Blunted Ventral Striatum Development in Adolescence Reflects Emotional Neglect and Predicts Depressive Symptoms

Supplemental Information

Study Procedures and Sample Description

Participants for this work were drawn from the Teen Alcohol Outcomes Study (TAOS) at the University of Texas Health Science Center at San Antonio (UTHSCSA). This project recruited 331 adolescents, age 11 to 15 years (age range at scan 1 = 11.88-15.45 years of age) in order to understand how genes, the environment, and neurobiology contribute to risk for psychopathology, with an emphasis on depression and alcohol use disorders. Participants with a family history of major depressive disorder (MDD), which is associated with increased risk for MDD and substance use disorders (1; 2), were over-sampled. For additional demographics, see Tables S1 and S2.

Participants with both a first- and second-degree relative with a history of MDD were classified as high risk (HR; *n* = 163 in the full TAOS sample; 59 HR in the analyses detailed in the main manuscript), and those with no first- or second-degree relatives with a history of MDD as low risk (LR; *n* = 168 in the full TAOS sample; 47 LR in the analyses detailed in the main manuscript). Sampling and recruitment procedures for TAOS are available in greater detail elsewhere (3-5). Written informed consent was first obtained from parents and then adolescent participants provided assent after being explained all study procedures in accordance with UTHSCSA's Institutional Review Board.

After providing consent/assent, participants without MRI contraindications (e.g., braces) completed in-person interviews, self-report behavioral assessments, a blood draw, and MRI scanning. Additional inclusion criteria required that participants be free of psychopathology, with the exception of an anxiety disorder diagnosis, at the baseline assessment. Diagnoses were assessed using the Schedule for Affective Disorders and Schizophrenia for School-Age

Children Present and Lifetime Version (KSADS-PL (6)). Participants were re-contacted annually to complete diagnostic interviews and questionnaires, and also underwent a follow-up MRI scanning session during the third wave of data collection. A small portion (16%) completed the second MRI scanning session at the fourth wave of data collection. Mean time between first and second scan was 2.09 years (SD = .37; range = 1.32-3.13 years; age range at scan 2 = 13.77-18.25 years of age).

Ventral Striatum (VS) Activity Paradigm

As described previously (7;8), all participants completed an fMRI card-guessing paradigm that consisted of three blocks each of predominantly positive feedback (80% correct guess), predominantly negative feedback (20% correct guess), and no feedback. Each block contained five trials and during each task trial, participants had 3000 milliseconds to guess, via button press, whether the value of a yet-to-be-presented card was lower or higher than 5. Responses were made via the index and middle finger, respectively. After each participant's response, the numerical value of the card was presented for 500 milliseconds and followed by outcome feedback (green upward-facing arrow for positive feedback; red downward-facing arrow for negative feedback) for an additional 500 milliseconds. A crosshair was then presented for 3000 milliseconds, for a total trial length of 7000 milliseconds. For the control blocks, participants were instructed to simply make button presses during the presentation of an "x" (3000 milliseconds), which was then followed by an asterisk (500 milliseconds) and a yellow circle (500 milliseconds). Each block was preceded by an instruction of "Guess Number" (positive or negative feedback blocks) or "Press Button" (control blocks) for 2000 milliseconds resulting in a total block length of 3800 milliseconds (38 seconds) and a total task length of 34200 milliseconds (342 seconds). To ensure that only participants who were actively engaged in the task and understood the experiment's instructions were included in analyses, participants were excluded if their mean % of feedback was <60% (for either positive or negative feedback). This

also made certain that similar numbers of trials for feedback type went into each fMRI parameter estimate.

MRI Acquisition

Structural MRI data were acquired with a T1-weighted MPRAGE sequence, with the following parameters: TR = 2200 milliseconds, TE = 2.8 milliseconds, slice thickness = 0.8 centimeters, and FOV = 256 millimeters. Functional (BOLD) MRI images were acquired using a gradient echo, echo planar imaging sequence with the following parameters: TR = 2000 milliseconds, TE = 25 milliseconds, FOV = 192 millimeters, matrix = 64 x 64, 34 slices, and a slice thickness = 3 centimeters.

BOLD fMRI Data Preprocessing

Functional data for each participant were realigned to the first volume in the time series to correct for head motion, spatially normalized into a standard stereotactic space (Montreal Neurological Institute (MNI) template) using a 12-parameter affine model (final resolution of functional images = 2 mm isotropic voxels), and smoothed with a 6-mm full-width half-maximum Gaussian filter. Voxel-wise signal intensities were ratio normalized to the whole-brain global mean.

Variability in single-subject whole-brain functional volumes was determined using the Artifact Recognition Toolbox (ART; http://www.nitrc.org/projects/artifact_detect). Individual whole-brain BOLD fMRI volumes were censored in first order models if 1) significant mean-volume signal intensity variation (i.e., within volume mean signal greater or less than 4 standard deviations of mean signal of all volumes in the time series), and 2) individual volumes where scan-to-scan movement exceeded 2 mm translation or 2-degree rotation in any direction. Participants with > 5% censored fMRI volumes were excluded from all analyses.

To deal with potential MR susceptibility artifacts and signal dropout, we employed a custom MATLAB script to check VS coverage. In brief, this script searched for the presence of signal in all voxels within a pre-defined anatomical region of interest (ROI) comprising the VS (two 10 mm spheres centered around ±12 12 -10, MNI coordinates) and output the percentage of non-missing voxel intensities within that volume for each individual participant. As detailed in and similar to Ref. (8), a coverage threshold of 90% of (non-missing VS) voxels was employed as an inclusion criteria for all participants' imaging scans. Of important note, this script used values reflecting the raw intensity of the signal recorded from voxels within the anatomical region of interest, which is completely independent from any specific task contrast.

For our second-level whole-brain analysis, correction for multiple comparisons was conducted with cluster-size thresholding based on Monte Carlo simulation using AFNI's 3dClustStim. Based on an initial (uncorrected) statistical threshold of $p = 0.005$, the number of comparisons in our imaging volume and the smoothness of our imaging data, a minimum cluster size of 189 voxels was required to yield a corrected $p \leq 0.05$.

