Winter 12-2019

Neuroticism and Stressful Life Events: Probing Mechanisms Underlying Vulnerability to Stress-Related Depression

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by

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A thesis presented to
The Graduate School
of Washington University in
partial fulfillment of the
requirements for the degree
of Master of Arts

December 2019
St. Louis, Missouri

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Acknowledgments

Thank you to my mentor, Dr. Ryan Bogdan, whose expertise, support, and guidance was instrumental to this process. Thank you to the St. Louis Personality and Aging Networks Lab and the Laboratory of NeuroGenetics for collecting the data used in this thesis. In particular, I want to thank the principal investigators, Dr. Thomas Oltmanns (SPAN: Study 1) and Dr. Ahmad Hariri (DNS: Study 2) for generously allowing me to use their data. I would also like to thank the members of my thesis committee, Dr. Ryan Bogdan, Dr. Renee Thompson, and Dr. Thomas Oltmanns. Finally, thank you to my friends, family, and the Behavioral Research and Imaging Neurogenetics Lab for the continual support.

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December 2019

ABSTRACT OF THE THESIS

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by

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Master of Arts in Psychology

Washington University in St. Louis, 2019

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Elevated neuroticism (N) potentiates the depressogenic effects of stressful life events (SLEs). We first replicate this association using longitudinal data (N=971 older adults) from the St. Louis Personality and Aging Network (SPAN) study. Here, SLEs prospectively predicted future depressive symptoms, especially among those reporting elevated N, even after accounting for prior depressive symptoms and previous SLE exposure (NxSLE interaction: $p=0.016$, $\Delta R^2=0.003$). These findings were further replicated in cross-sectional analyses of the Duke Neurogenetics Study (DNS), a young adult college sample with neuroimaging data (n=1,343: NxSLE interaction: $p=0.019$, $\Delta R^2=0.003$). Because evidence suggests that stress may promote depression by inducing reward-related neural dysfunction, we next tested whether neuroticism moderates the association between SLEs and reward-related ventral striatum (VS) activity in the DNS (N=1,195). Here, neuroticism moderated the association between SLEs and reward-related left VS activity such that individuals with high neuroticism who were also exposed to more SLEs had blunted left reward-related VS activation (NxSLE: $p=0.017$, $\Delta R^2=0.0048$), which was associated with a lifetime depression diagnosis ($r=-0.07$, $p=0.02$). These data suggest that

neuroticism may promote vulnerability to stress-related depression, and that sensitivity to stress-related VS dysfunction is a potential neural mechanism underlying this effect.

INTRODUCTION

The widespread prevalence and devastating impact of depression is starkly contrasted by our limited etiologic understanding of this complex disorder (Friedrich, 2017). Retrospective and prospective epidemiology research has strongly implicated stress exposure in the onset and maintenance of depression (Brown & Harris, 1978; Hammen, 2005; Kendler, Karkowski, & Prescott, 1999; Kessler, 1997) with evidence from experimental studies in humans and non-human animals that stress may induce depression (Anisman & Matheson, 2005; Bogdan & Pizzagalli, 2006; Hollon, Burgeno, & Phillips, 2015; Pizzagalli, 2014; Stanton, Holmes, Chang, & Joormann, 2019). However, there are vast individual differences in susceptibility to the depressogenic effects of stress, which has led to theoretically-guided (e.g., diathesis-stress and plasticity) investigations of individual difference factors (e.g., personality, biology, prior experience) that may moderate susceptibility to stress-related depression (Kendler & Karkowski-Shuman, 1997; Kessler, 1997; Mazure, 1998).

Neuroticism, which is a stable and heritable personality trait characterized by heightened negative emotionality and stress reactivity, is associated with depression risk (Jardine, Martin, Henderson, & Rao, 1984; Kendler & Myers, 2010; Kendler, Gatz, Gardner, & Pedersen, 2006; Smith et al., 2016), and moderates the association between stressful life events and depression (Kendler, Kuhn, & Prescott, 2004; Ormel, Oldehinkel, & Brilman, 2001). Initial longitudinal work by Ormel and colleagues showed that neuroticism potentiates the association between stressful life events and future depression and related characteristics among middle aged and older adults (Ormel et al., 2001; Ormel & Wohlfarth, 1991). This work has subsequently been replicated (Kendler et al., 2004) and extended to other stress phenotypes (e.g., chronic

stress;(Brown & Rosellini, 2011)), although not all studies have replicated this or related interactions (Brown & Rosellini, 2011; Wetter & Hankin, 2009) and the biological mechanisms that may underlie this vulnerability remain unclear.

