vs. punishments early after trauma were more important to the prediction of PTSD development a year later, compared to the amygdala activity and connectivity in response to punishments vs. rewards (Fig. 4f). While PTSD research to date has mostly focused on the NVS (e.g., fear, threat), our findings suggest the important role of the PVS in the risk of developing the disorder in the first year after trauma. Of note, the neural model of specific brain responses to reward and punishment is a simplification of the human positive and negative valence systems, involving multiple brain areas and networks and the interactions between them[1,111,112]. Future studies should examine the neural response using a network perspective or a data-driven whole-brain approach.

Beyond the association of PVS and NVS with overall PTSD symptom severity (i.e., CAPS-5 total scores), our results suggest a relationship between neurobehavioral abnormalities of these systems and specific clusters of PTSD symptoms, alluding to specific underlying mental processes. While NVS hyperactivation was associated mostly with symptom clusters of hyperarousal and intrusion, both at TP1 and TP3 (see Fig. 2 and 4), the PVS hypoactivation was particularly associated with avoidance symptoms (Fig. 4). Hyperarousal and intrusion are well-known as hallmarks of magnified threat processing in PTSD[7,113,114], while avoidance marks deficient reward processing[104,115,116], respectively standing for abnormally intensified NVS and weakened PVS. This finding suggests that the activation of NVS/PVS as early as one month after trauma could point to specific PTSD abnormalities a year later, thus guiding precise and personalized early intervention.

Interestingly, 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, displaying an overall progressive reduction in PTSD symptom severity, but large inter-individual variability[117–120]. An intermediary point of 6-months post-trauma might be too early to capture the tangible chronic PTSD subtype, whereas 14-months may portray a more stable representation of the chronic disorder, as it was shown to predict over 90% of the expected recovery from PTSD[121,122]. A

similar trend of null-results at TP2 was observed in a previous analysis of this data set examining neuroanatomical risk factors for PTSD[123].

The possible cognitive mechanism underlying imbalanced NVS/PVS in PTSD

The decrease in risky behavior was associated with both intrusion and avoidance symptoms (corresponding to NVS and PVS processing, respectively) (see Fig. 3), supporting the idea that risky choice index reflects a balance between the two systems. To further explore the relationship between risky choice bias and the neural mechanism of the valence systems, we employed an integrative moderation model. Results showed that a decrease in risky behavior over time (from TP1 to TP2) moderated the relationship between early hyperactive NVS (at TP1) and subsequent post-traumatic stress symptom development (at TP3) (Fig. 5 a&b). It remains to be determined what drives such a behavioral bias following traumatic stress exposure. Speculatively, a possible mechanism involves cognitive flexibility, the ability to change and adapt one's behavior in response to changing environments and stimuli[124,125]. Such flexibility may facilitate goal-directed behavior (e.g., approach or avoidance) that promotes the survival and wellbeing of the organism even in the face of danger[126-128]. Previous work has highlighted the importance of early cognitive flexibility compared to other neurocognitive domains,

as it was shown to be the most significant cognitive predictor of PTSD symptoms at 14-months post-trauma[129,130]. Furthermore, early neurocognitive intervention improved cognitive flexibility which in turn reduced PTSD symptoms, suggesting its role as a modifiable target preceding and underlying the development of post-traumatic psychopathology[130,131]. Hence, enhancement of cognitive flexibility may enable more risky approach behavior toward prospective rewards, possibly by recruitment of the positive system. This idea corresponds to theoretical accounts regarding the importance of PVS in stress recovery by broadening attention and building cognitive and social resources[132,133]. Future research may investigate cognitive flexibility as a potential mechanism of balance between neural PVS and NVS concerning the development of stress-related psychopathology. A common paradigm that captures both reward sensitivity and cognitive flexibility is the probabilistic reversal learning (PRL) paradigm[134–136]. Recent animal work using the PRL paradigm observed that while reward increased flexibility and learning, the presence of aversive punishing stimulus decreased learning performance, increased perseveration, and impaired error detection[137]. As stress is known to impair general learning mechanisms, Harms et al. (2017)[138] showed that stress-exposed adolescents performing the PRL paradigm learned associations of rewards and punishments more slowly (compared to typically developing peers), and showed profound deficits in reversing learned stimulus-response

associations. Finally, cognitive flexibility training improved reversal learning in the PRL paradigm and extinction retention memory (a hallmark cognitive effect of trauma)[139].

