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Altered Reward Function in Adolescent Depression: What, When, and How?

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Abstract

Background—Conceptual models and recent evidence indicate that neural response to reward is altered in depression. Taking a developmental approach to investigating reward function in adolescent depression can elucidate the etiology, pathophysiology, and course of depression, a disorder that typically begins during adolescence and has high rates of recurrence.

Methods—This conceptual review describes the *what*, *when*, and *how* of altered reward function in adolescent depression. With the goal of generating new, testable hypotheses within a developmental affective neuroscience framework, we critically review findings and suggest future directions. Peer-reviewed empirical papers for inclusion in this critical review were obtained by searching PubMed, PsycInfo, and ScienceDirect for the years 1990–2010.

Results—A pattern of low striatal response and high medial prefrontal response to reward is evident in adolescents and adults with depression. Given the salience of social stimuli for positive affect and depression, reward function might be especially disrupted in response to social rewards. Because of changes in the dopamine system and reward function with aging, altered reward function in depression might be more evident during adolescence than later in life; however, low reward function may also be a stable characteristic of people who experience depression. Mechanisms of altered reward function in depression could include disrupted balance of corticostriatal circuit function, with disruption occurring as aberrant adolescent brain development.

Conclusions—Future studies should examine responses to social rewards; employ longitudinal and prospective designs; and investigate patterns of functional connectivity in reward circuits. Understanding altered reward function in depression has potential implications for treatment development. A more rigorous approach to investigating anhedonia, threat-reward interactions, and comorbid anxiety will be valuable to future progress in describing the role of reward function in the pathophysiology of depression.

Keywords

depression; development; reward; brain function

Neural aspects of reward function have been conceptualized as critical to the etiology, development, pathophysiology, and treatment of depression (e.g., Forbes & Dahl, 2005; Hasler, Drevets, Manji, & Charney, 2004). This direction of research helps to shift the field away from a narrow focus on increased negative affect in depression and toward consideration of diminished positive affect, and it contributes to the search for mechanisms underlying mood and subjective experience.

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A developmental psychopathology perspective could be especially valuable to understanding the role of reward function in depression and to reconciling seemingly conflicting findings on this topic, such as mixed results on low striatal response to reward. Because depression typically begins during adolescence (Kessler, Avenevoli, & Merikangas, 2001), and adolescent depression confers a high risk of recurrence in adulthood (Lewinsohn, Rohde, Klein, & Seeley, 1999), adolescent depression provides a valuable scientific opportunity. Examining reward function during adolescent depression can elucidate the larger course of the disorder and place its etiology within the context of typical, dramatic changes in reward function that occur during this developmental period (Somerville, Jones, & Casey, 2010).

This review examines the evidence for *what* in particular about reward function is disrupted in adolescent depression, *when* in the development of depression reward function is disrupted, and *how* disruption in neural reward circuits occurs. We propose testable hypotheses to guide future work on this compelling topic, and we briefly consider how a deeper understanding of these issues may inform intervention strategies. To obtain material for this conceptual review, we searched for peer-reviewed empirical papers in English published between 1990 and 2010 using PubMed, PsycInfo, and ScienceDirect indices, with terms such as *depress*, reward*, *decision-making*, *dopamine*, *fMRI*, *striatum*, and *adolescen** (with the * wild card allowing retrieval of terms with the same stem, such as *depressed* and *depression*). Papers identified by the search were included if (1) they focused on topics relevant to the focus of the review (e.g., depression and striatal or medial prefrontal cortex (mPFC) response to reward; depression and decision-making behavior; adolescence and reward function; dopamine and depression), (2) used fMRI with a reward processing paradigm; (3) reported results of statistical tests; and (4) compared currently depressed and healthy control groups (e.g., not remitted depressed). Extending the stance of our previous reviews (Forbes, 2011; Forbes & Dahl, 2005; Forbes, et al., 2009), the specific goals of this review are to integrate recent neuroimaging findings; provide an overview of key related topics, such as reward-related decision-making; and develop an explicit foundation for future research.

What about Reward Function Is Disrupted?

This section reviews three literatures relevant to neural aspects of reward function in adolescent depression—functional magnetic resonance imaging (fMRI) of reward, reward-related decision-making behavior, and dopamine function—and then discusses methodological issues important to the neurobiology of reward function.

Neural Response to Reward

The neural circuitry of reward includes regions such as the striatum, orbitofrontal cortex, and amygdala (Haber & Knutson, 2010). Notably, because the dopamine neuromodulatory system plays a critical role in reward (Haber & Knutson, 2010), target regions of midbrain dopamine neurons, such as the striatum and mPFC, have been a focus of research on reward function in depression (see Figure 1).

