Ventral Striatum Reactivity to Reward and Recent Life Stress Interact to Predict Positive Affect

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Background: Stressful life events are among the most reliable precipitants of major depressive disorder; yet, not everyone exposed to stress develops depression. It has been hypothesized that robust neural reactivity to reward and associated stable levels of positive affect (PA) may protect against major depressive disorder in the context of environmental adversity. However, little empirical data exist to confirm this postulation. Here, we test the hypothesis that individuals with relatively low ventral striatum (VS) reactivity to reward will show low PA levels in the context of recent life stress, while those with relatively high VS reactivity will be protected against these potentially depressogenic effects.

Methods: Differential VS reactivity to positive feedback was assessed using blood oxygen level-dependent functional magnetic resonance imaging in a sample of 200 nonpatient young adults. Recent life stress, current depressive symptoms, and PA were assessed via self-report. Linear regression models were used to investigate the moderating effects of VS reactivity on the relationship between recent stress and state PA across participants.

Results: Recent life stress interacted with VS reactivity to predict self-reported state PA, such that higher levels of life stress were associated with lower PA for participants with relatively low, but not for those with high, VS reactivity. These effects were independent of age, gender, race/ethnicity, trait PA, and early childhood trauma.

Conclusions: The current results provide empirical evidence for the potentially protective role of robust reward-related neural responsiveness against reductions in PA that may occur in the wake of life stress and possibly vulnerability to depression precipitated by stressful life events.

Stressful life events are among the most reliable predictors of major depressive disorder (MDD) (1,2). However, while nearly everyone is confronted with stressful life events, the majority of the population does not subsequently develop depression. Uncovering the neurobiological basis of individual differences in relative vulnerability and resilience to the depressogenic effects of stress may provide unique insights into the pathophysiology of stress-related MDD.

Potential clues to the relationship between stress and depression can be garnered from extensive nonhuman animal research (3,4) and emerging human work (5,6), which converge to reveal that stress can induce anhedonia, a core symptom of MDD reflecting an inability to experience pleasure or respond to rewarding stimuli, and a general reduction in positive affect (PA). Since anhedonia is associated with relative reductions in reward-related brain function (7–10), it is reasonable to postulate that relative vulnerability to the depressogenic effects of stress is, at least in part, related to individual differences in neural responsiveness to reward. Accordingly, relatively increased responsiveness to reward, especially when robust to the detrimental effects of stress, has been hypothesized to confer relative resilience to stress-related psychiatric disorders, including MDD (11,12).

While reduced levels of PA are a hallmark of MDD, PA can vary independently of negative affect and other depressive symptomatology (13). At the same time, even subclinical reductions in PA can predict the development of full-blown depression, as well as general psychological well-being, particularly in the face of stress (14). Consistent with the idea that PA levels reflect the extent of one's pleasurable engagement with the environment (15), real-world PA has been found to correlate with the relative reward-related responsiveness of the brain's mesocorticostriatal system across both healthy and depressed individuals (16). Thus, PA and its temporal stability may serve as informative psychological markers with tractable biological substrates, which may help distinguish individuals at risk for or resilient to depression, particularly in the context of stress.

In the current study, we tested the hypothesis that reward-related reactivity of the ventral striatum (VS), a brain structure critically involved in reward processing and appetitive behaviors (17,18), would moderate the relationship between recent life stress and state PA. Specifically, we hypothesized that individuals with relatively low VS reactivity would show lower PA in the context of recent life stress, while those with high VS reactivity would display stable PA regardless of stress. A large cohort of nonpatient young adults ($n = 200$) underwent blood oxygen level-dependent (BOLD) functional magnetic resonance imaging (fMRI) during a number guessing paradigm previously demonstrated to elicit robust VS reactivity (19,20). The experience of recent stressful life events, as well as early childhood trauma, depressive symptoms, and PA (state and trait) were assessed using self-report questionnaires.

Methods and Materials

Participants

A total of 200 participants were included from the ongoing Duke Neurogenetics Study, which assesses a wide range of behavioral and biological traits among nonpatient, young adult, student volunteers. All participants provided informed consent in accordance with Duke University guidelines and were in good general health. Twenty-nine participants were excluded from analyses due to signal dropout in VS regions of interest (see below) and 1 partic-

ipant did not have valid self-report data due to programming error, leaving a final sample of 170 individuals (104 women; mean age: 19.55 ± 1.26).

