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ADHD (P ROBAEY, SECTION EDITOR)

Developmental Risk Relationships between ADHD and Depressive Disorders in Childhood

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Abstract Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder that is associated with significant difficulties in the executive control of behaviour and emotions. Risk for depression in ADHD youth is a logical concern. This narrative review examines what is known regarding sources of risk for depression in youth with ADHD in the areas of epidemiology, genetics, neuroanatomy, neuropsychological functioning, social functioning, maltreatment and the effects of psychopharmacologic treatments. Emphasis is placed on longitudinal studies across childhood to maximize relevance to the research question. Findings suggest that comorbidity between ADHD and depression is less than chance would predict in community studies, and shared risk for oppositional defiant disorder accounts for the association that is seen in clinical studies. ADHD and depression share few if any similarities in brain morphology and function. The risk of maltreatment, difficulties in parenting ADHD children and social functioning deficits likely account for substantial risk for depression and should be targets for interventions.

Keywords ADHD · Depression · Development · Childhood · Adolescence

This article is part of the Topical Collection on *ADHD*

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Introduction

Attention deficit hyperactivity disorder (ADHD) is a complex, heterogeneous neurodevelopmental disorder characterized by a delay or disturbance in the acquisition of skills in motor, social, language and cognitive domains. It is a very common disorder of childhood and persists into adulthood in the majority of persons. More recently, ADHD researchers have explored the impact of ADHD on emotional and psychological outcomes such as ability to regulate emotions, cognitions and risk for depression and suicide. As this literature continues to expand, it appears that youth with ADHD experience higher levels of mood and cognitive difficulties than their peers without ADHD, and these difficulties may have measurable neurobiological and social underpinnings [1].

For these reasons, it is important to consider the extent of the increased risk for depression and depressive symptoms in youth with ADHD, as well as to identify key risk factors which predict risk for depression in ADHD. As the median age at onset of ADHD temporally precedes depression from a developmental perspective, mechanisms of risk which can be identified in childhood are critical areas for intervention.

The aim of this review is to examine the possible and probable mechanisms of the presentation of depression in the context of childhood ADHD based on review of the literature. It is not a systematic review, and studies were excluded if they were published prior to 20 years ago. ADHD and major depression (MDD) as outcomes were measured by either a diagnostic interview or using a symptom severity measure. Prospective studies beginning in childhood were sought to provide the most robust evidence regarding developmental processes, although when such studies were absent, findings from cross-sectional studies of children and youth were included. Studies of adult depression or ADHD or retrospective studies were not included so as to reduce error from

differences in phenotypic characterization and retrospective reporting.

The paper is organized into sections reviewing risk factors from different content areas. Synthesis of possible mechanisms for risk of depression in the context of ADHD is presented in the discussion.

Epidemiology

ADHD affects 9 % of children [2], 70 % of whom will continue to meet diagnostic criteria into adolescence. It is significantly more prevalent in boys (M/F = 4–6:1), with sex differences reducing with increasing age. Clinical symptoms of ADHD vary throughout the lifespan. Twin studies indicate that hyperactive symptoms are more stable in early and middle childhood, whereas attention deficits are more stable in late childhood and adolescence [3]. Diagnostic criteria in DSM-5 [4] have been altered to reflect the fact that ADHD symptoms are now assessed at presentation in light of the evidence that symptoms can and do change over time and development and impairment from ADHD may emerge for the first time after age 7 [5].

Depression is also a complex psychiatric disorder characterized by the prominence of negative affect (sadness, anxiousness, irritability), sleep, interest/motivation and pleasure, but is not currently thought to be a neurodevelopmental disorder. The peak age of onset in adolescence is 12 [6]. Depression presents as an episode, yet is highly recurrent, and 75 % of previously depressed children or adolescents will again become depressed within 5 years [7]. Symptoms of depression also include difficulty with concentration and focus, but to constitute symptoms of depression, these cognitive aspects are temporally secondary to a period of depressed mood. Unlike ADHD, the prevalence of depression increases from childhood (1–2 %) to adolescence (2–24 %), and sex differences emerge at age 15 where depression is twice as common in girls [8].