Adolescents and adults with depression exhibit altered brain function in key reward-related areas in response to rewarding experiences (Table 1). In particular, findings have begun to converge on low reactivity to monetary reward in the striatum, a brain region associated with many aspects of reward processing (Balleine, Delgado, & Hikosaka, 2007; Haber & Knutson, 2010). Adolescents with depression exhibit reduced reactivity in the striatum in response to decision-making, anticipation, and outcome involving monetary reward (Forbes, et al., 2009; Forbes, et al., 2006). Adults with depression exhibit reduced reactivity in the striatum during decision-making (Smoski, et al., 2009), anticipation (Pizzagalli, et al., 2009;

Smoski, et al., 2009), and outcome (Pizzagalli, et al., 2009; Smoski, et al., 2009) involving monetary reward; in response to pleasant words (Epstein, et al., 2006) and pleasant facial expressions (Surguladze, et al., 2005); and when attempting to enhance positive affective state (Heller, et al., 2009).

In parallel with low striatal reactivity, some reward studies have reported that people with depression exhibit high reactivity in mPFC areas that are postulated to play a role in regulating reward response, including the anterior cingulate cortex (Knutson, et al., 2008) and nearby mPFC in adults (Keedwell, et al., 2005a) and adolescents with depression (Forbes, et al., 2009). Some studies, however, have reported that depression is associated with low response in this region (Epstein et al., 2006; Forbes et al., 2006; Smoski et al., 2009). Most recently, a study has reported that adult depression is associated with enhanced amygdala response to social reward (Davey et al., 2011). This finding is consistent with a finding on response to monetary reward in adolescent depression (Forbes et al., 2006). Findings on altered mPFC and amygdala response to rewarding stimuli in depression also could have implications for adolescent depression. Similarly, the developmental decrease in striatal function during attention to happy faces (Lindstrom et al., 2009) suggests that development of striatal response to other classes of reward could influence differences in adolescent depression.

Reward and Decision-Making

Reward function plays a critical role in decision-making because it influences motivation and learning. Consistent with reduced striatal response to reward described above, many behavioral studies have found that depression is associated with reduced sensitivity to rewarding outcomes during decision-making (Table 2). During gambling or monetary-reward tasks, adults with depression make decisions that are more conservative (Corwin, Peselow, Feenan, Rotrosen, & Fieve, 1990), slower (Kaplan, et al., 2006), and less flexible in the face of shifting contingencies (Cella, Dymond, & Cooper, 2010). Depression—and anhedonia in particular—is associated with failure to exhibit a response bias toward rewarded stimuli in signal detection tasks, in which one set of stimuli is subtly rewarded more frequently than another (Pizzagalli, Iosifescu, Hallet, Ratner, & Fava, 2008; Pizzagalli, Jahn, & O'Shea, 2005). In adolescents with depression, there is less distinction of high-magnitude and low-magnitude rewards under high-probability conditions (Forbes, Shaw, & Dahl, 2007) and less improvement in cognitive control with reward (Hardin, Schroth, Pine, & Ernst, 2007; Jazbec, McClure, Hardin, Pine, & Ernst, 2005).

Findings on decision-making in both adolescent depression and adult depression also have seeming inconsistencies. Adults with depression exhibit greater discounting of future rewards in intertemporal choice tasks (Takahashi, et al., 2008), which involve decisions between immediate, smaller-magnitude and delayed, larger-magnitude rewards and are thought to assess impulsivity. They may also exhibit shorter reaction time or better performance in choice tasks (Chase, Michael, Bullmore, Sahakian, & Robbins, 2010). Notably, adolescents with depression can appear to make faster, more impulsive decisions (Kyte, Goodyer, & Sahakian, 2005). Rather than enhanced reward function, however, such impulsivity could instead reflect pessimistic or inaccurate anticipation of future events, as well as altered PFC function, given the putative role of the PFC in planning and goal pursuit (Mushiake, et al., 2009). Depressive features must also be considered. For instance, probabilistic reversal reward learning in elderly adults with depression is disrupted for suicide attempters but not suicide ideators, with suicide attempters giving more weight to the last trial rather than to earlier patterns of outcomes (Dombrovski, et al., 2010). Also, blunting during reinforcement learning in a probabilistic decision-making task is positively associated with level of anhedonia (Chase, Frank, et al., 2010; Lempert & Pizzagalli, 2010).

Thus, it appears that in depression, there is difficulty integrating future rewards into current decisions.

Dopamine

At a molecular level, altered neural response to reward and altered decision-making behavior under rewarded conditions are likely to be subserved by changes in dopamine function. In fact, depression is postulated to be associated with disrupted dopamine signaling (see Dunlop & Nemeroff, 2007; Nestler & Carlezon, 2006 for reviews). Specifically, functioning in the mesolimbic pathway of dopamine neurons from the ventral tegmental area to the nucleus accumbens in the ventral striatum is proposed to play an etiologic role in depression (Nestler & Carlezon, 2006). Dopamine is implicated in typical affective response to reward and in rewarded behavior through projections of midbrain dopamine neurons to the striatum and medial prefrontal cortex (Haber & Knutson, 2010). Dopamine release is postulated to facilitate learning and goal-directed behavior by engaging both of these neural regions. A useful distinction in explaining the influence of dopamine neurons on reward-related behavior is that between *tonic* dopamine transmission, which provides a steady baseline level of dopamine regardless of external stimuli, and *phasic* dopamine transmission, which occurs in response to a stimulus. Goal-directed behavior has been associated with reduced phasic dopamine transmission in response to non-receipt of reward, with the phasic change serving to engage prefrontal regions in the service of changing current behavior (Sesack & Grace, 2010). In depression, difficulties with regulating mood flexibly or low behavioral activation could reflect reduced dopamine signaling. Evidence for this perspective includes findings from positron emission tomography and single photon emission computerized tomography studies, which can measure the density of dopamine receptors to infer the availability of dopamine in relevant regions such as the striatum (Cannon, et al., 2009). Animal models also provide evidence for this hypothesis: greater firing of ventral tegmental area dopamine neurons in rodents accompanies improvement in depressive-like behavior (Friedman, Friedman, Dremencov, & Yadid, 2008).

