Depression from childhood through adolescence: Risk mechanisms across multiple systems and levels of analysis.

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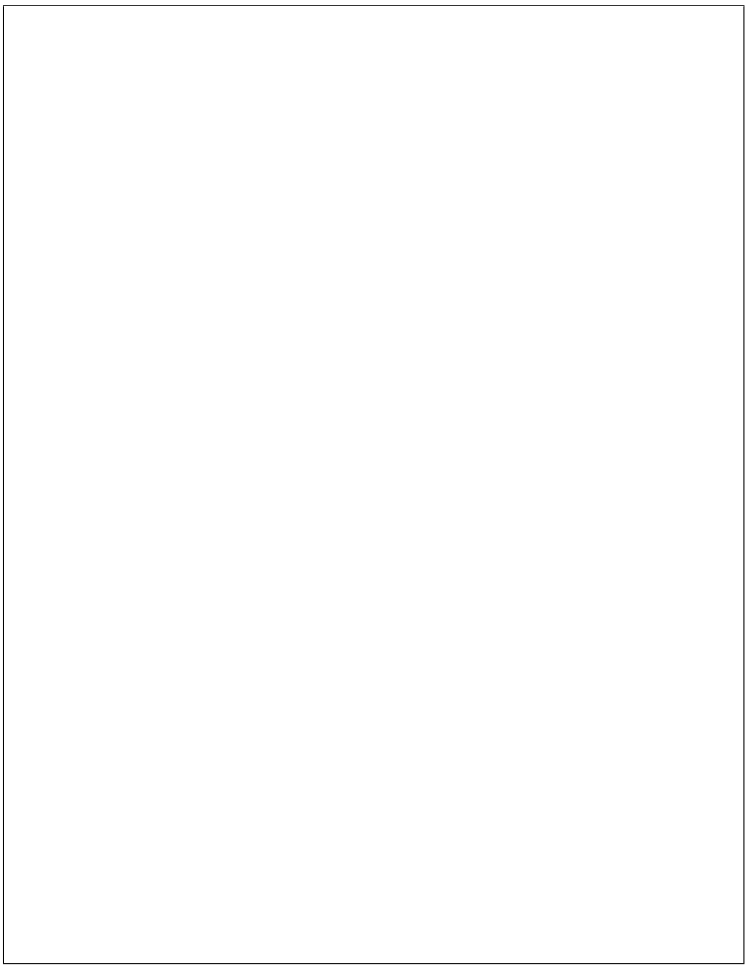

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Depression from childhood through adolescence: risk mechanisms across multiple systems and levels of analysis

Benjamin L Hankin

This paper selectively reviews recent research, especially in the last two years (2012–2014) in preschool, child, and adolescent depression. In particular, attention is paid to developmental epidemiology as well as risk factors and processes that contribute to depression trajectories over time. Emphasis is placed on a developmental psychopathology perspective in which risks are instantiated across multiple systems and levels of analysis, including genetics, stress contexts and processes, biological stress mechanisms, temperament, emotion, reward, cognitive factors and processes, and interpersonal influences. These risks dynamically transact over time, as they emerge and stabilize into relatively trait-like vulnerabilities that confer risk for the increasing rates of depression observed in adolescence. Overall, this summary illustrates that considerable progress has been made recently in understanding the complex developmental processes contributing to depression. Finally, a few gaps are highlighted as opportunities for future research.

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Depression is a common, debilitating, burdensome, and chronic mental health problem. Moreover, it is a developmental phenomenon. One of the major accomplishments in understanding depression has been the explicit recognition that it is a neurodevelopmental disorder. Modal onset of first episodes of depression most commonly occur in middle to late adolescence [1•,2], and many adult depressive episodes represent recurrences of adolescent-onset depression [3]. Compelling evidence shows that depression often begins much earlier than previously believed, including during preschool [4,5•]. Risk factors and processes first emerge, and then accumulate and crystalize over time, likely via dynamic developmental cascades starting with early adverse environments and then ongoing chronic and acute stressors that transact with these vulnerabilities across multiple systems and levels of analysis until these risks stabilize and consolidate. Indeed these developmental cascades can begin prenatally, as maternal emotional distress and stress physiology predict many of the developmental precursors that contribute to the emergence of pathways leading to vulnerabilities, and eventual enhanced risk to internalizing problems later in childhood and adolescence [6,7].

