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Adolescent Depression: Stress and Reward Dysfunction

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Abstract

Adolescence is a peak period for the onset of depression, and it is also a time marked by substantial stress as well as neural development within the brain reward circuitry. In the current review, we provide a selective overview of current animal and human research investigating the relationship among reward processes, stress, and depression. Three separate, but related, etiological models examine the differential roles that stress may play with regard to reward dysfunction and adolescent depression. First, the reward mediation model suggests that acute and chronic stress contribute to reward deficits, which in turn, potentiate depressive symptoms and/or increase the risk for depression. Second, in line with the stress generation perspective, it is plausible that premorbid reward-related dysfunction generates stress, in particular interpersonal stress, which then leads to the manifestation of depressive symptoms. Last, consistent with a diathesis-stress model, the interaction between stress and premorbid reward dysfunction may contribute to the onset of depression. Given the equifinal nature of depression, these models could shed important light on different etiological pathways during adolescence, particularly as they may relate to understanding the heterogeneity of depression. To highlight the translational potential of these insights, a hypothetical case study is provided as means of demonstrating the importance of targeting reward dysfunction in both assessment and treatment of adolescent depression.

Keywords

Major Depressive Disorder; Reward Circuitry; Stress Exposure; Stress Generation; Mesolimbic Pathway; Anterior Cingulate Cortex; Prefrontal Cortex

Adolescent depression is a major public health concern and is associated with significant emotional and socioeconomic burden.[1,2] The point prevalence of major depressive disorder (MDD) among adolescents is estimated between 3–8%.[3] Moreover, 40% of depressed adolescents experience a recurrent episode within 2 years of their initial diagnosis, and 70% will have a recurrence within 5 years.[3,4] Despite these alarming epidemiological data, the etiological and pathophysiological mechanisms contributing to adolescent MDD remain unclear.

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A preponderance of research has found that stress is a robust predictor of the onset, maintenance, and severity of MDD.[5] For example, in community samples of adolescent, adult, and elderly populations, approximately 80% of depressive episodes were preceded by stressful life events.[6–8] In addition, antecedent chronic stressors have been linked to poorer prognosis, more frequent relapse, and higher depressive symptoms.[9–12] Notably, for adolescents in particular, life stress plays a central role in MDD onset.[13,14] Adolescents experience a greater frequency of interpersonal stressors relative to younger and older individuals,[15] which may stem from a greater investment in peer relationships coupled with increased autonomy from parents. At the same time, deficient peer and parental relationships have been shown to generate relational stressors and subsequent depressive symptoms among adolescents, underscoring the need to examine interpersonal stressors as a pathway to adolescent depression.[16]

In addition to being a time of substantial interpersonal stress, adolescence is also a critical period of neurobiological growth within the brain reward circuitry (i.e., mesocorticolimbic regions).[17–20] During adolescence, the brain undergoes structural changes in gray and white matter subcomponents as well as subcortical regions, particularly in the basal ganglia.[21,22] Consistent with this notion, imaging studies have implicated key developmental differences in neurobiological regions critical for reward processing, namely the prefrontal and the mesolimbic cortex.[23,24] In this context, Casey and colleagues (2008) posit that prefrontal regions are less developed in comparison to the limbic systems in adolescent, and furthermore, that such discordant development may explain the critical role of reward circuitry in adolescent MDD, as the adolescent brain is learning and engaging reward with “more developed equipment” (i.e., mesolimbic system), while the “tools” to modulate reward responsiveness are not mature (i.e., prefrontal cortex).[25] Alternatively, Davey and colleagues suggest that prefrontal cortex development during adolescence increases the pursuit of reward (e.g., romantic relationships, status); however, failure to obtain these more complex goals ultimately suppresses the reward system and increases the likelihood of MDD.[18] Irrespective of the specific anatomical mechanisms, these theories suggest that the development of the reward circuitry plays a prominent role in the occurrence of depressive disorders, which is consistent with promising preliminary data indicating dysfunctional neural response to reward feedback as a predictor of adolescent depression.[26]