Intriguing findings from pharmacologic challenge studies provide an opportunity to illustrate claims about dopamine system function in depression. Seemingly at odds with postulated low dopamine function in depression, depression has been associated with greater sensitivity to stimulant drugs, which increase available dopamine. During amphetamine challenge, adults with depression report experiencing greater subjective rewarding effects (Tremblay, Naranjo, Cardenas, Herrmann, & Busto, 2002; Tremblay, et al., 2005) but exhibit *less* striatal response than healthy adults (Tremblay, et al., 2005). While these findings might suggest enhanced dopamine responding, differences in tonic and phasic dopamine neuron activity (Goto, Otani, & Grace, 2007) could also lead to the interpretation that depression involves low tonic dopamine levels, which disrupt the phasic dopamine response to reward. Alternatively, depression could alter dopamine response to different classes of rewarding stimuli, with lower response to natural rewards but enhanced response to drug rewards. The authors of these studies propose two possible neural mechanisms for these findings: (1) unusual glutamate transmission, which has been observed in depression (McCullumsmith & Meador-Woodruff, 2002) and which mediates dopamine response to amphetamine (Paladini, Fiorillo, Morikawa, & Williams, 2001); and (2) dopamine system compensation for low dopamine function (Tremblay, et al., 2005). Dopamine system changes reported in adult depression include increased density of D2 receptors—which is also associated with response to tricyclic and selective serotonin reuptake inhibitor (SSRI) antidepressant treatment (D'Haenen & Bossuyt, 1994; Ebert, Feistel, Loew, & Pirner, 1996; Klimke, et al., 1999)—and lower density of dopamine transporter (Klimek, Schenck, Han, Stockmeier, & Ordway, 2002; Meyer, et al., 2001). While the specific type of dopamine

system disruption is not revealed by these findings, they are consistent with altered dopamine function in depression.

Given the evidence for involvement of the dopamine system in depression, it can appear somewhat surprising that the most effective and widely used pharmacologic treatment for depression is selective serotonin re-uptake inhibitor medications (SSRIs; Masi et al., 2010). Medications targeting serotonin can "reverberate" in other monoamine systems, suggesting that dopamine function may be influenced indirectly by SSRIs (El Mansari et al., 2010). Several antidepressant medications such as pramipexole influence dopamine function directly (Dunlop & Nemeroff, 2007; El Mansari et al., 2010). Another pharmacologic issue worth mentioning in this context is that stimulant treatment for attention-deficit/ hyperactivity disorder, which increases dopamine function, can induce depression in a small subgroup of children.

Methodological Issues

Which types of rewards?—A compelling possibility is that reward function in depression is particularly disrupted in response to *social rewards*. Conceptually, depressed mood is seen as having a social function, for example by reducing one's dependence on the social group during times of strong competition for resources (Allen & Badcock, 2003). Developmental psychopathology and affective neuroscience perspectives emphasize the social changes of adolescence as facilitating the onset of depression (Davey, Yucel, & Allen, 2008). Social rewards elicit positive affect, which plays a central role in affiliation and social status (Bora, Yucel, & Allen, 2009), and reactivity in reward-related brain areas (Davey, Allen, Harrison, Dwyer, & Yucel, 2009). Notably, depression has an important association with social functioning, with loss of a romantic relationship as a typical triggering event for first episodes (Monroe, Rohde, Seeley, & Lewinsohn, 1999). Social stressors are viewed as strong influences on the development and course of depression in adolescents (Sheeber, Hops, & Davis, 2001).

Few studies of reward function in depression have focused on social rewards. This trend appears to be changing, with recent studies reporting that depression is associated with differences in neural response to autobiographical memory (Keedwell, et al., 2005b) and to face-processing during positive social feedback (Davey et al., 2011). Monetary reward is understandably more straightforward to study and can be understood in the context of reward paradigms used across species. But without examining the rewards that are most fundamental to human functioning, we may be missing a chance to understand the mechanisms and extent of reward dysfunction in depression. On a similar note, it will be important to gain enough insight into the normal function of the brain's reward systems and the commonalities of response to monetary and social rewards to achieve an understanding of how reward function might differ in response to different classes of rewards in depression.

fMRI paradigms—Differences in fMRI reward paradigms could explain the two notable exceptions to the pattern of low striatal response to reward in depression: one study reported no difference in striatal response (Knutson, Bhanji, Cooney, Atlas, & Gotlib, 2008) and another reported greater striatal response (Remijnse, et al., 2009). Paradigms differ in whether reward is contingent on performance (as in the Monetary Incentive Delay task) and in the way that trials are structured (e.g., anticipation, decision-making, and motor preparation might all occur in the same trial component). Importantly, developmental influences on reward function could also explain differences in findings. As described below, depression-related alterations in reward function might be more evident in adolescents than in adults.