Stress-induced anhedonia and alterations in reward-related neural circuitry may contribute to the depressogenic effects of stress (Pizzagalli, 2014; Stanton et al., 2019). The majority of this evidence comes from non-human animal models (i.e., rodents, non-human primates) showing that experimentally manipulated stress (e.g., early life stress, chronic mild stress, social defeat, threat-of-shock, maternal separation, immune challenge) reduces reward-related behavior (e.g., sucrose intake, self-administered rewarding brain stimulation, mobility in the forced swim test) (Anisman & Matheson, 2005; Chang & Grace, 2014; Felger et al., 2013; Kompagne et al., 2008; Tye et al., 2013). Emerging evidence suggests that stress-induced anhedonia may be conserved across species as stress exposure in humans is associated with anhedonic symptoms (Berenbaum & Connelly, 1993; Bogdan & Pizzagalli, 2009; Keller, Neale, & Kendler, 2007; Pizzagalli, Bogdan, Ratner, & Jahn, 2007), and experimentally-induced stress (e.g., threat-of-shock, social evaluation) can induce reward learning deficits (Berghorst, Bogdan, Frank, & Pizzagalli, 2013; Bogdan, Santesso, Fagerness, Perlis, & Pizzagalli, 2011; Bogdan & Pizzagalli, 2006; but see also Baranger et al., in preparation). Stress may promote depression and anhedonia by influencing neural circuits critical to reward processing. The corticostriatal circuit includes dopaminergic rich regions that show increased activation to motivating and rewarding stimuli, including the ventral tegmental area (VTA), ventral striatum (VS), dorsal striatum (DS), orbitofrontal cortex (OFC), and medial prefrontal cortex (PFC; (Chau, Roth, & Green, 2004; Haber & Knutson, 2010). This reward-responsive circuit is

sensitive to stress exposure; however, how stress impacts this circuit and in particular, response to reward, remains equivocal. For example, a wealth of evidence in rodents has reported that stress increases (Friedman et al., 2014), decreases (Chang & Grace, 2014), and/or results in no change (Chang & Grace, 2014) in VTA DA firing rates (Hollon et al., 2015). While many factors may contribute to these conflicting findings (e.g., regional specificity: DA projections to ventral striatum or medial PFC; types and duration of stress exposure), it is also possible that stress may decrease the number of active DA neurons but increase the activity of those that remain (Hollon et al., 2015; Stanton et al., 2019). Similarly, evidence from optogenetics studies shows that increasing phasic DA responses rescues stress-induced anhedonia but can also make animals more vulnerable to stress-induced anhedonia (Bekris, Antoniou, Daskas, & Papadopoulou-Daifoti, 2005; Chang & Grace, 2014; Chaudhury et al., 2013; Hollon et al., 2015; Tye et al., 2013). Neuroimaging studies in humans show that stress is correlated with blunted corticostriatal circuit activation to reward and that acute stress reduces reward-related activation, particularly in the ventral striatum (Corral-Frías et al., 2015; Kumar et al., 2014; Lincoln et al., 2019; Novick et al., 2018; Oei, Both, Van, & Van, 2014; Ossewaarde et al., 2011; Porcelli, Lewis, & Delgado, 2012; but see Gaillard et al., 2019; Treadway et al., 2017; van Leeuwen et al., 2019). Such findings mirror what has been found among individual with depression and anhedonic symptoms (Eckstrand et al., 2019; Heshmati & Russo, 2015; Keedwell, Andrew, WIlliams, Brammer, & Phillips, 2005; Pizzagalli et al., 2009; Smoski et al., 2009; Zhang, Chang, Guo, Zhang, & Wang, 2013; but see also Knutson, Bhanji, Cooney, Atlas, & Gotlib, 2008). Taken together, these data suggest that stress-related differences in reward-related ventral striatum activation represent a plausible neural mechanism linking stressful life event exposure and neuroticism to depression.

The Current Studies

Using data from two independent samples, we first attempt to replicate the finding that neuroticism potentiates the impact of stressful life events on depression. We then test whether neuroticism moderates the association between stressful life events and reward-related ventral striatum activation. To this end, we used longitudinal data from the St. Louis Personality and Aging Network Study (SPAN) study (n=971) to examine whether neuroticism potentiates the association between stressful life event exposure and subsequent depression after accounting for prior depressive symptoms and stressful life events. We also used cross-sectional data from the Duke Neurogenetics Study (DNS; n=1,195-1,343) to test whether those high in neuroticism are more susceptible to stress-related depression and blunted ventral striatum response to reward.

METHODS

Study 1

Participants

The St. Louis Personality and Aging Network (SPAN) study is an ongoing longitudinal protocol assessing a wide range of personality, health, social, and biological characteristics in a representative community sample of 1,630 older adults (N_{Female}=889; M_{Age}=60.07±2.74; *range*=55-65 at baseline) residing in the St. Louis, Missouri area. Recruitment procedures have been described in detail elsewhere (Oltmanns, Rodrigues, Weinstein, & Gleason, 2014). Each participant completed a 3-hour in-person assessment at baseline (*N*=1,630; baseline), and at 2 subsequent in-person follow-up sessions (IPFU1 n= 1,260, IPFU2 n=1,067; a 3rd is currently ongoing). Participants were also asked to complete a short sequence of mailed or online FU questionnaires every 6 months after entering the study. In this study, we use data collected from the IPFU1, and IPFU2 assessments to allow us to account for prior depressive symptoms and SLE exposure (n=971 nonmissing data on dependent and independent variables across assessments; **Table 1**). The protocol was approved by the Washington University in St. Louis Institutional Review Board. All participants provided written consent before participating and received $60 for each in-person visit.

Measures

The ***Beck Depression Inventory*** (BDI-II; (Beck, Steer, & Brown, 1996)) is a 21 item self-report measure of current depressive symptoms. Scores range from 0 to 63, with higher scores

indicating greater symptom severity (IPFU1: *N*=1,256; *M*=4.82 ± 6.163; α=0.902; IPFU2: *N*=1,053; *M*=5.34 ± 6.608; α=0.908).