As a whole, research suggests that stress and reward deficits (as well as the associated neural dysfunction) each contribute to the occurrence of adolescent MDD. However, given the temporal overlap of stress and neural development during adolescence, the interplay of these processes may confer the greatest vulnerability for the onset of MDD. Indeed, researchers have begun to disentangle the relationship between stress and reward processing as a means of better understanding adolescent MDD. In the current review, we provide a selective overview of current animal and human research, which was obtained by conducting a PubMed search using keywords including adolescent depression, reward processing, adolescent stress, brain reward circuitry. Three separate, but related, etiological models examine the differential roles that stress may play with regard to reward dysfunction and adolescent MDD. While the models are presented separately for the purpose of more clearly delineating the extant research, it bears mentioning that that the models are, in fact, interrelated. First, a large corpus of research has found that both acute and chronic stress

contributes to reward dysfunction, and these deficits, may then lead to the onset of MDD (see Figure 1A). Support for this *reward mediation model* has been found in animal models,[27] adults,[28,29] and to a lesser extent, adolescents.[30] Second, transactional models of MDD posit that individuals possess certain characteristics or engage in a specific pattern of behaviors that lead to the occurrence of stressors.[31] Specifically, adolescents characterized by pre-existing reward dysfunction may have a tendency to withdraw from peers or not attend to important social cues, and these deficits may in turn generate interpersonal or relational stressors (*stress generation model*). Over time, these accumulated stressors may lead to the onset of MDD (see Figure 1B). To date, research has explored cognitive[32] and interpersonal[16,33] predictors of adolescent stress generation; however, research has not examined the role that reward dysfunction exerts on the stress generation process. In this context, interesting findings have emerged examining the role of peer evaluation, which may shed important light on the role of reward dysfunction in the context of stress generation. Last, stress exposure models suggest that the interaction between premorbid vulnerability factors and stress leads to the development of MDD. Such a perspective is consistent with diathesis-stress models of MDD such as Beck's cognitive theory of depression.[34] Consistent with these etiological perspectives, we propose a *titration model* whereby the degree of vulnerability may be contingent on the magnitude of the stress as well as degree of reward dysfunction. Vulnerability may be operationalized in such a way that, for example, the greater reward dysfunction an individual possesses, the fewer stressful life events may be needed for depression to emerge. Conversely, less reward dysfunction may necessitate greater stress for depressive symptoms to arise. Within this diathesis-stress perspective, reward dysfunction alone may not predict depression, but rather, it is the interaction between reward deficits and stress, which may contribute to the occurrence of depression (see Figure 1C). Given the equifinal nature of MDD, these models may shed important light on different etiological pathways culminating in depression during adolescence, particularly as they may relate to understanding the heterogeneity of MDD. Over time, such insight may be used to develop more effective prevention, intervention, and treatment programs. Thus, in the final section of the current review paper, a hypothetical case study is provided as means of demonstrating the importance of targeting reward dysfunction in both assessment and treatment of adolescent depression.

Reward Dysfunction Model: The Impact of Stress on Reward Processes

In comparison to stress reactivity (i.e., stress generation) and stress exposure (i.e., diathesis-stress perspective) models, the impact of stress on reward dysfunction and subsequent depression has provided the most consistent findings across animal, adolescent, and adult research (see Figure 1A). These studies have utilized a variety of approaches to examine the impact of acute and chronic stress on reward-related neurotransmitters – particularly dopamine (DA) – especially as it relates to the associated impact of DA signaling within the reward brain circuitry (e.g., nucleus accumbens (Nacc), orbitofrontal cortex (OFC), ventral tegmental area (VTA)). Research with animals has provided an ideal setting to examine the impact of stress on reward functioning, and these studies have clearly demonstrated that stress negatively impacts reward processes. For example, chronically stressed animals show diminished appetitive behaviors, reduced DA release in the Nacc in response to palatable

food, and reduced DA transporter binding (a possible compensatory down-regulation stemming from reduced DA signaling) in the Nacc.[35–40] Further, stress-induced reduction in dopaminergic output from the Nacc has been associated with coping failures and maintenance of depression-like behaviors such as helplessness.[27] Importantly, pretreatment DA agonists are found to prevent the stress-induced reward processing deficits,[41] while antidepressant medication reverse these deficits.[39] These animal findings are intriguing in light of human neuroimaging evidence highlighting blunted Nacc activation to rewards in both adolescents[42] and adults[43] with MDD (see Figure 2A).

