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Archival Report

Orbitofrontal Cortex Activity and Connectivity Predict Future Depression Symptoms in Adolescence

Jingwen Jin, Ananth Narayanan, Greg Perlman, Katherine Luking, Christine DeLorenzo, Greg Hajcak, Daniel N. Klein, Roman Kotov, and Aprajita Mohanty

ABSTRACT

BACKGROUND: Major depressive disorder is a leading cause of disability worldwide; however, little is known about pathological mechanisms involved in its development. Research in adolescent depression has focused on reward sensitivity and striatal mechanisms implementing it. The contribution of loss sensitivity to future depression, as well as the orbitofrontal cortex (OFC) mechanisms critical for processing losses and rewards, remains unexplored. Furthermore, it is unclear whether OFC functioning interacts with familial history in predicting future depression.

METHODS: In this longitudinal study, we recorded functional magnetic resonance imaging data while 229 female adolescents with or without parental history of depression completed a monetary gambling task. We examined whether OFC blood oxygen level–dependent response and functional connectivity during loss and win feedback was associated with depression symptoms concurrently and prospectively (9 months later) and whether this relationship was moderated by parental history of depression.

RESULTS: Reduced OFC response during loss was associated with higher depression symptoms concurrently and prospectively, even after controlling for concurrent depression, specifically in adolescents with parental history of depression. Similarly, increased OFC-posterior insula connectivity during loss was associated with future depression symptoms, but this relationship was not moderated by parental history of depression.

CONCLUSIONS: This study provides the first evidence for loss-related alterations in OFC functioning and its interaction with familial history of depression as possible mechanisms in the development of depression. While the current functional magnetic resonance imaging literature has mainly focused on reward, the current findings underscore the need to include prefrontal loss processing in existing developmental models of depression.

Keywords: Adolescence, Depression, fMRI, Loss, Orbitofrontal, Parental history

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Major depressive disorder (MDD) is among the leading causes of disability worldwide. However, knowledge of pathological neural mechanisms involved in the development of MDD is limited, frustrating efforts aimed at early detection and intervention. A promising pathophysiological mechanism in depression is that of sensitivity to losses and rewards, with some studies showing reduced reactivity to rewards (1), increased reactivity to losses (2,3), or reduced reactivity to both rewards and losses (4). Importantly, studies show that these alterations in reward reactivity are evident in children and adolescents at high risk for developing depression (5,6) and prospectively predict worsening of depression symptoms (7–9). However, research on neural correlates of loss or reward sensitivity in adolescent depression is limited in that it has focused almost exclusively on reward sensitivity as well as striatal mechanisms that support it (1,5). In contrast, the role of loss sensitivity and its contribution to future depression remains poorly understood (10,11). This is a critical gap in the literature because loss sensitivity varies across development (11), contributes significantly to decision making, perhaps more strongly than reward sensitivity (12), and is strongly linked to anxiety and mood disorders (5,13,14).

As part of a distributed network critical for valence processing and valuation (15,16), the orbitofrontal cortex (OFC) plays an important role in processing salience and magnitude of losses as well as rewards (17–21). The OFC represents the complete dimension of subjective valence ranging from unpleasant to pleasant (22,23). Due to strong anatomical connectivity with sensory, striatal, limbic, and insular regions, the OFC plays a critical role in integrating loss- and reward-related information (19,24). Furthermore, adolescence might be a developmentally sensitive period for studying the OFC (25) and its relationship with future depression. Adults with history of or risk for depression show attenuated OFC activity for both rewards (7,26,27) and negative stimuli including losses (28,29) [for a review see (13)]. Relatively less is known about functional and effective connectivity of the OFC in adult depression, with studies showing greater connectivity of the

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OFC with the insula (30), the amygdala (31), and a distributed network including prefrontal and cingulate cortices (32), and this enhanced connectivity is associated with more severe depression symptoms (30,32). Despite prefrontal maturation in adolescence (33), adolescents and adults with and at risk for MDD show a similar pattern of prefrontal resting-state connectivity (34,35). However, it is unclear whether attenuated OFC activity and/or enhanced OFC connectivity during rewards and losses represent a premorbid risk that precedes the onset of symptoms or is the result of depression onset or treatment exposure, indicating a need for longitudinal research on OFC functioning prior to depression onset.