Stringent, Multilevel Quality Control Procedures

As noted above, participant's imaging data were excluded based on behavioral performance and imaging artifacts (large signal intensity variations as detected by ART, participant motion, or inadequate VS coverage). Across both imaging sessions, fifty-nine participants were excluded for inadequate behavioral responding (42 participants at Scan 1; 17 participants at Scan 2). Using dummy coding (for behavioral responding, included = 0, excluded = 1) and chi-square testing, we found this exclusionary criterion was equal across sex (for Scan 1: $\chi^2 = 1.96$, $p = 0.16$; for Scan 2: $\chi^2 = 1.33$, $p = 0.25$) and our risk groups (for Scan 1: $\chi^2 = 0.04$, $p = 0.84$; for Scan 2: $\chi^2 = 0$, $p = 1$). Using linear regression models where exclusion was dummy-coded (included = 0, excluded = 1), we found no relationship between this exclusionary criterion and

Childhood Trauma Questionnaire (CTQ) emotional neglect (EN) scores (for Scan 1: $p = 0.452$; for Scan 2: $p = 0.488$).

One-hundred and eleven participants (70 participants at Scan 1; 41 participants at Scan 2) had > 5% volumes flagged by ART (due to motion or extreme signal intensity values) and were also excluded. Using dummy coding (for ART censoring, included = 0, excluded = 1) and chi-square testing, we found this exclusionary criterion was equal across sex (for Scan 1: $\chi^2 = 0.087$, $p = 0.76$; for Scan 2: $\chi^2 = 0.57$, $p = 0.44$) and risk-group status (for Scan 1: $\chi^2 = 2.2$, $p = 0.14$; for Scan 2: $\chi^2 = 0.14$, $p = 0.7$). Using linear regression models where exclusion was dummy-coded (included = 0, excluded = 1), we found no relationship between ART exclusion and CTQ EN scores (for Scan 1: $p = 0.18$; for Scan 2: $p = 0.14$). No subjects (after behavioral and ART exclusion) were removed due to VS coverage issues.

Statistical Analyses Using Non-Parametric Methods

Additional statistical testing was employed to 1) check for data normality and 2) to deal with potential outliers for the relationships reported in the main manuscript. First, residuals from our regression models were subject to Shapiro-Wilk tests to examine normality. Residuals from the model examining changes in VS activity in relation to EN was normally distributed ($W = 0.9$, $p = 0.9$), as where residuals for the model examining changes in VS activity in relation to depressive symptoms ($W = 0.9$, $p = 0.8$). Second, robust regression models were also constructed examining changes in VS activity, EN, and depressive symptoms. These (and all other) robust regression models employed fast MM-estimation using the “lmrob” function from the “robust” package in the R environment (settings: max iterations of 50 reweighted least squares estimation; tuning chi of 1.54764, tuning psi of 4.685061).

Similar to the main manuscript, change in VS activity was measured by the residuals for a linear regression model (with Scan 2 as the dependent variable and VS activity for positive >

negative feedback for Scan 1 as the independent variable; reflecting the difference between observed VS activity and predicted scores for Scan 2). These non-parametric (robust regression) tests yielded similar statistics to the linear regression models detailed in the main manuscript. Change in VS activity was related to EN (β = -0.016, standard error (SE) = 0.005, t = -2.99, p = 0.003). Change in VS activity was also related to depressive symptoms at Scan 2 (β = -0.0068, SE = 0.0016, t = -4.319, p < 0.001).

Supplemental analyses were completed to confirm that subjects with extreme depression symptoms were not driving this basic relationship. Again, change in VS was operationalized as the residuals for a linear regression model with Scan 2 as the dependent variable and VS activity for positive > negative feedback for Scan 1 as the independent variable. Removing 5 participants with MFQ scores greater than 20, the relationship between VS change and depressive symptoms remains significant (robust regression β = -0.0088, SE = 0.003, t = -2.258, p = 0.026; scatterplot shown in Figure S1).

Analyses Employing Difference Scores of Activity

We conducted supplementary analyses using a difference score of VS activity, as opposed to a residualized change score, to index developmental changes in activity. For such investigations, Time 1 VS activity values (for positive > negative feedback) were subtracted from Time 2 VS activity (for positive > negative feedback). Larger values would therefore reflect a greater response to reward at Time 2. Looking at the relationship between this difference score and EN, we see a similar pattern to analyses using residualized change scores, with lower difference scores being related to greater exposure to EN (β = -0.193, p = 0.048; shown in Figure S2). Robust regression techniques with these variables found similar patterns (β = -0.014008, SE = 0.006851, t = -2.045, p = 0.04).

Turning to associations between this difference score and symptoms of depression at Scan 2, we again found similar effects to those obtained when using residualized change

scores. Lower change scores were related to greater symptoms of depression as reported on the MFQ (β = -0.227, p = 0.01; shown in Figure S3). These patterns remained consistent when using robust regression estimate techniques (β = -4.68, SE = 2.171, t = -2.157, p = 0.033). Employing statistical models similar to those discussed in the main manuscript, we found support for change in VS activity (as indexed by a difference score) mediating the relationship between EN and symptoms of depression (variance mediated by the VS = 0.13315; 95% confidence interval = 0.00209-1.05314, p = 0.05).

Statistical Analyses (Related to Potential Sex Differences)

Motivated by past reports of sex differences in the emergence of depression (9), we conducted exploratory analyses related to potential moderation of our effects by sex. Using regression models similar to those detailed in the main manuscript, we found the interaction of sex (as a dummy-coded factor) and emotional neglect was not related to VS change (as indexed by residualized VS change score p = 0.85 or a subtraction difference score of VS activity p = .9). Similarly, the interaction of sex and VS change was not related to depression symptoms (p = 0.3). Splitting the sample up into separate groups by sex, male and female participants had similar patterns of associations between EN, VS activity change, and depression (paralleling reports from the full sample). The correlation between EN and VS activity change did not differ for males versus females (for residual VS change score p = .6, for a subtraction difference score of VS activity p = .99). In relation to differences by sex, males and females did not differ on VS activity at Scan 1 (p = 0.98), Scan 2 (p = 0.32), residualized VS change (p = 0.32), VS difference (subtraction) score (p = 0.43), or levels of emotional neglect (p = .88).

