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Ventral Striatal Function Interacts With Positive and Negative Life Events to Predict Concurrent Youth Depressive Symptoms

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ABSTRACT

BACKGROUND: Life events and reward-system functioning contribute to resilience and risk for depression. However, interactions between life events and neural responses to reward and loss have not been previously investigated in relation to depression symptoms in child and adolescent populations.

METHODS: An unselected sample (N = 130) of 8- to 14-year-old girls (mean = 12.6 years) completed the Child Depression Inventory and a functional magnetic resonance imaging guessing task in which they won or lost money on each trial. Parents completed a measure of life events experienced by the child. Life events were separated by positive versus negative and whether they were likely related or unrelated to the daughter's behavior (i.e., dependent vs. independent, respectively). Multiple regressions tested whether the interaction between ventral striatal (VS) response to wins or losses and recent life events were associated with child-reported depressive symptoms.

RESULTS: A greater number of dependent positive life events related to decreased total depression symptoms when VS response to wins was robust. Conversely, a greater number of independent negative life events related to increased negative mood depression symptoms when VS response to losses was robust; this relationship was in the opposite direction when VS response to loss was low.

CONCLUSIONS: VS response to reward and loss were independent moderators of the relationship between recent life events (positive and negative, respectively) and depressive symptoms. Findings suggest that targeting neural responses (i.e., increasing responses to winning or decreasing responses to losing) may be important for both improving resilience and reducing risk in different environmental contexts.

Keywords: Adolescence, Depression, Loss, Positive events, Reward, Stress

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Exposure to different types of life events and neural response to rewards and losses are potent components of both depression risk and resilience. Environmental factors, including stressful life events and a lack of positive events, predict onset of depression (1) and relate to risk (2,3). Neural factors, including hyperresponsiveness to negative stimuli and hyporesponsiveness to positive stimuli, are also related to depression and are unique predictors of risk even in childhood and adolescence (4–6). Moreover, adverse early environments and stressful life events relate to decreased neural response to reward, suggesting a pathway linking these two sources of depression risk (7–9).

Despite these relationships, only a handful of studies have investigated whether neural responses to reward interact with life experiences to explain depressive symptoms. These studies suggest that adults showing reduced ventral striatal (VS) response to rewards versus losses are more vulnerable to the depressogenic effects of stress (10,11). However, given the focus in the literature on difference contrasts (e.g., positive vs. negative feedback) and stressful life events, it is unclear whether neural response to positive and negative feedback may interact with life events, both positive and negative, in different ways to affect liability for depression during late childhood and/or early adolescence. These are important questions given that responses within reward-related neural systems (12) and depressive pathology (13), particularly for female subjects, increase over adolescence (6); that changes in VS reward function may mediate relationships between early-life stress and adolescent depressive symptoms (14); and that blunted response to reward and enhanced response to loss show independent relationships with increased risk of depression in late childhood (6).

Diathesis-stress (15) and vantage-sensitivity (16) hypotheses are powerful frameworks for investigating how individual differences in biology might interact with the environment to predict mental health outcomes. These models hypothesize that some individuals (i.e., resilient or fixed) show normal mental health irrespective of their environment. Diathesis-stress frameworks typically highlight negative mental health outcomes for "vulnerable" individuals exposed to negative

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environments. Conversely, vantage-sensitivity frameworks emphasize the positive end of the spectrum, whereby certain individuals may show more positive outcomes in the context of a positive environment. In this study, we draw broadly on both diathesis-stress and vantage-sensitivity frameworks to make specific hypotheses regarding the differential effects of VS response to winning and losing on relationships between life events, both positive and negative, and girls' depressive symptoms during emerging adolescence.

Positive life experiences and environments, such as warm, positive parenting and close friendships, may be protective against depression (17), and emerging treatments for depression focus on increasing the frequency of positive experiences (18). Moreover, blunted striatal response to rewards, relative to response to losses or to control, is a key component of both adolescent depression and depression risk (19,20), and it prospectively predicts both the worsening of depressive symptoms (21,22) and the onset of major depressive disorder in previously healthy girls (5) during adolescence. Further, adolescents' experience of positive affect in their daily lives is related to striatal response to reward (23), suggesting a link between neural response to reward and the impact of positive daily experiences. These data raise the possibility that a robust neural response to reward may indicate the individuals who will show the greatest benefit from positive experiences, in terms of reduced depressive symptoms. This hypothesis is broadly consistent with vantage-sensitivity frameworks, but it differs in that low depressive symptoms are the proposed differential outcome of positive events, as opposed to an actively positive outcome, such as increased well-being (16). Given the increasing importance of social relationships in adolescence (24), we further hypothesize that positive events that are likely dependent on a girl's behavior (e.g., new friendship) will be more likely to relate to depressive symptoms than those that are likely independent of her behavior (e.g., parent getting a new job). As work in adults suggests that blunted response to reward versus loss is predicted by increased stress in early life (9), we will also test whether neural response to wins moderates effects of negative life events on depressive symptoms.

