Published in final edited form as:

Trends Cogn Sci. 2016 June ; 20(6): 456–468. doi:10.1016/j.tics.2016.04.002.

Reward Processing And Risk For Depression Across Development

Katherine R Luking, PhD¹, David Pagliaccio, PhD², Joan L Luby, MD³, and Deanna M Barch, PhD^{3,4,5,6}

¹The Psychology Department at Stony Brook University

²The Emotion and Development Branch at the National Institute of Mental Health

³The Department of Psychiatry at Washington University in St. Louis

⁴Department of Psychology at Washington University in St. Louis

⁵Department of Radiology at Washington University in St. Louis

⁶Neuroscience Program at Washington University in St. Louis

Abstract

Striatal response to reward has been of great interest in the typical development and psychopathology literatures. These parallel lines of inquiry demonstrate that while typically developing adolescents show robust striatal response to reward, adolescents with major depressive disorder (MDD) or those at high-risk for MDD show blunted response to reward. Understanding how these findings intersect is critical for the development and application of early preventative interventions in at-risk children, ideally before the sharp increase in the rate of MDD onset that occurs in adolescence. Robust findings relating blunted striatal response to reward and MDD-risk are reviewed and situated within a normative developmental context. We highlight the need for future studies investigating longitudinal development, specificity to MDD, and roles of potential moderators and mediators.

Keywords

Reward; Depression; Development

Depression and Response to Reward

Major depressive disorder (MDD) is a highly prevalent condition, affecting up to 16% of Americans during their lifetime [1], and is increasingly being diagnosed early in development with roughly 25% of MDD patients being less than 19 years old [1]. MDD is

Correspondence: Katherine R. Luking, Department of Psychology, Stony Brook University, Stony Brook, NY, 11794, ; Email: katherine.luking@gmail.com.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

also highly debilitating due to significant decrement in quality of life, loss of work productivity, increases in health care costs [2], and an average loss of over 20 years of life [3]. Although much work has been done to characterize MDD, less than half of MDD patients report obtaining adequate treatment [2]. Difficulties in treating MDD are due, in part, to the lack of a biological understanding of this clinically and etiologically complex disorder. To address these gaps researchers are increasingly investigating the neural processes and structure underlying MDD-risk. The underlying purpose of these studies is to identify neural endophenotypes for MDD (Box 1) or biomarkers of risk. Endophenotypes are heritable and reliable traits that help to bridge the gap between diagnostic presentation and genetic liability. Identifying endophenotypes would ideally shed light on key biological mechanisms contributing to MDD and MDD-risk, ideally guiding early diagnosis and mechanism-based preventative interventions.

Importantly, MDD is a particularly heterogeneous disorder where patients commonly present with any of a variety of symptoms including somatic complaints, heightened responses to negative or stressful events, low mood, and/or blunted behavioral or affective response to reward (i.e. anhedonia) [4]. Yet, as two MDD patients could present with wholly disparate symptom profiles, many researchers are now moving to focusing on specific symptom constructs and mechanisms, which often transcend diagnostic boundaries, [5] rather than examining MDD as a unitary construct. For example, there has been particular interest in examining whether blunted response to reward is a biomarker or endophenotype for MDD [6–8], particularly considering that anhedonia is one of the most treatment resistant components of MDD [9]. A focus on blunted response to reward as an endophenotype is highly consistent with the recent Research Domain Criteria (RDoC) framework that emphasizes a focus on core brain-behavior systems that may transcend traditional diagnostic boundaries [5]. In this review we focus on striatal response to the receipt of reward for the reasons outlined in Box 2, but acknowledge the importance of work that examines other aspects of reward processing, such as anticipation and learning. We also use the term striatal response to reward broadly with the important distinctions among differential functions associated with subregions of the striatum discussed briefly in Box 2, for in-depth discussion of these distinctions see [10].

Several specific criteria have been suggested in establishing endophenotype [11, 12] and importantly, blunted striatal response to reward meets many of these criteria in adult samples. First, for a trait to be a useful bridge between symptom presentation and genetic underpinnings, it must be associated with the disorder of interest. Meta-analytic work has confirmed that depressed individuals show blunted striatal responses to the receipt of rewards, as well as some evidence for blunting in response to anticipation of reward [13]. Second, endophenotypes must be state-independent and not confined to a current depressive episode. Blunted striatal response to reward is observed in remitted MDD [14]. Third, a proposed endophenotype should be enriched among non-affected family members relative to the general population, which has been shown for reward-related event related potentials (ERPs) [15, 16]. Fourth, endophenotypes must be heritable, and although heritability of striatal response to reward has not been examined, behavioral response to reward is approximately 46% heritable [17] and reward-related ERPs are familial [16], consistent with heritability. Fifth, familial co-segregation is required, where the endophenotype occurs to a

greater extent in depressed individuals or previously depressed family members compared to never depressed relatives. This has not been examined regarding striatal response to reward. Finally, reliability has been more recently added as an endophenotype criterion. Striatal response to reward shows mixed reports of reliability, with some studies reporting moderate reliability (intra-class correlations >0.5 [18, 19]), but others reporting poor reliability (intra-class correlations between -0.15 and 0.44 [20]).

Collectively this reviewed work suggests that blunted neural response to reward is a promising endophenotype of MDD. However, it is important to highlight that most of these criteria have only been examined in adults, with relatively few studies investigating pediatric MDD [21]. This gap in knowledge is particularly concerning given that the incidence of MDD begins to rise precipitously after age 10 [22] (Figure 1A), meaning that there is real need to identify markers of risk evident in childhood. Such early markers, which may manifest in developmentally specific ways, could help reveal mechanisms of early risk and identify key windows of vulnerability or opportunity for intervention, with the goal of developing and applying mechanism-based preventative mental health interventions. We feel that better integration of clinical and normative developmental frameworks are critical in achieving this aim. To this end, the current review summarizes the extant literature comparing striatal response to reward receipt in pediatric groups at relatively high- or low-risk for MDD based on familial MDD history (see Box 3 for discussion of risk definition) and highlights how this work relates to the normative development of striatal systems.

Typical Development and the Striatum

Increased affective and behavioral response to rewarding stimuli is a hallmark feature of adolescence that is conserved across species [23]. Striatal response to reward has been linked to reward-seeking behaviors as well as affective response to reward; these relationships and the details of striatal structure and function have been reviewed extensively [10, 24–26]. Given these links, adolescent changes in striatal structure and function are the focus of a burgeoning literature and several excellent reviews have been written focusing on adolescent changes in reward responsiveness [27–31]. Collectively, these reviews highlight both hypo- and hyper-activation of striatal response to reward during adolescence, relative to childhood and adulthood. The varying findings with regard to hypo- versus hyper-activation relate in part to task type, required behavioral response, and the component of reward processing examined (Box 2) [29]. For example, adolescents show striatal hypo-activation to reward cues relative to adults when inhibition of a primed behavior is required [32] or in response to anticipatory cues that predict a potential reward, e.g. [33]. Conversely, during receipt of reward feedback adolescents typically show striatal hyper-responsiveness relative to both younger and older ages [34–36] (Figure 1B). Longitudinal studies have also shown this inverted “u-shaped” quadratic relationship between age and ventral striatal response to reward [37, 38]. But, note that this pattern is not universally observed [39] with some studies reporting linear rather than quadratic trends [40].

