Review

Biological Psychiatry: CNNI

Vulnerability to Depression in Youth: Advances From Affective Neuroscience

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ABSTRACT

Vulnerability models of depression posit that individual differences in trait-like vulnerabilities emerge early in life and increase risk for the later development of depression. In this review, we summarize advances from affective neuroscience using neural measures to assess vulnerabilities in youth at high risk for depression due to parental history of depression or temperament style, as well as prospective designs evaluating the predictive validity of these vulnerabilities for symptoms and diagnoses of depression across development. Evidence from multiple levels of analysis indicates that healthy youth at high risk for depression exhibit abnormalities in components of the Research Domain Criteria positive valence systems, including blunted activation in the striatum during reward anticipation and feedback, and that some of these measures can be used to predict later symptoms. In addition, alterations in components of the Research Domain Criteria negative valence systems, including neural processing of sadness, loss, and threat, have been observed in risk for depression, though effects appear to be more task and method dependent. Within the social processes domain, preliminary evidence indicates that neural processing of social feedback, including heightened reactivity to exclusion and blunted response to social reward, may be related to depression vulnerability. These studies indicate that affective neuroscience can inform understanding of developmental pathways to depression and identify altered emotional processing among youth at high risk. We provide an integrated summary of replicated findings from this literature, along with recommendations for future directions and implications for early intervention.

Keywords: Affective neuroscience, Depression, Developmental psychopathology, EEG/ERP, fMRI, Risk

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Depression is a common psychiatric disorder and the second leading cause of disability worldwide (1,2), highlighting the importance of early intervention for youth at high risk (HR). Although rates of depression increase dramatically in adolescence and young adulthood (3–5), at least some trait-like vulnerabilities emerge earlier in life and increase risk for later depression (6,7). For example, at the behavioral and self-report level, maladaptive cognitive and affective styles, including hopelessness, rumination, negative attributions, and attentional biases for sad faces, have been observed among HR youth and/or shown to prospectively predict the development of depressive symptoms or diagnoses (5,6,8,9). More recent work has begun to apply affective neuroscience methods to identify early vulnerabilities for depression.

THE POTENTIAL OF AFFECTIVE NEUROSCIENCE FOR INFORMING VULNERABILITY RESEARCH

Neural and psychophysiological measures can provide relatively objective measures of emotional processing, offer insight into the brain circuitry underlying vulnerability, and add to levels of analysis of constructs of the Research Domain Criteria (10). There is also evidence that along with clinical and behavioral measures, neural measures account for additional variance in predicting future behavior, including clinical status and response to treatment (11), raising the possibility that these measures may aid in identifying youth at greatest risk. The goal of the current review is to synthesize initial efforts to apply affective neuroscience in understanding vulnerability to depression in children and adolescents. We highlight the potential of this work for informing early intervention work, as well as challenges in the field and needs for further research.

To rule out the possibility that altered emotional processing is a correlate of symptoms or consequence of a past depressive episode, we focus on studies of youth before the onset of the disorder, including both cross-sectional analyses of HR youth compared with those at lower risk (LR) and prospective studies examining predictors of future depressive symptoms or diagnoses, which are the most direct approach to examining precursors. With regard to HR designs, a common approach is studying offspring of parents with a history of depression, who are at an increased risk for developing the disorder themselves (12,13). These designs are complemented by studies of child temperament. Specifically, high negative emotionality (NE), characterized by sadness, irritability, and anxiety, and low positive emotionality

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(PE), characterized by positive affect, appetitive behavior, and sociability (14), have been linked to depression and prospectively predict later symptoms (15,16). Although NE may be a stronger predictor (hazard ratio = 1.31) than PE (hazard ratio = 0.96) of depression onset in adults (17), low PE in early childhood has been shown to prospectively predict increases in depressive symptoms (Cohen's d = .58–.85) (18), and the combination of low PE and high NE may be particularly predictive of depressive symptoms (18,19). When possible, we describe studies that tested specificity of effects for parental depression as opposed to other psychopathology or for temperament styles that may be relatively unique to depression, such as PE (20). Such designs provide insight into whether these vulnerabilities are specific to risk for depression or psychopathology more broadly.