Negative and stressful life events often precede (1) and are strong predictors of (25–27) depressive disorders and episodes, but not all individuals exposed to adverse events develop depression (28). Rather, specific neurobiological systems appear to moderate the depressogenic effects of negative life events (29), with genetic profiles related to increased stress reactivity predicting greater depression in adverse environments (30,31). However, it is unclear whether adolescents with heightened neural response to negative feedback show stronger relationships between the experience of negative events and depressive symptoms, which would be consistent with the diathesis-stress framework. Also, it is unclear whether different types of negative life events—for example, those likely dependent on an individual's behavior (e.g., relationship problems) versus those independent of an individual's behavior (e.g., experiencing a natural disaster)—may interact with neural diatheses in different ways to predict concurrent depressive symptoms during emerging adolescence (1). For example, social interactions and relationships, which are more likely to be dependent on a girl's behavior, are of increasing importance in adolescence; however, uncontrollable stress, which is likely independent of a girl's behavior, is particularly related to depression (32). As such, we do not have specific hypotheses regarding whether negative dependent versus independent events may show interactions with neural diatheses to promote depressive symptoms. Further, given work in adults suggesting that blunted response to reward versus loss interacts with stressful life events to predict anhedonia (11) or reduced positive affect (10) and that blunted response to reward versus loss in adulthood is predicted by increased stress in early life (9), we will also test whether neural response to wins moderates the effects of negative life events on depressive symptoms.

The current study examines whether neural response to positive feedback (i.e., monetary wins) and negative feedback (i.e., monetary losses) moderates relationships between the number of recent life events—positive or negative and dependent or independent—and current depressive symptoms. Consistent with a diathesis-stress framework, we hypothesize that increased negative life events coupled with greater VS deactivation to loss will be associated with the greatest severity of depression symptoms. As previous studies in children have linked behavioral and/or neural reactivity to loss, specifically to negative mood symptoms, we expect loss moderations to be strongest for these symptoms in particular (6,33). We also hypothesize that, broadly consistent with a vantage-sensitivity framework, increased positive life events coupled with greater VS activation to wins will be associated with the least severity of depression symptoms. The converse moderations (e.g., neural response to wins moderating effects of negative life events) will also be tested, as the adult literature has focused primarily on the difference between response to reward and response to loss, meaning that it is unclear whether one side of the difference score is the stronger moderator. We further hypothesize that win and loss moderations will show independent relationships with depressive symptoms, suggesting that reactivity to positive and negative feedback interacts with specific types of life events to exert unique effects on depressive symptoms, rather than reflecting two ends of the same risk/resilience spectrum.

METHODS AND MATERIALS

Participants

One hundred ninety-eight female subjects 8 to 14 years of age (mean = 12.46 years, SD = 1.79 years) and their parents participated in the current neuroimaging study. This sample was drawn from a longitudinal study investigating relationships among pubertal development, neural correlates of reward, and emerging symptoms of depression in girls beginning in late childhood and/or early adolescence [for recruitment methods, see Speed *et al.* (34)]. Participants were excluded from the current analyses if questionnaire data were missing (n = 47; stress questionnaires were added after the study had begun) or if functional magnetic resonance imaging (fMRI) data were of insufficient quality (excessive motion, n = 5; scanner sequence or other mechanical error, n = 16). Thus, data from 130 of the original 198 participants are included in current analyses. The final sample consisted of subjects 8 to 14 years of age (mean = 12.56 years, SD = 1.82 years); 82.3% of subjects were Caucasian, 6.9% were African American, 3.1% were Hispanic, 3.8% identified as "Other," and 3.9% chose not to respond (white vs. nonwhite, with white coded as 1, is used as a covariate of no interest in regression analyses). Informed assent and consent were obtained from the participant and their parent, respectively, prior to participation. The Stony Brook University Institutional Review Board approved the research protocol.

Life Events Measure

Parents completed the Child and Adolescent Survey of Experiences (CASE) (35). The CASE is designed to mirror interview-based measures of recent life events (36), and parent reports on the CASE relate well to interview-based measures (35). The CASE comprises 38 common life events for children and adolescents. For each event, parents indicate whether their child experienced that event during the previous 12 months, whether it was good or bad, and what impact it had. Importantly, event types are not "good" or "bad" a priori. Instead, an event's valence is determined by the parent's report of their child's experience (e.g., moving to a new house may be a positive or negative event). CASE positive (CASE-P) is the sum of good events and CASE negative (CASE-N) is the sum of bad events. Events can be further divided into independent events likely unrelated to the girl's behavior (e.g., moving to a new house) and dependent events likely related to the girl's behavior (e.g., doing well on a project or test). See the Supplement for independent and dependent event types.