The ***List of Threatening Experiences Questionnaire*** (LTE-Q; (Brugha & Cragg, 1990)) was used to assess the presence of recent stressful life events (e.g., personal serious illness, injury, or assault; death of a partner, parent, or child; fired from a job). The LTE-Q probes the presence of twelve events and three additional events (i.e., victim of serious crime, change in family responsibilities, other major event) that were included for the purposes of the SPAN study (Gleason, Powers, & Oltmanns, 2012). Endorsement of self-reported events was followed up by a phone interview with a research assistant to confirm event occurrence and recode data as needed (Gleason et al., 2012). The LTE-Q assessed the number of stressful life events that occurred in the 6 months prior to each assessment (IPFU1: *N*=1,253; *M*=0.65±0.825; *range*=0–4; IPFU2: *N*=1,067; *M*=0.66 ± 0.847; *range*=0-6).

The ***Revised NEO Personality Inventory*** (NEO PI-R; (Costa & MacCrae, 1992)) is a 240-item self-report questionnaire that assesses five personality domains: neuroticism, extraversion, openness, agreeableness, and conscientiousness. The 48-item neuroticism subscale (NEO-N), which was administered at IPFU1 was used in this study (*N*=1,260; *M*=68.9 ± 20.668; α=0.925).

Statistical Analyses

Linear regression analyses were used to assess whether neuroticism moderates the association between recent life stress and depression. Because recent life stress was only assessed at the IPFU1 and IPFU2 session, our analysis evaluated whether neuroticism assessed at IPFU1

interacted with recent life stress assessed at IPFU2 (i.e., stressful life events occurring in the preceding 6 months) to predict depression at IPFU2, as this allowed us to account for prior life stress and depressive symptoms assessed at IPFU1 in our analysis. Outliers were winsorized to ±3SDs before conducting analyses (*BDI:* IPFU1 n=22, IPFU2 n=27; *LTE:* IPFU1 n=8, IPFU2 n=7; *Neuroticism:* IPFU1 n=8). Prior to the computation of interaction terms, variables were mean centered so that main effects in these full models may be interpreted at the average moderator level. Analyses were conducted in three steps. First, we examined whether the neuroticism x recent life stress interaction was associated with depression without inclusion of any additional covariates other than main effects of neuroticism and recent life stress. Second, we included the following covariates: age, gender, self-reported race (i.e., white/not white, black/not black, Hispanic/not Hispanic), annual household income, prior depressive symptoms (i.e., BDI-II scores from IPFU1), and prior stressful life events (from IPFU1). Lastly, consistent with recommendations, covariate of no-interest x predictor variable interacts were further entered as covariates in our analyses (e.g., neuroticism x sex) to account for these potential confounds (Keller, 2014). Any significant interactions were probed using simple slope testing (-1 SD, average, +1 SD) as well as Johnson-Neyman tests. Analyses were conducted using list wise deletion using the SPSS v25 and the PROCESS v3.4 macro (Hayes, 2017).

Study 2

Participants

Following quality control procedures and exclusions**,** neuroimaging (N=1,195) and behavioral (N=1,344) data were available from young adult college students (M_{age}=19.72, *range*=18-22;

Table 2) were available for analyses from the Duke Neurogenetics Study (DNS). All participants provided written informed consent to a protocol approved by the Duke University IRB and were compensated $120 for their participation. Exclusion criteria for the DNS included: (1) medical diagnoses of cancer, stroke, diabetes, chronic kidney/ liver disease, or lifetime history of psychotic symptoms; (2) use of psychotropic, glucocorticoid, or hypolipidemic medication; (3) conditions affecting cerebral blood flow and metabolism (e.g., hypertension); and (4) not meeting quality control standards (e.g., having braces) for fMRI scanning (Swartz, Knodt, Radtke, & Hariri, 2015).

Measures

Self-report

Recent Stressful Life Events: A modified version of the ***Life Events Scale for Students*** (LESS; (Clements & Turpin, 1996)) was used to assess the presence of common stressful life events (e.g., death of a parent, pregnancy, failing a course) in the past 12 months. In addition to indicating whether a given event occurred, participants rated the subjective impact of each event from 1 (*minor impact*) to 4 (*severe impact*). To retain consistency with SPAN analyses, we used the total number of reported events (N=1,344, M=4.34 ± 2.978).

Neuroticism: The ***NEO PI-R*** (described in Study 1) was used to assess self-reported neuroticism (N=1,344; M=86.01 ± 22.520, α=0.924).

Depression: The 20-item Center for Epidemiologic Studies Depression Scale (CES-D) assessed depressive symptoms over the past week (N=1,345, M=10.06 ± 8.26). A clinical diagnosis of lifetime (i.e., current or past depression: n=68) and current (n=5) was assessed

through interview with a trained clinician using the lifetime electronic Mini International Neuropsychiatric Interview (Sheehan et al., 1998).

Neuroimaging

To probe reward-related ventral striatum (VS) activity, participants underwent six blocks of a commonly used card-guessing task while fMRI data were acquired (Delgado, Nystrom, Fissell, Noll, & Fiez, 2000; Forbes et al., 2009; Hariri et al., 2006; Nikolova, Bogdan, Brigidi, & Hariri, 2012). Blocks were presented in a pseudorandom order, each consisting of five predominantly positive (80% correct feedback) or predominantly negative (20% correct feedback) trials. Although participants were told their accuracy would impact their monetary earnings after the scanning session, all participants were given $10 for completing the task. During each trial, participants were shown the back of card and given three seconds to guess whether its value would be less than or greater than five; face cards were excluded to create the illusion of 50% probability for either choice. After the participant indicated their choice via button-press, the true value of the card was displayed for 500 ms, followed by 500 ms of appropriate feedback (i.e., a green “up” arrow for positive/ correct-feedback, and a red “down” arrow for negative/ incorrect feedback). A crosshair was then shown for an additional three seconds, giving each trial a total length of seven seconds. Each block also consisted of one incongruent trial to prevent participants from anticipating their feedback, and to maintain their motivation and attention. The six task blocks were interspersed with three control blocks in which participants viewed an “X” for three seconds, executed a button press, and then viewed an asterisk for 500 ms before being shown a yellow circle for a final 500 ms.