Statistical Analyses (Related to Familial Risk)

In line with past longitudinal neuroimaging research (10;11), linear mixed effect models were used to examine group differences in relation to familial risk status (e.g., having a first-degree

relative with a history of major depressive disorder). These models permit nesting of repeated measurements within subjects, allow for differences in the intervals of data collection, and can test effects of age rather than effect of wave. To test the hypothesis that the HR and LR groups differed in VS activity, a main effect of group, a main effect of age, and an age x risk group interaction were tested. The mixed linear effect model containing the age x risk group interaction did not provide a significantly better fit to the data relative to a null model with no predictors, $\chi^2(3, n = 366) = 1.083$, $p = 0.781$. Overall, these analyses indicated that there was not a significant main effect of risk group ($F_{(1,258)} = 0.057$, $p = .811$) or an age x risk group interaction for VS activity ($F_{(1,104)} = 0.049$, $p = .824$).

Analyses also examined whether levels of EN differed between groups; to test this possibility, linear regression models were constructed with EN as the dependent variable and risk group as the independent variables. Examination of these statistical models indicated no differences in levels of EN as a function of familial risk (Group $\beta = -0.019$, $t = -0.196$, $p = 0.845$). While past research has found lower reward brain activity in children and adolescents with a paternal history of depression (12;13), these previous reports have employed experimental paradigms with a number of important differences. First, these other research groups have deployed reward tasks with both anticipation and receipt of reward. The current work employed a block-design with only a receipt of reward phase. In addition, these past reports have employed event-related fMRI experiments with win, loss, and no-change events. Our work focused specifically on win versus loss conditions (positive versus negative feedback blocks). These variations likely contribute to the divergence in results.

Also of note, the most consistent findings across the prior work of Gotlib *et al.* and Forbes *et al.* appear to be differences in VS activation for high-risk participants during reward anticipation, which we were not able to investigate in the current study. The relationship between risk status and VS activity during receipt of rewards may be more complex. A recent investigation by Forbes *et al.* did not find a relationship between parental history and VS

activation during reward outcomes; instead, VS activation during reward outcome was related to the interaction of parental history (of depression) and self-reported levels of maternal warmth during development (14).

Statistical Analyses Focused on Recent Stressful Life Events

With a large body of research finding relationships between recent stressful events and depression (15;16), we examined the influence of recent stressful life events and the interaction between recent stress and EN on symptoms of VS reward activity. Recent stressful events were assessed using the Stressful Life Events Schedule (SLES) (17). For this measure, adolescent participants were interviewed regarding the occurrence of life events during the prior year. Each event was given a subjective rating of threat by the participant, as well as an objective rating by trained independent raters. This measure was collected at both baseline and second scanning sessions.

To interrogate potential relationships between VS activity, recent stress, and depression, we examined change in VS from Scan 1 to Scan 2 in relation to recent stressful life events. First, similar to the main manuscript, linear regression models were constructed with VS activity for positive>negative feedback for Scan 2 as the dependent variable and VS activity for positive>negative feedback for Scan 1 as the independent variable. Residuals for this model (the difference between observed VS activity and predicted scores for Scan 2) were our measure of VS change over time. Next, regression models were constructed with change in VS activity entered as the dependent variable and the CTQ EN subscale, the subjective subscale of the SLES, and the interaction of the two entered as dependent variables; two models were composed for SLES scores (one for Scan 1 recent stressful life events and another for Scan 2 recent stressful life events). These analyses found no association for change in VS and recent stressful life events (Scan 1 SLES $p = 0.29$; Scan 2 SLES $p = 0.45$). The interaction between

EN and recent life stress was also not related to VS activity at Scan 1 (p = 0.21) or Scan 2 (p = 0.12).

This result was slightly unexpected given that our group (8) has found recent life stress interacts with VS activity to predict self-reported state positive affect. However, the relationship between reward functioning and recent stress exposure may be more complex. First, differences may be due to the heterogeneity of stress in adolescence, with the types and magnitude of stressful events changing greatly during this developmental transition (18). Second, stress may impact the brain responses to aspects of reward that we are unable to probe with the current paradigm, as our task design only examined the receipt of reward (and not anticipation). Finally, recent work from Forbes' group did not find an association between life stress in adolescence and early adult reward-related VS activity (19). This research group instead found life stress was associated with brain activity in the mPFC. Future work employing broader probes of reward responding (both in regards to different psychological facets and different brain areas of interest) could clarify these inconsistencies.

Analyses Examining Other Forms of Child Trauma

Based on past work (3;4) from our laboratory, we focused on the EN subscale of the Childhood Trauma Questionnaire. We however conducted preliminary analyses examining reward-activity and other subscales and total summed score of this questionnaire (including physical abuse, sexual abuse, and physical neglect). The observed means and distributions of the CTQ were in line with previous reports (20;21). For the CTQ total scores, the mean was 31.51 (SD = 5.57, range = 25-54). Mean scores were highest for EN (mean = 7.716; SD = 2.68, range = 5-18). The means for other subscales were as follows: emotional abuse: 6.82 (SD = 2.1; range = 5-14.5), physical abuse: 5.92 (SD = 1.49; range = 5-15), sexual abuse: 5.15 (SD = 1.07; range = 5-15.5), and physical neglect: 5.89 (SD = 1.05; range = 5-9.5).

Bivariate correlations revealed no relationship between changes in VS activity for CTQ total score (r = -0.075, p = .44), emotional abuse (r = 0.072, p = 0.46), physical abuse (r = -0.013, p = 0.8), sexual abuse (r = -0.018, p = 0.85), or physical neglect (r = 0.13, p = 0.2). Such results may be in part due to the lower mean and reduced variability present within these subscales (compared to the EN subscale). Looking at difference scores (as opposed to a residualized change score), similar non-significant results were found between CTQ total score (p = 0.11) and other forms of trauma and VS change (emotional abuse p = 0.22; physical abuse p = .11; sexual abuse p = 0.6; physical neglect p = 0.35).

Controls for Additional Potential Confounds

Additional analyses were conducted to rule out the influence of other potential confounds not considered in analyses in the main manuscript. Controlling for all other subscales of the CTQ, the relationship between EN and changes in VS activity remains significant (β = -0.359, p = 0.001). Turning to mediation models, path analyses tested whether EN (X) was associated with depressive symptomatology (Y) and whether the observed association was mediated by changes in VS activity (M). These were similar to the main manuscript, but included other CTQ subscales (i.e., emotional abuse, sexual abuse, physical abuse, physical neglect), recent stressful life events (as indexed by the SLES at Scan 1 and Scan 2) and familial risk (parental history of MDD). Results remained significant when controlling for these factors (variance mediated by the VS = 0.18635; 95% confidence interval = 0.0104-0.853, p = 0.04).