All participants were free of the following study exclusions: 1) medical diagnoses of cancer, stroke, diabetes requiring insulin treatment, chronic kidney or liver disease, or lifetime history of psychotic symptoms; 2) use of psychotropic, glucocorticoid, or hypolipidemic medication; and 3) conditions affecting cerebral blood flow and metabolism (e.g., hypertension). Diagnosis of any current DSM-IV Axis I disorder or select Axis II disorders (antisocial personality disorder and borderline personality disorder), assessed with the electronic Mini International Neuropsychiatric Interview (21) and Structured Clinical Interview for the DSM-IV subtests (22), respectively, were not an exclusion, as the Duke Neurogenetics Study seeks to establish broad variability in multiple behavioral phenotypes related to psychopathology. No participants met criteria for either antisocial or borderline personality disorder, and 29 participants from our final sample ($n = 170$) met criteria for at least one Axis I disorder (Table S1 in Supplement 1). Since the exclusion of these individuals did not substantially alter our results, we present data from the entire sample in the main text (see Table S2 in Supplement 1 for analyses excluding individuals with Axis I disorders).

Ventral Striatum Reactivity Paradigm

As described previously (19), our blocked-design number guessing paradigm consisted of a pseudorandom presentation of three blocks of predominantly positive feedback (80% correct guess), three blocks of predominantly negative feedback (20% correct guess), and three control blocks. Participants were unaware of the fixed outcome probabilities associated with each block and were led to believe that their performance would determine a net monetary gain at the end of the scanning session. Instead, all participants received $10. We included one incongruent trial within each task block (e.g., one of five trials during positive feedback blocks was incorrect, resulting in negative feedback) to prevent participants from anticipating the feedback for each trial and to maintain participants' engagement and motivation to perform well (see Supplementary Methods and Materials in Supplement 1 for full task description).

BOLD fMRI Data Acquisition

Each participant was scanned using a research-dedicated GE MR750 3T scanner (General Electric, Fairfield, Connecticut) equipped with high-power high-duty cycle 50-mT per meter gradients at 200 Tesla per meter per second slew rate and an eight-channel head coil for parallel imaging at high bandwidth up to 1 MHz at the Duke-University of North Carolina Brain Imaging and Analysis Center (see Supplementary Methods and Materials in Supplement 1 for full data acquisition parameters).

BOLD fMRI Data Analysis

The general linear model of SPM8 (University College London, United Kingdom; http://www.fil.ion.ucl.ac.uk/spm) was used to conduct fMRI data analyses. Following preprocessing (Supplementary Methods and Materials in Supplement 1), linear contrasts employing canonical hemodynamic response functions were used to estimate differential effects of feedback (i.e., reward) from the contrast of positive feedback > negative feedback for each individual. Individual contrast images were then used in second-level random effects models accounting for scan-to-scan and participant-to-participant variability to determine mean condition-specific regional responses using one-sample t tests.

Because of the relatively extensive signal dropout and noise typically observed in the VS due to magnetic susceptibility associated with the region's proximity to tissue boundaries (23), only participants with greater than 90% signal coverage ($n = 170$) in bilateral VS anatomical regions of interest were included in analyses. This coverage check was independent of task-specific activation (Supplementary Methods and Materials and Figure S1 in Supplement 1). Whole-brain analyses were then conducted on participants with adequate signal to identify reward-related VS reactivity. A statistical threshold of $p < .05$, family-wise error whole-brain corrected, and ≥10 contiguous voxels was applied to the contrast of positive > negative feedback blocks for this analysis.

Mean BOLD values from VS clusters exhibiting a main effect of task were extracted using the volume of interest tool in SPM8. These extracted values were then entered into regression models using IBM SPSS Statistics 19.0 (SPSS Inc., Chicago, Illinois). Importantly, by extracting VS BOLD parameter estimates from the functional clusters activated by our paradigm rather than clusters specifically correlated with our independent variables of interest (i.e., depressive symptoms and PA), we preclude the possibility of any correlation coefficient inflation that may result when an explanatory covariate is used to select a region of interest (24). We have successfully used this conservative strategy in previous reports (25–27).