Scans were conducted using a GE MR750 3T scanner equipped with high-power high-duty-cycle 50-mT/m gradients at 200 T/m/s slew rate, and an eight-channel head coil for parallel imaging at high bandwidth up to 1 MHz at the Duke-UNC Brain Imaging and Analysis Center (BIAC). As an index of VS reward reactivity, we examined regions of the VS in which activity was greater for positive feedback than for negative feedback. Parameter estimates of reward-related activity in the left and right ventral striatum (LVS and RVS, respectively) were extracted from a 5 mm sphere centered on the maximal voxels identified from whole brain analysis ($p <$ .05 FEW, K_E=10) (Hariri et al., 2006).

Statistical Analyses

Similar to the statistical analyses presented in Study 1, moderation analyses evaluated whether neuroticism moderates associations between recent stressful life events and reward-related ventral striatum reactivity as well as depression. Linear models were used for all outcomes with the exception of lifetime depression history which adopted a logistic approach. Outliers on predictor variables were winsorized to ± 3SDs before conducting analyses (NEO-N: N=6; LESS: N=17, CES-D: N=25). We first tested whether this interaction was present when accounting for main effects but no other covariates. Second, we tested whether this interaction was robust to the inclusion of age, sex, perceived socioeconomic status, and self-reported ethnicity (i.e., White, Black, Asian, Hispanic). Perceived socioeconomic status was assessed by asking participants to place themselves on a ladder (0=lowest, 10=highest) relative to all other people in the United States (Adler, Epel, Castellazzo, & Ickovics, 2000). Third, we evaluated whether the interaction was robust to the inclusion of these covariates as well as the interaction between them and SLEs

and N to account for these potential confounds (Keller, 2014). Finally, we tested whether ventral striatum response to reward was associated with depressive symptoms and a clinical diagnosis of depression. Analyses were conducted using list wise deletion using the SPSS v25 and the PROCESS v3.4 macro (Hayes, 2017).

RESULTS

Study 1

Neuroticism (IPFU1) was positively correlated with stressful life event exposure (IPFU2: r=0.09) and depression (IPFU2: r=0.51), which was also related to stressful life event exposure (IPFU2: r=0.22), all ps<0.01. When only considering significant main effects of neuroticism and stressful life events, neuroticism measured at IPFU1 interacted with IPFU2 stressful life events to predict IPFU2 depression (n=971; b=0.03 [95% CI: 0.013, 0.049], p =0.0008, ΔR^2=0.0082; **Figure 1; Table 3**). This effect remained significant and directionally consistent when considering the main effects of age, gender, race, annual household income, IPFU1 depressive symptoms, and stressful life events prior to IFPU1 (n=911; b=0.02 [95% CI: 0.006, 0.037], p =0.01, ΔR^2=0.0037; **Table 3**) and when including these main effects and their interactions with neuroticism and stressful life events (e.g., prior depression x stressful life events; n=911; b=0.03 [95% CI: 0.008, 0.050], p=0.006, ΔR^2=0.0043; **Table 3**). Post-hoc simple slope testing revealed that SLEs were associated positively associated with depression among individuals with low (-1 SD), average, and high (+1 SD) neuroticism in a graded fashion such that higher levels of neuroticism potentiated this relationship (low: b = 0.65, p=0.021; average: b=1.27, p<0.0001, high: b=1.89, p<0.0001; **Figure 1**). Johnson-Neyman tests revealed that the relationship between stressful life events and depression was positively correlated among individuals with Neuroticism scores ≥ 45.71 (88.2% of sample).

Study 2

Neuroticism and recent stressful life events were each positively correlated with one another, depressive symptoms and a lifetime diagnosis of depression (*r*s=0.15-0.60, all ps<0.001), but not left or right ventral striatum response to reward (*r*s=-0.015 - -0.044, all ps >0.12). Consistent with Study 1, recent stressful life events moderated the association between neuroticism and depressive symptoms (n=1,343; b=0.0056 [95% CI: 0.001, 0.010], p =0.019, ΔR^2=0.0026; **Figure 2A; Table 4**). This effect remained significant and directionally consistent when considering age, gender, race/ethnicity, and perceived socioeconomic status (n=1,286; b=0.006 [95% CI: 0.0014, 0.0110], p =0.012, ΔR^2=0.0031; **Table 4**) and when including these main effects and their interactions with neuroticism and stressful life events (e.g., prior depression x stressful life events; n=1,286; b=0.0064 [95% CI: 0.0011, 0.0117], p =0.019, ΔR^2=0.0043; **Table 4**). Post-hoc simple slope testing revealed that SLEs were positively associated with depression among individuals with low (-1 SD), average, and high (+1 SD) neuroticism in a graded fashion such that higher levels of neuroticism potentiated this relationship (low: b = 0.28 [0.10, 0.45], p=0.002; average: b=0.40 [0.29, 0.52], p<0.0001, high: b=0.53 [0.39, 0.67, p<0.0001) in a graded fashion (**Figure 2A**). Johnson-Neyman tests revealed that the relationship between stressful life events and depression was positively correlated among individuals with Neuroticism scores ≥ 52.52 (92% of sample).