Exploratory Alternative Mediation Analyses

With our current study design, we were able to examine potential alternative explanatory pathways (i.e., do changes in depressive symptoms predict VS activation at time 2). To these ends, we first calculated change for depressive symptoms based on a linear regression, with MFQ at scan 2 entered as the dependent variable and MFQ at scan 1 entered as the

independent variable. Residuals for this model were saved and then used as an independent variable (along with age at scan 1 and scan 2 and sex) in a separate regression model with VS activity at Scan 2 entered as the dependent variable. In line with previous investigations, change in depression was related to VS activity at Time 2 (β = -0.286, $p < .005$). We also constructed mediation models to test whether EN (X) was associated with VS activity at Scan 2 (Y) and whether changes in depressive symptomatology mediated this relationship (M). No evidence however was found for change in depression as a potential mediator ($p > .21$; variance mediated by the change in depression = 0.226664; 95% confidence interval = -0.150653-0.927402).

Evaluating Potential Influences of Puberty on Reported Effects

To examine the potential confounding effects of pubertal maturation, we used data collected via adolescents' reports on the Pubertal Development Drawings (22). This self-report measure utilizes drawings based on Tanner's stages of development and illustrates male genitalia, male pubic hair, female breasts, and female pubic hair. This instrument has been shown to correlate well with physician examinations of pubertal development (23). At initial scanning session, female participants rated themselves on genitalia/breast development and pubic hair growth and boys on their genitalia development and pubic hair growth. Ratings from each participant were then entered into a confirmatory factor analysis to yield one composite measure of puberty for each participant. This single component accounted for 84.78% of the measurement variables and was then used as a covariate in a series of analyses. In a regression model with VS entered as the dependent variable, and puberty, sex, and EN entered as the independent variables, the relationship between pubertal stage and change in VS was not significant (β = -0.089, $p = 0.36$). In these models, similar to the main manuscript, EN was significantly associated with VS change (β = -0.241, $p = 0.01$). Examining associations between depression symptoms at Scan 2 and VS change (with MFQ at Scan 2 entered as the dependent variable

and puberty, sex, and VS change entered as the independent variables), puberty was not related to depressive symptoms (β = -0.02, p = 0.76). Again, similar to the main manuscript, VS change was related to MFQ at Scan 2 (β = -0.24, p = 0.01). Employing similar mediation models to those detailed in our primary analyses (here controlling for pubertal development in place of age), non-parametric bootstrapped models indicated the change in VS activity significantly mediated the association between EN and depressive symptoms (p < 0.05).

Child Maltreatment and Anxiety Symptoms

Similar to analyses detailed in the main manuscript, we also examined whether changes in VS activity mediated the effects of EN on anxiety. Path analyses tested whether EN (X) was associated with anxiety symptomatology (Y) and whether the observed association was mediated by changes in VS activity (M). Age (at Scan 1 and Scan 2), time between scans, sex, depression symptoms (Scan 2 MFQ) and anxiety symptomatology (Scan 1 SCARED) were included as covariates. These analyses found no evidence for VS mediation for symptoms of anxiety at Scan 2 (p = 0.5).

Supplemental regression models were conducted to examine EN, recent stressful life events (at each neuroimaging time point), and the interaction of these two factors in relation to anxiety (measured at Scan 2). These analyses indicated that this form of early life stress, recent stressful life events, and the interaction of these two forms of adversity were not associated with anxiety symptoms. This was true for Scan 1 (SLES at Scan 1, β = -0.108, p = 0.28; EN β = 0.022, p = 0.819; Interaction β = 0.039, p = 0.186) and also Scan 2 (SLES at Scan 2, β = 0.023, p = 0.819; EN β = 0.04, p = 0.69; Interaction β = 0.08, p = 0.076).

Statistical Analyses Unpacking Differences in Positive and Negative Feedback

With past reports linking EN to alterations in negative affective responding, we examined whether there were differential relationships for the processing of positive or negative feedback

with our variables of interest (EN; symptoms of depression at Scan 2). For these analyses, the contrasts of positive feedback > control blocks and negative feedback > control blocks were extracted in SPM for each subject. Change in VS activity was measured by the residuals for a regression model. In this case, two new separate regression models were constructed: one for positive feedback > control blocks, one for negative feedback > control blocks. In each model, VS activity for that specific valence of feedback greater than control blocks for Scan 1 was entered as the independent variable, while VS activity for that specific valence of feedback greater than control blocks for Scan 2 was the dependent variable. The residuals of these models therefore reflected the difference between observed VS activity (for either positive feedback > control blocks or negative feedback > control blocks) and were used in bivariate correlations in relation to our variables of interest. These analyses indicated a significant relation for change in VS activity for positive feedback > control blocks for EN (r = -0.209, p = 0.03) and depressive symptoms at Scan 2 (r = -0.259, p = 0.007). Interestingly, the VS for negative feedback > control blocks was not related to EN (r = -0.049, p = 0.6) or depressive symptoms at Scan 2 (r = -0.14, p = 0.12). Scatterplots for these relationships are shown in Figure S4. Using a non-independent correlation calculator, the correlation between emotional neglect and positive feedback > control blocks was found to be significantly different from the correlation between emotional neglect and negative feedback > control blocks (t = -2.1; p = 0.04). The Fisher r-z transform was not employed for these analyses as these correlations were from the same sample and also highly correlated (r = 0.6).

Exploratory Analyses Focused on Additional Regions of Interest

In service of probing brain regions involved with reward processing but that did not reach statistical significance in the analyses detailed in the main manuscript, we isolated regions of interest from NeuroSynth (neurosynth.org), an automated brain-mapping platform that uses text-mining, meta-analysis and machine-learning techniques to generate a large database of