Symptom Measures

Depressive Symptoms. Girls reported on their current depressive symptoms using the Children's Depression Inventory–Child Version (CDIC) (37). Sums of all 27 items (CDIC total score), as well as those for the six negative mood items and eight anhedonia items, are used in the current analyses. Parents reported on their own current depressive symptoms using the Beck Depression Inventory (38), with the total score from all 21 Beck Depression Inventory items used in the current analyses. Higher mean scores on both measures indicate greater severity of symptoms.

Anxiety Symptoms. Girls reported on their anxiety symptom severity using the 41-item Screen for Child and Anxiety Related Emotional Disorders (39). A higher total score indicates increased severity of anxiety symptoms.

Pubertal Development Measure

Both parents and daughters completed the Pubertal Development Scale (40) to rate the daughter's pubertal development. The Pubertal Development Scale assesses changes in height, body hair, skin, and breast development, as well as menarche, with higher mean scores indicating more advanced puberty. As maternal and daughter reports were highly correlated ($r = .89$), the mean of parent and daughter reports is used in all analyses.

fMRI Task Design

The doors task, a monetary guessing task, was similar to versions used in previous studies (41). Participants were presented with two identical doors and instructed to select the left or right door by clicking the left or right mouse button. Participants were told they could either win \$0.50 or lose \$0.25 on each trial, depending on their selection, and that they would receive the total amount of their winnings at the end of the experiment. The order of feedback events was predetermined such that all participants received exactly 50% win and 50% loss feedback events (30 of each type) presented in a pseudorandom order.

First, the image of the doors was presented (3000 ms). After stimulus offset, a fixation cross (+) was presented (600 ms), followed by feedback (1000 ms); a green arrow pointing upward (↑) represented win feedback, and a red arrow pointing downward (↓) represented loss feedback. Postfeedback intertrial interval (mean 3200 ms, minimum 1100 ms, maximum 11,600 ms) was followed by fixation (600 ms) signaling the next trial. See Figure 1A for a schematic of a single trial in the doors task and supplemental methods for task timing.

fMRI Data Acquisition

fMRI data were acquired using a 3T Siemens Trio whole-body scanner (Siemens, Erlangen, Germany). T2-weighted whole-brain volumes with an echo-planar imaging sequence sensitive to blood oxygen level–dependent signal were acquired (repetition time = 2100 ms, echo time = 22 ms, flip angle = 83°, matrix dimensions = 96 × 96, field of view = 224 × 224 mm, slices = 40, slice thickness = 3.5 mm, and gap = 0 mm). Statistical parametric mapping (SPM8; Wellcome Department of Cognitive Neurology, Institute of Neurology, London, United Kingdom) was used to perform standard preprocessing procedures with default parameters, including image realignment corrections for head movements, slice timing corrections for acquisition order, normalization to standard 2 × 2 × 2-mm Montreal Neurological Institute space, and spatial smoothing with a Gaussian full width at half maximum 8-mm filter. A block of fixation (21 seconds) preceded and followed the doors task for most participants (n = 152; 260 whole-brain volumes). The remaining participants (n = 25) experienced the same order of trials during the doors task but without the two fixation blocks (242 whole-brain volumes). Results were qualitatively similar when data from subjects without the additional fixation were excluded.

fMRI Data Processing and Analyses

All functional images were preprocessed using SPM8 (42). The initial six volumes were discarded for spin saturation. The ArtRepair toolbox (43,44) was used to correct motion artifacts by replacing affected volumes with a volume interpolated from the nearest unaffected volumes. Volumes with rapid movement above 1 voxel (2 mm) were identified and excluded. Participants were excluded from analyses if >20% of data were discarded. For each participant, the motion-corrected data were spatially realigned to the first volume. The T1-weighted structural image was coregistered to the mean functional image averaged across the realigned data and segmented into maps of pink matter, white matter, and cerebrospinal fluid, thereby generating the realignment parameters needed to normalize to the Montreal Neurological Institute echo-planar imaging brain template. The same normalization parameters were then applied to the realigned functional data to warp the images to Montreal Neurological Institute space. Finally, the