Fewer studies have focused on the biological mechanisms mediating this adolescent peak in striatal response to reward receipt. Those that do primarily use rodent or non-human primate models to investigate the dopaminergic (DA) or endocannabinoid systems, both of which

involve the ventral striatum and relate to incentive motivational and hedonic components of reward responding, respectively [26]. An excellent review of the literature examining age-related changes in DA signaling and incentive motivation suggests that increases in tonic striatal dopaminergic activity during adolescence, relative to childhood and adulthood, relate to increases in incentive/reward motivation during adolescence [41]. There is growing evidence from rodent models that endocannabinoid signaling is enhanced in adolescence relative to adulthood, [42] which in turn relates to enhanced social play [43, 44], a behavior that is heightened in adolescence. Reductions in endocannabinoid signaling can inhibit adolescent-typical patterns of behavior [45] and artificially enhancing endocannabinoid signaling can extend adolescent behavioral phenotypes into adulthood [44].

In human work, the role of puberty remains an important open question in this area. In particular, there are key open questions as to the relative effects of the biological process of sexual maturation versus chronological age in driving adolescent changes in striatal response to reward, as discussed in more detail below. Levels of gonadal hormones that rise during puberty, such as testosterone, do relate to ventral striatal response to reward [37]. However, human studies have not examined whether pubertal stage, typically assessed via changes in breasts/genitalia [46], or gonadal hormones mediate adolescent increases in striatal response to reward. In fact, there is evidence from rodent models that adolescent increases in dopamine receptor expression are not driven by gonadal hormones [47]. Future studies that contrast longitudinal change in age and physical development in humans are needed to establish the role of puberty in the functional maturation of striatal systems. See [48] for discussion of longitudinal relationships between striatal volume, reported reward response, and puberty.

Striatal Response to Reward in MDD-Risk

Nearly all published studies investigating striatal response to reward within never-depressed offspring of depressed versus healthy parents have reported blunted striatal response to reward receipt in high-risk groups (see Box 2 for discussion of reward tasks and relationships to striatal response). Blunted striatal response to reward in MDD-risk was found across different task types (e.g. instrumental versus passive), reward types (e.g. money versus happy faces), and maternal only versus parental MDD history (Table 1). Interestingly, group differences in striatal reward response, relative to a variety of control conditions, have been observed mainly in the ventral striatum (Table 1), though it should be noted that several studies restricted analyses to this region [49–51].

Only one published study did not report a significant difference in striatal response to reward between groups, although blunted responding to reward in the high-risk group was observed within the anterior cingulate and lateral orbital frontal cortex (OFC)/anterior insula [52]. This null effect of MDD-risk within the striatum may relate to the older age of the sample (aged 16–21 years; Table 1). It is possible that effects of MDD-risk on striatal reward response are greatest during the normative ‘peak’ in reward responding, typically observed in early/mid adolescence (Figure 1B/C); this hypothesis is discussed further below. However, it is also important to note that studies where high-risk groups show blunted striatal response to reward may be more likely to be published than those with null results.

Further, the effect sizes in the studies in Table 1 vary to some extent with sample size, with smaller studies showing somewhat larger effect sizes.

Blunted Reward Response in Predicting Depression

The studies discussed to this point have demonstrated cross-sectionally that blunted striatal response to reward is associated with MDD-risk based on maternal/parental history, particularly during adolescence. However, it is critical to establish whether blunted response to reward predicts longitudinal increases in depressive symptoms or new onset of MDD within individuals. Several studies have demonstrated that blunted striatal response to reward feedback [53, 54] and anticipation [55], along with striatal-related ERPs (i.e. feedback negativity) [56], prospectively predict worsening of depressive symptoms/disorder onset, even controlling for baseline symptoms. Importantly, these studies have typically been conducted in mid/late adolescence over a two-year follow-up window [54–56]. One study utilized a younger sample (11–13 years), but only observed a relationship between striatal function and future symptoms in adolescents with more advanced pubertal development [53]. As such, the early diagnostic/predictive value of striatum blunting is still unclear, as the available data do not speak clearly to whether striatal function in childhood also prospectively predicts worsening of symptoms/disorder onset. Further, it is unclear whether longitudinal change in striatal function mediates longitudinal changes in depressive symptoms. For example, it may be that blunting of striatal response to reward is part of the mechanistic pathway to depression, with blunted responding perhaps failing to buffer stress. Alternatively, blunted striatal response to reward and increased symptom severity, particularly from adolescence onward [57], may both mark increased risk, but may be driven by a third factor, with no direct causal relationship between blunted reward response and depression increases. Disentangling these possibilities may help inform whether blunted striatal reward response is a risk marker, mechanism, or both.

Studying Blunting and MDD-Risk: Developmental Considerations

Age

Many MDD-risk studies included individuals across wide age ranges, with the majority of published studies focusing on adolescence (Figure 1C), when a normative peak in striatal response to reward typically takes place (Figure 1B). This has made it difficult to assess whether high-risk individuals consistently show striatal blunting beginning early in development or whether striatal blunting worsens through adolescence. Only two studies to date have focused on risk-related reward blunting in childhood (i.e., participants through age 10), one using fMRI [58] and one using EEG [59]. Although both studies report blunted reward response in children of depressed mothers, the effect sizes are smaller relative to studies using the same card gambling task in adolescence [58, 60]. Though comparing effect sizes across these studies is confounded by differences in imaging parameters, paradigms, and power/sample size, the strongest evidence for blunted response to reward in high-risk groups has been observed during a period of heightened normative adolescent reward response. In fact, for the five studies using secondary rewards (consumed out of scanner), the reported effect sizes are strongly positively correlated with the mean sample age (Table 1).

Only one study has reported age differences in the relationship between striatal reward response and MDD-risk, here based on institutional rearing rather than family history. In this study, blunting of striatal response to happy faces was observed in high-risk adolescents but not in children [61].

Puberty

Puberty is quantified in a variety of ways in the literature. Some studies utilize a girl's first period (menarche) or a boy's first ejaculation to demarcate pre- versus post-puberty. Other studies focus on staged changes in genitalia and either breasts for females and voice/facial hair for males, known as Tanner Stages [62], that are typically assessed via questionnaire [46] or physical exam. Puberty is important to consider in addition to age given that high-risk groups tend to show earlier pubertal development [63], that advanced pubertal timing (i.e. earlier menarche or first ejaculation) is associated with adolescent depression [64, 65], and that blunted striatal response to reward is observed in adolescents who exhibit more advanced breast/genital development relative to their age [66]. As such, more advanced pubertal development could contribute to differences in striatal response to reward between high- and low-risk groups. Pubertal development was reported in only four of the nine MDD-risk studies discussed above [50, 58, 67, 68]. Although high-risk offspring tend show earlier pubertal onset in large-scale studies investigating puberty and psychopathology [63], MDD-risk was related to more advanced pubertal development in only one of the studies reviewed here [68]. Importantly, the effects of MDD-risk were unchanged when controlling for puberty [50, 67, 68]. Thus, it seems unlikely that more advanced self-reported pubertal development in high-risk groups (relative to low-risk groups) accounted for risk-related differences in striatal response.