mappings between neural and cognitive states (24). A key benefit of this approach is the ability to quantitatively distinguish forward inference (given a known psychological manipulation, one can quantify the corresponding changes in brain activity) from reverse inference (given an observed pattern of activity, one can determine the associated cognitive states). Reverse inference maps of the term “reward” were thresholded at 20% of their range to identify regions commonly activated during neuroimaging studies of reward, yielding four additional brain regions of interest. These four regions of interest (the brainstem, the caudate, and 2 clusters in ventral prefrontal cortex, vPFC; all shown in Figure S5) were then investigated in relation to our variables of interest (EN; depressive symptoms at Scan 2). No significant relationships were found between EN and change in reward activity for these regions of interest, using either residualized or difference score measures (brainstem residualized change $\beta = -0.065$, $p = 0.5$, caudate residualized change $\beta = -0.09$, $p = 0.36$, vPFC cluster 1 residualized change $\beta = 0.02$, $p = 0.7$, vPFC cluster 2 residualized change $\beta = 0.05$, $p = 0.58$, brainstem difference score $\beta = -0.10$, $p = 0.3$, caudate difference score $\beta = -0.08$, $p = 0.39$, vPFC cluster 1 difference score $\beta = 0.09$, $p = 0.34$, vPFC cluster 2 difference score $\beta = -0.12$, $p = 0.2$). Similarly, no significant relationships emerged between symptoms of depression and change in reward activity for these areas (brainstem residualized change $\beta = -0.092$, $p = 0.3$, caudate residualized change $\beta = -0.12$, $p = 0.21$, vPFC cluster 1 residualized change $\beta = 0.09$, $p = 0.3$, vPFC cluster 2 residualized change $\beta = 0.06$, $p = 0.5$, brainstem difference score $\beta = -0.03$, $p = 0.7$, caudate difference score $\beta = -0.04$, $p = 0.6$, vPFC cluster 1 difference score $\beta = 0.04$, $p = 0.6$, vPFC cluster 2 difference score $\beta = -0.01$, $p = 0.9$).

Exploratory Analyses Focused on Task-Based Connectivity

To more fully understand potential circuit-level interactions during reward processing, we examined task-based functional connectivity between the VS and the regions identified above by NeuroSynth (the brainstem, the caudate, and 2 clusters in vPFC) using the generalized

psychophysiological interaction (PPI) toolbox (25) in SPM. For these analyses, deconvolved time courses averaged across our VS region of interest (from our canonical task-based analyses) were extracted for each subject and entered into first-level statistical models that included a psychological regressor corresponding to positive feedback > negative feedback for the cards tasks detailed in the main manuscript, as well as the psychophysiological interaction term. Mean functional connectivity estimates were then extracted for four regions of interest for use outside of SPM. Four separate linear regression models were then constructed in R with PPI between the VS and each region of interest for Scan 2 as the dependent variable and VS-ROI PPI for Scan 1 as the independent variable. Residuals for this model (the difference between observed connectivity and predicted scores for Scan 2) were then examined in relation to our variables of interest (emotional neglect; depressive symptoms at Scan 2). Using these statistical models, we found no relationships between emotional neglect and change in functional connectivity between the VS and the brainstem ($\beta = -0.09$, $p = 0.33$), the caudate ($\beta = 0.02$, $p = 0.83$), and 2 clusters in vPFC (Cluster 1 $\beta = -0.05$, $p = 0.6$, Cluster 2 $\beta = 0.05$, $p = 0.57$). Similarly, there was no significant association between symptoms of depression at Scan 2 and change in functional connectivity between the VS and the brainstem ($\beta = -0.16$, $p = 0.11$), the caudate ($\beta = -0.04$, $p = 0.66$), and 2 clusters in vPFC (Cluster 1 $\beta = -0.10$, $p = 0.3$, Cluster 2 $\beta = -0.05$, $p = 0.6$).

Finally, motivated by a growing body of work showing the importance of amygdala-striatal interactions after stress exposure (26), we examined task-based functional connectivity between the VS and the amygdala. Similar to our other PPI analyses, mean functional connectivity estimates were extracted from masks of the left and right basolateral amygdala (BLA; from (27)). Past research has demonstrated differences in functional connectivity between BLA and central/medial amygdala ROIs using similar neuroimaging acquisition and processing parameters (27). Once PPI parameters were extracted for each BLA ROI, linear regression models were constructed with VS-BLA PPI (for left or right subregions) for Scan 2 as the

dependent variable and VS-BLA for Scan 1 as the independent variable. Residuals for this model (the difference between observed connectivity and predicted scores for Scan 2) were then examined in relation to our variables of interest (emotional neglect; depressive symptoms at Scan 2). Using linear regression models, we found a relationship between emotional neglect and change in VS-BLA connectivity, with greater emotional neglect being related to lower change (and potentially negative) coupling between the two regions (VS-Left BLA β = -0.223, t = -2.260, p = 0.026; VS-Right BLA β = -0.218, t = -2.19, p = 0.03; Figure S6). There was however no relationship between symptoms of depression at Scan 2 and change in VS-BLA connectivity (VS-Left BLA β = -0.169, t = -1.687, p = 0.094; VS-Right BLA β = -0.009, t = 0.09, p = 0.928). This effect was specific to connectivity between the VS and BLA subregion as there were no differences in connectivity between the VS and central nucleus of the amygdala (CeA), which is primarily responsible for driving autonomic changes in arousal (VS-Left CeA β = -0.06, t = -0.596, p = 0.552; VS-Right CeA β = 0.015, t = -0.151, p = 0.880).

These findings connect to recent research focused on the divergent signaling of corticolimbic and corticostriatal circuits in relation to negative mental health outcomes. For example, our research group recently demonstrated in a large cohort of young adults that problem drinking in the context of stress was related to two distinct neural phenotypes: 1) a combination of relatively low reward-related VS activity and high threat-related activity of the amygdala; or 2) a combination of relatively high VS activity and low amygdala activity (28;29). Decreasing VS-BLA connectivity may be indexing one (or both) of these neural phenotypes. Alternatively, recent research examining functional connectivity between the amygdala and VS has found increased connectivity between these regions for highly relevant (compared to less relevant) stimuli (30). Related to ideas advanced in the main manuscript, rewards may take on less relevance for individuals who have experienced greater EN and this may be indexed by decreased VS-BLA connectivity. These differences, if replicated, have important implications for understanding the development of depression and other forms of mood dysregulation.

Table S1. Demographic Information for Participants With Any Imaging Data.

	High Risk (Mean +/- SD)	**Low Risk (Mean +/- SD)**	**Test Statistics**
Age in Years at Scan 1 (*n* = 187)	13.67 +/- 0.98	13.64 +/- 0.94	*t* = -.231, *p* = 0.81
Age in Years at Scan 2 (*n* = 179)	15.73 +/- 0.95	15.65 +/- 1.04	*t* = -.598, *p* = 0.55
Sex at Scan 1 (Male, Female)	51 M, 49 F	48 M, 39 F	χ^2 = 0.18, *p* = 0.67
Sex at Scan 2 (Male, Female)	44 M, 46 F	45 M, 44 F	χ^2 = 0.005, *p* = 0.94

Table S2. Demographic Information for Participants With Both Imaging Time Points.