Animal studies have also demonstrated the deleterious effects of stress on reward function during developmentally sensitive periods. Specifically, chronic stress occurring early in development has been found to lead to long term dysfunction in the mesolimbic dopaminergic pathway, contributing to depressive-like behavior including reduced motivation to obtain rewards, reduced social motivation, and blunted acquisition and expression of Pavlovian appetitive conditioning.[44–50] Such early stress, however, does not affect other developmental processes such as eye opening and body weight, suggesting that reward processing might be especially sensitive to early adversity.[45] As a whole, animal studies have demonstrated behavioral and physiological markers of stress-induced reward dysfunction that mirror abnormalities seen in depressed individuals, which are especially pronounced in response to early stress. Thus, when stress occurs during developmentally sensitive periods, it may greatly impair reward processing and increase susceptibility to MDD.

The first evidence in humans linking stress exposure with reduction in reward responsivity was derived from samples of U.S. Army cadets and college students as they reported experiencing less pleasure following stressful events (field training exercises and final examinations, respectively) compared to a control situation (i.e., a non-stress period).[51] Notably, the same study also found that the deleterious effect of stress on hedonic capacity was particularly strong for subjects with family histories of MDD.[51] Expanding on these earlier findings, healthy adults exposed to both acute (e.g., threat of shock) and more prolonged (e.g., final examinations in high-school students) stress demonstrated a reduced ability to modulate behavior as a function of past reward, and such deficits correlated to impaired functioning in the prefrontal cortex.[28,52,53] Similar to the animal literature, the harmful impact of stress seems specific to reward processing, as acute stress in the form of threat of shock did not impair responses to aversive fearful faces[54] or the ability to learn from punishments.[55]

While comparatively fewer studies have examined the effect of stress on reward dysfunction in adolescence, child maltreatment and experimental manipulations in healthy youth may provide an interesting lens through which to examine this relationship. Echoing preclinical findings showing that exposure to early adversities can have deleterious long-term consequences on adult's reward responsiveness, Pechtel and Pizzagalli recently reported that women with a history of childhood sexual abuse were characterized by deficits in their ability to use previously rewarded – but not punished – information to guide decision making.[56] Along similar lines, relative to healthy individuals, adults with a history of childhood maltreatment rated rewarding cues as less positive and displayed diminished Nacc

response during anticipation of rewards but not punishments.[57,58] Finally, in healthy adolescents, a computer-based ball-tossing game was utilized to probe the impact of social exclusion as a stressor.[59] The results indicated that greater activity in the subgenual anterior cingulate cortex (ACC) was correlated with greater distress during social exclusion. Moreover, activity within the Nacc was associated with less distress, and in fact, Nacc activation was found to modulate subgenual ACC activity as well as individuals' level of social rejection sensitivity.[59]

Although these findings provide evidence that ongoing or early life stress is associated with decreased reward responsiveness, poor ecological validity (i.e., threat of shock manipulations within a lab setting versus early life adversity), and retrospective assessments of early life stress represent important limitations of these initial studies. To address these limitations, Admon and colleagues recently assessed healthy 18 year-old soldiers prior to deployment and prospectively followed them for 18 months following active duty in high conflict areas. Results indicated that following military stress there is a reduction in Nacc response to reward (see Figure 2B), and furthermore, such stress-induced reward responsiveness deficits are associated with higher levels of depressive symptoms following stress.[29] Similar to animal research, these data suggest that stress potentiates reward dysfunction and may increase susceptibility to depressive episodes, especially if stress occurs during developmentally sensitive periods. At the same time, while these findings have shed important light on the abnormal developmental trajectory, further research is warranted to better understand the pathways in which stress can induce reward dysfunction among children and adolescents.