Hormonal measures may provide a more reliable and mechanistic measure of pubertal development, although they are not without their own complexities. In fact, hormones have been shown to mediate relationships between scores on puberty rating scales and depression in girls [69]. Other developmentally relevant social factors, such as changes in need for affiliation, have also been suggested to contribute to increased risk for MDD during puberty (e.g. [70]). Even though need for affiliation increases during puberty/adolescence, changes in this process may not be captured in self-report of physical development, but could be of relevance to studies of reward responsivity. Thus, these may be important mediating or moderating factors to consider in future studies.

Possible Developmental Mechanisms

As discussed in the above section, increases in both tonic DA and endocannabinoid signaling are observed during adolescence and relate to adolescent changes in striatal function and reward-related behaviors. Interestingly both DA [71] and endocannabinoid [72] signaling are compromised in adult MDD. Further, pharmacological manipulations that reduce presynaptic DA [73, 74] or endocannabinoid signaling [75, 76] are sufficient to induce both depressive symptoms in non-depressed individuals and a blunting of ventral striatal response to reward. There is no work specifically investigating these neurotransmitters in pediatric depression or MDD-risk. Therefore, it is unclear whether, for example, high-risk offspring fail to show the developmentally typical increases in tonic DA

or endocannabinoid signaling, and thus resemble depressed adults. However, if high-risk offspring were to have altered tonic DA or endocannabinoid signaling, they may be more vulnerable to the anhedonic effects of stress given that: 1) an important function of the endocannabinoid system is to reduce glucocorticoid responses to stress [77]; and 2) blockade of cannabinoid receptors enhances stress-induced anhedonia [78]. Such vulnerability, in combination with increased exposure to psychosocial stress during adolescence, could contribute to the blunted striatal response to reward seen in high-risk adolescents. However, future studies in human are needed to test these hypotheses directly, particularly as the majority of this work has been conducted in animal models.

Confounds that May Explain Reward Blunting in MDD-Risk

Although the studies discussed here excluded offspring with a prior/current diagnosis of MDD, offspring of depressed mothers still tend to exhibit elevated sub-clinical depressive symptoms [58, 60, 67]. In adolescents, reduced positive affect and elevated depressive symptoms have been linked to blunted striatal response to reward [66]. As such, it is possible that group differences in striatal response to reward could simply reflect elevated subclinical depressive symptoms. Several studies have begun to examine this hypothesis by including MDD symptoms as predictors/covariates when testing risk effects, but have yielded opposing results. One study reported that elevated depressive symptoms reported by the offspring predicted blunted striatal response to reward receipt and that differences between high- and low-risk groups were no longer significant after controlling for symptoms [60]. However group differences remained significant for reward anticipation [60]. Conversely, several other studies [50, 58, 59, 67] reported risk-related blunting of response to reward even when controlling for offspring-reported depressive symptoms. Thus while depressive symptoms likely relate to striatal reward response, they do not necessarily explain differences between high- and low-risk groups.

Specificity of Blunted Striatal Responses

Specificity to MDD-Risk versus Disorder

For blunted striatal response to reward to be an endophenotype for MDD-risk, it should be observed in high-risk but healthy individuals as well as in depressed individuals. Two of the MDD-risk studies discussed above also included a currently depressed group to address this issue. Both studies reported similar striatal responses to reward, happy faces [68] or money [51] in healthy high-risk and depressed adolescents. These results suggest that blunted striatal response to reward is not simply a 'scar' of MDD, but rather is present to the same degree in never-depressed high-risk groups. However, as neither study reported what proportion of depressed adolescents also had depressed parents, future studies are needed to directly investigate whether current and familial MDD are independent predictors of adolescent striatal function, particularly as there is some evidence from ERP studies supporting this hypothesis in adults [15, 16].

Specificity to Reward

It is important to note that the striatum also responds to negative stimuli including punishment and loss of reward (for review see [10]). Although all of the MDD-risk studies discussed here included a negative feedback condition (loss of candy/money/points [51, 58–60, 67], aversive taste/picture [52], social rejection [50], or negative faces [49, 68]), only four studies reported on risk effects for both reward and negative feedback [49, 52, 58, 67] (note, [59] focused on the feedback negativity, which is the difference between loss- and gain-related ERPs). The four studies that investigated response to negative feedback all reported greater reactivity in high-risk groups. Specifically, high-risk children [58] and adolescents [67] both showed greater ventral striatal deactivation to loss of reward (relative to control conditions or fixation). These responses occurred during instrumental tasks and thus could possibly indicate enhanced negative prediction error signaling. In studies using face viewing or tasting paradigms, high-risk groups showed greater activation within the ventral striatum and amygdala [49] as well as lateral OFC [52] to negative stimuli. Whether the enhanced responding involved increased deactivation or increased activation depended on stimulus/paradigm type. Thus, while high-risk groups showed attenuated response to reward feedback, they also showed enhanced response to negative feedback within similar regions. In fact, there is evidence that risk-effects are significantly larger for ventral striatal response to loss than for response to reward feedback [58]. As such, striatal dysfunction in high-risk groups is not limited to reward feedback, although blunted patterns of striatal response do seem specific to reward, as high-risk groups show heightened responses to negative feedback.

Specificity to MDD-Risk Versus Other Disorder Risk

Although we operationalize a positive history of maternal MDD as ‘high-risk for depression’, maternal MDD also conveys increased risk for offspring psychopathology more broadly, particularly anxiety which tends to precede onset of MDD [79]. There have been two typical strategies in accounting for this general increased ‘risk’. Some studies exclude offspring with any psychiatric diagnoses [51, 52, 58, 60, 67, 68], whereas others exclude only for MDD but not other disorders [49, 50, 59]. Importantly, blunted striatal response to reward has been documented in high-risk groups independent of whether other diagnoses were exclusionary. Further, the effects of MDD-risk on striatal response/feedback negativity remain significant when controlling for anxiety symptoms [58, 59]. However, ERP studies focusing on specific anxiety symptoms have reported increased response to reward in social anxiety and blunted response to reward in generalized anxiety [80]. ADHD diagnosis/symptoms have also been related to blunted striatal response, here to reward anticipation [81]. Thus, well-powered studies are still needed to investigate possible specific or interactive effects of MDD-risk vs. other diagnoses on striatal function as well as longitudinal studies to examine whether blunted reward response specifically and differentially predicts onset of MDD versus other disorders.