Given the recognized importance of developmental processes for understanding depression, this paper takes an integrative developmental psychopathology perspective to better understand the multiple influences that may affect, and be affected by, depression across the early lifespan from preschool to childhood and into adolescence. Space limitations require an admittedly biased and selective viewpoint in which recent papers predominantly from the last two years (2012–2014) are preferentially reviewed. Additionally, this review focuses relatively more on recent areas of inquiry relevant for risk mechanisms (e.g., genetic influences, adverse childhood experiences (ACE), biological stress susceptibility) that are not as extensively covered in other papers in this special issue. This review explicitly adopts a developmental psychopathology perspective (cf. [8]), emphasizes that risk factors and mechanisms are likely instantiated across multiple systems and levels of analysis (e.g., genetic to neural to psychosocial influences all within environmental contexts), and highlights developmental processes, including emergence and stabilization of risk processes over time.

1. Developmental epidemiology

The most recent data regarding prevalence, severity, and comorbidity of adolescent clinical depression are provided by the National Comorbidity Study-Adolescent Supplement (NCS-A; [1]). Based on interview data with adolescents aged 13–18, lifetime and 1-year prevalence of Major Depressive Disorder (MDD) were 11.0% and 7.5%, respectively; for severe MDD, rates were 3.0% and 2.3%. MDD becomes increasingly more prevalent across adolescence, and this is especially so for girls relative to boys. MDD prevalence was independent of other sociodemographic features. Comorbidity with other disorders was common: 71.9% for all lifetime episodes and 63.7% for past year cases. Anxiety disorders were the most frequent. Although cross-sectional, these NCS-A data are consistent with other longitudinal, community-based depression studies (e.g., [2]). The well-known gender

difference in depression emerges in early adolescence [2], or mid-puberty [9]. Depression rates increase after the pubertal transition [9,10].

Moving earlier in age to complete the descriptive timeline of depression trajectories, clinical depression begins as early as preschool. By age 3, 1.8% of preschoolers in a community sample had MDD [4]. Longitudinal follow-up demonstrates predictive validity and clinical significance as preschool depression continues into childhood. Consistent with homotypic continuity, preschool depression predicted MDD later in childhood and early adolescence [5•]. Consistent with heterotypic continuity, preschool MDD predicted later childhood anxiety disorders and ADHD [5•,11]. Early onset preschool depression proved to be a more robust predictor of childhood depression than maternal MDD or traumatic life events [5•]. Other prospective predictors of later school-aged MDD (assessed at age 6) include preschool irritability [12], prior anxiety, poor inhibitory control, poor peer functioning, parental psychopathology and lower education, and early and recent stressful events [13].

In sum, the developmental epidemiological findings in depression clearly show that MDD can begin early in life, be identified and diagnosed with similar (albeit not developmentally isomorphic), reliable, and valid criteria as used with adolescents and adults. MDD rates then increase in prevalence from childhood into adolescence. At the same time, it is important to note that there are both continuities and discontinuities in depression trajectories over time and in the underlying mechanisms [14]. Thus, it is important to carefully identify latent trajectories of depression across time and salient developmental stages (e.g., pubertal transition) and investigate potential sequential and integrative interplay among genetic, neural, psychosocial, and environmental contextual processes contributing to progressions in depression.

2. Genetics

Telomerase length (TL) is shortened in many, albeit not all, studies with depressed adults [15]. Telomeres, which cap the end of chromosomes, shorten with each cell division and have been shown to erode more in the context of chronic stress, such as childhood adversity [15]. In a longitudinal study, persistent internalizing disorders, including MDD, from age 11 to 38 predicted shortened TL at age 38 in a dose-dependent way in men [16•]. Gotlib [17•] demonstrated that TL was shortened in never-depressed daughters at high familial risk for depression compared to controls, and eroded telomeres related to cortisol reactivity to laboratory stress.

Methylation of particular genes is an epigenetic mechanism postulated to explain how environmental experiences across key developmental periods can affect later risk to depression (e.g., [18]). For example, one longitudinal study showed maternal stress during the first year of a child's life was related to DNA methylation when the children were in middle adolescence and that some of these epigenetic effects varied by child sex [19]. Also, ACE, especially maltreatment, affects risk to depression via G × E processes [20•], and this may occur by epigenetic changes in biologically plausible genes (e.g., *BDNF*, *NR3C1*, and *FKBP5*) relevant for stress susceptibility systems in maltreated children [21,22]. Finally and consistent with the emphasis on connecting risk across multiple systems and units of analysis, methylation of *5-HTTLPR* predicted threat-related amygdala reactivity [23•].