A Stress Generation Perspective: The Impact of Reward Dysfunction on Stress Onset

A large corpus of research has examined the stress generation effect, which seeks to disentangle the reciprocal relationship between stress and depression.[31] Such research stems from Hammen's seminal work, which shows that previous depressive episodes in adult women predict subsequent MDD as a result of generating a greater number of interpersonal, but not non-interpersonal, stressors.[60] Inherent to the stress generation framework is the belief that an individual possesses certain characteristics or behaviors that lead to the occurrence of dependent interpersonal stressors (i.e., stressors in which an individual is at least partly responsible for the occurrence). To date, research has demonstrated the role of stress generation in predicting diagnoses of depression in children and adolescents,[61] adult men,[62] and adult women[63]. More recent research has explored cognitive[32] and interpersonal[16,33] predictors of stress generation, but the direct link between reward dysfunction and stress generation, as a potential etiological pathway of MDD, has not to be examined. Therefore, direct evidence for the stress generation is scarce. Nevertheless, as reward dysfunction negatively affects both approach and avoidance tendencies, there is reason to believe that reward deficits may generate interpersonal or relational stressors. In part, individuals possessing avoidance-related deficits may withdraw and/or isolate from social situations to the frustration of partners, family and friends. Alternatively, youth exhibiting approach-related dysfunction may not respond to salient social cues, and despite

proactive efforts, may paradoxically "push people away." Over time these accumulated interpersonal stressors may lead to the onset of MDD (see Figure 1B).

Recent peer evaluation studies provide an interesting medium to delineate the relationship between reward dysfunction and stress generation. To do so, researchers have employed a chat room task, which simulates the transient online peer evaluations occurring on various social media sites (e.g., Facebook). While the administrations of the tasks vary, participants typically create a user profile detailing personal interests. Then, participants are made to believe that this profile will be shared with other adolescents at participating sites, and these youth will thus have an opportunity to determine whether they will accept or reject a participant's invitation to chat online. After completing the offline portion of the chat room paradigm, which includes participants generating their own bank of peer acceptances and rejections, participants return to the lab 1–2 weeks later, and fMRI data are collected while participants are shown the same pictures of adolescents from the previous session. After each picture is displayed, teens are alerted as to whether they were "accepted" or "rejected" by their peers. Following each acceptance or rejection trial, participants are also asked to indicate the level of distress the trial elicits. To date, the chat room task has generated a number of interesting findings. While "rejected" trials are consistent with the reward mediation model (i.e., Figure 1A) in which stress triggers reward dysfunction, acceptance trials that elicit a blunted reward response may simulate a stress generation effect. For example, when examining healthy adolescents ages 9–17, Guyer and colleagues (2012) reported greater caudate and putamen activity following acceptance feedback, which is consistent with greater striatal responses to positive emotion.[64] Future peer evaluation neuroimaging studies would benefit from examining adolescents exhibiting a blunted acceptance response or hypoactivation within the striatum, as this may indicate a preexisting reward deficit. A potential consequence of not "experiencing" acceptance in social situations is that such adolescents may act in ways that disrupt relationships thereby potentiating interpersonal stressors. The accumulation of this stress over time may contribute to the occurrence of depressive symptoms. In line with this approach, peer evaluation neuroimaging studies could, ultimately, highlight potential neurobiological mechanisms that lead to greater relational stressors, which may increase vulnerability to MDD.