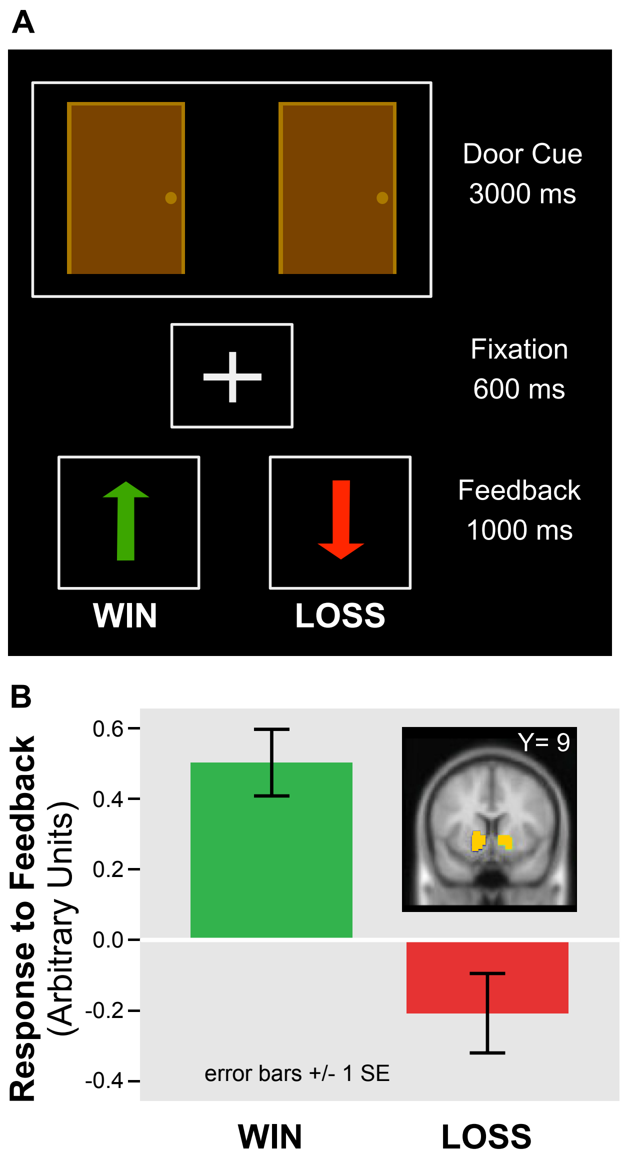

Figure 1. Doors task and ventral striatal response to feedback. **(A)** Schematic of a single doors task trial. **(B)** Ventral striatal regions of interest were identified using win/loss contrast. Participants showed activation to receipt of win feedback (green) and deactivation to receipt of loss feedback (red) within the bilateral ventral striatum.

functional data was spatially smoothed with an isotropic Gaussian kernel of full width at half maximum of 8 mm.

Event-related fixed-effects general linear models were created for each participant. Onsets of door cue, win feedback, and loss feedback were modeled separately for the first and second half of the task. VS response to win/loss during the first half was only weakly correlated with that in the second half of the task (Spearman–Brown coefficients: left/right VS win = 0.32/0.26, left/right VS loss = 0.36/0.24), and the VS response in the first half of the task showed superior internal consistency (45). As such, the current analyses were planned to focus on VS responses to feedback receipt during the first half of the task, a strategy reported in the reward fMRI literature (23). Exploratory analyses focusing on responses during the second half of trials are reported in Supplemental Tables S1 and S2.

To examine activation to win feedback versus baseline (implicit) and loss feedback versus baseline (implicit), we created *t* contrasts from each participant's general linear models. Second-level mixed effects for each event type were created to examine between-subjects effects. A win $>$ loss contrast was also computed and a one-way *t* test for win $>$ loss, thresholded (familywise error $p < .01$, cluster size > 20), was used to identify VS regions of interest independent of our question of interest. As such, current analyses focus on response to feedback within the bilateral VS regions of interest (−13,7,−8, and 13,7,−8) (Figure 1B). Individual participants' responses to win and loss feedback (vs. baseline) were extracted from the VS regions of interest using the MarsBaR toolbox (46) and used in subsequent analyses. As in previous child studies using win/loss guessing tasks, VS regions showed activation to win feedback and deactivation to loss feedback (Figure 1B) (6).

Moderation Analyses

Three hierarchical linear regressions using mean centered variables were conducted in SPSS 22.0 (IBM Corp., Armonk, NY) to examine whether VS function moderates relationships between recent life events and current depressive symptoms. As dependent variables of the three regressions (CDIC total score, CDIC negative mood subscale, and CDIC anhedonia subscale) were related, matrix spectral decomposition was used to identify the number of effective independent variables, here 1.68, and the *p*-value threshold needed for an α of .05, here $p < .029$ (47).