There has been considerable controversy and mixed evidence regarding candidate gene-environment interactions (G × E) predicting depression, but more recent studies that have clearly characterized particular developmentally salient stressful environments have proven successful at predicting prospective elevations of depression in adolescence. For example, interpersonal stressors, especially chronic family stress, enhances the effect of *5-HTTLPR* on later depression during adolescence (e.g., [24,25]). Additionally, early ACE affects more proximal stressors in childhood and adolescence, and this stress sensitization process is moderated by genetics. For example, *5-HTTLPR* and *CRHR1* enhanced the effect of early ACE (over the first five years of life) sensitizing recent chronic stress to predict depression at age 20 years [26•].

Genetic influences not only affect risk via G × E mechanisms but also through gene-environment correlations (rGE), in which particular stressful contexts are more likely to be experienced for particular individuals at enhanced genetic susceptibility. While less research has directly investigated rGE relative to G × E [27], recent work illustrates the importance of both types of gene-environment interplay. For example, emotionally or sexually maltreated youth at genetic risk (*5-HTTLPR*) experienced more dependent, especially interpersonal, proximal events (i.e., stress generation) prior to MDD [28]. Behavioral genetic research shows that both depressive symptoms and particular stress contexts, including parenting and family stress, are moderately heritable, thus indicative of rGE, and that G × E co-exists alongside this rGE in that risk to depressive symptoms is stronger among children with enhanced genetic risk who also experience family stress [29]. Expanding on this latent rGE process with parenting, other molecular rGE research shows that more attuned parents (i.e., those who were less neurotic and more extraverted) provided more sensitive, responsive, and warm parenting for their children at greater genetic risk [30]. Thus, these genetically influenced parent-child relationships and parental socialization processes affect child risk mechanisms via stress, neural, and interpersonal processes (see later), thus providing another example of risk instantiated via multiple systems and levels of analysis.

3. Stress contexts and processes

ACE confers enhanced risk and an adverse course of MDD over the lifecourse. Using data from NCS-A to investigate the impact of multiple childhood adversities (CA), distress disorders, including MDD, were most associated with emotional abuse, sexual abuse, parental mental illness, parental criminality, parental divorce, and family violence; overall CAs accounted for 32.2% of distress disorders [31•]. Moreover, childhood maltreatment predicted persistent and recurrent MDD [32].

In addition to ACE, chronic stress and acute episodic events exhibit bi-directional transactions with depression and other risk factors. These effects can occur via stress amplification, stress generation, and stress sensitization processes. Stressful life events increase across adolescence, especially after the pubertal transition [10], when more interpersonal stressors occur. As more stress is experienced and in developmentally relevant social contexts, depression is more likely to ensue via the main effect of stress or via various vulnerabilities interacting with the rise in stress through stress amplification processes. More recent multivariate studies have examined which particular individual differences most strongly predict prospective dependent, especially interpersonal, events. Interpersonal risks (e.g., co-rumination and attachment) and elevated levels of multiple psychopathologies most strongly predicted dependent interpersonal stressors, and this effect was stronger for girls [33]. Regarding stress sensitization processes, maltreated adolescents, especially those who were emotionally abused, reported lower stress severity prior to MDD onset [34]. Also consistent with stress sensitization, longitudinal research shows that idiographic dependent stressors predicted future depressive symptoms after youths' first onset of MDD in the transition from early to middle adolescence [35]. Finally and consistent with a more nuanced developmental psychopathological perspective, which stress mechanism (e.g., sensitization, amplification) is operating to contribute effective risk to later depression may depend upon age of first MDD onset and exposure to ACE [36].

4. Biological stress processes

The Limbic Hypothalamic Pituitary Adrenal (LHPA) axis is one biological intermediate process that may undergird stress sensitivity. Cortisol, the end product of the LHPA system, is dysregulated in depression. The cortisol awakening response predicts prospective onsets of MDD during adolescence, although the strength of the effect decays over time [37]. Cortisol reactivity to a laboratory challenge is also dysregulated in youth, including in preschoolers with high internalizing symptoms [38] as well as children and adolescents, although the direction of dysregulation (i.e., cortisol hyporeactivity to hyperreactivity) may change across the pubertal transition [39].