Specificity to MDD is also a question on the parental side of the risk equation. MDD is highly comorbid with other disorders, including substance abuse/dependence and anxiety disorders. Thus, it is likely that many depressed parents also had comorbid disorders. Only a few studies have conducted analyses investigating whether response to reward within high-

risk offspring differed based on the presence of other types of parental psychopathology [58, 68]. These post-hoc analyses yielded null-results, but were relatively underpowered and should be interpreted with caution. One study directly investigated parental MDD, anxiety, and their interaction as unique predictors of offspring reward response (here feedback negativity) [59]. Despite robust relationships between parental MDD and striatal blunting, blunting was not observed among offspring of mothers with anxiety only or with comorbid depression and anxiety. This result suggests that blunted reward response may be a specific marker of familial liability for MDD. Other large studies in adults have suggested that blunted reward-related ERPs (i.e. frontal asymmetry and feedback negativity) specifically relate to familial liability for MDD versus panic disorder [15] or familial low positive affect versus elevated negative affect [16]. Importantly, these ERP measures related to familial 'risk' over and above the proband's diagnostic status or symptoms.

Specificity to Familial MDD Versus Other Risk Factors

As discussed in Box 3, a number of other environmental factors, such as early life deprivation or trauma, also increase risk for MDD. No studies, to our knowledge, have investigated whether familial MDD and other risk factors are unique predictors of striatal response to reward or whether factors, like parenting or stress exposure, may instead mediate effects of familial MDD on reward responsivity. However, it does seem that blunted striatal response to reward also characterizes groups at high-risk for MDD based on severe early life deprivation, such as that experienced in orphanages abroad [61]. There is also emerging evidence that parenting may moderate the relationship between maternal MDD and offspring response to reward. Specifically, reduced levels of positive parenting during early childhood, either reduced warmth [82] or authoritative parenting [83], predict worsened blunting of ERP/striatal response to reward, particularly in high-risk offspring. These results indicate that a lack of positive parenting may convey added risk for children already at high-risk via familial MDD. Future studies are needed to parse these potentially mediating and moderating effects of familial MDD and other risk factors on striatal response to reward.

Behavioral Significance of Blunted Response to Reward

Relatively little work has focused on why blunted response to reward is linked to negative mental health outcomes. We know that greater striatal reward response predicts both greater real world positive affect in adolescents' daily life [84] and reduced levels of depressive symptoms [66]. However, it is unclear to what degree blunted striatal reward response is a mediator (e.g. increasing anhedonic symptomology), moderator (e.g. exacerbating effects of other risk factors, such as stress), or epiphenomenal marker (i.e. not being mechanistically involved) of MDD/MDD-risk. For example, adults with blunted ventral striatal response to reward show greater reductions in positive affect when experiencing stress [85]. It may be that individuals with blunted response to reward are less able to use reward experience to buffer effects of/recover from stress. They may also show even greater reductions in reward response following stress (i.e. stress-induced anhedonia). If so, reward responding may be an important resilience factor and potential treatment target allowing patients to experience greater positive affect or more adaptively react/recover from life stressors, which often precede onset of depressive episodes.

Concluding Remarks and Future Perspectives

Studies comparing never depressed groups at high- and low-risk for MDD routinely document relationships between MDD-risk and blunted striatal response to reward. The strongest evidence for this relationship has been observed during mid adolescence, a time when striatal response to reward peaks in typically developing populations. Longitudinal studies beginning in childhood are needed to explicitly examine whether the relationship between MDD-risk and striatal response changes/strengthens over adolescent development.

Together the studies reviewed here suggest that blunted striatal response to reward is a promising endophenotype for MDD-risk in adolescence given that risk-related differences in striatal function are not explained by confounding factors, such as advanced puberty or elevated depressive/anxious symptoms, seems to be specific to familial depression versus anxiety, and are present to a similar extent in depressed and never-depressed high-risk groups. However, future studies in pediatric groups examining other endophenotype features such as heritability, familial co-segregation, and reliability are still needed to fully evaluate whether blunted striatal response to reward constitutes a useful developmental endophenotype for MDD. Future studies are also needed to evaluate this relationship over a broad developmental range and to investigate the specificity and potential mechanisms of this relationship as well as relationships to mental health outcomes. Together such studies would establish whether blunted striatal reward response is a robust marker of MDD-risk in early childhood, as it seems to be in adolescence, and is thus a potential target for preventative intervention. This is a critical future direction if we hope to preclude the development of the depressive pathology that is such a burden for those who suffer from this illness.

Acknowledgments

This research was supported in part by the Intramural Research Program of the NIMH (DP) as well by NIMH Grants MH098454 (JLL & DMB), MH090786 (JLL & DMB), and MH097767 (KRL).

Glossary

Major Depressive Disorder (MDD)	mood disorder characterized primarily by feelings of sadness and/or loss of interest
Anhedonia	the reduced ability to experience pleasure or interest
Puberty	the biological process of sexual maturation
Endophenotype	a genetic epidemiology term that is used to separate behavioral symptoms into more stable phenotypes with a clear genetic connection
Co-segregation	when an endophenotype occurs more in depressed individuals or previously depressed family members compared to never-depressed relatives

References

1. Kessler RC, et al. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of general psychiatry*. 2005; 62:593–602. [PubMed: 15939837]
2. Simon GE. Social and economic burden of mood disorders. *Biological psychiatry*. 2003; 54:208–215. [PubMed: 12893097]
3. Colton CW, Manderscheid RW. Congruencies in increased mortality rates, years of potential life lost, and causes of death among public mental health clients in eight states. *Prev Chronic Dis*. 2006; 3:A42. [PubMed: 16539783]
4. APA. *Diagnostic and Statistical Manual of Mental Disorders*. American Psychiatric Publishing; 2013.
5. Insel T, et al. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. *The American journal of psychiatry*. 2010; 167:748–751. [PubMed: 20595427]
6. Proudfit GH. The reward positivity: from basic research on reward to a biomarker for depression. *Psychophysiology*. 2015; 52:449–459. [PubMed: 25327938]
7. Bogdan R, et al. Neurogenetics of depression: a focus on reward processing and stress sensitivity. *Neurobiology of disease*. 2013; 52:12–23. [PubMed: 22659304]
8. Pizzagalli DA. Depression, stress, and anhedonia: toward a synthesis and integrated model. *Annual review of clinical psychology*. 2014; 10:393–423.
9. Calabrese JR, et al. Methodological approaches and magnitude of the clinical unmet need associated with amotivation in mood disorders. *Journal of affective disorders*. 2014; 168:439–451. [PubMed: 25113957]
10. Haber SN, Knutson B. The reward circuit: linking primate anatomy and human imaging. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*. 2010; 35:4–26. [PubMed: 19812543]
11. Gould TD, Gottesman II. Psychiatric endophenotypes and the development of valid animal models. *Genes, brain, and behavior*. 2006; 5:113–119.
12. Gottesman II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. *The American journal of psychiatry*. 2003; 160:636–645. [PubMed: 12668349]
13. Zhang WN, et al. The neural correlates of reward-related processing in major depressive disorder: a meta-analysis of functional magnetic resonance imaging studies. *Journal of affective disorders*. 2013; 151:531–539. [PubMed: 23856280]
14. McCabe C, et al. Neural representation of reward in recovered depressed patients. *Psychopharmacology*. 2009; 205:667–677. [PubMed: 19529923]
15. Nelson BD, et al. Biomarkers of threat and reward sensitivity demonstrate unique associations with risk for psychopathology. *Journal of abnormal psychology*. 2013; 122:662–671. [PubMed: 24016008]
16. Weinberg A, et al. Blunted Neural Response to Rewards as a Vulnerability Factor for Depression: Results From a Family Study. *Journal of abnormal psychology*. 2015 epub ahead of print.
17. Bogdan R, Pizzagalli DA. The heritability of hedonic capacity and perceived stress: a twin study evaluation of candidate depressive phenotypes. *Psychological medicine*. 2009; 39:211–218. [PubMed: 18507876]
18. Wu CC, et al. Affective traits link to reliable neural markers of incentive anticipation. *NeuroImage*. 2014; 84:279–289. [PubMed: 24001457]
19. Plichta MM, et al. Test-retest reliability of evoked BOLD signals from a cognitive-emotive fMRI test battery. *NeuroImage*. 2012; 60:1746–1758. [PubMed: 22330316]
20. Fließbach K, et al. Retest reliability of reward-related BOLD signals. *NeuroImage*. 2010; 50:1168–1176. [PubMed: 20083206]
21. Kerestes R, et al. Functional brain imaging studies of youth depression: a systematic review. *NeuroImage. Clinical*. 2014; 4:209–231. [PubMed: 24455472]
22. Beesdo K, et al. Mood episodes and mood disorders: patterns of incidence and conversion in the first three decades of life. *Bipolar disorders*. 2009; 11:637–649. [PubMed: 19689506]