The first step, model 1, for all regressions included VS response to wins, VS response to losses, the number of positive independent events (P_{IND}), the number of positive dependent events (P_{DEP}), the number of negative independent events (N_{IND}), the number of negative dependent events (N_{DEP}), the interaction between VS win and each of the four life event types, the interaction between VS loss and each of the four life events types, and covariates of no interest (age, Pubertal Development Scale, Screen for Child and Anxiety Related Emotional Disorders, Beck Depression Inventory, maternal education level, and race—white vs. nonwhite). In regressions in which negative mood and anhedonia subscales of the CDIC are the dependent variable, the other subscale was also included as a covariate to investigate the specificity of effects to that symptom construct. The second step, model 2, included all two-way interactions between the independent variables and covariates to control for potential confounds (48). The PROCESS macro version 3.0 (49) for SPSS was used to implement the Johnson–Neyman technique for model 1, and the interact function within the jtools R package (50) was used to graph significant two-way interactions from model 1.

RESULTS

Relationships Between Life Events, Depressive Symptoms, and VS Responses

See Table 1 for descriptive statistics and Table 2 for correlation coefficients. Parental depressive symptoms related positively to the number of negative events parents reported their child experienced in the previous 12 months (CASE-N). Neither CASE-P nor CASE-N related significantly to child anxiety or depressive symptoms (all $r < .15$). CASE-P related to CASE-N ($r = .22$), but only the former related to VS response to win feedback ($r = -.19$); neither CASE score related loss.

Depressive symptoms were not significantly related to VS response. However, as expected, offspring depressive symptoms were significantly related to parent depressive symptoms and offspring anxiety symptoms.

Interactions Between Life Events and VS Function Predict Concurrent Child Depressive Symptoms

Response to Reward Moderates the Relationship Between P_{DEP} Life Events and Total Depressive Symptoms. The number of P_{DEP} life events experienced in the previous 12 months interacted with VS response to wins to predict concurrent total child depressive symptoms (CDIC total score) (Table 3; Figure 2A). This interaction remained significant ($\beta = -.40$, $t_{79} = -2.34$, $p = .022$) in model 2 (Supplemental Table S3).The conditional effect of P_{DEP} events on general depressive symptoms was significant when VS response to wins was >0.18 (Supplemental Figure S1; see Supplemental Table S4 for Johnson–Neyman results when using life events as the moderator). As such, the experience of a greater number of P_{DEP} events was protective only in the context of a robust VS response to reward.

Table 1. Descriptive Statistics for Demographic Variables, Symptom Measures, Ventral Striatal Response, and Life Events

	Mean	SD	Minimum	Maximum
Age, Years	12.65	1.81	8.08	14.99
Pubertal Development Scale Score	2.74	0.80	1	3.9
Maternal Education Level[a]	4.92	1.02	3	7
CDIC Total Score	8.15	8.28	0	38
CDIC negative mood subscale score	2.13	1.96	0	9
CDIC anhedonia subscale score	2.21	2.37	0	9
SCARED Total Score	20.87	11.62	0	58
BDI Score	6.16	7.07	0	31
Win	0.53	1.30	−3.28	5.30
Loss	−0.20	1.52	−5.37	5.67
CASE-P, Number	4.68	2.11	0	12
CASE-P_{IND}, number	1.16	1.15	0	6
CASE-P_{DEP}, number	2.65	1.21	0	8
CASE-N, Number	2.23	2.09	0	9
CASE-N_{IND}, number	1.35	1.35	0	5
CASE-N_{DEP}, number	0.61	0.93	0	4

BDI, Beck Depression Inventory; CASE, Child and Adolescent Survey of Experiences; CDIC, Child Depression Inventory–Child Version; DEP, dependent; IND, independent; N, negative; P, positive; SCARED, Screen for Child and Anxiety Related Emotional Disorders.

[a]Maternal education measure was coded as follows: 1 = eighth grade or less, 2 = some high school, 3 = high school degree/general equivalency diploma, 4 = some college/two-year degree, 5 = four-year degree, 6 = master's degree, 7 = doctoral degree.

Remaining interactions between VS function and life events were not significantly related to general depressive symptoms.

Response to Loss Moderates the Relationship Between N_{IND} Life Events and Negative Mood Symptoms. The interaction between the number of N_{IND} events experienced in the previous 12 months and VS response to loss significantly related to child negative mood symptoms, above and beyond child anhedonic symptoms (Table 3; Figure 2B). This interaction remained significant ($\beta = -.37$, $t_{72} = -2.32$, $p = .023$) in model 2 (Supplemental Table S3). The conditional effect of N_{IND} events on negative mood symptoms was significant when VS response to loss was <-2.72 or >0.29 (Supplemental Figure S1). As such, girls who both experienced a greater number of N_{IND} events and showed heightened VS response to loss (i.e., more negative response or greater deactivation) reported increased negative mood symptoms. However, when response to loss feedback is reduced, the experience of a greater number of N_{IND} events may lead to reduced depressive symptoms. Thus, experience of a greater number of N_{IND} life events is a risk factor for increased depressive symptoms, but only in the context of VS hyperresponsiveness to loss.