Conclusion

This study provides a mechanistic neurobehavioral investigation of PVS and NVS in a large cohort of recent trauma survivors that also takes into consideration dynamics in post-traumatic stress symptoms during the first year following trauma. Results include specific behavioral and neural patterns (activation and connectivity) at one-month after trauma, associated with symptom severity at the same time and predictive of post-trauma psychopathology development over a year later. This work also revealed connections between these neurobehavioral indices and specific symptom clusters, suggesting different NVS/PVS processes underlying different clinical phenotypes of PTSD. As the neurobehavioral mechanisms of the human response to positive and negative outcomes are intrinsically linked, novel therapeutic strategies for PTSD should benefit from addressing symptoms on both fronts. While most interventions and treatments for PTSD focus on reducing the hyperactive negative valence system, strategies aiming to increase the positive valence system may further promote stress resilience and recovery[109].

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Ethics: The study was approved by the ethics committee in the local Medical Center (Reference number 0207/14). All participants gave written informed consent in accordance with the Declaration of Helsinki, and received financial remuneration at the end of each time-point (TP1, TP2 and TP3). The study was registered under ClinicalTrials.gov database

(registration ID#: NCT03756545; https://clinicaltrials.gov/ct2/show/NCT03756545).

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Tables

Table 1. Participants' demographic and clinical characteristics. The table summarizes characteristics of participants included in the final analyses across the 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.

	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)	

Figures Titles and Legends

Figure 1. Safe or Risky Domino Choice (SRDC) Paradigm. Each round of the game is composed of four intervals. First, the participant choose which chip to play next (i.e., decision-making), either a matching choice (e.g., a chip with least one of the master chip's numbers) or a non-matching choice. Next, he moves the cursor to the chosen chip and places it facing down adjacent to the master chip (i.e., decision-execution). The participant then waits for the opponent's response (i.e., anticipation of an outcome) and sees whether the opponent challenges

this choice by uncovering the chosen chip or not (i.e., response to outcome). Participant's choices and opponent's 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 Indicators of Positive and Negative Valence Systems for Post-Traumatic Stress Symptom Severity Shortly after Trauma Exposure. **a.** Partial regression scatter plots depicting the relation between CAPS-5 total scores at TP1 (y-axis) and mean beta values for the left and right amygdala activation in response to punishments vs. rewards (x-axis). Values on axes are unstandardized residuals. 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 mean beta values for the left and right ventral striatum activation in response to rewards vs. punishments (a-axis). Values on axes are unstandardized residuals. The anatomical ventral striatum 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 mean beta values for the right amygdala – left lateral OFC

connectivity in response to punishments vs. rewards at TP1 (x-axis). Values on both axes are unstandardized residuals. 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.

Figure 3. Behavioral Indicators of Positive and Negative Valence Systems for Post-Traumatic Stress Symptom Severity Shortly after Trauma Exposure. a. Boxplots with individual data points representing average risky choice index (%) for individuals which met PTSD diagnosis at TP1 and those who did not ('PTSD', n=97, dark gray; 'No PTSD', n=35, light gray). **b.** Partial regression plot depicting the relation between individuals' risky choice indexes at TP1 (%, x-axis) and their total CAPS-5 scores (y-axis) at TP1, while controlling for effects of age, gender and trauma type (covariates). Values on both axes are unstandardized residuals. 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: 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.