In addition to promising neuroimaging data, there is also a growing empirical literature linking genes and reward dysfunction, which suggests that there may be an additional pathway contributing to the stress generation effect. For example, the DA D2 receptor gene (DRD2) has been called the "reward gene" by some researchers, as it is believed that A1 allele carriers on this gene have a greater likelihood of developing disorders characterized by reward deficiencies including depression.[65–67] Critically, children carrying A1 allele exhibit more social problems and are more withdrawn, suggesting that a genetic predisposition may account for reward-related deficits.[68] In line with this assumption, adults carrying the A1 allele on the DA D2 receptor gene (DRD2) exhibit reduced striatal responsivity to reward and impaired reward learning.[69–72] Interestingly, other genetic polymorphisms on the D3 and D4 DA receptors were also associated with MDD, acting as a "phenotypic modifier for MDD".[73,74] In a related study, Nikolova and colleagues (2011) recently demonstrated that a genetic profile for DA signaling based on five different polymorphic loci better explained variability in reward-related Nacc reactivity than single genes, suggesting that a better

understanding of DA deficiency may be mediated by the integrative effect of several genes (see Figure 2C).[75] As a whole, these findings strongly suggest that the inheritance of alleles that encode neuronal receptors and transporters of DA may impact reward processing. Such genetic variability may thus contribute to reward dysfunction even prior to stress exposure, and reward deficits may in turn lead to the development of interpersonal stressors, and ultimately increase susceptibility for future MDD.

Altogether, the pioneering neurobiological and genetics research described above has provided kindling for a "new chapter" in stress generation research, and in doing so, has developed an important bridge between clinical psychology and neuroscience. At the same time, future research is needed to ascertain the specific neurobiological mechanisms and genetic vulnerabilities that underlie reward deficits as this may, ultimately, provide key information about the etiology of stress generation.

A Titration Perspective: The Relative Effect of Reward Dysfunction and Stress

Diathesis-stress perspectives of MDD have often followed a titration model whereby the interaction of the relative magnitude of stress and a premorbid vulnerability are accounted for in determining one's likelihood of developing MDD (i.e., moderation framework; see Figure 1C). For example, the hopelessness theory of depression asserts that individuals possessing less negative inferential styles (i.e., internal, stable, and global) require more stressful life events to confer vulnerability for hopelessness depression.[76] Monozygotic twin studies provide an interesting platform to examine the titration perspective given the shared genetic makeup and at times, environmental backgrounds. Such overlap has allowed researchers to disentangle the interrelationships among genes, stress, and psychopathology. For example, Kendler and Halberstadt (2012) completed extensive interviews with 14 pairs of monozygotic twins presenting with a discordant history of MDD.[77] Interestingly, relative to the unaffected twins, the co-twins reported that depressive episodes were triggered by traumatic life events, romantic upsets, and diminished intimacy. These findings suggest that, despite shared genetic risk, stressful life events significantly increased one's susceptibility to MDD. Conversely, in a twin study of adolescents between the ages of 11–17 (n = 780 pairs), the presence of Val66Met genotype (a polymorphism in the brain-derived neurotrophic factor (BDNF) gene associated with the onset of MDD) did not predict depressive symptoms.[78] However, the interaction between Val66Met and stress was significantly associated with higher levels of depressive symptoms, suggesting that genes moderate the relationship between life events and subsequent depressive episodes.[78] Taken together, these studies suggest that vulnerability to MDD may be the results of both stress and genetic factors; however, these studies do not adequately examine the role of reward dysfunction.

As mentioned previously, individuals possessing the A1 allele on the DRD2 gene are more likely to develop reward dysfunction. However, it is also important to note that following exposure to stress, A1 allele carriers report a higher prevalence rate of psychopathology and greater comorbidity.[79,80] Furthermore, while stress exposure models suggest that stress triggers reward dysfunction leading to the development of mental illness,[81,82] it is clear that stress severity alone does not determine the onset of psychiatric illness, which leaves room

for additional factors such as premorbid vulnerability. In support of this notion, Bogdan et al. (2011) found that genetic variation of the corticotropin-releasing hormone type 1 receptor gene (CRHR1), a key component of HPA axis activity that regulates stress response, modulates the ability to learn from rewarding signals in an acute stress – but not no-stress – condition.[83] In other words, stress-induced reward responsiveness deficits were greatest in healthy carriers of a genetic variants previously associated with increased MDD risk.[83] These findings may suggest that genetic predispositions underlying reward dysfunction and stress response may increase susceptibility to future depression during times of stress exposure, which is consistent with the titration perspective in that the interaction between stress and premorbid reward dysfunction is believed to contribute to the onset of depression.