More recent studies have progressed to examine developmental origins of such altered cortisol responses. Early ACE and more recent traumatic events were associated with children's cortisol reactivity patterns ([40]; see [41] for review). Additionally, candidate genes relevant for stress susceptibility (e.g., *FKPB5*, *CRHR1*) interact with ACE to predict cortisol reactivity in adolescence [42,43]. Parents' depression and various aspects of child temperament predicted longitudinal cortisol reactivity in middle childhood [44]. Cortisol reactivity exhibits moderate trait-like stability over time, and particular genetic variants for stress susceptibility, especially 5-*HTTLPR* and *CRHR1*, predict greater cortisol stability [45•]. Also consistent with this review's emphasis on integrating risk across multiple systems and levels of analysis, parental depression history and child cognitive vulnerability interacted to predict cortisol reactivity [46].

Stressful contexts also contribute risk to depression via another intermediate biological process—altered immune system and inflammation processes via social signal transduction [47]. ACE, including childhood maltreatment, contributes to allostatic load, via biological embedding and altered immune system functioning [41]. A longitudinal study of adolescent girls showed that those with ACE exhibited significant coupling and bi-directional effects between depression and inflammatory biomarkers (IL-6 and C-Reactive Protein) [48•]. Another longitudinal study of a birth cohort showed that IL-6, assessed at age 9, predicted MDD by age 18 [49].

5. Temperament, emotion, and reward

Predominant temperament models propose that negative (NEM) and positive emotionality (PEM) contribute to affective reactivity while effortful control (EC) comprises the capacity to regulate and control these affective responses. Considerable research indicates that negative constitutes a potent affective temperamental risk to depression [50]. Likewise, lower PEM, including disrupted reward functioning, predicts later depression [51], and this effect may increase through the pubertal transition [52,53]. Poor EC, as a main effect, also predicts later depression [13]. Importantly, EC also synergistically interacts with the affective temperament components to contribute to depression risk, such that high NEM, low PEM, and low EC related to high depressive symptoms [54].

Emotion is also disrupted in youth depression. Children of depressed mothers displayed increased pupil dilation when exposed to sad faces [55]. Boys at familial depression risk exhibited enhanced sensitivity to recognize sad faces in an emotion morph task [56]. Last, currently clinically depressed, but not remitted or control, youth misclassified happy and sad emotion faces as angry in an emotion morph task [57]. These findings suggest that

currently depressed, or those at enhanced risk, display biased perceptions of emotion faces.

These associations between depression and temperament dimensions, emotion, and reward, also have been examined at other levels of analysis. A review of neuroimaging studies in child and adolescent depression found abnormal activations in ventromedial and orbitofrontal frontal regions, the amygdala, and the anterior cingulate [58•]. This ''extended medial network'' is broadly associated with reward processing, emotion processing, cognitive control, emotion recognition, and resting-state functional connectivity. Reward processing, an important feature of PEM and depression risk, has been investigated neurally via psychophysiology [59] and fMRI [51]. Lowered feedback negativity (FN), a psychophysiological index of reward, predicted prospective MDD onset over 2 years among previously never depressed girls [60•].

Relations with depression and temperament, emotion, and reward have also been integrated across multiple systems, and these findings further demonstrate the complex, transactional developmental pathways that confer risk across systems to contribute to depression's etiology. For example, parental negative affective, parent psychopathology, and child EC predict youths' LHPA axis dysregulation [61,62]. Additionally, maternal warmth, assessed in early childhood and later in early adolescence, predicted male offspring's neural activity (e.g., mPFC, caudate, striatum) during reward and loss tasks years later in young adulthood [63]. Also of interest, different neural areas are activated in response to potential rewards in the context of low parental warmth (increase in rewards in mPFC, striatum, and amygdala) relative to peer victimization (decrease in reward response in mPFC) [64•]. Early parenting and parental MDD affected offspring's reward processing neurally as assessed psychophysiologically via error-related negativity [65].

6. Cognitive factors and processes

A recent comprehensive review shows that many cognitive vulnerabilities contribute risk to depression cross-sectionally and longitudinally and that many, albeit not all, cognitive risks appear to be transdiagnostic predictors and not specifically associated with risk to depression per se [66]. Self-reported cognitive products (e.g., dysfunctional attitudes, negative cognitive style, rumination) predict prospective increases in depressive symptoms and MDD in youth, often via vulnerability–stress interactions in which cognitively vulnerable youth are more likely to become depressed when experiencing stressors. Additionally, cognitive processes, including deficits in executive function as well as biased attention and memory, are concomitantly associated with depression.