The rate of co-occurrence of ADHD and depression is significantly greater than chance would predict. A meta-analysis of epidemiological studies of comorbidity found that depression is 5.5 times more likely to co-occur with ADHD than in its absence [9]. Associated disorders are common when ADHD and depression co-occur, and indeed, youth with ADHD typically have three additional diagnoses by adolescence [10]. In a series of elegant analyses of very large epidemiological samples, Angold and colleagues have repeatedly demonstrated that the association between ADHD and depression is not significant when controlling for other comorbid disorders and does not persist over 2-year follow-up at any point in childhood [11]. Oppositional defiant disorder (ODD) comorbidity accounts for bulk of the association developmentally [11, 12], whereas comorbidity with social anxiety disorder and generalized anxiety disorder may increase the risk of depression in ADHD. This means that an important mediator of the risk for depression in ADHD is ODD or oppositional symptoms. ODD is currently seen as a disorder of emotional dysregulation [13], and the magnitude of this comorbidity highlights the role of the executive functioning deficits of ADHD to emotional dysregulation.

The story of ADHD and depression comorbidity is different in clinical studies. Comorbidity is significant cross-sectionally and appears to persist over time based on significant odds of association between ADHD and depression in clinical samples of ADHD youth. Out of seven studies including 4300 children, five of these studies reported odds of association between ADHD and depression greater than 3, some as great as 13 across 5–10 follow-up, even when controlling for depression, and in many studies, multiple comorbidities including ODD, at baseline [14–20]. A more direct relationship between ADHD and depression in clinical samples may be related to the severity of the symptoms and associated complex social difficulties which bring youth into a clinical setting; however, it still remains that youth with ADHD in clinical samples have multiple comorbidities, most commonly ODD [21].

Possible Mechanisms for the Relationship Between ADHD and Depression

Biological Risk Processes

Genetics

ADHD has strong genetic contributions with heritability estimated at 79–90 % from twin studies [22]. While no single gene for ADHD has yet reached genome-wide significance, the dopamine receptor DRD4 is the most strongly implicated in the pathogenesis of ADHD [23] Depression appears to be less heritable (40 %) than ADHD [24]. While a substantial literature has targeted the role of serotonin in the etiology of depression, the precise role of the complex repeat polymorphism within the 5HT gene promoter region (5HTTLPR) remains inconsistent across studies.

Brain Structure and Function

Neuroimaging studies of ADHD have identified atypical cortical connections primarily involving frontal striatal circuits, smaller brain volumes, reductions in prefrontal cortical thicknesses and anomalies in the shape of subcortical structures, specifically the basal ganglia, hippocampus, amygdala and cerebellum. In fMRI studies, children with ADHD were found to experience hypoactivation in fronto parietal and ventral attention networks supporting deficits of executive

functioning (EF)—specifically cool EF [25]. Hyperactivation in the default network at rest and visual circuits were suggestive of defective connectivity among neuronal networks. Interestingly, no fMRI evidence for the involvement of regions related to motivation or emotion such as the ventral striatum, OFC or amydala despite the clinical recognition of emotion and motivational dyfunctions in ADHD subjects. Recent evidence suggests a more global brain dysfunction versus more localized effected regions. Longitudinal studies suggest delayed cortical maturation with clinical outcomes associated with differences in cortical developmental trajectories.

Key neural networks implicating the fronto-limbic and stress response systems are believed to underlie the core symptoms of childhood MDD, [7] although recent findings of other brain networks (parietal-temporal) and their connections are also implicated. A meta-analysis of studies found convergent volumetric abnormalities in paediatric depressed samples that together implicate a cortico limbic network dysfunction in MDD children in areas subserving emotional regulation [26]. These findings are congruent with results in adults with MDD.

In a fMRI study of pre-schoolers, Gaffrey et al. [27] found right lateralized elevated amygdala activity during emotional face processing for positive and negative expressions in depressed 4- to 6-year-olds. Amygdala hyperactivity was also associated with parental reports of emotion regulation and negative affect in these young children. These findings lend additional support to the subcortical limbic-related abnormalities associated with depression in both children and adults.

Neuropsychological Functioning

ADHD has been extensively studied from a neuropsychological perspective and has been recognized as a primary disorder of EF [25]. ADHD-related EF deficits are frequently associated with the regions in the dorsolateral prefrontal cortex that regulate inhibitory motor control functions [28]. Nikolas & Nigg [29] undertook EF research examining inhibitory control, working memory and response variability performance in affected ADHD subjects, their unaffected family members and normal controls. EF deficits, most notably response inhibition deficits, were present in the unaffected parents and siblings of ADHD subjects but not evident in normal controls conveying a familial risk for ADHD. These findings were not attributed to age, sex or comorbidity. Interestingly, these deficits did not persist into adolescence for non-affected siblings but were still present in youth with ADHD, further supporting a hypothesis of delayed brain maturation in ADHD.