Remaining interactions between VS function and life events were not significantly related to negative mood symptoms.

Neither VS Function and Life Events nor Their Interaction Significantly Relates to Anhedonic Symptoms. No interaction between VS response to either win or loss feedback with any type of life event was significantly related to CDIC anhedonia subscale score over and above CDIC negative mood subscale score (Table 3; Supplemental Table S4).

DISCUSSION

The goal of this study was to examine whether VS response to monetary wins and losses moderate relationships between the experience of significant life events and depressive symptoms in female subjects during late childhood and/or early adolescence. Findings suggest that recent experiences of P_{DEP} and N_{IND} life events relate to severity of depressive symptoms in the context of heightened VS sensitivity to feedback of the same valence. Response to win feedback specifically moderated the relationship between general depressive symptoms and positive events likely dependent on the girl's behavior; response to loss feedback specifically moderated the relationship between negative mood symptoms and negative events likely independent of the girl's behavior. Together, these results suggest that there might be independent pathways of resilience and risk for depressive symptoms during the adolescent transition that depend on VS function and type of life experiences.

In this study, girls with robust response to reward showed a relationship between P_{DEP} events and reduced general depressive symptoms. This finding is broadly consistent with a vantage-sensitivity framework in which some individuals are more sensitive to the effects of a positive environment on positive outcomes (16); however, it should be noted that here the outcome was a lack of a negative outcome, depressive

Table 2. Correlations Between Model Predictors and Symptom Measures

	1	2	3	4a	4b	4c	5	6	7a	7b	7c	8a	8b	8c	9	10
1. Age																
2. PDS	0.78[b]															
3. Maternal Education	0.04	0.02														
4a. CDIC Total Score	0.24[b]	0.33[b]	0.02													
4b. CDIC Negative Mood Score	0.22[a,c]	0.31[b,c]	0.02[c]	0.87[b,c]												
4c. CDIC Anhedonia Score	0.17	0.28[b]	0.02	0.86[b]	0.68[b]											
5. SCARED	0.15	0.22[a]	−0.04	0.63[b]	0.59[b]	0.58[b]										
6. BDI	0.00	0.04	−0.15	0.13	0.01	0.08	0.01									
7a. CASE-P	0.10	0.12	0.08	−0.07	−0.04	−0.09	−0.15	−0.06								
7b. CASE P_{IND}	−0.03	0.03	−0.05	0.02	0.04	0.00	−0.07	−0.05	0.72[b]							
7c. CASE P_{DEP}	0.07	0.08	0.11	−0.12	−0.07	−0.11	−0.16	−0.01	0.78[b]	0.20[a]						
8a. CASE-N	0.15	0.22[a]	−0.05	0.13	0.10	0.14	0.08	0.26[b]	0.22[a]	0.11	0.19[a]					
8b. CASE N_{IND}	0.05	0.14	−0.07	0.07	0.02	0.10	0.05	0.28[b]	0.14	0.01	0.17	0.85[b]				
8c. CASE N_{DEP}	0.20[a]	0.24[b]	−0.05	0.13	0.11	0.11	0.08	0.14	0.22[a]	0.18[a]	0.13	0.72[b]	0.32[b]			
9. Win	−0.06	−0.08	−0.16	−0.16	−0.21[a]	−0.12	−0.04	0.04	−0.19[a]	−0.14	−0.16	0.06	0.05	0.09		
10. Loss	−0.12	−0.17	−0.04	−0.15	−0.14	−0.09	−0.05	0.02	0.02	0.03	0.07	0.01	0.00	0.02	0.46[b]	
11. White vs. Nonwhite[c]	1.81 (128)	1.15 (128)	1.15 (128)	−0.34 (37.3)	−0.47 (128)	−1.43 (128)	−2.24 (128)[a]	0.50 (128)	1.60 (128)	−0.02 (128)	1.42 (128)	1.36 (128)	1.94 (128)	−0.02 (128)	3.47 (36.2)[b]	1.90 (128)

Values are Pearson's *r*.

Equal variance assumed for all variables except CDIC total score and win.

BDI, Beck Depression Inventory; CASE, Child and Adolescent Survey of Experiences; CDIC, Child Depression Inventory−Child Version; DEP, dependent; IND, independent; N, negative; P, positive; PDS, Pubertal Development Scale; SCARED, Screen for Childhood Anxiety Related Emotional Disorders.

[a] $p < .05$.

[b] $p < .01$.

[c] *t* statistics and (*df*) from independent samples *t* test reported for white vs. nonwhite subjects.