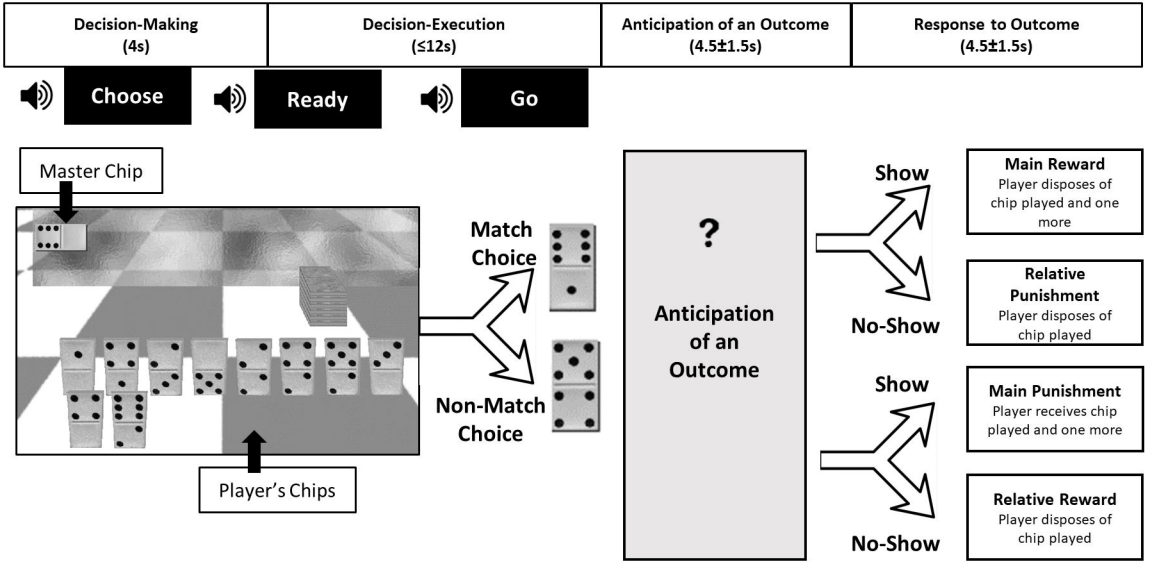
Figure 4. Neural abnormalities of PVS and NVS predict first-year PTSD development. a. Partial regression scatter plot depicting the relation

between CAPS-5 total scores at TP3 (y-axis) and mean beta values for the left amygdala activation in response to punishments vs. rewards at TP1 (x-axis), while controlling for effects of age, gender and trauma type (covariates). Values on both axes are unstandardized residuals. On the left, a bar plot presenting the 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 mean beta values for the right ventral striatum activation in response to rewards vs. punishments at TP1 (x-axis), while controlling for covariates (see in a). On the left, a bar plot presenting the correlations between right ventral striatum's activation and all four PTSD symptom clusters at TP1 according to CAPS-5. 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 mean beta values for the right ventral striatum – right vmPFC connectivity in response to rewards vs. punishments at TP1 (x-axis), while controlling for covariates (see in a). The corresponding predefined anatomical ROIs, right VS (green) and right vmPFC (yellow), are presented next to the plot. **d. Explainable machine learning.** On the right, Absolute feature importance as calculated by SHAP, pointing to the importance of

neural features at TP1 in predicting CAPS-5 total scores at TP3. The larger the SHAP value, the more important the feature is to discriminate between individuals with different symptom severity (CAPS-5 total scores). On the left, 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). 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).

Figure 5. Integrative modeling of brain, behavior and PTSD development. **a.** Integrative moderation model of neural NVS, behavior and clinical symptoms: behavioral change in risky choice index (from TP1 to TP2) significantly moderated the relation between valence specific left amygdala activation at TP1 and PTSD symptoms at TP3, beyond age, gender, trauma type and initial symptom severity. **b.** Conditional effects of TP1 left amygdala's activation to punishments vs. rewards on TP3 CAPS-5 total scores at different values of n=90 individuals' change in risky choice index (TP2-TP1) (blue = more risky behavior, Mean-1SD; green= no change in risky behavior, Mean; red = less risky behavior, Mean+1SD). All variables were centered prior to the analysis. Change in risky choice index is presented as a categorical variable with 3 levels for

illustration purposes, even though it was used as continuous variable in the analyses. *p >.05