These cognitive products and processes have been integrated within other levels of analysis and systems, including genetics (e.g., [67]), stress biology (e.g., [46]), cognitive/affective neurosciences (e.g., [68,69]), and interpersonal influences. For example, successful cognitive reappraisal protects against the depresogenic G × E effect (5-*HTTLPR* × stress) [70]. Negative parenting contributes to children's attentional bias to negative emotional stimuli [71].

Finally, longitudinal research with repeated measures of cognitive risks demonstrates moderate stability in negative self-referential thinking [72] as well as cognitive products [73] over time in children and adolescents. These findings suggest that cognitive vulnerabilities may be relatively trait-like, intermediate risk processes that emerge and stabilize before the large surge in depression rates observed during middle to late adolescence.

7. Interpersonal influences

Developmental social contexts, and the salience of relationships, normatively change from preschool into childhood and adolescence. Still, despite the normative increase and emphasis in peer relations during adolescence, parent-child relationships remain important as positive parental relationship quality continued to buffer against the depressogenic effects of peer stress from childhood through adolescence [74]. In adolescence, peer and romantic relationships take on increasing salience and potential to contribute to depression via peer and romantic stress. A particularly potent interpersonal predictor of depression, especially in the context of interpersonal relationships, is co-rumination, the process of emotionally rehashing negative emotion in close social relationships [75,76]. Regarding romantic stress, results from a family-based design showed that only sexual activity in a non-romantic relationship predicted adolescent depression after controlling for genetic and shared familial confounds [77•].

More recently, work has increasingly integrated neural processes with parenting, socialization, and peer influences. Exposure to positive parenting behavior is associated with specific neural areas and circuitry (e.g., anterior cingulate, vlPFC) in adolescent offspring, and these neural areas are reduced in depressed adolescents exposed to their own parents' positive behavior [78•]. Additionally, longer duration of maternal negative emotion affected similar neural areas in her child in response to lack of peer acceptance [79]. Social information processing systems, including affective and motivational processes linked to peers and romantic partners, are hypothesized to become more sensitive and reactive with the transition through puberty [52]. Consistent with this, sensitivity to social evaluation increases across adolescence, as evidenced by pupillary reactivity [80] and

fMRI-based neural activation [81•], to peer rejection in a virtual chatroom task, and these multi-level risk processes relate to enhanced vulnerability to adolescent depression.

8. Future directions

First, theoretical work is needed to coherently synthesize and integrate the rapidly accumulating knowledge of risk factors across multiple levels and over the lifespan so that a more succinct, focused conceptual model of key etiological risk factors and mechanisms can be articulated. The literature reviewed here does not presently offer a clear theoretical depiction of the core mechanisms contributing to the ontogeny of depression over time. This review enumerated many factors and processes that potentially provide suggestive, compelling clues upon which to build and articulate a more integrative, coherent theoretical model of the development of depression.

Second, continued longitudinal, preferably multi-wave repeated measures, research is still needed to more rigorously examine the extent to which the various risk factors and mechanisms reviewed here function as potential causes, correlates, and/or consequences to rising trajectories of depression over time. Many of the studies are cross-sectional, and as such cannot address issues of temporal precedence and possible causal risk mechanisms. Additionally, further longitudinal research is needed to investigate developmental processes in these core risk factors and mechanisms, including: the extent to which these risks and depression affect each other over time in dynamic, transactional, and cascading processes; and developmental origins along with the relative degree of stability and change occurring over time for these risk.

Finally, the degree to which many of these risk mechanisms predict depression specifically, versus comorbid conditions more transdiagnostically, is not well understood. Better understanding and predicting developmental sequential comorbidity trajectories of depression with commonly co-occurring disorders represents an important area of inquiry. For example, depression co-occurs with many, albeit not all, anxiety disorders, and recent work summarizes three potential temporal pathways through which depression and anxiety can affect each other [82]. Accordingly, different potential processes and models (e.g., [83]) can then be evaluated to better ascertain which particular risk mechanisms predict depression specifically versus transdiagnostically and in what ways.

Conflict of interest

Author has no biomedical financial interests or potential conflicts of interest.

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