Self-Report Measures

Depressive Symptoms and PA. Participants completed the Center for Epidemiologic Studies-Depression (CES-D) scale (28). Based on previous factor analytic studies (29,30) and a confirmatory factor analysis in the current sample (Supplementary Methods and Materials in Supplement 1), four subscales were computed: 1) positive affect (CES-D PA), 2) negative affect (CES-D NA), 3) somatic features (CES-D SF), and 4) interpersonal functioning (CES-D IP). Trait PA was assessed using the positive emotions subscale of the extraversion dimension of the NEO Personality Inventory-Revised (31).

Stressful Life Events. To assess recent life stress, we administered a modified version of the Life Events Scale for Students (LESS) (32) (Supplementary Methods and Materials in Supplement 1). This modified version of the scale asks participants to indicate whether they experienced common stressful life events within the past 12 months; in addition, for each event that occurred, participants reported on the impact it had on their lives on a 1 to 4 scale (with 4 being the highest). The impact scores were set to zero for events that did not occur. We derived three main variables of interest from the LESS: 1) LESS total number of events; 2) LESS highest impact, reflecting the highest impact associated with any event that occurred within the past year; and 3) LESS average impact, capturing the average impact of all events that occurred within the past year. To ensure the specificity of our results to current life stress, we assessed early life trauma using the Childhood Trauma Questionnaire (CTQ) (33) and used this measure as a covariate in regression analyses.

Statistical Analyses

Regressions using LESS and VS reactivity as independent variables and CES-D PA scores as a dependent variable were conducted within IBM SPSS Statistics 19.0. Significant interactions were probed using the Johnson-Neyman method (34), as implemented in the SPSS MODPROBE macro (35), to calculate the range of VS reactivity values for which stress is significantly correlated with PA. Rather than probing the interactions at specific values of the moderator variable (in this case, VS reactivity), the Johnson-Neyman method

Table 1. Effects of Gender and Age on Self-Report Variables and VS Reactivity

	Gender Effects				Age Effects	
	Men (n = 66)	Women (n = 104)	t	p	b	p
CES-D						
PA	8.92 (2.64)	8.67 (2.96)	−.56	.58	−.032	.68
NA[a]	.79 (.78)	.98 (.79)	−1.58	.12	.148[b]	.054[b]
SF	3.83 (3.09)	4.35 (3.38)	−1.00	.32	.040	.60
IP[a]	.36 (.48)	.34 (.49)	.32	.76	.059	.45
Total[a]	2.13 (.75)	2.22 (.77)	−.75	.45	.062	.42
Trait PA	20.09 (4.55)	21.17 (5.46)	−1.34	.18	−.059	.45
CTQ Total[a]	3.50 (.18)	3.56 (.24)	−1.87[b]	.064[b]	.081	.29
LESS						
Number	4.56 (3.41)	4.63 (3.12)	−.13	.90	−.057	.46
HI	2.89 (1.29)	2.91 (1.04)	−.11	.91	−.115	.13
AI	2.08 (.92)	2.22 (.77)	−1.08	.28	−.133[b]	.083[b]
rVS (a.u.)	.13 (.18)	.07 (.18)	2.17[b]	.032[b]	−.046	.55
lVS (a.u.)	.12 (.20)	.07 (.19)	1.47	.14	−.015	.85

AI, average impact; a.u., arbitrary units; CES-D, Center for Epidemiological Studies-Depression; CTQ, Childhood Trauma Questionnaire; HI, highest impact; IP, interpersonal functioning; LESS, Life Events Scale for Students; lVS, left ventral striatum; NA, negative affect; PA, positive affect; rVS, right ventral striatum; SF, somatic features; VS, ventral striatum.

[a]Log-transformed to normalize distribution.

[b]Significant or trend-level effects.

allows for calculating the entire range of moderator variable values for which the focal predictor (i.e., the other interacting variable, LESS) is significantly correlated with the dependent variable (CES-D PA) (see Figure S3 in Supplement 1 for results from analyses probing the interaction at VS reactivity values of 1 SD below the mean, mean, and 1 SD above the mean).