Most interestingly, the interaction between neuroticism and SLEs was significantly associated with left, but not right, reward-related VS activation, with adjustment for multiple testing (i.e., 2 hemispheres; *Left:* b=-0.0002, p=0.017, ΔR^2=0.0048, **Figure 2B**; Right: b=-0.0001, p=0.099, ΔR^2=0.0023; **Table 5**). Identical results were found when considering age, sex,

race/ethnicity, and perceived socioeconomic status as covariates (b=-0.0002, p=0.018, ΔR^2=0.0047) and when further adding their interactions with SLEs and neuroticism (b=-0.0002, p=0.026, ΔR^2=0.0041; **Table 5**). Post-hoc simple slope testing revealed that SLEs were negatively coupled with left reward-related VS activation only among individuals with high (i.e., +1SD) neuroticism(b=-0.004, p = 0.03 (AVG: b=-0.0006, p =0.70, -1SD: b=0.003, p = 0.22; **Figure 2B**). Further, Johnson-Neyman tests revealed that the negative association between SLEs and reward-related left VS activation arose among individuals who had higher neuroticism scores ≥104.40 (20.6% of sample). Finally, left, but not right reward-related ventral striatum reactivity was negatively correlated with a lifetime diagnosis of clinical depression, but not current depressive symptoms in the absence of covariates (Lifetime depression diagnosis: left r=-0.07, p = 0.02, right r=-0.04, p = 0.20, **Figure 2C**; CES-D: left r=-0.003, p = 0.93, right r=-0.014, p = 0.63). The association with lifetime depression remained when including age, sex, race/ethnicity, and perceived SES in the model (n=1,182: b=-1.79, p =0.023).

DISCUSSION

Two primary findings emerged from the present study. First, in a sample of older adults followed longitudinally (Study 1), we find evidence that neuroticism interacts with stressful life events (SLEs) to confer susceptibility to later depression. More specifically, SLEs are correlated with prospective depression and this relationship is potentiated among those with elevated neuroticism, even after accounting for depression and SLE exposure at baseline. This finding was replicated in cross-sectional analyses in a sample of young adult college students (Study 2). Second, in the sample of young adult college students, we find that neuroticism also moderates the association between recent stressful life event exposure and reward-related left ventral striatum (VS) response. Among those with greater neuroticism, recent stressful life events were negatively correlated with reward-related VS activation, which was correlated with lifetime history of a depression diagnosis, but not current depressive symptoms. Collectively, these findings suggest that neuroticism may potentiate risk for stress-related depression and that blunted VS response to gains relative to losses may be a neural mechanism through which this vulnerability arises.

Stress is a common experience that is one of the most robust predictors of depression (Hammen, 2005; Kessler, 1997). However, not everyone exposed to SLEs will suffer from depression. In a replication of prior work (Kendler et al., 2004; Ormel et al., 2001; but see also Brown & Rosellini, 2011; Wetter & Hankin, 2009), we find that heightened neuroticism confers susceptibility to stress-related depression in longitudinal analyses of an older sample in Study 1 and cross-sectional analyses of a young college sample in Study 2. Longitudinal epidemiological work suggests that the frequent comorbidity of anxiety and depression is characterized by

sequential comorbidity in which anxiety typically precedes the development of depression (Pine, Cohen, Gurley, Brook, & Ma, 1998; Rice et al., 2017; Wetherell, Gatz, & Pedersen, 2001); but see also evidence for depression preceding generalized anxiety disorder as well: (Moffitt et al., 2007; Pine et al., 1998). Anxiety and depression are both characterized by negative affect, a major component of neuroticism, but depression is uniquely characterized by deficits in positive affect (Watson et al., 1995). In light of evidence that: 1) general anxiety symptoms often precede the development of depression, 2) stressful life events potentiate the association between neuroticism and depression, and 3) stress can induce reward processing dysfunction, it is possible that depression risk conferred by neuroticism is partially attributable to stress-related reward dysfunction. Consistent with this putative mechanism, in Study 2, we find that the association between stressful life events and left reward-related VS reactivity is moderated by neuroticism, such that those with elevated neuroticism and greater stressful life event exposure had reduced reward-related VS reactivity, which, in turn, was associated with clinical depression.

How neuroticism confers increased susceptibility to stress-related reductions in VS activation to reward is unclear, but some speculation can be advanced based on emergent data from non-human animal models. For example, anhedonic-like behavior in rodents induced by early life stress is mediated by reward-related activation of corticotropin releasing hormone [CRH] neurons in the central nucleus of the amygdala that typically mediate anxiety-related behavior (Bolton et al., 2018). Elevated amygdala activity and connectivity at rest, which can be induced by CRH infusion into the central amygdala in non-human primates (Kalin et al., 2016), has been inconsistently associated with neuroticism (Servaas et al., 2013; Silverman et al., 2019; Stein, Simmons, Feinstein, & Paulus, 2007) with evidence from one experiment that neuroticism

is only correlated with increased amygdala reactivity under a stress manipulation (Everaerd, Klumpers, van Wingen, Tendolkar, & Fernández, 2015). In the context of evidence that amygdala and VS activation interact to influence stress-related psychiatric outcomes (e.g.,(Nikolova, Knodt, Radtke, & Hariri, 2016), this represents one possible mechanism through which the interaction of neuroticism and stress may promote attenuated reward-related ventral striatum activity. Alternatively, and not mutually exclusive, evidence suggests that natural rewards inhibit stress-induced increases in CRH signaling in the paraventricular nucleus [PVN] of hypothalamic-pituitary-adrenal (HPA) axis, to blunt anxiety-like behavior in rodents (Yuan et al., 2019). It is possible that reward does not have such anxiolytic effects in individuals with high trait neuroticism, which then results in less engagement of this circuitry, particularly under stress.