	High Risk (*n* = 59)	**Low Risk (*n* = 47)**	**Test Statistics**
Sex (Male, Female)	28 M, 31 F	27 M, 20 F	$\chi^2 = 0.68$, $p = 0.4$
Race (White/Non-White)	34 W, 25 NW	31 W, 16 NW	$\chi^2 = 0.45$, $p = 0.5$
Age In Years at Scan 1 (Mean +/- SD)	13.77 +/- 0.95	13.55 +/- 0.94	$t = 1.1$, $p = 0.24$
Age In Years at Scan 2 (Mean +/- SD)	15.87 +/- 1.02	15.62 +/- 1.06	$t = 1.2$, $p = 0.22$
Time in Years Between Imaging Sessions	2.1 + / - 0.35	2.07 +/- 0.41	$t = 0.435$, $p = 0.66$

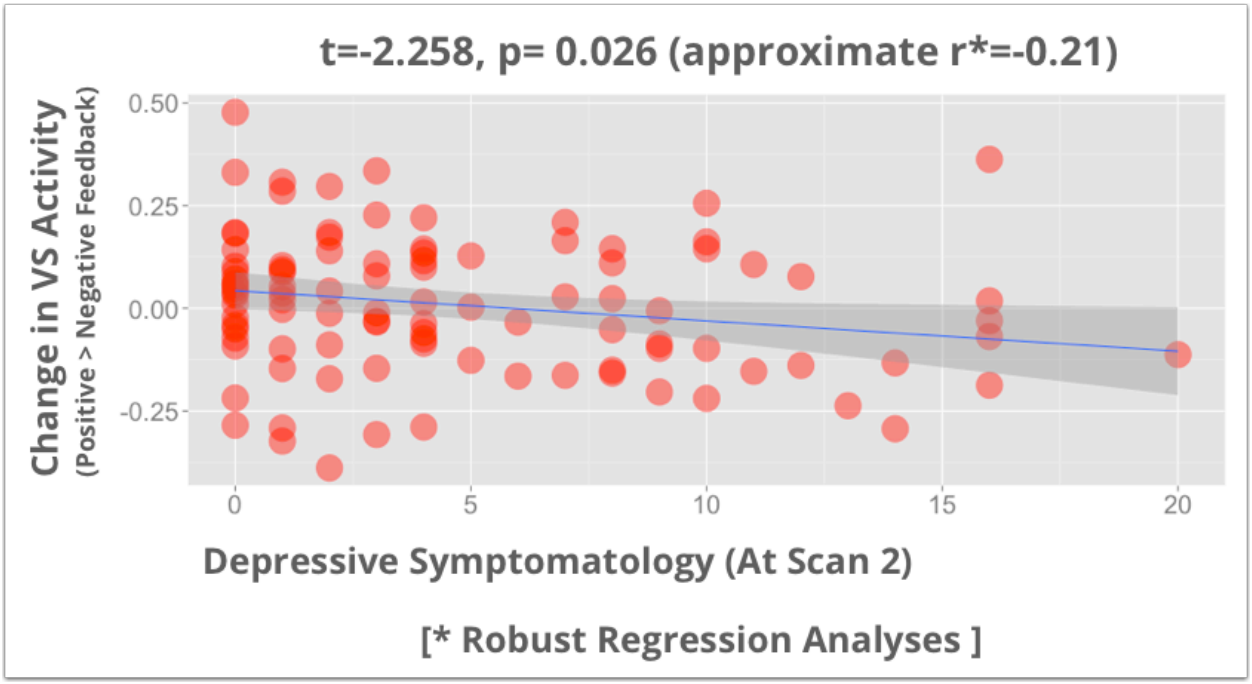

Figure S1. Scatterplot showing change in VS activity (vertical axis) and depressive symptoms at Scan 2 (horizontal axis) for a subsample of participants where depressive symptoms were ≤ 20 on the Mood and Feelings Questionnaire.

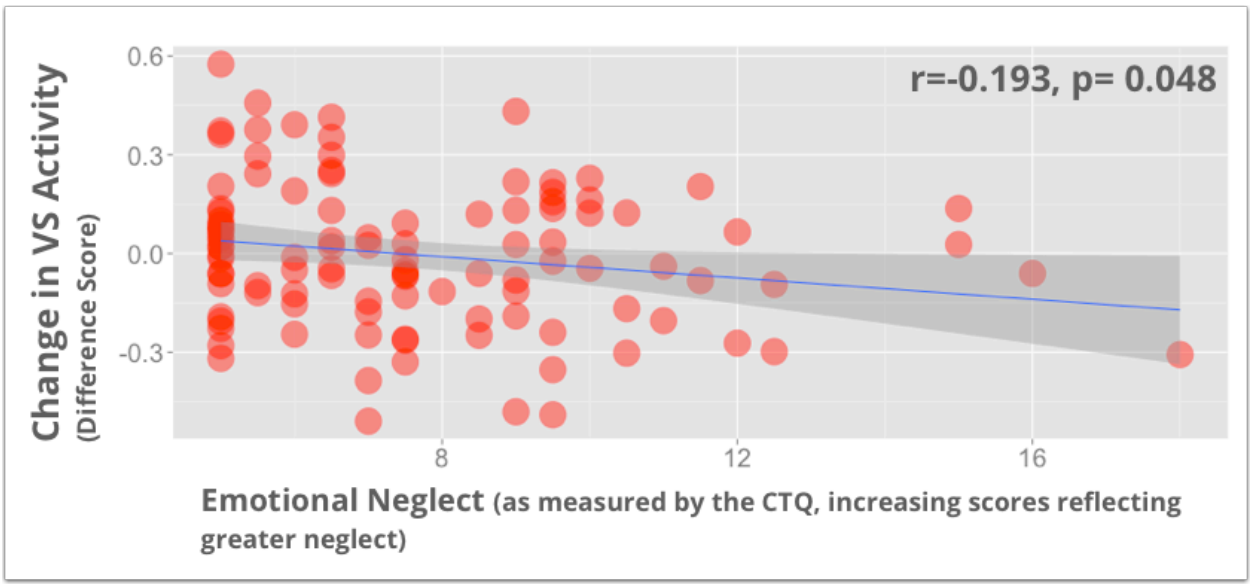

Figure S2. Scatterplot showing change in VS activity using a change score subtraction (vertical axis) and emotional neglect (horizontal axis).