Decision-Making
(4s)
Decision-Execution
(≤12s)
Anticipation of an Outcome
(4.5±1.5s)
Response to Outcome
(4.5±1.5s)
Choose
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Master Chip
Player's Chips
Match
Choice
Non-Match
Choice
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Anticipation
of an
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Show
No-Show
Main Reward
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Player receives chip played and one more
Relative Reward
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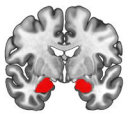
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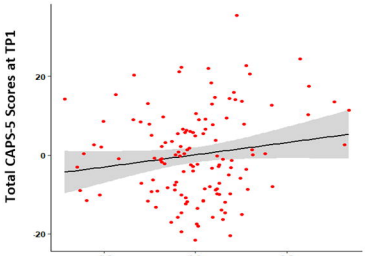
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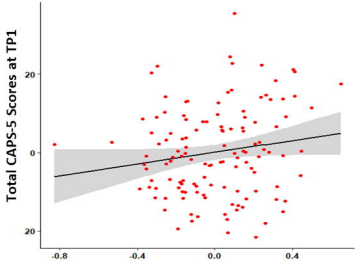
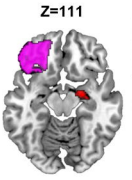
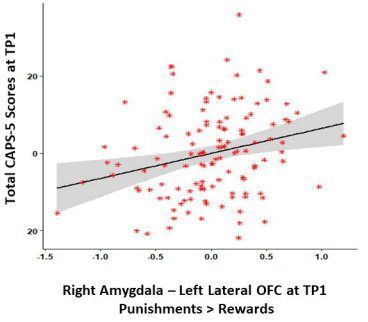
Total CAPS-5 Scores at TP1
Left Amygdala Activation at TP1
Punishments > Rewards

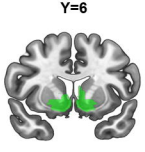

n=128, r=-0.162, p=0.035
Total CAPS-5 Scores at TP1
Right Amygdala Activation at TP1
Punishments > Rewards

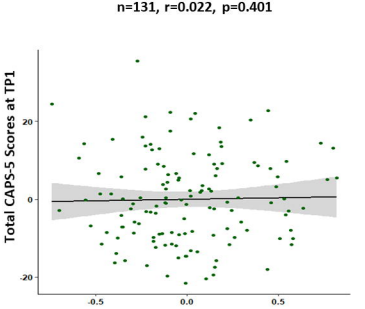
c

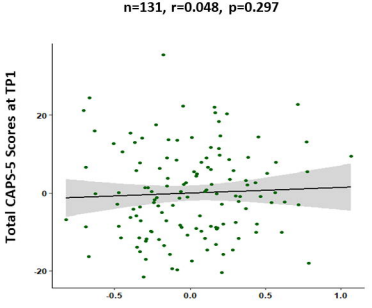

Z=111

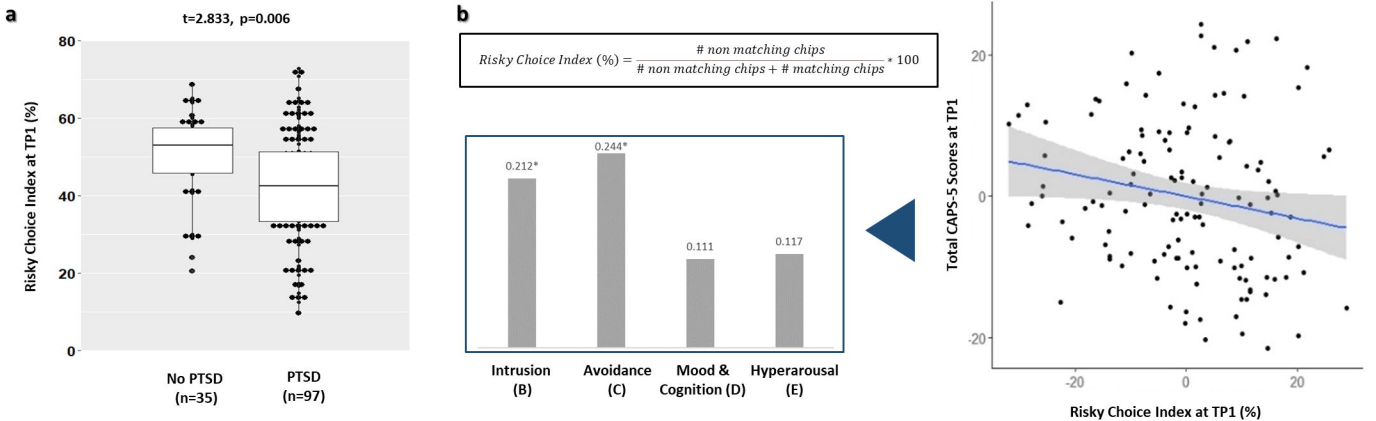

n=124, r=0.254, p=0.005
Total CAPS-5 Scores at TP1
Right Amygdala – Left Lateral OFC at TP1
Punishments > Rewards