Limitations and Considerations

The present studies are characterized by several limitations that should be considered when interpreting these results. First, Study 1 and Study 2 are characterized by samples that are vastly different in age and other demographic factors. While this is a strength with regard to generalizability for our finding that neuroticism moderates the association between stressful life events, it remains unclear whether the association with reward-related ventral striatum response is also present at later ages. Second, the analyses in Study 2 were cross-sectional in nature. It will be important for future studies to examine whether the N x SLE interaction is prospectively associated with future reward-related ventral striatum reactivity and depression at this developmental time. Third, we evaluated cumulative life events; in light of evidence that stressor type and duration can differentially impact depression and related neural circuitry (Brown &

Rossellini, 2011), it is important for future work, with greater power, to evaluate different dimensions of stress exposure. Fourth, ventral striatum response to reward was only associated with lifetime clinical depression and not current depressive symptoms.[1] It is possible that reduced ventral striatum response to reward may only be a marker of clinically significant depression risk. Lastly, growing evidence suggests that the test-retest reliability of task-related fMRI activation, including that elicited by this task, is poor (Elliott et al., 2019). While longer scan durations may improve reliability, the vast majority of individual difference studies in the literature, as well as ongoing large-scale data collection efforts (e.g., Adolescent Brain Cognitive Development [ABCD] Study, (Casey et al., 2018), are not characterized by such scans. As such, the utility of task-related fMRI for understanding individual differences as currently implemented in this study and the majority of the field, should garner increased skepticism. With that said, our associations between ventral striatum response to reward and depression risk are consistent with prior reports in the literature.

Conclusions

In two independent datasets, we examined the link between stressful life events, neuroticism, and depression. Older adults with greater levels of neuroticism are at increased risk for future depression, particularly in the context of more stressful life events. Cross-sectional analyses in a young adult sample also found that neuroticism potentiates the link between stress and depression. Finally, in Study 2, we find that reduced reward-related ventral striatum activation to reward was associated with depression diagnosis. Taken together, these studies provide

[1] Notably, there were too few cases with a current diagnosis of depression (n=5) to permit meaningful analyses. However, there was evidence that blunted left ventral striatum response to reward was associated with current depression diagnosis, r=-0.055, p =0.059.

additional evidence that neuroticism moderates the depressogenic effects of stress and raises the intriguing possibility that differences in reward-related neural circuitry may be a mechanism through which this risk is conferred.

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Figure 1. The Neuroticism x Stressful Life Event Interaction is Prospectively Associated with Depression in Older Adults