Sample characteristics—Discrepant findings could occur also occur because of participant characteristics. Adolescents with depression differ in their clinical presentation, with variability in the experience of symptoms, such as anhedonia, or other forms of psychopathology, such as anxiety. As discussed in Conclusions below, considering these features, as well as integrating research on reward function and threat function, will provide a more thorough picture of reward function.

Multi-method assessment—Assessing reward function across its components is critical to capturing it comprehensively and elucidating its role in depression. Like other affective processes, reward function includes physiological (e.g., brain function), behavioral (e.g., displayed positive affect), and subjective components (e.g., experience of pleasant mood; e.g., McManis et al., 2001). Differences in neural aspects of reward function are most powerfully understood when they are examined in the context of their associations with mood (e.g., feeling happy) or behavior (e.g., performance on a computer task with prizes). For example, we recently reported that greater reactivity in a region of the striatum associated with adolescent depression was correlated with higher levels of subjective positive affect measured in natural environments (Forbes, et al., 2009). Another innovative developmental study found that adolescents whose mothers displayed more punitive behavior in response to adolescents' positive affect had larger orbitofrontal cortex volume (Whittle, et al., 2009). Both of these studies also illustrate the value of emphasizing assessment of reward in ecologically valid, personally relevant ways. It will be exciting for future studies to investigate the links between neural components of reward function in adolescent depression and well-documented behavioral characteristics, such as less-frequent expression of positive affect (Sheeber, et al., 2009) and lower subjective positive affect in laboratory and natural settings (Joiner & Lonigan, 2000).

When in Development Is Reward Function Altered?

Depression and the Normal Development of Reward Function

Adolescence may be the developmental period at which reward function in depression is most strikingly disrupted. First episodes of depression are likely to occur during adolescence (Lewinsohn, Clarke, Seeley, & Rohde, 1994), when normative levels of reward function are higher than during childhood or adulthood (Somerville, et al., 2010). Behavioral and phenomenological findings both suggest that it could be value to place altered reward function in depression into a context of normal development. Specifically, altered reward function is more characteristic of early than later episodes of depression (Nandrino, Dodin, Martin, & Henniaux, 2004), adolescent anhedonia predicts later major depressive disorder (Pine, Cohen, Cohen, & Brook, 1999), and low positive affect during adolescents' depressive episodes predict recurrence (Joiner, Lewinsohn, & Seeley, 2002).

Normal Development of Reward Function during Adolescence—Adolescence is a sensitive period for the development of depression and, for reward function, a time of *more and less*. On one hand, adolescents tend to engage in more high-risk, reward-seeking behaviors than either children or adults (see Somerville, et al., 2010), to report more sensation-seeking (Steinberg, et al., 2008), and to experience rewards more intensely (Ernst, et al., 2005; Steinberg, 2008). These findings are echoed in rodent research (e.g., Laviola, Macri, Morley-Fletcher, & Adriani, 2003). On the other hand, adolescents have low levels of momentary positive affect e.g., (Larson, Moneta, Richards, & Wilson, 2002), are often bored, and show substantial, increasing levels of depressive symptoms (Sawyer, et al., 2009). Adolescents show altered striatal response to reward in comparison to children or adults (Bjork, et al., 2004; Ernst, et al., 2005; Forbes, Ryan, et al., 2010; Galvan, et al., 2006), and greater neural response to reward in regions implicated in social cognition and

self-perception, such as the mPFC (Bjork, et al., 2004; Forbes, Ryan, et al., 2010). Adolescents' greater striatal response to reward prediction error, which is mediated by dopamine neurons (Cohen, et al., 2010), suggests that the development of dopamine function is critical to changes in reward function. Similarly, the simultaneous development of the dopamine system and neural reward circuits during adolescence has been postulated to trigger depression in those who are vulnerable (Davey, et al., 2008). Puberty, with its influence on behavioral (Forbes & Dahl, 2010) and neural (Forbes, Ryan, et al., 2010) changes in reward function—as well as on the development of depression (Angold & Costello, 2006)—likely contributes to this developmental pattern.

Changes in Reward Function during Adulthood—In contrast to adolescence, adulthood may involve decreases in reward function. Aging is associated with difficulty learning reward associations (Mell, et al., 2005), decreased total earnings in reward decision-making (Brown & Ridderinkhof, 2009), and low subjective positive affect (e.g., Kunzmann, 2008). The dopamine system undergoes reductions in receptor density, and there are shifts in patterns of reward-related brain function and the association between midbrain and prefrontal activation (Dreher, Meyer-Lindenberg, Kohn, & Berman, 2008). Striatal function in particular appears to decline (Dreher, et al., 2008; Mell, et al., 2009; Schott, et al., 2007). These aging-related changes could close the reward function gap between people with depression and people without depression during late adulthood, obscuring differences.