23. Spear LP. The adolescent brain and age-related behavioral manifestations. *Neuroscience and biobehavioral reviews*. 2000; 24:417–463. [PubMed: 10817843]
24. Haber SN, Gottfried JA. *Neuroanatomy of Reward: A View from the Ventral Striatum. Neurobiology of Sensation and Reward*. 2011
25. Berridge KC. From prediction error to incentive salience: mesolimbic computation of reward motivation. *The European journal of neuroscience*. 2012; 35:1124–1143. [PubMed: 22487042]
26. Berridge KC, et al. Dissecting components of reward: ‘liking’, ‘wanting’, and learning. *Current opinion in pharmacology*. 2009; 9:65–73. [PubMed: 19162544]
27. Galvan A. Adolescent development of the reward system. *Frontiers in human neuroscience*. 2010; 4:6. [PubMed: 20179786]
28. Spear LP. Rewards, aversions and affect in adolescence: emerging convergences across laboratory animal and human data. *Developmental cognitive neuroscience*. 2011; 1:392–400. [PubMed: 21918675]
29. Richards JM, et al. A systematic review of fMRI reward paradigms used in studies of adolescents vs. adults: the impact of task design and implications for understanding neurodevelopment. *Neuroscience and biobehavioral reviews*. 2013; 37:976–991. [PubMed: 23518270]
30. Wahlstrom D, et al. Neurobehavioral evidence for changes in dopamine system activity during adolescence. *Neuroscience and biobehavioral reviews*. 2010; 34:631–648. [PubMed: 20026110]
31. Geier C, Luna B. The maturation of incentive processing and cognitive control. *Pharmacology, biochemistry, and behavior*. 2009; 93:212–221.
32. Geier CF, et al. Immaturities in reward processing and its influence on inhibitory control in adolescence. *Cereb Cortex*. 2010; 20:1613–1629. [PubMed: 19875675]
33. Bjork JM, et al. Adolescents, adults and rewards: comparing motivational neurocircuitry recruitment using fMRI. *PloS one*. 2010; 5:e11440. [PubMed: 20625430]
34. Van Leijenhorst L, et al. Adolescent risky decision-making: neurocognitive development of reward and control regions. *NeuroImage*. 2010; 51:345–355. [PubMed: 20188198]
35. Galvan A, et al. Earlier development of the accumbens relative to orbitofrontal cortex might underlie risk-taking behavior in adolescents. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2006; 26:6885–6892. [PubMed: 16793895]
36. Silverman MH, et al. Neural networks involved in adolescent reward processing: An activation likelihood estimation meta-analysis of functional neuroimaging studies. *NeuroImage*. 2015; 122:427–439. [PubMed: 26254587]
37. Braams BR, et al. Longitudinal changes in adolescent risk-taking: a comprehensive study of neural responses to rewards, pubertal development, and risk-taking behavior. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2015; 35:7226–7238. [PubMed: 25948271]
38. Lamm C, et al. Longitudinal study of striatal activation to reward and loss anticipation from mid-adolescence into late adolescence/early adulthood. *Brain and cognition*. 2014; 89:51–60. [PubMed: 24485273]
39. Bjork JM, et al. Incentive-elicited brain activation in adolescents: similarities and differences from young adults. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2004; 24:1793–1802. [PubMed: 14985419]
40. Hoogendam JM, et al. Different developmental trajectories for anticipation and receipt of reward during adolescence. *Developmental cognitive neuroscience*. 2013; 6:113–124. [PubMed: 24055865]
41. Luciana M, et al. Dopaminergic modulation of incentive motivation in adolescence: age-related changes in signaling, individual differences, and implications for the development of self-regulation. *Dev Psychol*. 2012; 48:844–861. [PubMed: 22390660]
42. Rodriguez de Fonseca F, et al. Presence of cannabinoid binding sites in the brain from early postnatal ages. *Neuroreport*. 1993; 4:135–138. [PubMed: 8453049]
43. Trezza V, et al. Endocannabinoids in amygdala and nucleus accumbens mediate social play reward in adolescent rats. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2012; 32:14899–14908. [PubMed: 23100412]