Finally, depression is etiologically heterogeneous, with evidence suggesting differences in etiopathophysiological processes between more and less familial/genetic forms (36). Familial history of depression is one of the most important risk factors for depression, and it is associated with altered reward sensitivity in adolescents (5,6,37). However, few studies have explored whether abnormalities in OFC functioning interact with vulnerability imposed by familial history of depression to predict future depression. In the current longitudinal study, we used functional magnetic resonance imaging (fMRI) and a monetary gambling task to examine OFC blood oxygen level–dependent response, an indirect measure of neural activity (38), and OFC connectivity during loss and win feedback in a large cohort of female adolescents who were free of lifetime depressive disorders and who were assessed for depression again 9 months later. We hypothesized that 1) attenuated OFC activity and enhanced OFC functional connectivity with striatal, limbic, and insular regions for losses and wins will be correlated with greater depression symptoms concurrently and will predict depression symptoms 9 months later, even after controlling for concurrent depression, 2) parental history of depression (parental-history) will moderate the relationship between OFC activity and connectivity with future depression symptoms, such that the association is stronger for groups with high versus low risk for depression, and 3) measures of OFC activity and connectivity will independently predict depression symptoms in both cross-sectional and prospective analyses.

METHODS AND MATERIALS

Participants

A total of 261 female adolescents (mean age = 15 years 3 months, SD = 7 months) and their parents from the larger Adolescent Development of Emotions and Personality Traits project participated in the current study. The project cohort consisted of female adolescents during a developmental stage marked by a sharp increase in depression onset (39–41) (see the Supplement). Participants and their parents gave informed assent and consent, respectively, and all families were financially compensated for participation. After the baseline assessment (wave 1), participants were invited for follow-up clinical assessments every 9 months and fMRI at first follow-up (wave 2). See Supplement for details. Because we aimed to examine predictors of depression, participants with a lifetime history of MDD or dysthymia were excluded during initial screening. The exclusion of 32 participants due to data quality issues resulted in a final set of 229 subjects, 49 high risk (HR) and 180 low risk (LR), based on whether their participating parents met criteria for a lifetime history of either MDD or dysthymia (Supplement). Additional analyses were conducted defining the HR group based on family history reports of depression in nonparticipating parents (Supplement).

Clinical Measures

At baseline (wave 1), lifetime history of MDD or dysthymic disorder was determined based on the Structured Clinical Interview for DSM-IV (42) conducted with the participating biological parent (Supplement). Mood and anxiety symptoms in adolescents were measured using a new-generation factor-analytically derived Inventory of Depressive and Anxiety Symptoms (IDAS-II) (43). Relationship of OFC activity was examined with IDAS-II dysphoria scores at wave 2 (Dys_{w2}) and wave 3 (Dys_{w3}) because this scale captures core symptoms of depression (9,43) as well as other IDAS-II anxiety and depression-related scales (Supplement).

Experiment Paradigm: The Doors Task

Participants performed a modified version of a previously used forced-choice monetary gambling task (44) to probe neural response to loss- and reward-related monetary feedback (Figure 1A). Participants chose between two doors presented simultaneously and received feedback of loss or win with 50/50 probability (Supplement). The losses were purposefully set at half as large as wins due to prior data suggesting a 2 times loss aversion ratio (45). Choice and response time were recorded. Although the outcome of each trial was predetermined and independent of performance, participants were informed that they could gain between $0 and $10 depending on success rate. All participants were paid $6 after the scan.

Behavioral Data Analyses

For each subject, we computed the percentage of times the subject switched the choice of door on the next trial ($n + 1$) based on whether the door in the current trial (n) yielded loss feedback (loss-switch) or win feedback (win-switch). We compared win-switch and loss-switch using a paired-samples t test. We also examined choices across time (Supplement).

fMRI Data Acquisition and Preprocessing

Whole-brain functional and structural MRI images were acquired using gradient echo T2*-weighted echo planar images on a Siemens Trio 3T MRI whole-body scanner (Siemens, Erlangen, Germany). All functional images were spatially realigned, motion corrected, normalized to standardized space, and spatially smoothed using Statistical Parametric Mapping software (SPM8; http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). See the Supplement for details regarding image parameters and preprocessing.

fMRI Data Analyses

Subject-Level Model. A general linear model was estimated by convolving blood oxygenation level–dependent hemodynamic response function with stick (delta) function