However, based on two other perspectives, depression and aging could interact to produce the opposite pattern: greater divergence in reward function between healthy and depressed adults with aging. Adults with depression undergo more rapid aging and higher rates of aging-related illness and cognitive decline (Rapp, et al., 2010). In addition, the kindling hypothesis (Post, 2007)—which postulates that episodes occur more spontaneously and are more severe with the progression of affective disorders—could predict that reward function becomes more unusual with clinical course. Future longitudinal studies are critical for settling this issue.

Depression and Individual Differences in Reward Function

From a different perspective, stable individual differences in reward function could lead some people to have low reward function *throughout* the lifespan, regardless of episode status. Low reward function has been proposed as a candidate endophenotype of depression, reflecting evidence that it is a risk characteristic that is likely to be heritable, not immediately evident in behavior, present regardless of illness state (i.e., before, during, and after depressive episodes), and predictive of onset (Hasler, et al., 2004). Consistent with this view, nondepressed offspring of depressed parents, a population at high risk of developing depression (Goodman, 2007), exhibit reduced reward-related brain function in response to monetary (Gotlib, et al., 2010) and social reward (Monk, et al., 2008). Reward-related decision-making predicts later depressive disorders in adolescents, even when adjusting for previous depression (Forbes, et al., 2007). In those with depression, reward-related brain function does not seem to improve appreciably between episodes or after treatment (McCabe, Cowen, & Harmer, 2009), and behavioral sensitivity to catecholamine depletion is greater (Hasler, et al., 2009). Prospective studies and studies of high-risk groups are needed to disentangle stable individual differences and episodic changes in reward function. The seeming paradox between low reward function as both a stable individual difference and a characteristic more evident in depression during adolescence is illustrated by Figure 2, which depicts level of reward function with development and indicates that normal developmental change in reward function could reveal depression-related differences most clearly during adolescence.

How Is Reward Function Disrupted in Adolescent Depression?

One clue about the mechanisms by which reward function may be disrupted in depression is the pattern, described above, of frontostriatal function: low reactivity in the striatum plus high reactivity in the mPFC. As indicated by our preliminary findings on treatment response in adolescent depression, this pattern also appears to be predictive of worse response to treatment (Forbes, Olino, et al., 2010). In addition, the effortful regulation of positive affect reduces frontostriatal connectivity in adults with depression (Heller, et al., 2009), and behavioral activation therapy alters neural response in both the striatum and mPFC (Dichter, et al., 2009).

There are several possible patterns of disruption in neural circuits including the striatum and mPFC in depression. One possibility, suggested by findings that depressed adolescents tend to dampen positive affect (Feldman, Joormann, & Johnson, 2008), is that a typical initial response to reward occurs in the striatum but is over-regulated by the mPFC, resulting in attenuated intensity and duration. Relatedly, adults with depression exhibit negative, top-down functional connectivity between the ventromedial prefrontal cortex and the amygdala while processing happy faces (Almeida, et al., 2009). A second possibility is that the striatum is less reactive to reward, and increased mPFC function reflects signaling to enhance neural response or elicit dopamine release. Support for low striatal reactivity includes findings of low dopamine release in depression (Martin-Soelch et al., 2008, cf Price & Drevets, 2010). Support for the mPFC's role in dopamine release includes rodent findings that stimulation of the mPFC elicits greater activity in the ventral tegmental area (e.g. Taber & Fibiger, 1993). A third possibility is that both regions have altered function: the initial striatal response to reward is diminished and, in parallel, the mPFC is excessively engaged in self-processing. Given the mPFC's role in processing self-relevant material (Passingham, Bengtsson, & Lau, 2010) and in the *default mode network* that is more active in depressed than healthy adults at rest (Sheline, et al., 2009) and during affective processing (Grimm, et al., 2009), the mPFC might be engaged in the negative, self-focused ruminations that are considered a hallmark of the development of depression (Hankin, et al., 2009). This tendency could lead to difficulty shifting away from self-focused processing in the presence of external rewards. Characterizing the association of these two reward-related brain areas will require additional functional connectivity studies, as well as prospective and longitudinal designs.

Another issue is how this pattern of neural function arises. Developmentally, the typical changes in reward function during adolescence could lead to altered function in frontostriatal circuits that persists over time and launches some adolescents onto a trajectory of depression. Consistent with this view, achieving balance among prefrontal and subcortical affective regions is considered a key developmental task of adolescence (Ernst & Fudge, 2009), and the rapid changes in both reward and executive function systems during adolescence has been conceptualized as etiologically relevant for depression (Davey, et al., 2008).

Conclusions

Treatment Implications

While far from providing practical guidance for diagnosis or intervention, findings on reward function in adolescent depression ideally have potential clinical implications by suggesting targets for treatment. To illustrate, the three proposed neural mechanisms leading to altered reward-related brain function suggest different and possibly promising approaches. If reward function is disrupted through over-regulation of striatal response by mPFC, an mindfulness intervention, as applied to chronic adult depression, might aim to

reduce over-regulation (Kuyken, et al., 2008). If reward function is disrupted through low initial striatal response to reward, perhaps initial reactivity could be strengthened through pharmacologic means. If mPFC is ineffective at enhancing striatal response, this circuit could be targeted through training to savor pleasant experiences (McMakin, Siegle, & Shirk, In Press).