44. Schneider M, et al. Enhanced Functional Activity of the Cannabinoid Type-1 Receptor Mediates Adolescent Behavior. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2015; 35:13975–13988. [PubMed: 26468198]
45. Agoglia AE, et al. Cannabinoid CB1 receptor inhibition blunts adolescent-typical increased binge alcohol and sucrose consumption in male C57BL/6J mice. *Pharmacology, biochemistry, and behavior*. 2016; 143:11–17.
46. Petersen AC, et al. A Self-Report Measure of Pubertal Status: Reliability, Validity, and Initial Norms. *Journal of Youth and Adolescence*. 1988; 17:117–133. [PubMed: 24277579]
47. Andersen SL, et al. Pubertal changes in gonadal hormones do not underlie adolescent dopamine receptor overproduction. *Psychoneuroendocrinology*. 2002; 27:683–691. [PubMed: 12084661]
48. Urošević S, et al. Pubertal status associations with reward and threat sensitivities and subcortical brain volumes during adolescence. *Brain and cognition*. 2014; 89:15–26. [PubMed: 24512818]
49. Monk CS, et al. Amygdala and nucleus accumbens activation to emotional facial expressions in children and adolescents at risk for major depression. *The American journal of psychiatry*. 2008; 165:90–98. [PubMed: 17986682]
50. Olino TM, et al. Social Reward in Youth at Risk for Depression: A Preliminary Investigation of Subjective and Neural Differences. *Journal of child and adolescent psychopharmacology*. 2015; 25:711–721. [PubMed: 26469133]
51. Sharp C, et al. Major depression in mothers predicts reduced ventral striatum activation in adolescent female offspring with and without depression. *Journal of abnormal psychology*. 2014; 123:298–309. [PubMed: 24886004]
52. McCabe C, et al. Neural processing of reward and punishment in young people at increased familial risk of depression. *Biological psychiatry*. 2012; 72:588–594. [PubMed: 22704059]
53. Morgan JK, et al. Neural response to reward as a predictor of increases in depressive symptoms in adolescence. *Neurobiol Dis*. 2013; 52:66–74. [PubMed: 22521464]
54. Telzer EH, et al. Neural sensitivity to eudaimonic and hedonic rewards differentially predict adolescent depressive symptoms over time. *Proceedings of the National Academy of Sciences of the United States of America*. 2014; 111:6600–6605. [PubMed: 24753574]
55. Stringaris A, et al. The Brain's Response to Reward Anticipation and Depression in Adolescence: Dimensionality, Specificity, and Longitudinal Predictions in a Community-Based Sample. *The American journal of psychiatry*. 2015; 172:1215–1223. [PubMed: 26085042]
56. Bress JN, et al. Blunted neural response to rewards prospectively predicts depression in adolescent girls. *Psychophysiology*. 2013; 50:74–81. [PubMed: 23252717]
57. Angold A, et al. Puberty and depression: the roles of age, pubertal status and pubertal timing. *Psychological medicine*. 1998; 28:51–61. [PubMed: 9483683]
58. Luking K, et al. Depression Risk Predicts Blunted Responses To Candy Gains And Enhanced Responses To Candy Losses In Healthy Children. *Journal of the American Academy of Child and Adolescent Psychology*. 2016
59. Kujawa A, et al. Neural reactivity to rewards and losses in offspring of mothers and fathers with histories of depressive and anxiety disorders. *Journal of abnormal psychology*. 2014; 123:287–297. [PubMed: 24886003]
60. Olino TM, et al. Reduced reward anticipation in youth at high-risk for unipolar depression: a preliminary study. *Dev Cogn Neurosci*. 2014; 8:55–64. [PubMed: 24369885]
61. Goff B, et al. Reduced nucleus accumbens reactivity and adolescent depression following early-life stress. *Neuroscience*. 2013; 249:129–138. [PubMed: 23262241]
62. Marshall WA, Tanner JM. Growth and physiological development during adolescence. *Annu Rev Med*. 1968; 19:283–300. [PubMed: 4297619]
63. Ellis BJ, Garber J. Psychosocial antecedents of variation in girls' pubertal timing: maternal depression, stepfather presence, and marital and family stress. *Child development*. 2000; 71:485–501. [PubMed: 10834479]
64. Kaltiala-Heino R, et al. Early puberty is associated with mental health problems in middle adolescence. *Social science & medicine*. 2003; 57:1055–1064. [PubMed: 12878105]
65. Kaltiala-Heino R, et al. Pubertal timing, sexual behaviour and self-reported depression in middle adolescence. *Journal of adolescence*. 2003; 26:531–545. [PubMed: 12972267]

66. Forbes EE, et al. Healthy adolescents' neural response to reward: associations with puberty, positive affect, and depressive symptoms. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2010; 49:162–172. e161–165. [PubMed: 20215938]
67. Gotlib IH, et al. Neural processing of reward and loss in girls at risk for major depression. *Archives of general psychiatry*. 2010; 67:380–387. [PubMed: 20368513]
68. Kerestes R, et al. Altered neural function to happy faces in adolescents with and at risk for depression. *Journal of affective disorders*. 2015; 192:143–152. [PubMed: 26724693]
69. Angold A, et al. Pubertal changes in hormone levels and depression in girls. *Psychological medicine*. 1999; 29:1043–1053. [PubMed: 10576297]
70. Cyranowski JM, et al. Adolescent onset of the gender difference in lifetime rates of major depression: a theoretical model. *Archives of general psychiatry*. 2000; 57:21–27. [PubMed: 10632229]
71. Dunlop BW, Nemeroff CB. The role of dopamine in the pathophysiology of depression. *Archives of general psychiatry*. 2007; 64:327–337. [PubMed: 17339521]
72. Gorzalka BB, Hill MN. Putative role of endocannabinoid signaling in the etiology of depression and actions of antidepressants. *Prog Neuropsychopharmacol Biol Psychiatry*. 2011; 35:1575–1585. [PubMed: 21111017]
73. Capuron L, et al. Dopaminergic mechanisms of reduced basal ganglia responses to hedonic reward during interferon alfa administration. *Archives of general psychiatry*. 2012; 69:1044–1053. [PubMed: 23026954]
74. Pessiglione M, et al. Dopamine-dependent prediction errors underpin reward-seeking behaviour in humans. *Nature*. 2006; 442:1042–1045. [PubMed: 16929307]
75. Christensen R, et al. Efficacy and safety of the weight-loss drug rimonabant: a meta-analysis of randomised trials. *Lancet*. 2007; 370:1706–1713. [PubMed: 18022033]
76. Horder J, et al. Reduced neural response to reward following 7 days treatment with the cannabinoid CB1 antagonist rimonabant in healthy volunteers. *The international journal of neuropsychopharmacology / official scientific journal of the Collegium Internationale Neuropsychopharmacologicum*. 2010; 13:1103–1113.
77. Riebe CJ, Wotjak CT. Endocannabinoids and stress. *Stress*. 2011; 14:384–397. [PubMed: 21663537]
78. Rademacher DJ, Hillard CJ. Interactions between endocannabinoids and stress-induced decreased sensitivity to natural reward. *Prog Neuropsychopharmacol Biol Psychiatry*. 2007; 31:633–641. [PubMed: 17258369]
79. Weissman MM. Recent advances in depression across the generations. *Epidemiologia e psichiatria sociale*. 2006; 15:16–19. [PubMed: 16584099]
80. Kessel EM, et al. Neural reactivity to monetary rewards and losses differentiates social from generalized anxiety in children. *Journal of child psychology and psychiatry, and allied disciplines*. 2015; 56:792–800.
81. Scheres A, et al. Ventral striatal hypo-responsiveness during reward anticipation in attention-deficit/hyperactivity disorder. *Biological psychiatry*. 2007; 61:720–724. [PubMed: 16950228]
82. Morgan JK, et al. Maternal depression and warmth during childhood predict age 20 neural response to reward. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2014; 53:108–117. e101. [PubMed: 24342390]
83. Kujawa A, et al. Early Parenting Moderates the Association between Parental Depression and Neural Reactivity to Rewards and Losses in Offspring. *Clinical psychological science : a journal of the Association for Psychological Science*. 2015; 3:503–515. [PubMed: 26167423]
84. Forbes EE, et al. Altered striatal activation predicting real-world positive affect in adolescent major depressive disorder. *The American journal of psychiatry*. 2009; 166:64–73. [PubMed: 19047324]
85. Nikolova YS, et al. Ventral striatum reactivity to reward and recent life stress interact to predict positive affect. *Biological psychiatry*. 2012; 72:157–163. [PubMed: 22534456]
86. Williamson DE, et al. First episode of depression in children at low and high familial risk for depression. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2004; 43:291–297. [PubMed: 15076262]