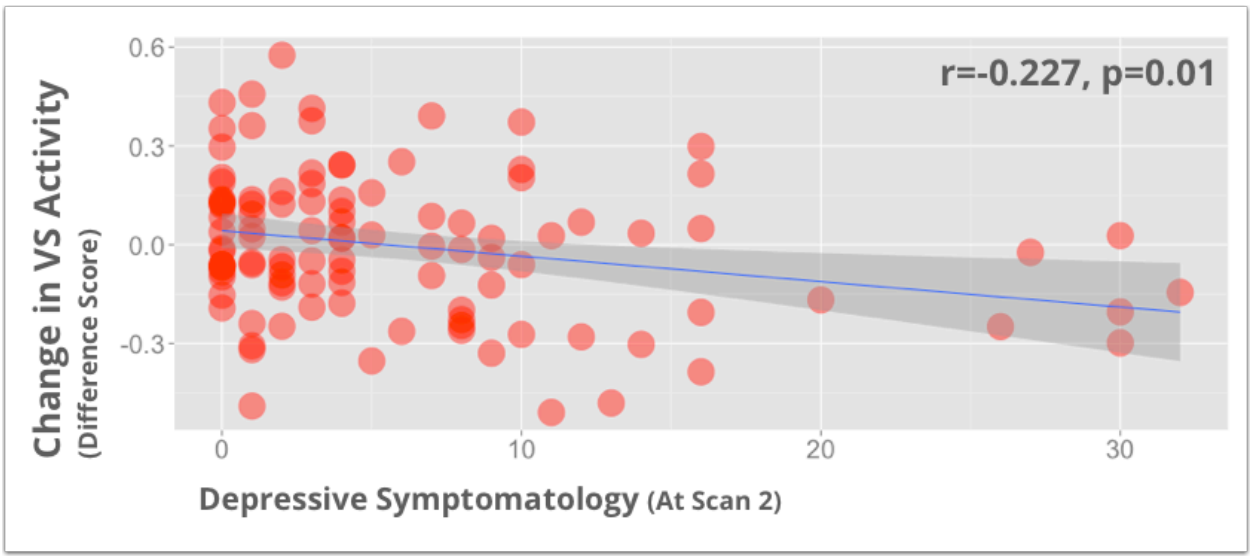

Figure S3. Scatterplot showing change in VS activity using a change score subtraction (vertical axis) and depressive symptoms at Scan 2 (horizontal axis).

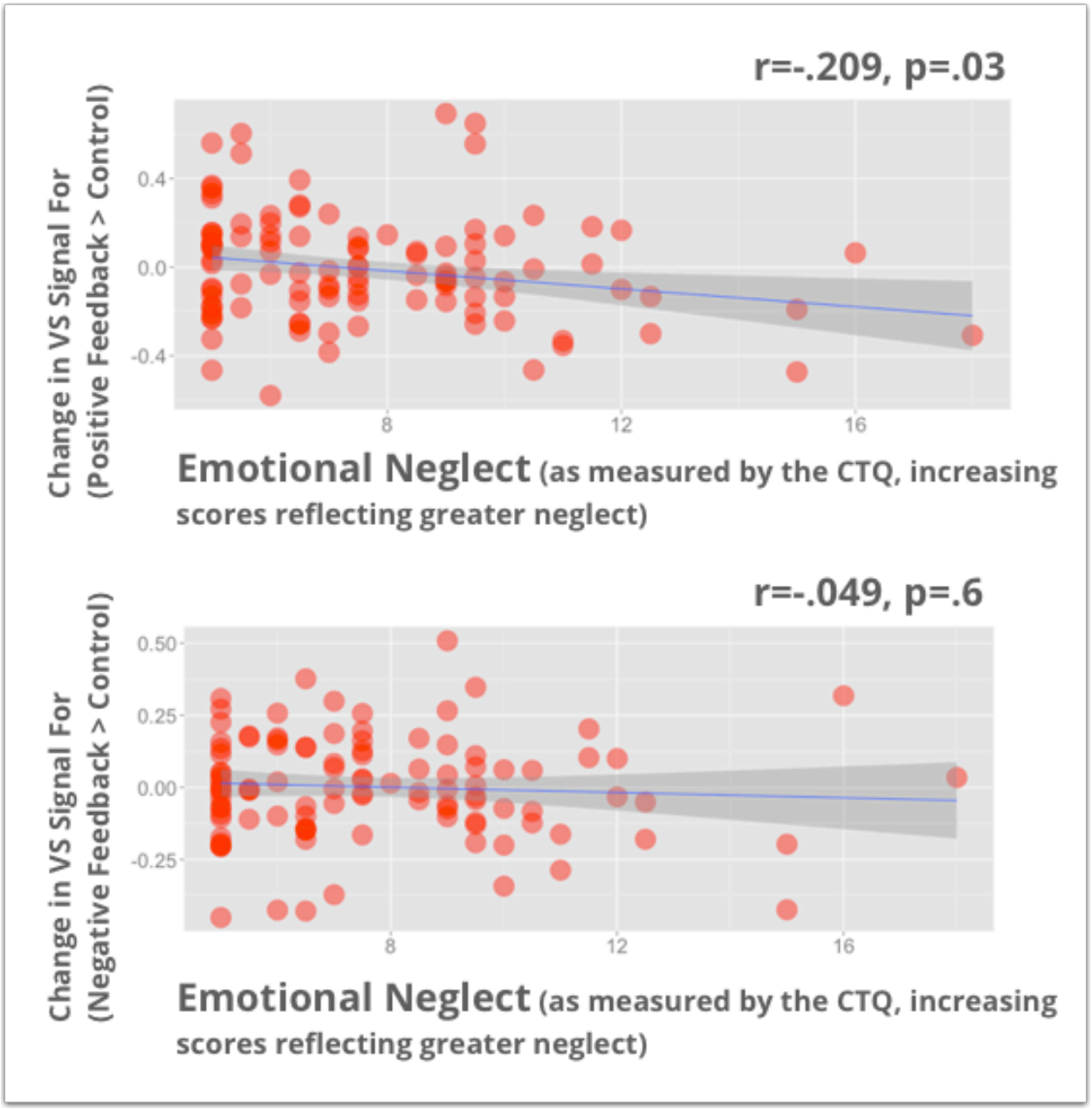

Figure S4. Scatterplots showing EN (horizontal axis; both panels) and change in VS activity (vertical axis in top panel for positive feedback > control blocks; vertical axis in bottom panel for negative feedback > control blocks).

