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Neural response to reward as a predictor of increases in depressive symptoms in adolescence

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ABSTRACT

Adolescence is a developmental period characterized by significant increases in the onset of depression, but also by increases in depressive symptoms, even among psychiatrically healthy youth. Disrupted reward function has been postulated as a critical factor in the development of depression, but it is still unclear which adolescents are particularly at risk for rising depressive symptoms. We provide a conceptual stance on gender, pubertal development, and reward type as potential moderators of the association between neural response to reward and rises in depressive symptoms. In addition, we describe preliminary findings that support claims of this conceptual stance. We propose that (1) status-related rewards may be particularly salient for eliciting neural response relevant to depressive symptoms in boys, whereas social rewards may be more salient for eliciting neural response relevant to depressive symptoms in girls and (2) the pattern of reduced striatal response and enhanced medial prefrontal response to reward may be particularly predictive of depressive symptoms in pubertal adolescents. We found that greater vmPFC activation when winning rewards predicted greater increases in depressive symptoms over 2 years, for boys only, and less striatal activation when anticipating rewards predicted greater increases in depressive symptoms over 2 years, for adolescents in mid to late pubertal stages but not those in pre to early puberty. We also propose directions for future studies, including the investigation of social vs. monetary reward directly and the longitudinal assessment of parallel changes in pubertal development, neural response to reward, and depressive symptoms.

Introduction

Rates of depressive episodes rise significantly during adolescence with age 15 found to be the peak age of onset (Lewinsohn et al., 1994). Not only do many adolescents experience their first depressive episode during this time period, many additional adolescents experience subthreshold rises in depressive symptoms that are nevertheless distressing and interfere with adolescent development (Lewinsohn et al., 2000). This increase in depressive symptoms during adolescence appears normative in some ways (Sawyer et al., 2009) but there are also individual differences in the increase.

Much research has been conducted to delineate risk factors that may contribute to risk for onset of clinical depression during adolescence (Cicchetti and Toth, 1998; Davey et al., 2008; Forbes and Dahl, 2005). Depression is characterized by a number of symptoms including elevated negative affect and disturbances in sleep and appetite, but it is consistently distinguished from other affective disorders by dysregulation in positive affect and low reward responding (for review, see Forbes and Dahl, 2005). Accordingly, adolescents with Major Depressive Disorder (MDD) have less striatal response and more ventral medial prefrontal cortex (vmPFC) response to monetary reward (Forbes et al., 2006, 2009). Similarly, adolescents at risk for MDD (via familial history) also have less striatal response to pleasant stimuli (Monk et al., 2008) and monetary reward (Gotlib et al., 2010). These findings suggest that reward-related changes may be related to rises in depressive symptoms in youth during adolescence prior to onset of clinical levels of depression.

According to Davey et al.'s (2008) developmental model of depression, social (e.g., greater peer affliation) and neural (e.g., reward circuitry maturation) developmental changes in adolescence result in reward-related changes that may increase risk for depression during this time period. These concurrent neural and social changes during adolescence make pursuit of rewards not only more valued but also more purposeful, leading to increased use of executive function to set and work toward abstract goals involving social rewards (Davey et al., 2008). As a result, challenges or failures in obtaining dearly-valued social goals (e.g., becoming romantically involved with someone, joining a high-status peer group) can put vulnerable adolescents on a trajectory toward disrupted reward responding and, eventually, depression. Feedback to the developing dopamine system at this sensitive time in development might then lead to disrupted neural reward function and, then, depressive symptoms (Davey et al., 2008).

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What is not explained by Davey et al.'s (2008) model is why some adolescents show clinically significant increases in depressive symptoms during adolescence, whereas others do not, despite these normative social and neural developmental changes. The current paper postulates that individual differences in reward function early in adolescence could predict increases in depressive symptoms—placing some adolescents at greater risk for developing clinical levels of the disorder in the future—and that the association between reward function and depression may be moderated by gender, pubertal development, and reward type. Specifically, we postulate that less striatal response and more vmPFC response to anticipation and gain of rewards during adolescence increases adolescents' risk for depression during this developmental time period. Moreover, we hypothesize that this brain-behavior association unfolds in the context of pubertal development and the combination of gender and reward type, with status rewards as more salient to boys and affiliative rewards as more salient to girls.

Our goal is to put forward a more detailed conceptual model of reward function in the development of adolescent depression, rather than to offer a definitive explanation for the emerging gender difference in *the prevalence rate* of adolescent depression or the increase in depression with pubertal changes. Therefore, addressing other important etiological issues such as the role of stressful life events or cognitive bias toward negative information on depression is beyond the scope of this paper. We offer a conceptual model for putative differing mechanisms of risk—based on disrupted reward systems in differing contexts—for depression depending on adolescent characteristics (e.g., gender, pubertal stage). We outline previous literature on reward-related regions, the striatum and vmPFC, and their association with the development of depression. In addition, to provide proof of concept for our model that could inspire future research, we describe preliminary empirical support for the role of gender and pubertal development as moderating factors of reward-depression associations, and we raise questions that may be tested empirically in future research.