Table 3. Multiple Regressions Examining Moderating Effects of Ventral Striatal Function on the Relationship Between Life Events and Depressive Symptoms

	CDIC Total Score			CDIC Negative Mood Subscale Score			CDIC Anhedonia Subscale Score		
Independent Variable	β	*t*	*p*	β	*t*	*p*	β	*t*	*p*
Constant		3.72	<.001		3.91	<.001		5.47	<.001
Win	.08	0.60	.552	−.02	−0.17	.864	.19	1.36	.176
Loss	−.17	−1.09	.280	−.07	−0.47	.639	−.07	−0.44	.662
CASE P_{IND}	.12	1.63	.105	.06	0.91	.365	.04	0.52	.606
CASE P_{DEP}	−.13	−1.78	.077	−.02	−0.31	.754	−.09	−1.20	.233
CASE N_{IND}	−.05	−0.63	.530	−.10	−1.50	.137	.06	0.83	.410
CASE N_{DEP}	.05	0.69	.492	.06	0.91	.363	−.01	−0.17	.869
CASE P_{IND} × Win	−.05	−0.59	.558	−.09	−1.15	.254	.09	0.95	.344
CASE P_{DEP} × Win	−.29[a]	−2.38[a]	.019[a]	−.16	−1.44	.152	−.20	−1.59	.114
CASE N_{IND} × Win	−.07	−0.72	.475	−.04	−0.42	.673	.03	0.30	.765
CASE N_{DEP} × Win	.04	0.39	.697	.07	0.82	.413	.03	0.28	.780
CASE P_{IND} × Loss	.02	0.18	.860	.10	1.19	.238	−.07	−0.71	.481
CASE P_{DEP} × Loss	.03	0.24	.813	−.11	−0.98	.332	.08	0.63	.532
CASE N_{IND} × Loss	−.20	−1.92	.058	−.25[a]	−2.70[a]	.008[a]	−.01	−0.08	.939
CASE N_{DEP} × Loss	.09	0.91	.365	.02	0.25	.800	.04	0.39	.699
Age	.00	−0.04	.970	.02	0.15	.878	−.06	−0.58	.563
PDS	.18	1.63	.105	.12	1.16	.249	.13	1.19	.238
SCARED	.62	8.97	<.001	.38	5.15	<.001	.24	2.67	.009
BDI	.14	1.93	.056	.01	0.11	.912	.06	0.83	.409
Education	.03	0.49	.628	−.02	−0.24	.812	.05	0.68	.495
White vs. Nonwhite	.08	1.14	.258	.08	1.24	.218	−.09	−1.28	.203
CDIC Subscale				.39	5.06	<.001	.50	5.06	<.001
Model Statistics	$F_{20,109}$ = 7.16, $p < .001$, adjusted R^2 = .49			$F_{21,108}$ = 9.68, $p < .001$, adjusted R^2 = .59			$F_{21,108}$ = 6.40, $p < .001$, adjusted R^2 = .47		

See Supplemental Table S3 for model 2, which also includes interactions between independent variables of interest and all covariates.

BDI, Beck Depression Inventory; CASE, Child and Adolescent Survey of Experiences; CDIC, Child Depression Inventory−Child Version; DEP, dependent; IND, independent; N, negative; P, positive; PDS, Pubertal Development Scale; SCARED, Screen for Childhood Anxiety Related Emotional Disorders.

[a]Interactions where $p < .029$.

symptoms. As girls with blunted response to reward were unable to capitalize on the benefits of positive experiences, risk-mitigation and treatment strategies focusing on increasing positive experiences may be most beneficial among high-reward responders. Moreover, targeting neural response to reward and positive experiences concurrently may provide a synergistic impact on depressive symptoms. Further, encouraging positive experiences specifically linked to a girl's behavior (i.e., dependent events) may be particularly important, as dependent events specifically were protective in the context