Consideration of reward function in adolescent depression raises the issue of personalized interventions. Reward function is not uniformly disrupted in adolescents with depression (Forbes, et al., 2009), and response to treatment is also variable (Kennard, et al., 2006). Greater attention to potential endophenotypes and biomarkers can contribute to understanding which adolescents will respond to which treatments (Brent & Maalouf, 2009). Investigating reward function can be a model for this approach. Recently, we have reported in a small sample of adolescents with depression that reward-related brain function before treatment with either cognitive behavioral therapy or cognitive behavioral therapy plus selective serotonin reuptake inhibitors predicted both severity and symptoms post-treatment and rate of anxiety symptom reduction during treatment (Forbes, Olino, et al., 2010). This is the first study to identify a potential biomarker of treatment response in adolescent depression.

We do not intend to suggest that the study of reward function in depression has led the field to a point at which we will use fMRI scans to diagnose depression or to select the most effective treatment in adolescents. In addition, findings on brain function have yet to lead to efficacious treatments. Instead, we make the optimistic prediction that understanding the neural mechanisms underlying altered reward function can lead us to a better description of the pathophysiology and, ultimately, to treatments addressing the mechanisms of depression.

Recommendations for Future Research

There is much to be done to understand the role of reward function in the development of depression. An important example is the need for a more rigorous, empirical definition of *anhedonia* and a conceptual model for its association with reward function in depression. Anhedonia is considered a core symptom of depression (American Psychiatric Association, 1994) is present in 76% of adolescents with depression (Lewinsohn, Pettit, Joiner, & Seeley, 2003), may have important predictive value for depression in young people, and is associated with reduced striatal response in adult depression (Keedwell, et al., 2005a). But the construct's definition is inconsistent, with varying attention to physical, social, and motivational features (Chapman, Chapman, & Raulin, 1976), as well as to its reflection of unusual appetitive or consummatory processes of reward function (Snaith, 1993). Anhedonia is often understood to reflect a complete absence of the experience of pleasure, but clinical impressions indicate that such an affective state is rare in adolescents and that low motivation to obtain reward—rather than low experience of pleasure once reward is obtained—might be a more appropriate focus. As an example of a fruitful approach, a recent review has proposed that anhedonia occurs in depression through alterations of decision-making processes that are associated with motivational or "wanting" aspects of reward function and mediated by dopamine function (Treadway & Zald, 2010). Defining anhedonia in terms of neural, behavioral, and subjective aspects of reward function; examining its association with different components of reward processing; understanding it in developmental context; and improving its measurement could strengthen the foundation for research on reward function in depression.

The *interplay of threat and reward systems* is a critical topic, given the role of positive affect in regulating negative affect (Garland, et al., 2010) and the emphasis of early studies on depression's association with bias toward feedback about failure (Elliott, et al., 1997). Peer-reared monkeys, who exhibit behavior similar to human anxiety and depression, exhibit

heightened behavioral response to reward (Nelson, et al., 2009). This finding was interpreted as evidence of a possible attempt to regulate negative affect with reward-related behavior. Similarly, the recent report that genes relevant to endocannabinoid function are associated with both reduced neural response to threat and enhanced neural response to reward (Hariri, et al., 2009) point to common genetic pathways for influencing the two affective systems. Also, the context of altered reward function could be considered more carefully. For instance, we have recently examined depression effects on striatal response to reward anticipation based on the outcome of the previous trial (Olino, et al., in press).

Finally, the role of *comorbid anxiety* in reward function in depression has been ignored, despite the frequent co-occurrence of the two types of affective disturbance (Kessler, et al., 2008). Both types of disorders are postulated to involve disrupted threat processing (Clark & Watson, 1991), and neuroimaging evidence supports this claim (Britton et al., 2011; Savitz & Drevets, 2009). Although affective models of psychopathology claim that only depression is associated with altered reward function (Clark & Watson, 1991), recent evidence indicates that reward function is also altered in anxiety. Contrary to depression, adolescent anxiety is associated with greater striatal response to reward anticipation (Bar-Haim, et al., 2009). Anxiety could thus involve enhanced sensitivity to potential feedback or uncertainty. Because the amygdala, a key region in threat circuits, influences the nucleus accumbens (McGinty & Grace, 2008), and adolescents' reward-related striatal function predicts reduction in anxiety symptoms with treatment (Forbes, Olino, et al., 2010), enhanced striatal reactivity in anxiety could reflect vigilance for threat. With this intriguing pattern of findings on reward and anxiety, further research on reward function has the potential to provide insights on the differences between anxiety and depression.

Summary

We hope that our attempts to interpret the extant literature and to identify central themes will provoke thought and discussion and will, ideally, inspire future studies. While our hypotheses have necessarily gone beyond the implications of the present evidence, we believe that they can have some value for conceptualizing and investigating reward function in depression.