87. Nikolova YS, et al. Multilocus genetic profile for dopamine signaling predicts ventral striatum reactivity. *Neuropsychopharmacology* : official publication of the American College of Neuropsychopharmacology. 2011; 36:1940–1947. [PubMed: 21593733]
88. Barch, DM., et al. Mechanisms of Motivational Deficits in Psychopathology. In: Simpson, EH.; Balsam, P., editors. *Current topics in behavioral neurosciences*. Springer; 2015. p. 1-45.
89. Liljeholm M, O'Doherty JP. Contributions of the striatum to learning, motivation, and performance: an associative account. *Trends in cognitive sciences*. 2012; 16:467–475. [PubMed: 22890090]
90. Knutson B, et al. Dissociation of reward anticipation and outcome with event-related fMRI. *Neuroreport*. 2001; 12:3683–3687. [PubMed: 11726774]
91. Delgado MR, et al. Tracking the hemodynamic responses to reward and punishment in the striatum. *Journal of neurophysiology*. 2000; 84:3072–3077. [PubMed: 11110834]
92. Foti D, Hajcak G. Depression and reduced sensitivity to non-rewards versus rewards: Evidence from event-related potentials. *Biological psychology*. 2009; 81:1–8. [PubMed: 19162124]
93. Schultz W. Predictive reward signal of dopamine neurons. *Journal of neurophysiology*. 1998; 80:1–27. [PubMed: 9658025]
94. Delgado MR, et al. Dorsal striatum responses to reward and punishment: effects of valence and magnitude manipulations. *Cognitive, affective & behavioral neuroscience*. 2003; 3:27–38.
95. Silk JS, et al. Peer acceptance and rejection through the eyes of youth: pupillary, eyetracking and ecological data from the Chatroom Interact task. *Social cognitive and affective neuroscience*. 2012; 7:93–105. [PubMed: 21775386]
96. Kendler KS, et al. Toward a comprehensive developmental model for major depression in women. *The American journal of psychiatry*. 2002; 159:1133–1145. [PubMed: 12091191]
97. Gavin AR, et al. The associations between socio-economic status and major depressive disorder among Blacks, Latinos, Asians and non-Hispanic Whites: findings from the Collaborative Psychiatric Epidemiology Studies. *Psychological medicine*. 2010; 40:51–61. [PubMed: 19460189]

Box 1**Goals of Endophenotype Studies**

Having good endophenotypic measures may help in the early diagnosis and treatment of MDD. Ideally, identifying robust endophenotypes will help improve the specificity of identifying at-risk individuals who will ultimately develop MDD. This is particularly important given that although risk factors such as maternal history of MDD relate to significantly increased odds of an individual developing MDD, a large proportion of individuals with a maternal history will never develop MDD themselves, i.e. approximately 47% of offspring of depressed mothers will develop MDD [79, 86]. Further, identifying particular endophenotypes and understanding their relationships to the development of depression will help in the development of specific mechanism-based interventions or in personalizing treatment plans to individuals.

The heterogeneous nature of MDD often makes it difficult to study the disorder in a mechanistic way. Thus, focusing on a particular construct or endophenotype, i.e. blunted reward responding, may be particularly helpful in identifying the mechanisms of inter-generational transmission of MDD, i.e. examining genetic and environmental factors that contribute to reward processing deficits rather than MDD writ large. The identification of key mechanisms underlying MDD could also help identify novel mechanism-based treatments, i.e. targeting particular neural systems or cognitive differences. There are also hopes that brain-based endophenotypes may provide more sensitive measures than behavioral or questionnaire-based measures, if they serve to provide more direct assessment of key neural mechanisms of interest, though this is an open empirical question.

The identification of endophenotypes may also provide targets for genetic association studies; again, endophenotypes ideally would serve as a less heterogeneous and more mechanistic outcome than MDD diagnosis. Although this has not been explored in large-scale genetic studies, there is some evidence, for example, that differences in dopamine-related genes predict variance in striatal response to reward [87]. This type of genetic work could then be extended to investigate the role of dopamine system genes in MDD risk and intergenerational transmission of MDD more specifically.

Box 2**Reward Processing and Neuroimaging in MDD-Risk**

The striatum/basal ganglia play a vital role in a number of cognitive and motivational processes that are impaired in MDD [88], such as goal-directed action, reward learning, and hedonic response [10, 89]. The majority of reward studies investigating MDD-risk use tasks derived from the basic neuroscience literature, e.g. Monetary Incentive Delay Task [90] or Card Gambling/'Doors' Task [91, 92]. These tasks include a motor response, and delivery of reward feedback, with some tasks also presenting an anticipatory cue. The anticipatory cue, which is presented at the beginning of the trial, indicates either the feedback options, e.g. whether a given trial could result in a gain (versus no change) or no change (versus a loss), or the probability of reward. Striatal response to the cue is thought to index reward anticipation or 'wanting' and relate to motivational processes [10, 25, 26]. The ventral striatum in particular shows robust response to cues that predict reward [90], a processes is mediated by dopaminergic signaling [93]. Conversely, neural response to feedback signaling reward gain, particularly within the ventral striatum, is thought to index hedonic responses or 'liking' of reward, a process mediated largely by opioid and endocannabinoid systems [10, 25, 26]. However, it should be noted that portions of the dorsal striatum also show activation to receipt of reward feedback in these tasks [94].

The tasks described above typically use secondary rewards such as money, points, or representations of candy pieces that are delivered post scan. Other risk studies using primary rewards, such as presented images of happy faces [49, 68] or images and taste of chocolate experienced in the scanner [52] either passively present these rewarding stimuli [49, 52] or require a stimulus-dependent response [68], e.g. gender discrimination of emotional faces. Finally, the chatroom interaction task [95], where adolescents' invitations to 'chat' with a peer are either accepted or rejected, has been used to more naturalistically investigate social acceptance as a reward [50]. In all of these studies, reward receipt occurs when the stimulus is consumed (i.e. happy face is viewed, chocolate tasted, or acceptance indicated), which typically elicits activation within the ventral striatum.

Given that reward anticipation was not present/manipulated across all tasks, the current review focuses on findings relating to reward receipt. However, it is important to note that relationships to depression risk may differ for other types of reward tasks involving more complex learning strategies or responses and that anticipatory deficits may also confer unique risk for depression.