Results

Sample Demographics

There were no significant effects of gender or age on any self-report measure (Table 1). However, several trend-level effects

emerged (Table 1). In addition, consistent with previous literature (36), men had higher right VS reactivity compared with women (p = .032). Finally, race/ethnicity had a significant effect on CES-D total and all CES-D subscales except interpersonal functioning (Table 2). To account for the potentially confounding effects of these demographic variables, all analyses were conducted with and without age, gender, and race/ethnicity (dummy coded) as covariates in addition to current Axis I diagnosis and trait PA. Analyses with trait PA as a covariate were conducted on n = 169 participants because of missing NEO Personality Inventory-Revised scores in one individual resulting from a programming error.

Table 2. Effects of Race/Ethnicity on Self-Report Measures and VS Reactivity

	Caucasian (n = 75)	African/African American (n = 31)	Asian/Asian American (n = 45)	Biracial or Multiracial (n = 11)	Other (n = 8)	F	p
CES-D							
PA	9.48 (2.66)[a]	8.13 (2.99)[a]	7.78 (2.87)[a]	9.90 (2.21)[a]	8.63 (2.67)	3.60	.008[a,b]
NA[c]	.67 (.73)[a]	1.10 (.87)[a]	1.01 (.78)[a]	1.16 (.63)[a]	1.34 (.70)[a]	3.40	.011[a,d]
SF	3.60 (2.77)[a]	5.71 (3.88)[a]	3.64 (3.35)	5.27 (3.50)	4.50 (2.67)	3.05	.019[a,e]
IP[c]	.31 (.46)	.42 (.54)	.31 (.48)	.41 (.60)	.48 (.42)	.55	.70
Total[c]	1.98 (.75)[a]	2.43 (.79)[a]	2.25 (.79)	2.47 (.51)	2.18 (.77)	2.88	.024[a,e]
Trait PA	20.75 (5.61)[a]	21.65 (4.89)[a]	19.02 (4.43)[a]	22.90 (4.32)[a]	24.13 (3.04)	2.99	.020[a,f]
CTQ Total[c]	3.43 (.18)[a]	3.63 (.20)[a]	3.60 (.24)[a]	3.61 (.23)[a]	3.61 (.22)[a]	8.58	<.001[a,d]
LESS							
Number	4.56 (2.96)	4.94 (3.08)	3.80 (3.00)	5.64 (4.27)	6.75 (4.86)	2.00	.097
HI	2.87 (1.12)	3.10 (.83)	2.71 (1.34)	3.36 (1.03)	3.00 (1.15)	1.02	.40
AI	2.10 (.78)	2.30 (.62)	2.03 (1.00)	2.52 (.73)	2.49 (1.08)	1.44	.22
rVS (a.u.)	.10 (.18)	.06 (.16)	.11 (.21)	.08 (.13)	.09 (.14)	.35	.84
lVS (a.u.)	.08 (.21)	.07 (.16)	.09 (.24)	.10 (.12)	.11 (.15)	.11	.98

AI, average impact; a.u., arbitrary units; CES-D, Center for Epidemiological Studies-Depression; CTQ, Childhood Trauma Questionnaire; HI, highest impact; IP, interpersonal functioning; LESS, Life Events Scale for Students; LSD, least significant difference; lVS, left ventral striatum; NA, negative affect; PA, positive affect; rVS, right ventral striatum; SF, somatic features; VS, ventral striatum.

[a]Significant differences between groups.

[b]Caucasian > Asian/Asian American and African/African American; Biracial/Multiracial > Asian/Asian American, *p*s < .024, LSD corrected.

[c]Log-transformed to normalize distribution.

[d]All groups > Caucasian, *p*s < .05, LSD corrected.

[e]African/African American > Caucasian, *p* = .002, LSD corrected.

[f]African/African American > Asian/Asian American, *p* = .009, LSD corrected.
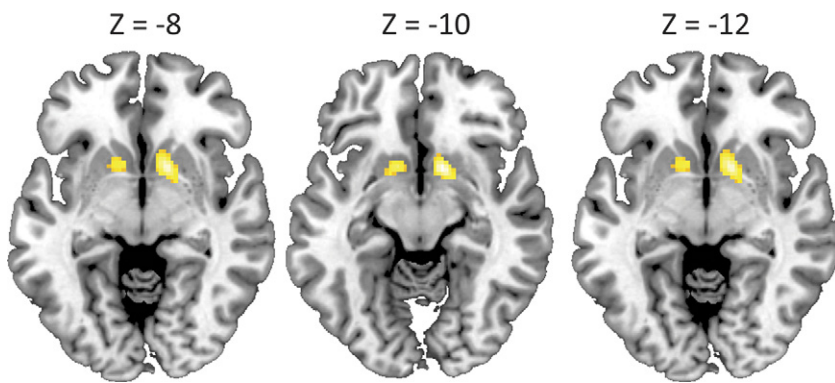
Z = -8   Z = -10   Z = -12