In a qualitative review of 33 neuropsychological studies, Vilgis et al. [30] found little evidence of an association between EF deficits in multiple cognitive domains among children and adolescents with MDD, while EF deficits have been consistently evident in ADHD children and adolescents. In a meta-analysis of 17 studies of cognitive function in children and adolescents with MDD, Wagner et al. [31] found no deficits in go/no go inhibitory task performance among MDD children relative to healthy controls but reported impairments in cognitive interference control as measured by the Stroop task. Cognitive interference control deficits have also been reported in ADHD children and adolescents but with greater variability than the motor control deficits associated with ADHD. Differences of EF performance may advance the search for greater specificity of functional deficits associated with each disorder and their related neurobiological networks.

Sex Differences

The core symptoms of attention and impulsivity are known to vary within and among healthy and ADHD males and females with neuroimaging evidence of sex-specific anatomical and functional differences [32]. Sex can also influence the severity, age of onset, clinical course, comorbidities and underlying neurobiology of ADHD as well as depression. In ADHD, males are believed to be more impaired in behavioural inhibition and girls more deficient in planning, attention and information processing and possibly have more learning disorders [21, 33]. No clear sex differences in depression phenotypes have been documented. Overexpression of Y-linked genes is one hypothesis of male/female sex differences in ADHD [22]. In depression, estradiol effects at puberty may influence amygdala and serotonin circuitries placing girls at greater risk for depression [34].

Psychotropic Medication Treatment Response

A few studies have examined the effects of psychostimulants on ADHD and/or depressive symptoms. The use of combination therapy including treatments for both ADHD and MDD has been shown to improve both ADHD and depressive symptoms [35–37]. Monotherapy with treatments for ADHD in children comorbid for ADHD and MDD resulted in the improvement of ADHD symptoms, but no significant improvement in depressive symptoms [38, 39]. Studies have produced varied results when looking at antidepressant monotherapy for comorbid ADHD and depression. Findling et al. [40] found that fluoxetine or sertraline monotherapy were effective for treating depressive symptoms, but not ADHD symptoms. Davis et al. [41] and Quintana et al. [42] both observed an improvement in both ADHD and depressive symptoms when administering bupropion or fluoxetine as monotherapies in youth with comorbid ADHD and depression.

A limitation to generalizability of the findings is that the samples are selected clinical samples and they are small. As such, power to detect significant differences in treatment response from these studies is not sufficient. Larger studies are

needed. Inattentive symptoms also appear to be more strongly predictive of depression than hyperactivity symptoms [13], suggesting that identifying inattentive symptoms may be important for identifying youth with ADHD who are most likely to benefit from depression prevention interventions. Studies focusing on predominantly inattentive youth, or the specific impact on inattentive symptoms, would address this possibility.

While antidepressant treatment may alleviate depressive and ADHD symptoms in clinically depressed children, it is not known whether stimulant treatment will significantly reduce depressive symptoms in youth who do not have depression. Further research is needed.

Environmental Risk Processes

Social Functioning

Children with ADHD suffer from difficulties in peer relationships, and approximately 50 % of these children experience multiple instances of peer rejections [43, 44]. The sociometric assessment (peer ratings) data from the multimodal treatment study of ADHD (MTA) demonstrated that children and adolescents with ADHD who have fewer friends are less well liked and more often receive an overall rejected social status than their non-ADHD peers [43, 44]. Similar findings have been reported for youth with depression [44] although the magnitude of the peer rejection problem in depressed youth has been subjected to less scrutiny.

Hoza and colleagues suggest that symptoms of hyperactivity and impulsivity characteristic of ADHD likely cause children to be overbearing in social contexts, leading to peer rejection [43, 45]. Inattentive symptomology is thought to limit the acquisition of social skills that children typically acquire through observational learning [46].

A model is hypothesized to explain the relationship between ADHD and social functioning deficits and risk for depression whereby social skill deficits associated with ADHD may be risk factors for depressive symptoms directly or indirectly through their effects on social relationship functioning [46, 47]. One cross-sectional community study has shown that children's social competence moderated the relationship between ADHD and depression [3]. Others have shown that those with comorbid ADHD and depression are more impaired in their social relationships when compared to their ADHD-only counterparts [48]. This latter study also showed that the inattentive symptoms explained the total influence of depression in the ADHD-depressed group suggesting that the inattention symptoms accounted for the high levels of depression in this group.