Treatment Implications: Designing a Clinic for the Future

Within our selective review of the literature, we presented three separate, but related, models delineating the relationship among stress, reward dysfunction, and adolescent MDD. Given the equifinal nature of MDD, we believe that insights from these models may shed important light on different etiological pathways culminating in depression during adolescence, particularly as they may relate to understanding the heterogeneity of MDD. Over time, such insights may be used to develop more effective prevention, intervention, and treatment programs. Therefore, in the proceeding section we describe a hypothetical case study as means of demonstrating the importance of targeting reward dysfunction in both assessment and treatment of adolescent depression. Although there is a preponderance of caveats to the vision outlined below for the *Clinic for the Future* (including economic and empirical obstacles), it is important to evaluate *how* translational research may one day shape our approach to understanding psychopathology and designing intervention.

Hypothetical Case Study

D.D. is an 18 year-old male reporting recurrent MDD. Specifically, D.D. experienced his first depressive episode at age 13, and to date, has experienced 3 other episodes, each persisting for approximately 4 months. In the current episode, D.D.'s symptoms include depressed mood, anhedonia, fatigue, insomnia, feelings of worthlessness, and inattention. Prior to the depressive episode, D.D. was an accomplished runner, and it was not uncommon for him to run 5–6 miles daily. However, since the onset of this most recent episode, D.D. struggles to get out of bed in the morning for school. While reserved, D.D. has a close-knit group of friends. In recent months, however, he has begun to withdraw socially and has exhibited a heightened sensitivity to peer criticism. Such withdrawal and peer conflict has contributed to the recurrence of his depressive symptoms and is consistent with a stress generation model of MDD.[31]

During the initial clinical assessment, D.D. was asked to undergo a brief neuroimaging session in which he completed a social evaluation task (i.e., peer acceptance versus rejection) while fMRI data were collected. This task was selected given D.D.'s diminished motivation and avoidance-based behavior, especially around peers. Consistent with research examining blunted reward response to positive social stimuli,[64] D.D. demonstrated decreased Nacc activity in response to peer acceptance. These findings suggest that D.D.'s positive social experiences may not be reinforced, decreasing his likelihood of pursuing

these opportunities, and thus, potentially contributing to the recurrence and maintenance of his depressive symptomology. Given D.D.'s symptom and neural profile, he received a combination of cognitive behavior therapy coupled with a novel *reward retraining* task relying on neurofeedback. During cognitive behavior therapy, D.D. worked collaboratively with his therapist: (a) creating and adhering to behavioral schedules – with a particular emphasis on being active during the weeks following the initial sessions, (b) completing thought records to challenge negative automatic thoughts and underlying schemas, and (c) developing mastery in resolving interpersonal discord. During his biweekly fMRI and neurofeedback sessions, D.D. was instructed to focus on raising a visual bar presented on a computer screen. In fact, through real-time fMRI analysis, the bar represented D.D.'s level of Nacc activation, and the *reward retraining* was intended to "recondition" reward dysfunction by targeting hypoactivation within the Nacc, a critical factor in the etiology of D.D.'s depressive episode. Over the ensuing weeks, CBT and *reward retraining* neurofeedback were found to be effective in reducing D.D.'s depressive symptoms, and given the improvements across symptoms, behavior, and neural functioning, it is believed that the likelihood of MDD recurrence has also been reduced.