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Abbreviations

mPFC medial prefrontal cortex

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Key Points

- Altered reward function is postulated to be critical to the development and pathophysiology of depression.
- This review proposes that (1) physiological, behavioral, and subjective aspects of reward function are disrupted; (2) altered reward function is most evident in adolescent depression and is stably low in those with depression; and (3) altered reward function is related to the pattern of reactivity of the striatum and medial prefrontal cortex.
- A more comprehensive understanding of mechanisms of reward function in adolescent depression will help to develop and personalize treatments.
- Future research should include longitudinal and cross-sectional designs employed prospectively and across clinical course.

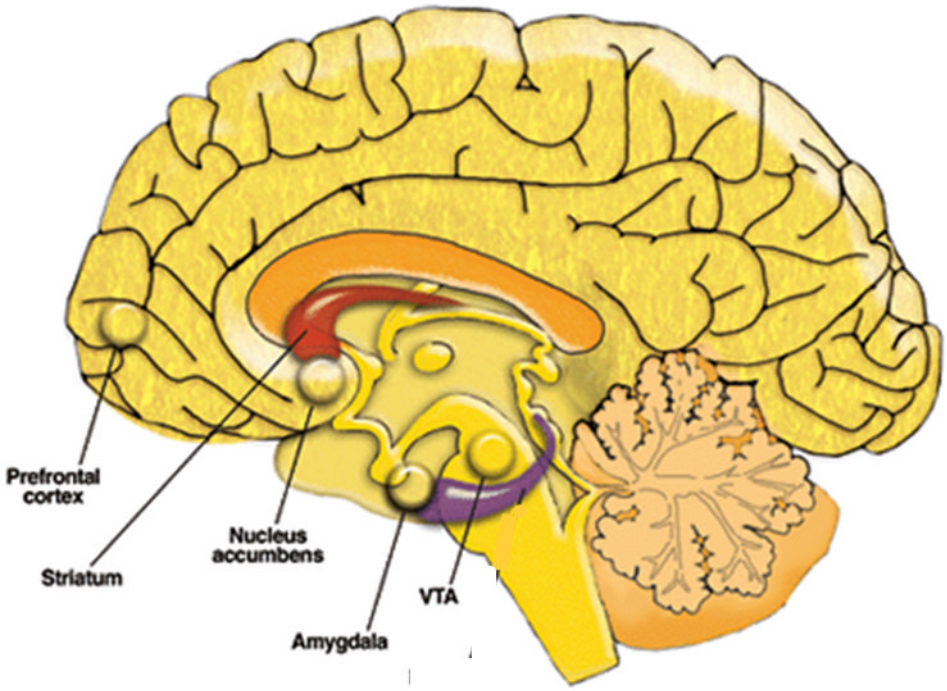

Figure 1.
Neural reward circuitry, with an emphasis on regions found to have altered function in depression. Adapted from Clapp et al., 2008.

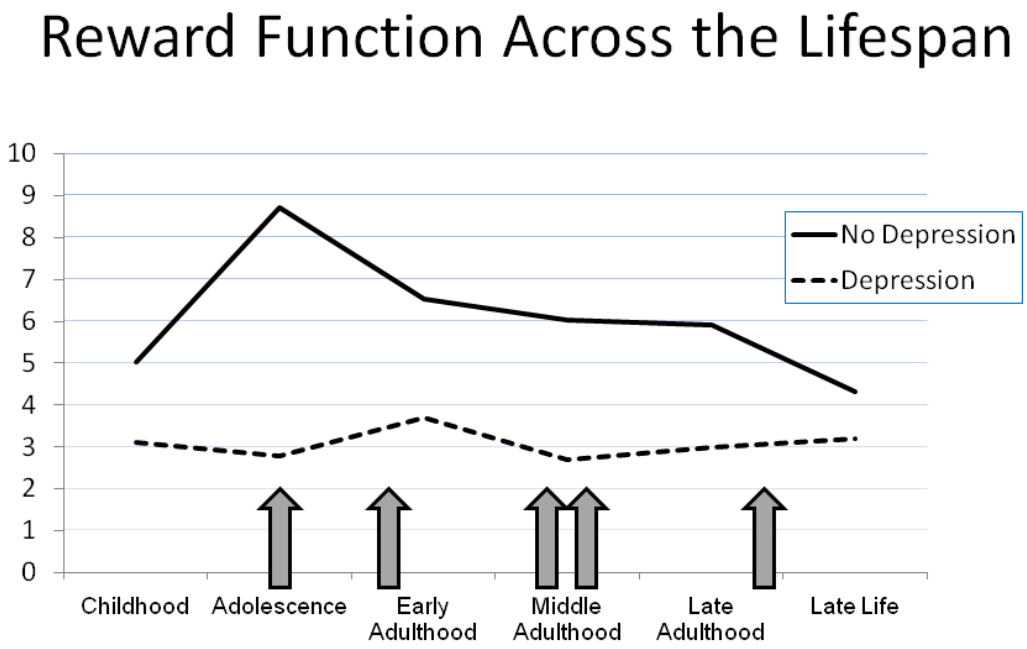

Figure 2.

