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

Jamie L. Hanson, Ahmad R. Hariri, and Douglas E. Williamson

ABSTRACT

BACKGROUND: Emotional neglect is associated with multiple negative outcomes, particularly increased risk for depression. Motivated by increasing evidence of reward-related ventral striatum (VS) dysfunction in depression, we investigated the role of developmental changes in VS activity on the emergence of depressive symptomatology as a function of emotional neglect.

METHODS: We examined relationships between longitudinal neuroimaging of reward-related VS activity, assessments of mood, and measures of emotional neglect in 106 participants first scanned between ages 11 to 15 and then 2 years later.

RESULTS: We found that greater levels of emotional neglect were associated with blunted development of reward-related VS activity between the first and second assessments (as indexed by lower residualized change scores). Additionally, we found that decreases in this reward-related VS activity were related to greater depressive symptomatology and partially mediated the association between emotional neglect and subsequent depressive symptomatology.

CONCLUSIONS: Our results provide an important demonstration that blunted development of reward-related VS activity as a function of emotional neglect predicts the emergence of depressive symptoms in adolescents. Further, our results are consistent with emerging evidence for the importance of reward-related VS dysfunction in the etiology and pathophysiology of depression. These results are a first step toward developing the ability to predict, prevent, and treat stress-related psychopathology through the targeting of specific neural phenotypes.

Keywords: Depression, Early life stress, Emotional neglect, fMRI, Longitudinal, Neurodevelopment

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Early life stress (ELS) is associated with compromised physical and mental development, as well as long-term physical and mental difficulties (1). In regard to mental health, meta-analyses suggest over a 65% increase in the risk for major depressive disorder (MDD) following ELS such as abuse or neglect (2). Though well studied and well replicated in psychological and epidemiological research, the exact neurobiological mechanisms mediating the association between such adverse experiences and later depression remain unclear. ELS is associated with sensitization of the neuroendocrine stress response (3) and such differences may be amplified by genetic variation (4). However, further mechanistic clarification is crucial for advancing efforts to establish predictive biomarkers of relative risk and resilience. Targeted neurobiological investigations, particularly those employing neuroimaging, could also aid in developing the next generation of intervention strategies.

In considering the various forms of ELS, psychological maltreatment, such as emotional neglect (EN) may be of particular concern, as this adversity is prevalent, often goes unreported, and is associated with a twofold increase in adolescent mental illness (5–7). Emotional neglect, which is characterized by emotional unresponsiveness, unavailability, and limited emotional interactions between parent and child (8), has been associated with the development of a host of psychological difficulties including increased shame, humiliation, anger, and feelings of worthlessness (9). Furthermore, EN has been found to be one of the "most predictively potent maltreatment type(s)" with strong links to symptoms of MDD (5,10).

To date, the majority of investigations into neural mechanisms of risk related to forms of ELS have focused on dysfunction of brain circuits involved with threat processing and stress responsiveness such as the amygdala (11,12). However, emerging research further implicates dysfunction of reward-related neural circuitry in the pathophysiology of depression (13). Central in this neural circuitry is the ventral striatum (VS), a subcortical structure supporting reward responsiveness and learning (14). VS dysfunction has been theorized to underlie symptoms of MDD (including anhedonia and apathy), and neuroimaging studies have reported decreased reward-related VS activity in depressed individuals (15,16). Furthermore, there is evidence that psychological factors protective against MDD, including maintaining

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optimism and a positive self-concept, are associated with increased activity of the VS and interconnected neural circuitry (17). In support of these clinical studies, preclinical animal models have found associations between depressive behavior and VS functioning as assessed by levels of transcription factors and gene expression (18,19). Further work has found antidepressive-like effects after manipulation of VS neurobiology, such as changing the levels of transcription factors or the firing rates of neurons that project to the VS (20,21), again underscoring a central role of the functioning of this brain region in the pathophysiology of depression.

Despite the links suggested by the work described above, few investigations have directly examined associations between EN, VS dysfunction, and depression. One study reported behavioral deficits in reward processing in children who suffered maltreatment (22). A small number of additional descriptive studies have noted lower VS activity in samples of children (23,24) or in adults that have suffered maltreatment (25). The dearth of clinical research in this area is further surprising, given robust findings from preclinical models linking ELS to alterations in reward-related neural circuitry, particularly dopaminergic modulation of VS activity (26,27). Additionally, changes in reward-related behaviors, such as weakened conditioned place preferences, have been consistently noted in these preclinical models of ELS (28).