Figure 1. Reward-related ventral striatum reactivity. Statistical parametric map illustrating bilateral ventral striatum activation clusters for the contrast positive > negative feedback overlaid onto a canonical structural brain image in the axial plane. Montreal Neurological Institute coordinates and statistics ($p < .05$, family-wise error whole-brain corrected and ≥ 10 contiguous voxels): left hemisphere: $x = -12$, $y = 10$, $z = -10$, $t = 6.19$, $p = 2.12 \times 10^{-9}$, right hemisphere: $x = 12$, $y = 10$, $z = -8$, $t = 7.31$, $p = 4.85 \times 10^{-12}$; $k_E = 446$.

VS Reactivity

Consistent with previous studies (19,20), our paradigm elicited significant reward-related (i.e., positive > negative feedback) bilateral VS reactivity (Figure 1). The only additional clusters surviving this correction were two small clusters in the bilateral rostral anterior cingulate cortex (Figure S1 in Supplement 1). Because there was a small area of contiguity between the left and right VS activation clusters, we extracted BOLD signal values from 5 mm spheres built around the peak voxels in each hemisphere (left: $x = -12$, $y = 10$, $z = -10$; right: $x = 12$, $y = 10$, $z = -8$).

VS Reactivity, Stress, and PA

In support of our hypothesis, there was a significant interaction between right VS reactivity and LESS highest impact scores ($\Delta R^2 = .045$, $b = .500$, $p = .0054$, Cohen's $f^2 = .049$), such that higher LESS impact was associated with lower CES-D PA for participants with relatively low VS reactivity (bottom 28.2%, $n = 48$) but not for those with high VS reactivity (remaining 71.8%, $n = 122$) (Figure 2A). Importantly, the interaction term explained significant CES-D PA variance above and beyond the main effects of VS reactivity ($b = .318$, $p = .14$) and LESS ($b = .217$, $p = .26$). Furthermore, the interaction remained significant after controlling for age, gender, race/ethnicity, CTQ total, Axis I diagnosis, and trait PA ($\Delta R^2 = .033$, $b = .450$, $p = .0095$, Cohen's $f^2 = .034$). In addition, the interaction remained significant when LESS number of events and CES-D non-PA scores, computed by subtracting CES-D PA from CES-D total, were added to the model individually (LESS: $\Delta R^2 = .031$, $b = .441$, $p = .011$, Cohen's $f^2 = .032$; CES-D: $\Delta R^2 = .026$, $b = .401$, $p = .012$, Cohen's $f^2 = .027$) or simultaneously ($\Delta R^2 = .026$, $b = .403$, $p = .013$, Cohen's $f^2 = .027$). A similar pattern emerged on the left side ($\Delta R^2 = .035$, $b = .444$, $p = .014$, Cohen's $f^2 = .036$); however, the interaction between LESS highest impact and left VS reactivity was not equally robust to the inclusions of covariates and was reduced to a statistical trend after their addition to the model ($\Delta R^2 = .016$, $b = .313$, $p = .075$).

Similar to LESS highest impact, LESS number of events also interacted with right VS reactivity ($\Delta R^2 = .030$, $b = .152$, $p = .024$, Cohen's $f^2 = .03$) (Figure 2B) to predict significant variability in CES-D PA above and beyond the main effects of VS reactivity ($b = .327$, $p = .13$) and LESS ($b = .100$, $p = .14$). Specifically, LESS number of events was associated with lower PA only for participants with relatively low VS reactivity (bottom 34.7%, $n = 59$) but not for those with high VS reactivity (remaining 65.3%, $n = 111$). The interaction remained significant when age, gender, race/ethnicity, CTQ scores, Axis I diagnosis, and trait PA were added as covariates ($\Delta R^2 = .023$, $b = .138$, $p = .032$). As with LESS highest impact, we found a similar pattern on the left side ($\Delta R^2 = .025$, $b = .125$, $p = .040$, Cohen's $f^2 = .026$), which, however, was reduced to a trend when covariates were included in the model ($\Delta R^2 = .018$, $b = .111$, $p = .057$). Unlike

LESS highest impact, however, the number of events by right VS reactivity interaction was not robust to the inclusion of covariates in the sample excluding participants with current Axis I diagnosis (Table S3 in Supplement 1). Life Events Scale for Students average impact did not interact with VS reactivity to predict CES-D PA (p values $> .20$).