Box 3**Defining Depression Risk**

The neuroimaging literature most frequently uses maternal history of depression as a marker of depression risk. This risk factor is easily assessed and robust; offspring of depressed parents are approximately three times more likely to develop MDD themselves than the offspring of non-depressed parents with approximately 47% of high risk and 14% of low-risk offspring developing MDD [79, 86]. However, there are a number of other important factors known to increase risk for MDD, including genetic factors, early life stress/trauma, and low social support [96], among others. Importantly, some risk factors, such as low socioeconomic status [97] and early puberty [63], are more prevalent in families with MDD making it difficult to separate genetic and environmental sources of risk and their respective relationships with neural function. Although many studies attempt to match high- and low-risk groups on factors such as socioeconomic status or exposure to stress, it may be important to consider these as potential mediation or moderating factors of the MDD-risk effects observed in fMRI studies.

Outstanding Questions Box

- Does the relationship between MDD-risk and striatal response to reward change over development? How is risk for MDD related to longitudinal change in striatal function over development?
- How specific is blunted striatal reward response to MDD-risk/pathology versus other disorders, e.g. anxiety, substance use disorder, or ADHD? Does striatal blunting relate to transdiagnostic anhedonia in high-risk groups, which would address questions posed by the Research Domain Criteria (RDoC) initiative?
- Is blunted reward responsivity related to the development of specific symptom profiles/clusters, e.g. anhedonia versus negative mood, again in line with the RDoC initiative?
- Do responses to receipt of different types of rewards (e.g. primary versus secondary, social versus non-social) or other components of reward processing (e.g. anticipation) add to our understanding of MDD-risk?
- Does blunted striatal response to reward moderate or buffer effects of other MDD-risk factors, such as stress/trauma, on depressive symptoms?
- How does blunted reward responsiveness act in the mechanisms of inter-generational transmission of MDD? Does a 'normative' reward response mark/confer resilience among high-risk offspring? Will examining reward responsivity help identify individuals who are have particularly high risk?
- What are the mechanisms mediating the relationship between familial risk for MDD and striatal reward response, i.e. why do high-risk offspring show blunted response to reward? Can we more clearly identify the role of specific neurotransmitter systems, such as dopaminergic and endocannabinoid systems? Can we parse genetic versus environmental factors, such as parenting and stress exposure? Are these potential targets for intervention?

Trends Box

- Offspring of depressed mothers are at increased risk for developing depression and show blunted responses to reward relative to low-risk peers within the dorsal and ventral striatum.
- The strongest evidence for the relationship between depression-risk and blunted striatal response to reward has been found during mid adolescence, a time in development when healthy low-risk groups show maximal striatal response to reward.
- Blunted striatal response to reward is not simply a consequence of experiencing depression, as both never depressed high-risk adolescents and currently depressed adolescents show similarly blunted striatal response to reward relative to low-risk controls.
- Blunted striatal response to reward may specifically relate to maternal depression, and not maternal anxiety.
- Blunted striatal response to reward may co-occur with enhanced responses to loss of reward or punishment in high-risk groups.

Figure 1.

MDD Onset, Striatal Response to Reward Receipt, and the Number of Studies Investigating MDD-Risk and Reward Response All Increase During Adolescence

A – Red dotted line indicates the cumulative age of onset for individuals with Unipolar Depression (i.e. with Major Depressive Episode (MDE) but without Manic Episodes (ME)), onset of MDEs begins to sharply increase around age 12–15, HE=Hypomania. Reprinted from Bipolar Disorders, 11/6, Beesdo, K., Hofler, M., Leibenluft, E., Lieb, R. Bauer, M.,

Pfennig, A., Mood episodes and mood disorders: patterns of incidence and conversion in the first three decades of life, 637–49, Copyright (2009), with permission from Wiley [22].

B – Striatal response to monetary reward versus non-reward shows a quadratic (i.e. inverted u-shape) relationship with age from childhood through young adulthood. Peak striatal response is observed around 12 to 15 years of age. Reprinted from Neuroimage, 51/1, Van Leijenhorst, L., Gunther Moor, B., Op de Macks, Z. A., Rombouts, S. A., Westenberg, P. M., Crone, E. A., Adolescent risky decision-making: neurocognitive development of reward and control regions, 345–55, Copyright (2010), with permission from Elsevier [34].

C – Ages of participants in reviewed MDD-risk and reward neuroimaging studies (circle = mean age; whiskers = min/max ages). The majority of participant groups in MDD-risk and reward studies have a mean age between 12 and 15 years. LR=Low-Risk, HR=High-Risk, solid line studies report striatal blunting to reward feedback in HR groups.

Table 1

Striatal Reward And Depression Risk Studies

Study	Reward and Task Type	Contrast	Striatal Finding	Cohen's d	LR n (HR n)	Age Range	Mean Age	% Female	Risk Definition
Luking et al 2016 [58]	Candy – CGT	R-B R-N	LR>HR	0.82	32 (16)	7–10	9.2	52	Maternal MDD
Kujawa et al 2014 [59] *	Money - Doors	R-L	LR>HR	0.22	252 (155)	9	9.2	45	Maternal MDD
Gotlib et al 2010 [67]	Points for Prizes - MID	R-N	LR>HR	1.43	13 (13)	10–14	12.5	100	Maternal MDD
Olino et al 2015 [50]	Social Acceptance – Chat Task	R-C	LR>HR	0.92	30 (17)	10–16	13.0	57	Parent MDD
Sharp et al 2014 [51]	Money - CGT	R-B	LR>HR	1.13	19 (19)	10–16	13.4	100	Maternal MDD
Monk et al 2008 [49]	Happy Faces – Passive	R-L	LR>HR	0.61	22 (17)	10–18	14.1	50	Parent MDD
Kerestes et al 2016 [68]	50% Happy Faces – Gender Discrimination	R-B	LR>HR	NR	43 (38)	8–17	14.5	57	Parent MDD/BP
Olino et al 2014 [60]	Money - CGT	R-B	LR>HR	1.57	12 (14)	12–17	15.7	73	Maternal MDD
McCabe et al 2012 [52]	Chocolate Taste/Picture – Passive view/taste	R-C	LR=HR	NR	25 (25)	16–21	18.9	64	Parent MDD

Note: Cohen's d was calculated using t-statistics/degrees of freedom when d was not reported. When multiple striatal regions were identified in a given study, we report the Cohen's d for the striatal region with the strongest risk effect. Shaded studies used secondary rewards with a lump sum of the reward (money, points, candy pieces) delivered out of scanner; these studies also all happened to focus on maternal MDD specifically to define risk.

* Electroencephalogram Study using Feedback Negativity, R=Reward, N=Neutral/Non-Reward, L=Loss of Reward or Fearful Face; C=Control Task/Stimulus; CGT=Card Gambling Task, MID=Monetary Incentive Delay, LR=Low Risk, HR=High Risk, NR=not reported, MDD=Major Depressive Disorder, BP=Bipolar Disorder.