In terms of methods, we focus on neural measures (i.e., physiological and circuit levels of analysis) of responses to emotional information, within the research domains (10) of positive valence systems (PVSs), negative valence systems (NVSs), and social processes. Recent functional magnetic resonance imaging (fMRI) studies have provided insight into neural circuits involved in emotional processing in HR youth. This work is complemented by studies of event-related potentials (ERPs) derived from the electroencephalogram (EEG). ERP measures are economically measured across development, allowing for assessment of large samples of youth, and offer improved temporal resolution, which provides insight into multiple stages of stimulus processing (see Table 1 for a summary of measures). We first present a comprehensive review of this literature (Table 2), followed by summaries of replicated findings emerging across two or more studies (Table 3). Finally, we discuss the potential for identifying youth at greatest risk and informing early intervention, as well as directions for future research.

POSITIVE VALENCE SYSTEMS

Reward Processing

Within PVSs, a relatively large literature has examined ERP and fMRI measures of reward processing as vulnerabilities for depression. The reward positivity (RewP) ERP component, also referred to as the feedback negativity, appears as a relative positivity approximately 250 to 300 ms following reward feedback compared to loss (21,22). RewP can be reliably assessed across development (23) and correlates with self-report and behavioral measures of reward sensitivity (24), as well as activation in the ventral striatum and medial prefrontal cortex (PFC) (25). There is growing evidence that reduced reward reactivity, as measured by RewP, may be a vulnerability for depression. That is, 9-year-old children with a maternal history of depression but not maternal anxiety exhibited a blunted RewP compared with LR children, even when controlling for subthreshold child symptoms (26). A similar pattern was observed in a smaller sample of HR adolescents who reported increases in sad mood following a mood induction (27). RewP has also been linked to temperamental risk, with low observed and self-reported PE predicting a blunted RewP in a large sample of children (28). Finally, in two studies of adolescent girls, reduced RewP prospectively predicted the first onset of depression when accounting for baseline symptoms (29,30) and appeared to be a relatively specific vulnerability for depression rather than anxiety (29).

In addition, evidence from fMRI indicates that healthy youth with a parental history of depression or who are low in PE exhibit reduced activation in subcortical regions involved in reward processing, including ventral and dorsal striatum in anticipation of (31–33) and following receipt of reward (31–35) compared with LR youth. Furthermore, one study indicated that reduced activation in ventral striatum during

Table 1. Overview of Neural Measures Used to Examine Positive and Negative Valence Systems and Social Processes in Depression Vulnerability Research

Measure	Affective Process	Possible Neural Circuit
fMRI		
BOLD signal in reward systems	Wanting and liking rewards, decision making, reward learning (94,95)	Striatum, anterior insula, amygdala, thalamus, PCC, PFC, ACC, OFC (94,95)
BOLD signal in threat/ negative emotion systems[a]	Identifying, appraising, and regulating responses to threat and negative emotions (96,97)	Amygdala/hippocampus, insula, striatum, thalamus, PCC, ACC, supplementary motor area, PFC, occipitotemporal cortex (97,98)
ERPs		
RewP	Processing reward outcomes, reinforcement learning (99)	Striatum, medial PFC (25,100)
LPP	Sustained attention toward salient stimuli, activation of motivational systems (37,101)	Occipitotemporal cortex, amygdala/hippocampus, insula, temporal pole, OFC, PFC (102,103)
ERN	Performance monitoring, cognitive control, sensitivity to errors/endogenous threat (55,56,104)	ACC (104)
P300	Stimulus evaluation and attentional allocation (105)	Frontal and temporal/parietal regions; correlated with activation in insula and medial frontal gyrus (105–107)

ACC, anterior cingulate cortex; BOLD, blood oxygen level–dependent; ERN, error-related negativity; ERPs, event-related potentials; fMRI, functional magnetic resonance imaging; LPP, late positive potential; OFC, orbitofrontal cortex; PCC, posterior cingulate cortex; PFC, prefrontal cortex; RewP, reward positivity.

[a]We have separated reward and negative emotion systems to parallel the order of the review and distinct literatures on reward processing and negative mood/face processing in depression vulnerability; however, these systems overlap, with common neural circuitry involved in emotional processing regardless of valence (98).