Control Analyses

To ascertain the specificity of our findings to the CES-D PA subscale, we conducted a regression using LESS and VS reactivity as predictors of CES-D non-PA scores, computed by subtracting CES-D PA from CES-D total. As hypothesized, this model resulted in a main effect of LESS (number of events or highest impact) on non-PA depressive symptoms (b coefficients $> .090$, p values $< .001$) but no significant effect of VS reactivity or VS reactivity by LESS interaction (p values $> .25$). Further demonstrating the specificity of our findings to CES-D PA, no LESS measure interacted with VS reactivity to individually predict any specific non-PA CES-D subscale (p values $> .05$).

Underscoring the specificity of our results to recent life stress, CTQ (total or emotional neglect subscales) scores did not interact with VS reactivity to predict CES-D PA or any of the other CES-D subscales (p values $> .16$). In addition, neither the LESS nor the CTQ or any of their subscales had a direct effect on VS reactivity (p values $> .16$).

Discussion

Consistent with theoretical predictions that robust responsiveness to reward may protect against the depressogenic effects of stress (12), we provide empirical evidence that recent life stress interacts with reward-related ventral striatum reactivity to predict self-reported state positive affect. Specifically, we show that recent life stress is associated with decreased PA only in individuals with relatively low VS reactivity. In those with relatively high VS reactivity, levels of PA did not vary as a function of life stress. This interaction effect was robust to the effects of age, gender, race/ethnicity, childhood trauma, trait PA, and current psychopathology.

Despite numerous studies implicating reward system dysfunction in MDD (7–10,37), little is known about how differences in reward-related brain function influence depressive symptomatology in the context of environmental adversity. Results from the current investigation suggest that individual differences in reward system reactivity may shape one's propensity to experience reductions in PA in the wake of recent life stress. Long-term prospective studies investigating interactions between life stress and individual differences in VS reactivity are needed to evaluate if this pattern is associated with vulnerability for developing MDD. However, the relevance of this putative risk pathway is corroborated by extant
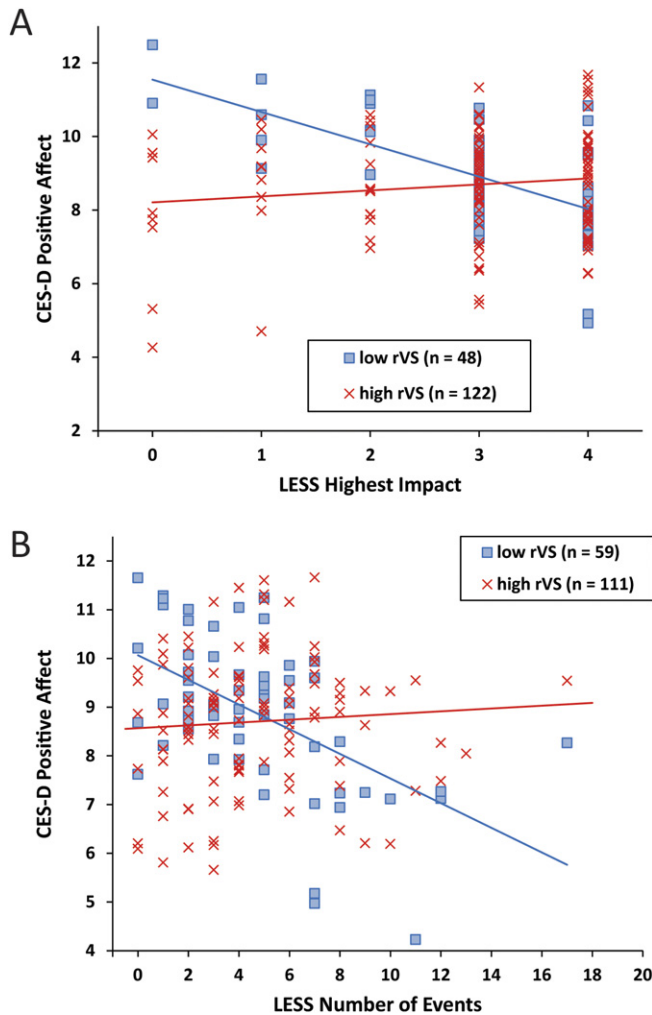
Figure 2. Reward-related ventral striatum (VS) reactivity moderates the relationship between recent life stress and current levels of positive affect. Stress ([**A**]: Life Events Scale for Students [LESS] highest impact, [**B**]: LESS number of events) was associated with lower state positive affect in participants with relatively low (blue line) but not high (red line) right VS reactivity. Removal of the two participants reporting 17 life events from the analyses did not change the significance of the LESS number of events by VS reactivity interaction term ($\Delta R^2 = .033$, b = .207, $p = .018$). In order to allow overlapping points to be displayed, the plotted values are adjusted for gender, age, and race/ethnicity. CES-D, Center for Epidemiological Studies-Depression; rVS, right ventral striatum.