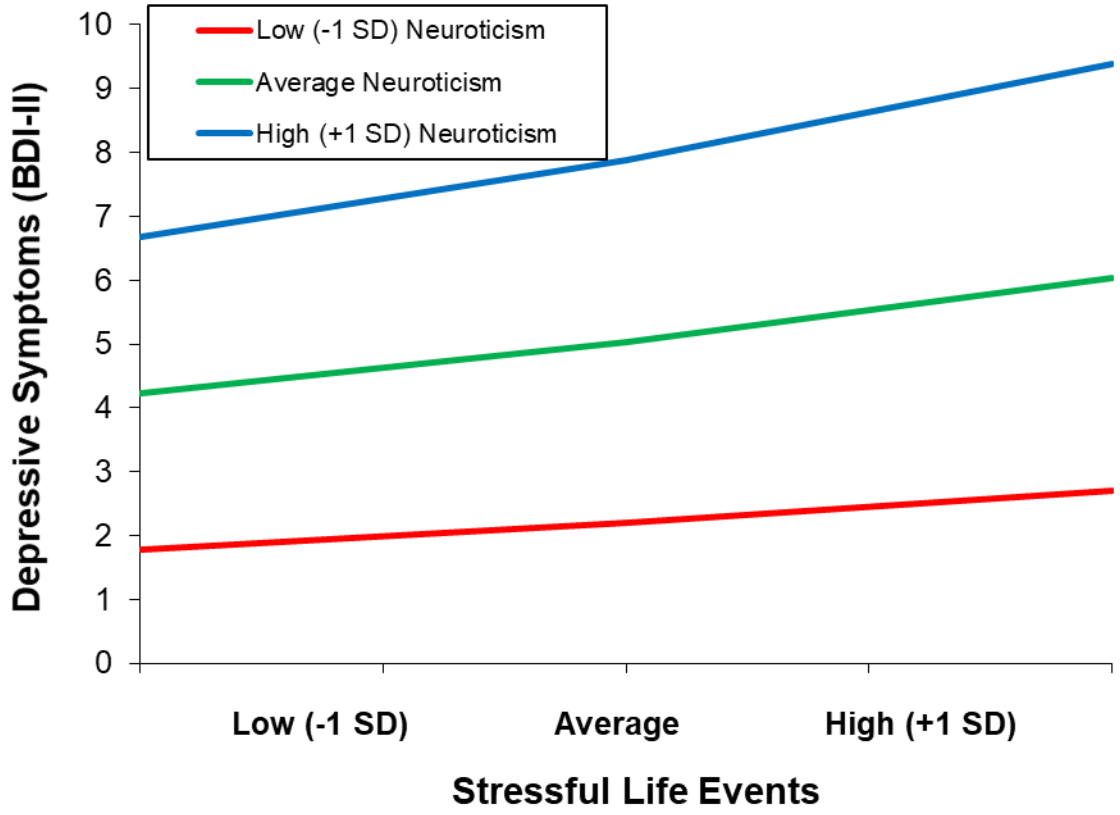

Figure 2. Neuroticism, Stressful Life Events, Reward-related Ventral Striatum Activation, and Depression in Young Adult College Students.

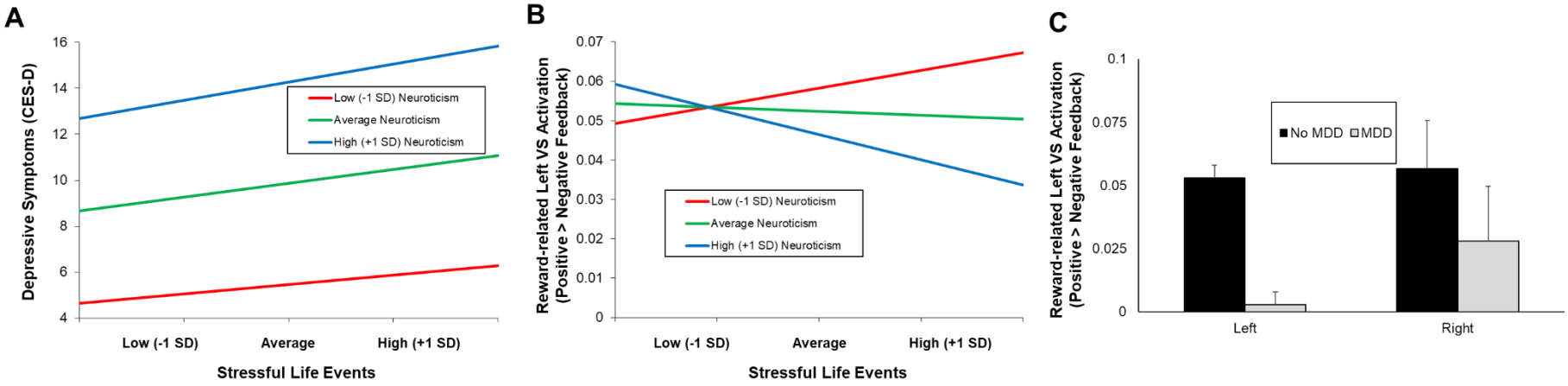

Table 1. Demographic Information (Study 1)

	Baseline	IPFU1	IPFU2
N	1,630	1,260	1,067
Gender, female (%)	889 (*54.5*%)	--	--
Age	60.067 ± 2.735	--	--
White (%)	1061 (65.1%)	--	--
Black (%)	516 (31.7%)	--	--
Hispanic (%)	30 (1.8%)	--	--
Annual Household Income*	3.90 ± 2.19	--	--
Neuroticism (NEO-N)	72.201 ± 20.720	68.98 ± 20.685	--
Recent Stressful Life Events (LTE-Q)	--	0.65 ± 0.825	0.66 ± 0.847
Depressive Symptoms (BDI-II)	5.23 ± 6.036	4.82 ± 6.163	5.34 ± 6.608

*Income was self-reported on the following scale: 1 = under $20k; 2 = $20k - $39,999; 3 = $40k - $59,999; 4 = $60k - $79,999; 5 = $80k - $99,999; 6 = $100k - $119,999; 7 = $120k - $139,999; 8 = $140k or more.

Table 2. Demographic Information (Study 2)

	Baseline
N	1,343
Gender, female (%)	771 (57.3%)
Age	19.71 ± 1.26
White (%)	586 (44.5%)
Black (%)	357 (27.1%)
Asian (%)	357 (26.5%)
Hispanic (%)	136 (10.3%)
Perceived SES*	7.45 ± 1.69
Neuroticism (NEO-N)	86.01 ± 22.52
Recent Stressful Life Events (LTE-Q)	4.34 ± 2.98
Depressive Symptoms (CES-D)	10.06 ± 8.26
Depression Diagnosis (Lifetime)	68 (5.1%)
Depression Diagnosis (Current)	5 (0.4%)

*Perceived socioeconomic status was assessed by asking participants to place themselves on a ladder (0=lowest, 10=highest) relative to all other people in the United States.