Not all studies support this hypothesis. Mrug et al. [44] examined ADHD and depression, as it relates to social relationships, by examining a subset of participants from the MTA study across ages 7 to 15. Their results showed that childhood peer rejection in children with ADHD was not related to depressive symptoms in middle adolescence. It may be that some children with ADHD are at reduced risk for depression due to their overly positive self-perceptions and self-appraisal of their peer status as these children typically hold inaccurate, positive appraisals of their social functioning [44, 49]. However, this seemingly protective self-appraisal might be specific to children that exhibit the more externalizing behaviours of ADHD.

Maltreatment

Maltreatment is defined as an adverse childhood experience characterized by abuse, neglect, victimization and/or isolation [50]. Any of these forms of maltreatment are recognized as critically important risk factors for mental and physical health problems, substance abuse, social impairment, unemployment, delinquency, school dropout and even early pregnancy [51]. Each of these outcomes has been predicted by ADHD and depressive disorders, making tests of the specific impact of various forms of maltreatment on ADHD or depression challenging.

In their review of the behavioural characteristics of children who have been exposed to emotional abuse and neglect, Maguire et al. [52] noted an association between both exposures and ADHD in seven of nine selected studies. This review also identified associations between maltreatment exposures and IQ, literacy, numeracy and language skills. These cognitive outcomes are similarly predicted by ADHD, therefore further research is needed which examines the complex relationships between ADHD, maltreatment and their interactions to cognitive and mood outcomes of children.

Peer victimization (bullying) is also an important concern for children with ADHD. Yang et al. [53] demonstrated a prospective association between involvement in bullying and ADHD in 10-year-olds. Children with ADHD were 3.5 times more likely to be a bully and 5.0 times more likely to be a victim than their peers. Bacchini [54] and others suggest that certain features of ADHD (such as poor problem-solving skills) render children more likely to be involved in peer victimization, as either a bully or a victim.

Literature on the impact of negative parenting styles (i.e. harsh, inconsistent) on risk or course of ADHD far surpasses the data on abuse and neglect. Parenting style is an important predictor of the learning of self-regulation in youth with ADHD [55]. The only prospective study on the topic across early childhood found that parental hostility expressed as demeaning, critical and sarcastic behaviours was predictive of ADHD, as were decreased involvement, poor supervision and inconsistent discipline [56]). These authors did not examine the specificity of these parenting styles to ADHD as opposed to other symptoms

nor were ADHD symptoms controlled for at baseline. Child temperament and parent factors are also important aspects of risk process. Child conscientiousness reduces the impact of inconsistent discipline on children's inattention symptoms, whereas the impact of parental supervision on hyperactivity-impulsivity symptoms is mediated by the child's emotional reactivity. Parental supervision was found to have no impact on inattentive symptoms [57]. Deault [58] has shown that ADHD symptoms strongly predict frequency of parental punishment which in turn predicts increased symptoms of the disorder. The presence of parent mental health difficulties predicts both the use of physical punishment and rates of children's disruptive behaviours [59].

Strong linkages between various forms of maltreatment and depressive symptoms have been noted in several prospective studies. A child's experience of abuse (physical, emotional or sexual) perpetrated by a parent increases rates of depression in adolescence by two- to fivefold [51, 60]. Kim and Cicchetti [61] examined mechanisms of how maltreatment influences the risk of depression. They showed that physical abuse was negatively related to initial levels of self-esteem whereas physical abuse and physical neglect were positively associated with depressive symptoms. Emotional abuse was predictive of change in depressive symptoms over time. Several cross-sectional studies have noted associations between reduced emotional responsiveness (positive reinforcement and minimal eye contact) between family members [62], intrusiveness, overprotection, control and inconsistency [1, 63] and depressive symptoms in children. Consistent with this, insecure attachment to, or negative schema of, the mother predicts depression in youth exposed to maltreatment [63, 64].

Several groups have found that peer victimization in childhood predicts short-lived and persistent depressive symptoms [65–67], future use of antidepressants and psychiatric hospitalizations for depression [68]. The opposite effect has also been observed [69]. A meta-analysis by Reijntjes [70] has found that both directions of effects are significantly associated, suggesting a reciprocal association between victimization and depression.

Discussion

Conclusion

This review identified that the relationship between ADHD and depression is not as well understood as one might suspect. First, follow-up studies showed relatively small measures of association between the disorders over time suggesting that the risk for depression is not high as clinical comorbidity studies might predict. Based on the content areas examined, several main points are highlighted which may inform clinical research and practice.