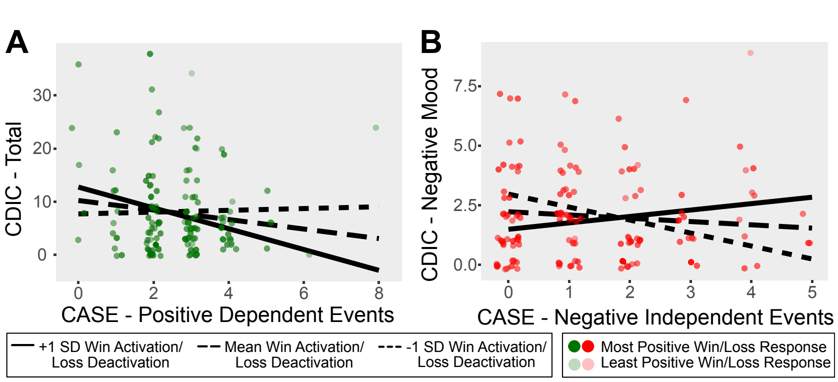

Figure 2. Ventral striatal (VS) response to win/loss feedback moderates relationships between life events and depressive symptoms. **(A)** Total positive dependent events on the Child and Adolescent Survey of Experiences (CASE) were associated with fewer total depressive symptoms on the Child Depression Inventory–Child report (CDIC) when VS activation to win feedback was robust. **(B)** Negative independent events on the CASE were associated with greater CDIC negative mood when VS deactivation to loss feedback was robust and with decreased CDIC negative mood when VS deactivation to loss was weak. Lines indicate the predicted relationship between depressive symptoms and life events when VS win activation or VS loss deactivation is one standard deviation above the mean (solid line), at the mean (dashed line), or one standard deviation below the mean (dotted line). The opacity of individual data points indicates the level of the moderator, with 100% opacity indicating the most positive VS response to win (green points) or loss (red points) within the sample.

of robust reward response. More work is needed to determine why dependent events specifically showed this effect. One possibility is that positive events linked to a girl's own behavior (e.g., winning a prize at school) may be more related to depressive symptoms through increased self-esteem (51). Another possibility is that dependent events, which are more likely to be social and/or interpersonal in nature (e.g., new friendship), may both serve as a better buffer against depression (17) generally and be more salient, particularly during adolescence.

Negative life events likely independent of girls' behavior related specifically to negative mood symptom severity, though the direction of this effect varied by VS response to loss. A greater number of negative independent events related to increased negative mood symptoms for girls showing robust VS response to loss (i.e., strong VS deactivation to loss). However, for girls characterized by minimal loss-related deactivation, a greater number of N_{IND} events related to decreased negative mood symptoms. The first finding complements other diathesis-stress findings where individuals with genotypes associated with enhanced reactivity within stress or affective neural systems are more sensitive to the depressogenic effects of stress or negative environments (30,31). Here it may be that girls who are more reactive to negative feedback are more likely to employ depressogenic cognitive strategies, such as increased rumination, when negative events are unrelated to their behavior (52). This finding is also in line with findings in the literature that specifically link uncontrollable stress to depression (32). However, mechanisms supporting the second finding are less clear. One possibility is that girls with lower sensitivity to negative feedback may interpret stressors over which they have little control as external challenges to be approached and overcome, leading to greater self-efficacy and reduced negative mood. Additional studies are needed to further explore the mechanisms of this moderation, particularly in the case of resilient outcomes.

Together, these results suggest that insofar as it may be difficult to intervene on environmental factors unrelated to an individual's behavior, focusing on neural response to loss in prevention and treatment efforts may be a compelling intervention option. For example, reducing responses to negative stimuli via attention bias modification (53) may be a particularly important target for preventive interventions in late childhood and early adolescence, as enhanced VS deactivation to loss is both observed in healthy children at high familial risk for major depressive disorder (6), and related to negative outcomes in the context of negative events in the current study.

Although this study has several strengths, including controlling for both parent depressive symptoms and child-reported anxiety, using different reporters and methodologies for each of the independent variables and outcomes of interest, and investigating unique effects of positive versus negative events and reactivity, there are limitations. Parental report of whether events were good or bad may be biased by parental factors and may not match the child or adolescent's experience, and this bias may vary with age; indeed, this may explain unexpected correlations between parent-reported positive or negative events and child-reported depressive symptoms and response to wins. Similarly, the accuracy and completeness of parent reports of child or adolescent life events may differ over the age range included here (8–14 years), and as child or adolescent report on the CASE was not collected, we cannot control for this possibility. Future studies with both child and parent report of life events are needed for this age range. Further, we were unable to investigate whether these more recent experiences may have reflected environments earlier in development. Thus, longitudinal studies with multiple reporters are needed to examine the temporal relationships between VS response to win or loss feedback, different types of life events, and depressive symptoms as well as whether the nature of these relationships change over development. The parent study from which the current sample was drawn recruited only female subjects. As such, we were unable to examine whether VS function similarly moderates relations between life events and depression in male subjects, and future studies are needed to examine possible sex differences in these effects. Future studies should also examine whether similar relationships are observed in adolescents with clinical levels of depression, more extreme life events, and regions beyond the ventral striatum. Finally, replication of these results by future studies would increase confidence in current findings, which were somewhat limited by sample size and model complexity.

Conclusions

In conclusion, relationships between recent life events and depressive symptoms differ depending on VS function in female subjects during emerging adolescence. Interventions designed to enhance VS activation to reward and reduce VS deactivation to loss may be useful strategies for augmenting the protective effects of positive life events and reducing the deleterious effects of negative life events during this particularly vulnerable developmental stage.

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