research demonstrating that reward system reactivity in nondepressed adults is shaped by various genetic and environmental factors known to modulate depression vulnerability. Specifically, VS reactivity in healthy adults is regulated by polymorphisms within dopaminergic genes (19,27) that have also been linked to differential depression susceptibility, particularly in the context of environmental adversity (38,39). In addition, both early life stress and experimentally manipulated acute stress have been linked to reductions in reward-related neural reactivity (40,41) and increased risk for depression (42). Drawing on our current results, we speculate that reward-related VS reactivity may further interact with recent life stress to modulate stress-related reductions in PA and potentially risk for depression.

Contrary to prior findings demonstrating that early life stress reduces neural responses to reward in adults (40), we found that

neither early childhood trauma, as assessed by the CTQ, nor recent life stress had a direct effect on VS reactivity. It is worth noting, however, that participants in the current sample were not specifically selected for childhood trauma experience and were primarily high-functioning college students with little endorsed childhood trauma exposure. Thus, it is possible that only severe childhood trauma or chronic stress of a magnitude outside the range present in the current sample would result in significant reduction in adult neural responsiveness to reward.

As hypothesized, the interaction between VS reactivity and stress was most robust when predicting PA (i.e., CES-D PA), rather than general depressive symptoms as measured by the other subscales of the CES-D. This suggests that VS reactivity may be protective against decreases in PA specifically, rather than depression in general, possibly by conferring resiliency to stress-related hedonic impairments. Moreover, because anhedonia and reductions in PA are a defining feature of other stress-related psychopathology, such as posttraumatic stress disorder, our findings may not be specific to MDD resilience. In fact, the results we report are also consistent with studies suggesting that pre-existing individual differences in neural responsiveness to reward correlate with resilience to posttraumatic stress disorder in the face of trauma (43). Nonetheless, since we used a nonclinical sample in this study, direct translation of the observed patterns into vulnerability and resilience for psychopathology cannot be assumed until confirmed by prospective longitudinal studies mapping the etiology of clinical disorders.

In addition to the specificity of our results to PA, our findings were strongest when using the LESS highest impact metric, rather than total number of events or average impact. Importantly, the results involving LESS highest impact scores remained significant when controlling for number of events, suggesting that the effects of the event with the highest impact may override the independent and/or additive effects of multiple less impactful stressful events. Moreover, the results with LESS number of events did not survive when individuals with current psychopathology were removed from analyses. While the additivity of stressful life events has long been the subject of debate in the literature (44), some empirical support does exist for the notion that once a highly impactful event has occurred, the depressogenic effects of minor events may become negligible (2). Future research employing interview-based stress measures (45) embedded within a prospective longitudinal design may be necessary to corroborate the credibility of this postulation.