Conceptual model of reward function across the lifespan, depicted separately for depressed and non-depressed populations. Arrows indicate timing of hypothetical depressive episodes. Between-group differences are most evident during adolescence, when levels of reward function are particularly high in the non-depressed group. At the same time, reward function in the depressed group is fairly stable across development and clinical course. Units are arbitrary.

Table 1

Studies of Depression and Neural Response to Reward

Authors	Task	Findings			Supports Low Reward Function?
		Striatum	mPFC	Other	
		Studies with Adolescents			
Forbes et al., 2006	Monetary guessing task	MDD < comparison during decision-making/anticipation and outcome[a]	MDD < comparison[a]	amygdala: MDD > comparison during outcome	Yes
Forbes et al., 2009	Monetary guessing task	MDD < comparison during anticipation and outcome (both: −6, 18, 3)	MDD > comparison during outcome (−4, 60, 3)		Yes
		Studies with Adults			
Davey et al., 2011	Social feedback about likeability	No group difference	MDD > comparison for faces vs. fixation (−14, 50, −2); (6, 32, −2)	amygdala: MDD > comparison (72, −36, −12)	No
Epstein et al., 2006	Pleasant words	MDD < comparison (−15, 15, −6) (15, 6, −3)	MDD < comparison[b]		Yes
Heller et al., 2009	Positive affect regulation task	MDD < comparison (−9, 12, 0)	N.A.		Yes
Keedwell et al., 2005a	Pleasant autobiographical memory		MDD > comparison (10, 51, 4) (−1, 33, 51)		
Keedwell et al., 2005b	Pleasant autobiographical memory	MDD < comparison (18, −4, 20)	MDD > comparison (−25, 4, 42); (−22, −7, 42)		Yes
Knutson et al., 2008	Monetary Incentive Delay task	No group difference	MDD > comparison during anticipation (−11, 11, 34) and outcome (8, 40, 4)		Mixed
Pizzagalli et al., 2009	Monetary Incentive Delay task	MDD < comparison during anticipation (−28, −13, −2) and outcome[b]	N.A.		Yes
Smoski et al., 2009	Wheel of Fortune monetary reward task	MDD < comparison during decision-making (−8, 6, 6) and anticipation (−18, −16, 22)	MDD < comparison during decision-making (−14, 44, 48)	orbitofrontal cortex: MDD > comparison during decision-making (26, 30, −16)	Yes
Surguladze et al., 2006	Pleasant facial expressions	MDD < comparison (22, 11, −2)	No group difference		Yes

[a] peak voxel not reported because analyses tested group differences in mean function of anatomically defined regions of interest

[b] peak voxel coordinates not reported, although both papers depicted clusters in figures. Pizzagalli et al. stated regions as bilateral caudate and left nucleus accumbens; Epstein et al. stated regions as left dorsomedial frontal gyrus

Note. MDD: major depressive disorder. Coordinates for the peak voxel of the cluster for group difference results are noted under each finding. All coordinates are in Talairach space, except for those for the studies by Pizzagalli et al., 2009 and Davey et al., 2011, which are in Montreal Neurological Institute space. N.A. Not applicable because the region was not included in analyses of group differences.

Table 2

Studies of Depression and Decision-Making under Reward Conditions

Authors	Tasks	Findings	Supports Low Reward Function?
Forbes et al., 2007	Reward-contingent decision task	Choice of "risky" option: depression group showed no difference between high-probability/low-magnitude and high-probability/high-magnitude conditions	Yes
Hardin et al., 2007	Reward antisaccade task	Performance: MDD < comparison Latency: improved with reward in comparison group but not MDD	Yes
Jazbec et al., 2005	Reward antisaccade task	Inhibitory efficiency: improved with reward in comparison but not MDD	Yes
Kyte et al., 2005	Decision making task	Speed of decisions when betting points: MDD > comparison	No
Cella et al., 2010	Iowa gambling task	Contingency-shift phase: MDD less perceptive of shifts from punishment to reward contingencies	Yes
Chase, Frank, et al., 2010	Probabilistic selection task	RT: MDD < comparison Blunted learning during practice: positive correlation with anhedonia	Yes
Chase, Michael, et al., 2010	Cued reinforcement reaction time task	Total points: MDD > comparison Likelihood of reaching threshold: MDD > comparison Errors: MDD < comparison	No
Corwin et al., 1990	Signal detection task	Response bias: MDD more conservative than comparison	Yes
Kaplan et al., 2006	Cambridge Gamble Task	Decision-making latency: MDD > comparison	Yes
Lempert & Pizzagalli, 2010	Intertemporal choice	Delay discounting: negative association with anhedonia	Yes
Pizzagalli et al., 2008	Signal detection task	Response bias toward rewarded stimuli: MDD < comparison	Yes
Pizzagalli et al., 2005	Signal detection task	Response bias toward rewarded stimuli: negatively correlated with depressive symptoms	Yes
Takahashi et al., 2008	Intertemporal choice task	Impulsivity: MDD > comparison	No

Note. MDD: major depressive disorder. RT: reaction time.

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