The limited available research, though informative, has not investigated whether differences in reward-related VS function specifically predict later mood disturbances related to EN or other types of ELS. Prospective work is critically needed, particularly during adolescence. Initial episodes of depression are likely to occur during this developmental transition (29,30), conferring greater risk for MDD in adulthood (31). Furthermore, focusing on reward during this time period may be particularly important, given that anhedonia and low positive affect in adolescence predicts later MDD (32–34). Emotionally unresponsive caregiving during childhood and adolescence could influence the development of this circuitry, leading to difficulties in emotion processing and regulation (35,36). When examining these possible developmental pathways, it will be important to carefully consider seminal studies examining structural brain development that have found trajectories of neurobiological change may be more predictive of outcomes than a single measurement at one time point (37). Here, we report on such a prospective study. Specifically, we used longitudinal neuroimaging and behavioral data to test the hypothesis that changes in reward-related VS activity would mediate the relationship between emotional neglect and the emergence of later depressive symptomatology. We predicted that higher levels of EN would be related to greater decreases in reward-related VS activity over time and that this change in activity would partially explain the association between depressive symptoms and EN. Finally, we examined neural responses to specific valences of feedback (i.e., positive or negative) to more fully understand potential relationships between EN, symptoms of depression, and VS activity. Based on past theoretical and empirical reports linking lower VS activity to anhedonic elements of depression, we predicted lower VS activity to positive feedback in individuals reporting higher levels of EN.

METHODS AND MATERIALS

Participants

Longitudinal data were available for 106 adolescents (51 female adolescents; mean age at scan 1 = 13.67 years; range at scan 1 = 11.88–15.45 years of age) who were initially recruited as part of a study designed to investigate factors contributing to risk for psychopathology, with an emphasis on depression and alcohol use disorders. After providing consent/assent, adolescent participants without magnetic resonance imaging (MRI) contraindications (e.g., braces) then completed in-person interviews, self-report behavioral assessments, and MRI scanning. Participants were re-contacted annually to complete diagnostic interviews and questionnaires and also underwent a follow-up MRI scanning session (mean time between scanning sessions = 2.09 ± .37 years; range = 1.32–3.13 years; age range at scan 2 = 13.77–18.25 years). A distinctive feature of our recruitment and sampling strategy was an ability to capture increases in rates of depression between adolescence and early adulthood (38,39), while also recognizing that symptoms of MDD (which predict later full-blown diagnoses) often emerge before age 14 (40).

Inclusion criteria required that all participants be free of psychopathology, with the exception of anxiety disorder diagnoses, at the baseline. Diagnoses were assessed using structured clinical interviews (41). Sixteen participants had an anxiety disorder at the start of the project and nine participants developed MDD between neuroimaging scans. Within the study population, participants with a family history of MDD were oversampled. Those with both a first- and second-degree relative with a history of MDD were classified as high risk, and those with no first- or second-degree relatives with a history of MDD were classified as low risk.

Measures of Depression and Anxiety

Depressive symptoms were measured with the child-report version of the Mood and Feelings Questionnaire (42). Anxiety symptoms were assessed with the child version of Screen for Child Anxiety Related Disorders (43). Both of these self-report measures have high internal consistency and test-retest reliability (43,44).

Emotional Neglect

EN was assessed using the Childhood Trauma Questionnaire (45), which ascertains the experience of different trauma types. In line with prior research in this sample (46), the EN subscale exhibited greater variability in scores. This measure was collected at the baseline scanning session and the second scanning session and then averaged together to yield a composite measure of EN. Analyses were also conducted related to stressful life events occurring during the past year assessed using the interviewer-based Stressful Life Events Schedule (47) and are presented in Supplement 1.

Ventral Striatum Activity Paradigm

To probe reward circuitry, participants completed a functional MRI (fMRI) card-guessing paradigm consisting of three blocks each of predominantly positive feedback (80% correct guess),