Toward an Improved Understanding of Corticobasal Ganglia Reward Circuitry in Adolescent Depression

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Adolescence is a period of heightened risk for major depressive disorder (MDD) and represents an opportune time to identify neural markers implicated in the emergence of depression. One of the most promising risk factors has been diminished striatal response to the anticipation and receipt of reward in adolescents at familial risk for MDD (1). The striatum, however, is embedded in a larger corticobasal ganglia reward processing circuit: cells in cortical areas, particularly the orbitofrontal cortex (OFC), insular cortex, and anterior cingulate cortex, receive and integrate multimodal sensory information that are inputs to the dorsal and ventral striatum (2). The OFC is critical for evaluating the representations of conditioned stimuli and translating this information, along with the motivational signals computed in the striatum, into goal-directed behavior. Only one study to date has found blunted reward-related responses in OFC (as well as in the insula and anterior cingulate cortex) in a sample of adolescents and young adults with familial risk (3). Given the protracted development of the OFC during adolescence and its central role in the corticobasal ganglia reward circuit, key questions regarding the OFC in the etiology of adolescent MDD remain: 1) Is reward-related function of the OFC a marker of (familial) risk for depression in adolescents? 2) Does reward-related function of the OFC prospectively predict subsequent depression in adolescents (above and beyond blunted striatal responses)? and 3) Are specific patterns of reward processing (e.g., blunted reward responses versus enhanced loss sensitivity) differentially associated with depression subtypes? Answering these questions may have important implications for determining whether specific patterns of reward processing confer increased risk for MDD onset, whether they are potential treatment targets, and/or whether they represent moderators of clinical significance (e.g., moderators of intervention or treatment response).

In this issue of Biological Psychiatry: Cognitive Neuroscience and Neuroimaging, results from a longitudinal study by Jin et al. (4) bring us closer to filling these gaps. The authors use a guessing task that has been tested extensively in electrophysiology research (5); however, for the present study, low- and high-risk adolescents completed the task while functional magnetic resonance imaging (fMRI) data were acquired to probe activation to win and loss feedback within the OFC. Depressive symptoms in all participants were then assessed 9 months later. Although the authors found no differences between risk groups on OFC activation or functional connectivity, reduced loss-related OFC activation was selectively associated with greater subsequent depressive symptoms (even after controlling for baseline levels). Importantly, this finding was moderated by familial risk: adolescents with positive parental history exhibited significant associations between reduced loss-related OFC activation and increased subsequent depressive symptoms. Stronger functional coupling between the OFC and posterior insula during the processing of losses also predicted greater future depression symptoms; however, unlike OFC activation to loss, this association was not moderated by parental history of depression. Finally, OFC–posterior insula connectivity during losses improved statistical predictions of future depressive symptoms above and beyond the significant effects of baseline depressive symptoms, loss-related OFC activation, parental history of depression, and the interactive effects of loss-related OFC activation and positive parental history. Taken together, these results suggest that while reduced loss-related OFC activation may be a potentially meaningful predictor of subsequent depression in individuals with heightened risk, OFC–posterior insula connectivity may represent an additional risk factor that is independent of familial history. Indeed, the posterior insula is a key node in the corticobasal ganglia circuit and receives and encodes sensory (particularly aversive and nociceptive) inputs that are integrated along with signals in OFC (2); stronger coupling between these regions during losses may therefore represent a neurocognitive bias for negative stimuli that increases vulnerability to the development of MDD.

Interestingly, while Jin et al. reported evidence of reduced striatal responses to wins in the high- versus low-risk females, there were no associations between reward-related activation in striatum and concurrent or prospective depressive symptoms. Until recently, blunted striatal responses to reward using familial high-risk designs have mostly been identified in the context of cross-sectional comparisons (1), and thus it is unclear whether these known differences contribute to MDD onset vulnerability. While one study found that reduced ventral striatum activation to reward was associated with greater depressive symptom severity in adolescents [although not among individuals with MDD (6)], only one fMRI study to date has observed that aberrant ventral striatal responses to reward prospectively predicted subthreshold and clinical depression in previously psychiatrically healthy adolescents (7). Moving forward, it will be important to determine whether OFC activation and connectivity is implicated above and beyond striatal dysfunction and, more broadly, whether aberrant activation or connectivity patterns within these respective regions reflect different subtypes of depression. Addressing this issue may then provide promising clinical targets,
Commentary

particularly as it relates to targeting key precision medicine initiatives (6).

The findings reported by Jin et al. also highlight the unique role of loss sensitivity in adolescents (particularly females) at familial risk for MDD. It is notable that in previous studies (with samples containing both males and females), familial psychiatric history was not a significant factor in the association between striatal activation to rewards and depressive symptoms (6,7). Of relevance to this issue are results from a recent study examining fMRI responses to the anticipation of rewards and losses in mothers with and without a history of MDD and their never-depressed adolescent daughters (6). While several cortical, basal ganglia, and limbic regions were sensitive to rewards and losses, only heightened putamen responses to the anticipation of losses showed a significant concordance between mother–daughter dyads. The results suggest the potential heritability (e.g., genetic, biological, and environmental) of these deficits and may partially explain why offspring of parents with an MDD history show altered reward processing.

Presently, there is no clear understanding whether loss-related activation in corticobasal ganglia circuits is specific to females with a parental history and whether they may be more robust predictors of MDD relative to neural responses to rewards. Answering these questions will require future neuroimaging studies to have sufficient power to test sex-specific pathways and to develop behavioral tasks with the necessary sensitivity to dissociate the unique contributions of reward and loss. In the present study by Jin et al., participant behavior was affected by task design; there was a significantly higher percentage of switching choices after trials with loss compared with win outcomes. Moreover, this effect grew stronger over the course of the experiment. The study was unfortunately not designed to examine neural responses during these “switch” trials; however, probing these conditions may clarify the link between activation and connectivity of the corticobasal ganglia circuit and dissociable aspects of reward processing (and potentially, reward-based reinforcement learning). In this context, the adoption of trial-by-trial computational modeling for choice behavior is a fast-growing and important area for future research (10). For example, less adaptive switching or less sensitivity to sustained consecutive reward (or loss) feedback may provide insight into latent cognitive constructs, such as reward error prediction or feedback sensitivity, that can be quantified with computational models of behavior. These model parameters that represent latent cognitive constructs can then be used as regressors in an fMRI study to identify their neural correlates at the group level (high- vs. low-risk, MDD vs. control subjects) or, provided there are a sufficient number of trials, even at the level of an individual. With this approach, researchers will have the ability to more precisely elucidate the neural mechanisms of internal representations relevant to dissociable aspects of reward processing; such information may ultimately be useful for not only understanding risk mechanisms of adolescent MDD, but also for characterizing subtypes of MDD and, in turn, identifying and selecting personalized treatment targets.

In summary, findings from Jin et al. add to a growing body of literature that suggests that disruptions in corticobasal ganglia reward circuits increase the risk for MDD during adolescence by altering adaptive reward processes. Whether reduced striatal responses to anticipated outcomes, reduced cortical responses to outcome feedback, or atypical connectivity among these regions during either of these processes is a premorbid depressive state in adolescents who develop depression remains an outstanding question and, critically, a key issue to target in future research.

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