1. Epidemiologic studies argue against a direct increase in risk for depression associated with ADHD diagnosis but highlight the relationship between ODD and depression as critical. In the community, ODD is more strongly predictive of risk for depression and oppositional youth in these settings merit screening for depression. While screening for ADHD is also important, the yield would be expected to be less than in clinical settings. In clinical samples, the magnitude of this comorbidity highlights the role of the executive functioning deficits of ADHD to emotional dysregulation. The high rate of multimorbidity in clinical studies of youth with ADHD supports the profound impact of ODD as an indicator of emotional dysregulation, as a clinical referral correlate for youth with ADHD [21]. There may be aspects of ADHD severity and associated features in clinical samples which increase risk for depression, and emotional dysregulation may be an important one. The bottom line is the critical importance of screening ADHD youth for the risk of depression in clinical settings, whereas the yield will be lower in other settings.
2. There is of yet no substantial shared abnormalities in brain structure, functioning or genetic underpinnings common to MDD and ADHD. Interference control may be commonly impaired in depression and ADHD, although the functional correlates of this may differ across the groups. The neural networks primarily implicated in ADHD primarily involve the front-striatal, fronto-parietal and fronto-cerebellar networks and their connections which govern inhibitory motor/behavioural control processes. The ventro medial/limbic circuitries and reward pathways (nucleus accumbens) connecting motivating and attentional executive functions are more commonly affected in childhood depression but inconsistently affected in some ADHD samples. These emotional circuits may implicate a shared pathology among these two unique disorders, particularly relevant for the emotional dysregulation common to both disorders. Research about the neural correlates of emotional dysregulation in ADHD is building promisingly, whereas it is preliminary in depression.
3. Pharmacologic treatments for ADHD do not appear to be effective for treatment of depressive symptoms, although symptoms of ADHD may improve in depressed youth whose depressive symptoms respond to antidepressants. The pharmacologic studies to date suggest that depression must be treated separately from ADHD symptoms. This is sensible given the overall findings of the review. Inattention or hyperactivity that is secondary or coincident with depressed or anxious mood may be a

different symptom cluster that may respond to antidepressant medication. Our current knowledge about the psychopharmacology of inattention is very small and deserves specific attention.

4. Peer relationship problems affect both groups and undoubtedly increase risk for depression, particularly in adolescence. As youth enter adolescence, tremendous change occurs at the biological and social level, including an increased focus on peer versus family acceptance. Living with ADHD and/or struggling with low mood places youth at significant increased social vulnerability possibly due to both lack of skill or desire or ability to obtain support. This is an important time for clinical and school professionals to ensure that social functioning is optimized through support and facilitation for youth with ADHD or depression. More research is needed about sensitive times to intervene and which child, adolescent or family focused interventions are likely to help the most.
5. Maltreatment has broad detrimental effects on children, and children with ADHD may be at significantly increased risk for maltreatment.

Inconsistent or harsh parenting and peer victimization have each been implicated as forms of maltreatment associated with risk for ADHD and depression. As parental inconsistency is influenced by individual and family factors which may be associated with ADHD such as affective and behavioural impulsivity or ODD, assessment of ADHD, ODD and depression across family members may be important for reducing instances of maltreatment. Screening and intervening for ADHD in very young children make tremendous sense particularly in high risk families where both genetic and social stressor predisposition is high.

More work is needed to include measures of maltreatment in follow-up, basic science and treatment studies to understand both the psychological sequelae of maltreatment and child factors which increase or protect against nefarious outcomes. Cussen et al. [71] note the possibility that children with ADHD are at increased risk for abuse and may be a subset of children for whom schools and clinics coordinate efforts to screen for abuse and support the family system where possible. It is also important for clinicians to assess for psychopathology in general, but ADHD in particular, in youth who have been exposed to trauma.

Limitations of the review include the separation of the sections into biological and environmental risk processes; this dichotomy does not exist in reality. To add an additional section on plausible interactive effects would be ideal, although difficult to assimilate. This would hopefully be possible in the next few years. Studies are needed which specifically aim to measure such reciprocal or cascade effects to understand how ADHD and depression are influenced. The review also did not include a section on psychological (family, parent or individual) treatment effects on both symptom outcomes. Although important, it was not deemed to be integral for this review. A recent review by Tarver and colleagues [72] suggests that parenting interventions are beneficial for multiple child outcomes and further highlights the importance of family/multimodal treatment interventions for youth with ADHD to potentially reduce the risk for depression.

Compliance with Ethical Standards

Conflict of Interest Jeannette LeGris, Khrista Boyla, Victoria Stead, Kaitlyn Beyfuss and Allison Chan declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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