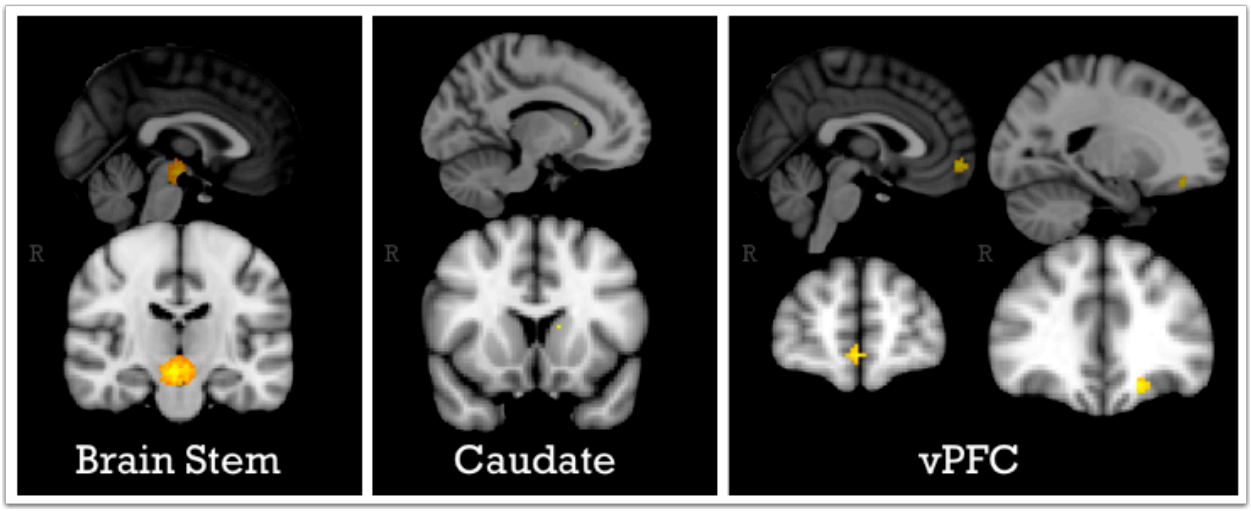

Figure S5. Additional brain areas examined in relation to our variables of interest. These four clusters (in three regions of interest) were isolated based on automated meta-analyses from NeuroSynth of “reward” (neurosynth.org)

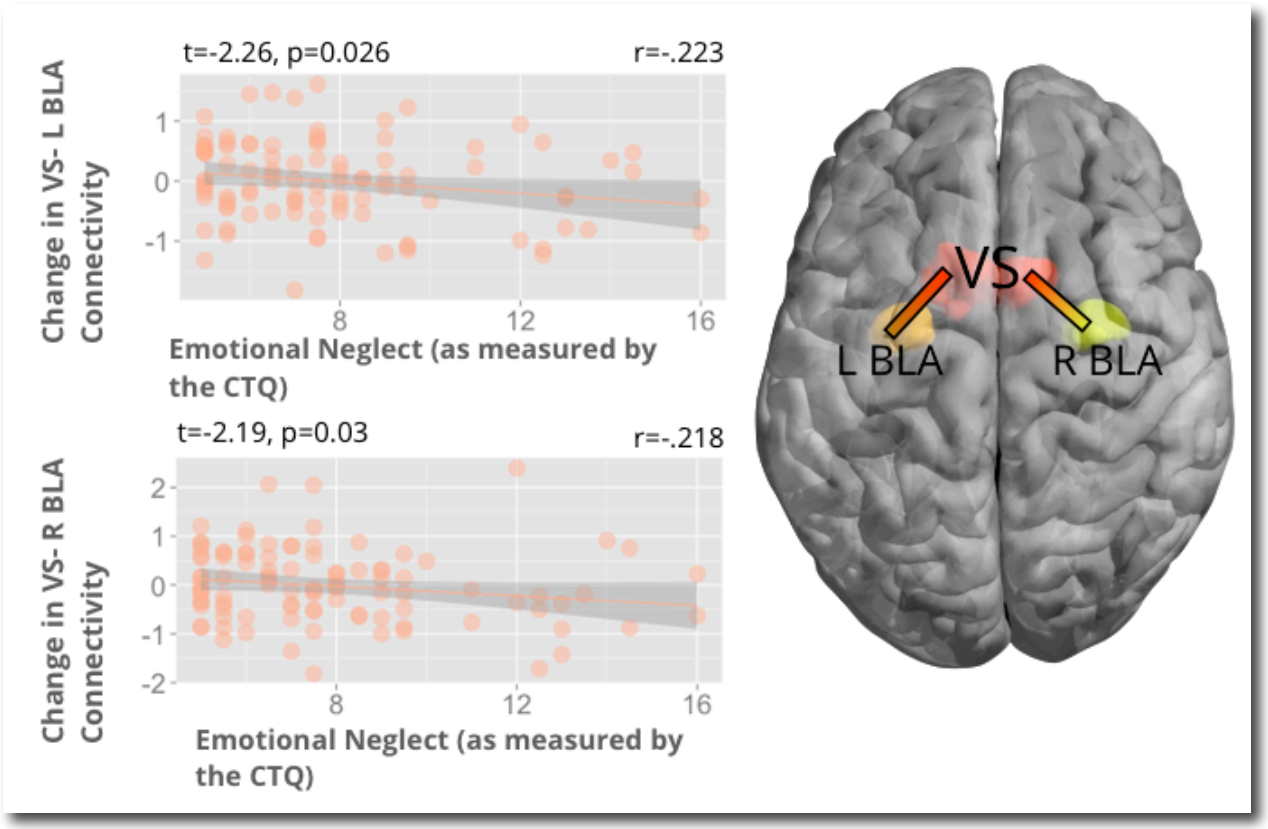

Figure S6. Data from psychophysiological interaction analyses between VS and basolateral portions of amygdala (BLA) activity. Scatterplots showing change in VS-BLA connectivity (vertical axis) and emotional neglect (horizontal axis) are shown for the left (top) and right amygdala (bottom), respectively.

Supplemental References

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