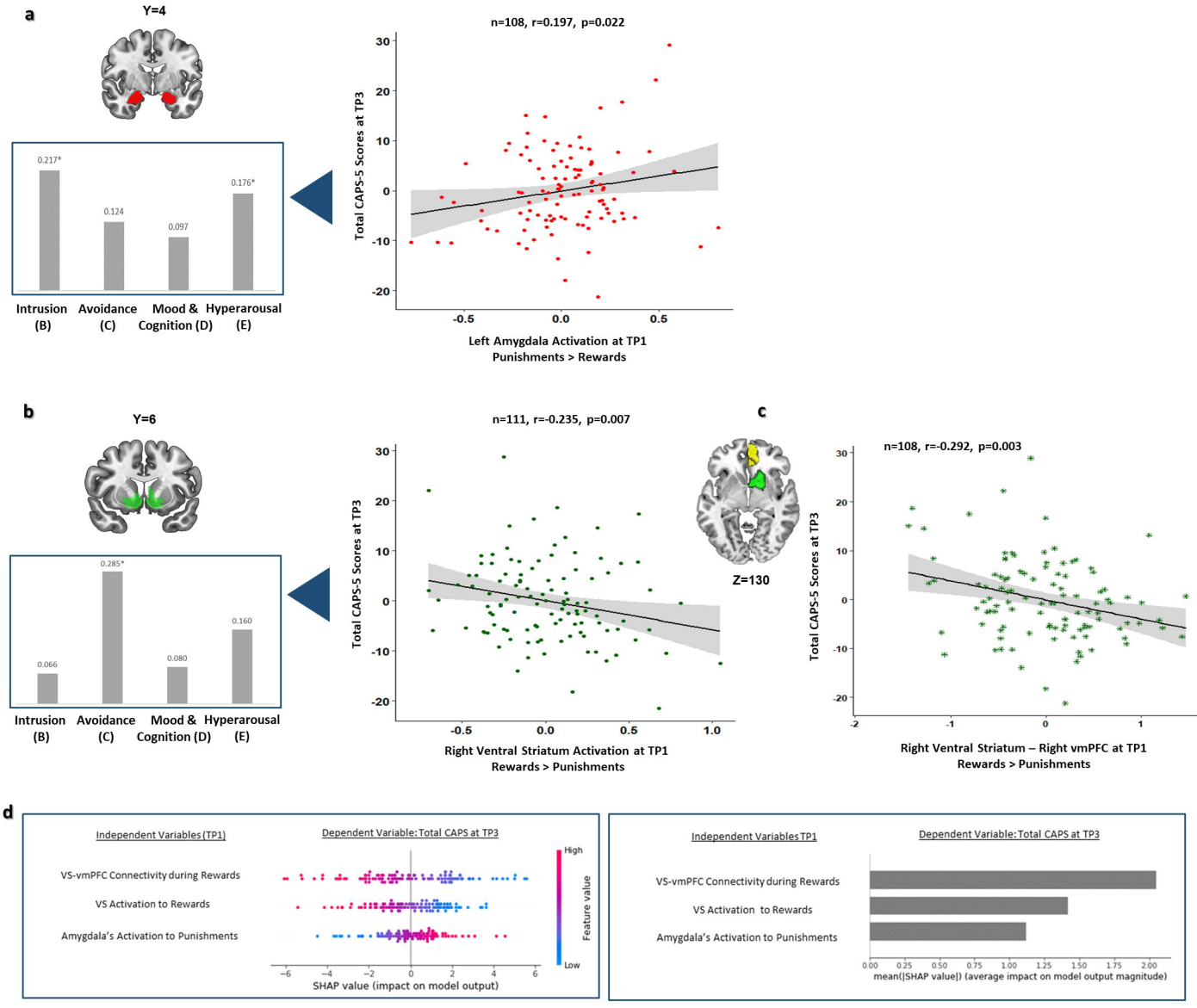
b

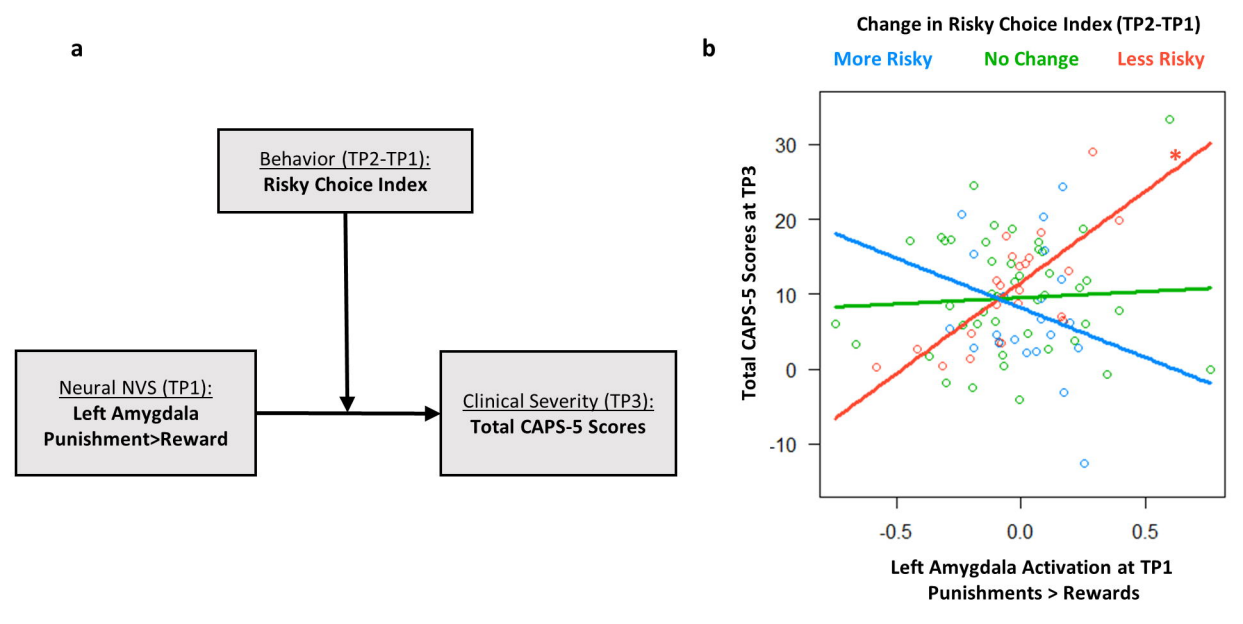

Y=6


n=131, r=0.022, p=0.401
Total CAPS-5 Scores at TP1
Left Ventral Striatum Activation at TP1
Rewards > Punishments


n=131, r=0.048, p=0.297
Total CAPS-5 Scores at TP1
Right Ventral Striatum Activation at TP1
Rewards > Punishments


a
t=2.833, p=0.006
Risky Choice Index at TP1 (%)
80
60
40
20
0
No PTSD
(n=35)
PTSD
(n=97)
b
Risky Choice Index (%) = # non matching chips / (# non matching chips + # matching chips) * 100
0.212*
0.244*
0.111
0.117
Intrusion
(B)
Avoidance
(C)
Mood &
Cognition (D)
Hyperarousal
(E)
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 (%)


a
Y=4
0.217*
0.124
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
0.066
0.285*
0.080
0.160
Intrusion (B)
Avoidance (C)
Mood & Cognition (D)
Hyperarousal (E)
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)


a
Behavior (TP2-TP1):
Risky Choice Index
Neural NVS (TP1):
Left Amygdala
Punishment>Reward
Clinical Severity (TP3):
Total CAPS-5 Scores
b
Change in Risky Choice Index (TP2-TP1)
More Risky
No Change
Less Risky
Total CAPS-5 Scores at TP3
30
20
10
0
-10
*
-0.5
0.0
0.5
Left Amygdala Activation at TP1
Punishments > Rewards