Table 3. Neuroticism x Stressful Life Event Interaction is Associated with Depression: Regression Results (Study 1)

	No Covariates Other Than Main Effects		**Typical Covariates**		**Typical Covariates and Covariate x Predictor Interaction**	
Variable	*b*	*p*	*b*	*p*	*b*	*p*
Neuroticism (N)	**0.14**	**<0.001**	**0.06**	**<0.001**	**0.10**	**0.01**
SLEs	**1.29**	**<0.001**	**0.76**	**<0.001**	-2.25	0.10
Age	--	--	0.05	0.32	-0.01	0.94
Gender	--	--	0.53	0.06	-1.29	0.20
White	--	--	-1.72	0.06	1.40	0.63
Black	--	--	-1.22	0.20	-1.64	0.09
Hispanic	--	--	0.25	0.80	0.71	0.48
Income	--	--	-0.05	0.48	-0.29	0.25
Prior Depression (PDep)	--	--	**0.52**	**<0.001**	**0.29**	**0.01**
Prior SLEs (PSLE)	--	--	0.19	0.29	-0.43	0.51
NxAge	--	--	--	--	0.001	0.69
NxGender	--	--	--	--	**0.03**	**0.05**
NxWhite	--	--	--	--	-0.05	0.19
NxBlack	--	--	--	--	-0.03	0.53
NxHispanic	--	--	--	--	0.08	0.10
NxIncome	--	--	--	--	0.003	0.35
NxPDep	--	--	--	--	**0.003**	**0.03**
NxPSLE	--	--	--	--	0.01	0.26
SLExAge	--	--	--	--	-0.04	0.50
SLExGender	--	--	--	--	0.46	0.20
SLExWhite	--	--	--	--	**2.81**	**0.04**
SLExBlack	--	--	--	--	**3.38**	**0.01**
SLExHispanic	--	--	--	--	-1.83	0.16
SLExIncome	--	--	--	--	-0.11	0.22
SLExPDep	--	--	--	--	-0.08	0.94
SLExPSLE	--	--	--	--	-0.06	0.76
NxSLE	**0.03**	**0.008**	**0.02**	**0.01**	**0.03**	**0.01**

Table 4. Neuroticism x Stressful Life Event Interaction is Associated with Depression: Regression Results (Study 2)

	No Covariates Other Than Main Effects		**Typical Covariates**		**Typical Covariates and Covariate x Predictor Interaction**	
Variable	*b*	*p*	*b*	*p*	*b*	*p*
Neuroticism (N)	**0.20**	**<0.001**	**0.19**	**<0.001**	0.06	0.67
SLEs	**0.40**	**<0.001**	**0.38**	**<0.001**	1.17	0.24
Age	--	--	-0.09	0.50	-0.61	0.27
Gender	--	--	-0.63	0.07	-0.83	0.56
White	--	--	-0.98	0.16	0.006	0.998
Black	--	--	0.44	0.59	-4.53	0.20
Asian	--	--	-0.42	0.56	-1.58	0.61
Hispanic	--	--	-0.83	0.31	-0.68	0.85
SES	--	--	**-0.28**	**0.01**	0.01	0.98
NxAge	--	--	--	--	0.008	0.22
NxGender	--	--	--	--	0.01	0.41
NxWhite	--	--	--	--	-0.006	0.87
NxBlack	--	--	--	--	0.05	0.25
NxAsian	--	--	--	--	0.02	0.51
NxHispanic	--	--	--	--	0.008	0.84
NxSES	--	--	--	--	-0.005	0.23
SLExAge	--	--	--	--	-0.04	0.46
SLExGender	--	--	--	--	-0.21	0.08
SLExWhite	--	--	--	--	-0.12	0.59
SLExBlack	--	--	--	--	0.19	0.47
SLExAsian	--	--	--	--	-0.20	0.37
SLExHispanic	--	--	--	--	-0.18	0.50
SLExSES	--	--	--	--	0.05	0.15
NxSLE	**0.006**	**0.019**	**0.006**	**0.012**	**0.006**	**0.02**

Table 5. Neuroticism x Stressful Life Event Interaction is Associated with Reward-related Left Ventral Striatum Activation: Regression Results (Study 2)

	No Covariates Other Than Main Effects		**Typical Covariates**		**Typical Covariates and Covariate x Predictor Interaction**	
Variable	*b*	*p*	*b*	*p*	*b*	*p*
Neuroticism (N)	-0.0003	0.23	-0.0002	0.34	-0.0035	0.35
SLEs	-0.0006	0.70	-0.0008	0.67	-0.042	0.13
Age	--	--	**-0.007**	**0.09**	-0.019	0.21
Gender	--	--	**-0.03**	**0.003**	-0.04	0.30
White	--	--	0.012	0.55	0.20	0.30
Black	--	--	0.013	0.57	0.12	0.21
Asian	--	--	0.015	0.47	**0.27**	**0.001**
Hispanic	--	--	-0.002	0.93	0.17	0.09
SES	--	--	-0.002	0.54	-0.004	0.73
NxAge	--	--	--	--	0.0003	0.11
NxGender	--	--	--	--	0.0001	0.83
NxWhite	--	--	--	--	**-0.0032**	**0.0009**
NxBlack	--	--	--	--	**-0.0026**	**0.023**
NxAsian	--	--	--	--	**-0.0036**	**0.0003**
NxHispanic	--	--	--	--	**-0.0032**	**0.0057**
NxSES	--	--	--	--	-0.0001	0.52
SLExAge	--	--	--	--	-0.0026	0.06
SLExGender	--	--	--	--	0.0009	0.79
SLExWhite	--	--	--	--	**-0.015**	**0.0098**
SLExBlack	--	--	--	--	**0.022**	**0.0042**
SLExAsian	--	--	--	--	0.0084	0.18
SLExHispanic	--	--	--	--	**0.019**	**0.010**
SLExSES	--	--	--	--	0.05	0.15
NxSLE	**-0.0002**	**0.017**	**-0.0002**	**0.018**	**-0.0002**	**0.026**