To be very clear, the assessment and treatment described above are not presently in practice, and significant advancements are needed before such approaches could conceivably be utilized on an individual basis. Notably, although neurofeedback is a relatively new field, previous studies have shown that it improves self-regulation of emotion networks in healthy and MDD individuals,[84–86] highlighting substantial promise. Of particular relevance here, these improvements were achieved by successfully targeting regions prominently implicated in the pathophysiology of MDD, including the subgenual PFC,[84] amygdala,[85] and ventromedial PFC.[86] For example, in a recent proof-of-concept study that included four neurofeedback sessions, eight individuals with MDD learned to up-regulate the ventrolateral PFC, an area critically implicated in positive affective experience.[86] Even more promising, neurofeedback targeting the ventromedial PFC has also been associated with increased ventral striatal activation to positive stimuli (see Figure 2D), highlighting improvements in a larger network within the brain reward pathway.[86]

In sum, at present, integrating neural assessments into everyday clinical practice is not empirically supported. However, as the National Institute of Mental Health Strategic Plan has emphasized the need to develop "new, brain-behavior-environmental targets for intervention research" and to "broaden the focus of what is meant by outcome measures in treatment research," forward progress is anticipated. In the end, bridging the divide between clinical psychology and neuroscience may lead to more effective prevention, intervention, and treatment programs.

Future Directions

Despite an improved understanding of adolescent MDD, there are key empirical gaps, particularly with respect to understanding age- and gender-related differences in MDD. Specifically, adolescence is the peak period for the onset of MDD, and gender differences that arise in mid-adolescence perpetuate throughout adulthood. Additionally, a diagnosis of MDD is characterized by large heterogeneity, which directly impacts the course for the

disorder and the approach to treatment. Therefore, future research is warranted to better address these issues.

Age and Gender

Between the ages of 12 and 18, there is a near fivefold increase in the prevalence of MDD with approximately 20% of adolescents experiencing a depressive episode.[87] Further, after the age of 14, girls report twice as many depressive episodes compared to boys, and this 2:1 ratio persists throughout adulthood.[88] Despite these alarming data, little is known about factors that increase vulnerability in youth and, particularly, females. Structural and functional neuroimaging studies, however, may provide key insight about why adolescence is a critical developmental window to examine the onset of MDD and gender differences that arise therein. Specifically, whereas the females' total brain volume peaks at 10.5 years, the males' brain does so at 14.5 years.[89–91] While the brain volumes converge in the early twenties, there remain important differences pertaining to structure and function that persist throughout the life course.[91–95] These sexually dimorphic changes may have implications for processing and regulating emotional stimuli, and therefore, puberty may provide a unique opportunity to examine *how* differential neurobiological activity increases vulnerability to MDD. For example, in a recent study examining puberty, gender-specific neural response to reward, and adolescent depressive symptoms, Forbes and colleagues (2010) indicated that advanced pubertal maturation was associated with less striatal and more medial PFC activity during rewarding trials, which is the same pattern of results she found in adults.[42] In addition, the study highlighted important hormonal differences as testosterone was positively correlated with reward anticipation in boys, but negatively associated with striatal reactivity in both girls and boys during rewarding outcomes.[42] Despite these promising results, additional research is warranted to better understand the integrative effect pertaining to puberty, neural development, reward functioning, and MDD.

MDD Heterogeneity

Given the heterogeneity of MDD, researchers have sought to identify behavioral indicators and biomarkers in order to improve diagnostic and treatment efforts. One promising area of research has been the study of anhedonia, which is considered to be a trait marker (i.e., a characteristic that is not state dependent)[96,97] and endophenotype (i.e., an intermediate marker more closely associated with neurobiological and environmental risk factors than the syndrome itself)[98] of MDD. The study of anhedonia has led researchers to examine reward processing deficits, especially as it relates to characterizing neural abnormalities that may potentiate reward dysfunction. Such efforts have contributed to fuel the development of the National Institute of Mental Health's Research Domain Criteria initiative to underscore the importance of examining broad dimensions of abnormal functioning across symptoms, behaviors, genes, and neurobiology as a means of identifying core underpinnings of psychopathology.[99,100] It is expected that the identification of underlying mechanisms that cut across disorders may enable researchers and clinicians to develop more effective prevention and intervention programs.