While linear regression analyses conducted separately for the right and the left VS activation clusters yielded convergent results, the VS reactivity × stress interaction effect was more robust in the right hemisphere. Such asymmetries are not uncommon in the literature (46,47) and may reflect intrinsic differences in neurotransmitter regulation of VS function across the two hemispheres (48–51). However, the precise biological mechanisms mediating such lateralized effects are currently unknown. Alternatively, it is possible that, perhaps due to its visuospatial component, our task preferentially recruited the right VS. Although a paired-samples *t* test directly comparing activation in the peak two voxels in the left and right VS was not significant in the current sample ($p = .29$), our whole-brain voxel-wise analysis showed that the peak activation voxel on the right side was somewhat more strongly activated than the peak voxel on the left side (right: $t = 7.31, p = 4.85 \times 10^{-12}$; left: $t = 6.19, p = 2.12 \times 10^{-9}$). Consistent with this notion, we have previously found right-hemisphere specific correlations between reward-related VS reactivity, as assessed by the same task, and variability in behavioral measures of impulsivity (19,20). Further

research is necessary to determine the functional significance of these lateralized effects.

The current study is not without limitations. Most importantly and as highlighted above, while trait PA has been found to be predictive of depression risk (14,52,53), the direct relevance of these findings to understanding depression vulnerability and resilience, particularly over long periods of time, is limited. The clinical significance of the findings is also limited by the fact that we focused on high-functioning nonpatient young adult participants, who may be more resilient than the general population. This could at least partially explain why we did not find a main effect of recent life stress on either depressive symptomatology more generally or PA levels specifically. Thus, caution must be used in interpreting the broader clinical significance of these findings until replicated in the context of more severe mood pathology.

Another potential limitation of the present study lies in the instrument we used to assess tress. Specifically, we used a self-report retrospective measure of stressful life events occurring in the past 12 months. This questionnaire did not ask participants to indicate the specific time when each event occurred, leaving us unable to differentiate between more proximal and distal events (54) or evaluate potential "kindling" effects (55). However, prior studies have shown that stressful life events can have detrimental effects on psychological well-being for up to a year following their occurrence (32,56). In addition, the appraisal of an event's impact, as conveyed by LESS highest impact scores, at the time of study completion (i.e., when VS reactivity and CES-D PA were assessed) provides an index of subjective importance of a life event, which may be more informative than its proximity in time. Nonetheless, given the retrospective nature of our self-report measure of stressful life events, we cannot rule out the possibility that these events affected subsequent measures of VS reactivity. However, prior research suggests that VS reactivity is a temporally stable neural phenotype. Specifically, studies have shown that VS reactivity as assessed by this task correlates with temporally stable personality and behavioral traits such as impulsivity (19) and delay discounting (20). In addition, we have previously shown that the same neural phenotype is under the direct influence of polymorphisms within several dopaminergic genes, suggesting this phenotype may be relatively independent of environmental effects (19,27). Finally, systematic effects on VS reactivity would be expected to manifest as direct correlations between LESS scores and VS reactivity in the current sample and all such correlations were nonsignificant.

Finally, recent studies have demonstrated that reward processing may not be a unitary phenomenon (17), and our task does not allow for differentiation between brain function during different phases of reward processing (e.g., reward anticipation, outcome, and learning). Relatedly, we focused our analyses on state positive affect levels, which capture overall happiness but do not tap directly into motivational aspects of reward processing or reward learning. In light of studies showing reduced reward responsiveness and reward-based learning in the context of stress (5,57), it is possible that the relatively low levels of positive affect we observed as a function of recent stressful life events and relative hyporesponsiveness of the VS may, in fact, be due to stress-related reductions in motivation to pursue rewards or a reduced ability to learn from prior reinforcement. Future studies using tasks allowing for greater specificity on both the behavioral and neural level could identify discrete components of reward processing that may better explain the specific mechanisms underlying stress-related variability in positive affect and associated psychopathology risk.

These limitations notwithstanding, the current study is the first empirical demonstration that robust neural reactivity to reward

may protect against stress-related reductions in positive affect. Given that impairments in PA are cardinal features of mood disorders in general and MDD in particular, the current work provides a useful framework for future research to investigate the relevance of these pathways in the expression of clinical dysfunction. Additional work establishing molecular adaptations in the reward system that may mediate resilience to stress-related hedonic impairments holds promise not only to enhance our understanding of vulnerability and resilience to depression but also to ultimately inform advances in treatment and prevention strategies for MDD and other stress-related psychopathology. Such research may benefit specifically from combining laboratory stress manipulations with multimodal positron emission tomography/fMRI imaging to measure reward-related brain function alongside dopamine release (58), while also taking into account genetic variants affecting neurotransmission within the VS (59).

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