Striatal Activation

The striatum is a region of the brain typically associated with positive affect and reward (Forbes, 2009; Haber and Knutson, 2009). Function of the striatum appears to be relatively specific, with activation in the striatum found in response to reward win but not reward loss in many studies (for review, see Knutson and Greer, 2008). In adolescents without diagnoses of depression, striatal response is positively associated with subjective positive affect and inversely associated with depressive symptoms (Forbes et al., 2009, 2010). Previous research has demonstrated that, similar to adults with depression (Epstein et al., 2006; Smoski et al., 2009), adolescents with clinical diagnoses of depression show less striatal activation during a reward decision-making task compared to healthy adolescents (Forbes et al., 2006, 2009). Indeed, a recent meta-analysis conducted by our group indicates that low striatal response to monetary reward is consistent across studies of adult and adolescent depression (Olino and Forbes, in preparation).

Adolescents may be showing reward-related differences in striatal reactivity prior to onset of depression, and these patterns of neural response, especially during periods of developmental sensitivity, may even be predictive of depression. While previous findings (Forbes et al., 2006, 2009, 2010) indicate associations between depression and neural response to reward, they do not provide us with information about *when* reward-related developmental changes occur in relation to rise of depressive symptoms. Studies of adolescents at risk for depression (Gotlib et al., 2010; Monk et al., 2008) have reported less response to reward in the striatum compared to low risk adolescents, suggesting that alterations in reward function could precede the onset of clinical levels of depression. However, because these studies did not examine changes in depressive symptoms in their samples, more research examining adolescents' striatal reactivity is needed to clarify whether these neural differences in reward function subsequently predict later *increases* in depressive symptoms.

vmPFC activation

The vmPFC plays an important role in the regulation of affect and may foster the formation of and pursuit of abstract social and emotional goals (e.g., establishing social status, initiating a romantic relationship; Davey et al., 2008). In addition to abstract reward processing, many subregions of the vmPFC (i.e., the Anterior Cingulate (ACC), Brodmann area (BA) 32, and medial BA 10) have been associated with the processing of self-performance and self-mastery in relation to others (Amodio and Frith, 2006; Haber and Knutson, 2009; Masten et al., 2011). The ACC, in particular, plays a role in reward decision making and self-evaluation in social contexts and is highly interconnected with the ventral striatum, among other brain regions (Haber and Knutson, 2009). Greater activation in the ACC during social peer-rejection fMRI paradigms has been associated with depressive symptoms (Masten et al., 2011).

Depressive symptoms may putatively be associated with distorted self-perception of the ability to obtain rewards successfully, with excessive focus on the loss of status or on difficulties obtaining reward. Indeed, increased mPFC response to reward has been associated with depression in adults (Knutson et al., 2008) and adolescents (Forbes, 2009), possibly reflecting difficulty regulating striatal response or disengaging from self-focused cognition during rewarding experiences (Forbes and Dahl, 2012). The vmPFC has reciprocal connections with the striatum, and, given the inverse relation of cortical and striatal dopamine function (Grace, 1993), is thought to serve a regulatory role for the striatum (Price and Drevets, 2010). In terms of development of symptoms, some adolescents may be at greater risk for rises in depressive symptoms because of increased activation in these self-processing areas (Forbes et al., 2010).

Other regions have also been implicated in reward processing, including the amygdala and orbitofrontal cortex (OFC; Haber & Knutson, 2009). Whereas our conceptual framework focuses on the ventral striatum (due to its role in affective experience in pleasant and rewarding stimuli) and the vmPFC (due its cognitive and regulatory role in reward seeking and attainment), research has also found that monetary and social rewards are associated with activation in the amygdala and OFC (e.g., Davey et al., 2010; Monk et al., 2008). Imaging studies that examine the association between reward-related differences and risk for depression should consider these regions as well.

Moderating Factors: Gender and Reward Type, Pubertal Development

In order to provide a more comprehensive conceptual model of reward function in adolescent risk for depression, we postulate that the association of reward-related changes and depressive symptoms is moderated by (1) gender differences in response to specific types of reward and (2) pubertal development. We provide more detail on these hypotheses below.

Gender and reward type

Although girls are at greater risk for depressive symptoms than boys starting at adolescence (Essau et al., 2010), boys also experience an increase in depressive symptoms during this time period (Cicchetti and Toth, 1998), and depression disrupts the academic and social functioning of both male and female adolescents (Lewinsohn et al., 2000). Many conceptual models have studied the impact of negative life events and stressors in girls in order to explain the emergence of depression (Hankin et al., 2007). However, this research has originated from models of stress in the etiology of depression. From a reward function perspective, it is not only important to examine whether neural response to reward is related to depression but to elaborate on how different types of reward may be relevant to depression (Forbes, 2009), and