Of note, anhedonia itself encompasses a broad array of reward processes and motivational components. Treadway and Zald (2011) suggest that consummatory (i.e., goal-directed

behavior) and motivational (i.e., force driving one's actions toward a desired goal) processes associated with anhedonia significantly differ with respect to neurobiological processes and may result in the manifestation of different types of symptoms.[101] Despite these important differences, within the current review, reward dysfunction is utilized ubiquitously without highlighting these important, fine-grain differences. Nevertheless, these distinct reward processes may have important implications for the proposed models. Namely, it may be that different reward processes are more closely associated with stress dysfunction, stress reactivity, or stress exposure. For example, early adversities have been shown to negatively affect anticipatory as opposed to consummatory processes,[57] suggesting that stress can impact specific reward components. At present, further research is needed to better delineate the relationship between specific reward processes, susceptibility to stress, and vulnerability to depression as this may have important etiological and treatment consequences.

Summary

Recent research has made significant advancements in unpacking etiological mechanisms critically implicated in adolescent MDD. Each of the three models outlined above provide a distinct, but related, starting point to better integrate clinical psychology and neuroscience research. Building a bridge between these two fundamental sciences will only serve to improve our understanding of the onset, maintenance, recurrence of adolescent MDD. In time, advancements in our understanding will fuel more effective prevention and treatment programs, which will ease the untold economic and emotional cost associated with adolescent MDD.

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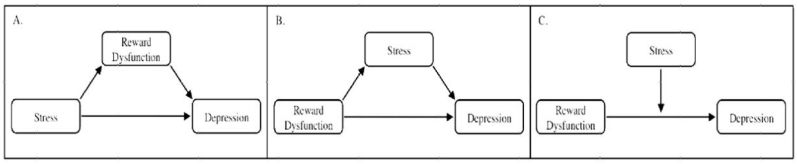

Figure 1.

Examining the Relationship among Stress, Reward Dysfunction, and Depression

Note. (A) Reward Mediation Model; (B) Stress Generation Model, (C) Titration Model

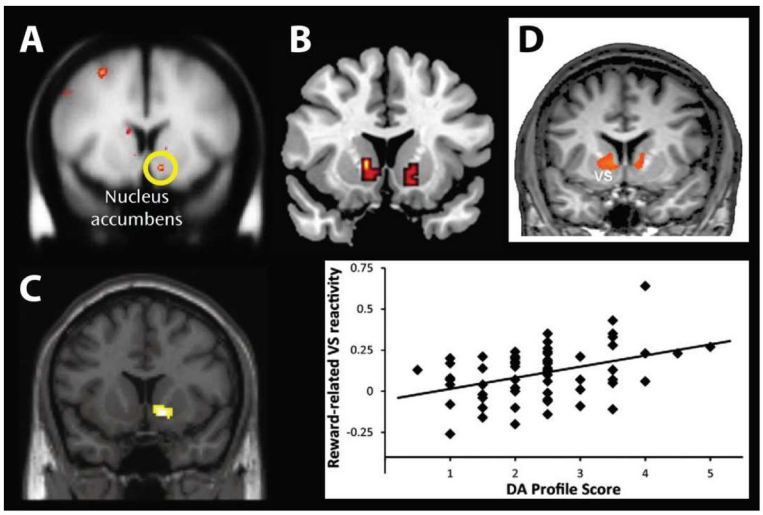

Figure 2.

Exemplary findings implicating ventral striatal regions (particularly the nucleus accumbens) in the pathophysiology of major depression. (**A**) Relative to healthy controls, unmedicated MDD subjects show reduced ventral striatal activation to reward feedback (Pizzagalli et al., 2009; Reprinted with permission from The American Journal of Psychiatry, (Copyright ©2009). American Psychiatric Association.); **(B)** Among Israeli soldiers, combat exposure is associated with reduced ventral striatal activation to reward relative to before combat exposure (Admon et al., 2013); **(C)** Among healthy controls, a genetic score for DA signaling based on five different polymorphic loci predicted 10.9% of the variance in ventral striatal reactivity during a gambling task (Nikolova et al., 2011); and **(D)** Among individuals with MDD, neurofeedback targeting the ventromedial PFC was associated with secondary increases in ventral striatal activity to positive stimuli (Linden et al., 2012). All figures reproduced with permission from each publisher and corresponding author.