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Future Directions in Vulnerability to Depression among Youth: Integrating Risk Factors and Processes across Multiple Levels of Analysis

Benjamin L. Hankin

University of Denver

Abstract

Depression is a developmental phenomenon. Considerable progress has been made in describing the syndrome, establishing its prevalence and features, providing clues as to its etiology, and developing evidence-based treatment and prevention options. Despite considerable headway in distinct lines of vulnerability research, there is an explanatory gap in the field ability to more comprehensively explain and predict who is likely to become depressed, when, and why. Still, despite clear success in predicting moderate variance for future depression, especially with empirically rigorous methods and designs, the heterogeneous and multi-determined nature of depression suggests that additional etiologies need to be included to advance knowledge on developmental pathways to depression. This paper advocates for a multiple levels of analysis approach to investigating vulnerability to depression across the lifespan and providing a more comprehensive understanding of its etiology. One example of a multiple levels of analysis model of vulnerabilities to depression is provided that integrates the most accessible, observable factors (e.g., cognitive and temperament risks), intermediate processes and endophenotypes (e.g., information processing biases, biological stress physiology, and neural activation and connectivity), and genetic influences (e.g., candidate genes and epigenetics). Evidence for each of these factors as well as their cross-level integration is provided. Methodological and conceptual considerations important for conducting integrative, multiple levels of depression vulnerability research are discussed. Finally, translational implications for how a multiple levels of analysis perspective may confer additional leverage to reduce the global burden of depression and improve care are considered.

Several years ago, I was doing psychotherapy with a depressed adolescent girl, and she described her mood and depression as “an ogre.” A few weeks later while I was watching *Shrek* with my own children, we laughed at the scene when Shrek is walking through a field with Donkey on their way to battle the dragon, and Shrek explains to Donkey, “Ogres are like onions. Onions have layers; Ogres have layers! Get it?” This juxtaposition leads to a metaphor of clinical depression as an ogre, a potentially dark and scary condition, and its

Correspondence concerning this article should be addressed to Benjamin L. Hankin, Department of Psychology, University of Denver, 2155 South Race Street, Denver CO 80208. Internet correspondence can be addressed to ben.hankin@psy.du.edu. Phone: 303-871-7468.

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etiology may best be understood as being comprised of multiple layers, or levels. As a field, child and adolescent clinical scientists have made considerable progress in describing depression, establishing its prevalence and features, providing clues as to its etiology, and developing evidence-based treatment and prevention options (for reviews, see Abela & Hankin, 2008a). However, much of this progress has been based on inquiries that usually are at one level of analysis and exclusive of other possible coherent integrations across multiple levels or perspectives. Despite considerable progress in distinct lines of vulnerability research, there is an explanatory gap in our ability to more comprehensively explain and predict who is likely to become depressed, when, and why. Overall, the field lacks a more complete understanding of multiple levels of analysis that can bridge together accessible, observable risks to molecular genetic influences and their connection through various intermediate processes (or endophenotypes; Gottesman & Gould, 2003).

There are likely many reasons for the current state of affairs in which there appears to be a ceiling for the amount of variance of youth depression that we can currently explain. First, there has been excessive and exclusive concentration on one vulnerability theoretical model to the exclusion of meaningful integration with other vulnerabilities. Many investigators focus on their own comfortable set of constructs and processes as well as their familiar measures, methods, and approaches. Clearly, the lack of interdisciplinary training and knowledge base is a primary reason for the paucity of integrated, multidisciplinary research; there is a strong need for improvements in training, including broad and deep skills and knowledge across behavioral sciences, cognitive and affective neurosciences, molecular neuroscience, and psychiatry (Insel & Wang, 2010). Second, many of the methodological features that characterize much of the research on depression vulnerability study preclude a deeper and more rigorous empirical investigation. Third and related, repeated use of the same, traditional conceptual models, instead of considering and testing refined and more advanced, alternative conceptual models, hampers progress, calcifies and reinforces the present state of knowledge, and does not permit testing of newer conceptual vulnerability models across multiple levels of analysis.

One possible approach to addressing these issues involves greater integration across multiple levels of analysis of depression vulnerabilities across the lifespan. The primary purpose of this paper is to advocate for this perspective. By doing so, I hope this stimulates some promising future research that will “unpeel the onion” and promote a more complete understanding of the etiological connections among the multiple levels of risk to depression among youth, or the “ogre,” that this depressed girl described.

Overview of this paper

As many psychiatric disorders, including depression, are multiply determined, a singular focus on one etiological risk at a single level of analysis is unlikely to provide a complete understanding of the many pathways leading to the development of this disorder. I first illustrate this point with a very succinct review of cognitive vulnerability theories of depression (e.g., Abramson, Metalsky, & Alloy, 1989; Beck, 1967, 1987; Nolen-Hoeksema, 1991) and evidence for these models as predictors of depression in youth. These etiological models were initially developed to characterize adult depression, but have more recently

been investigated in children and adolescents using fairly rigorous empirical designs and approaches. This review is intended to make the point that even such rich conceptual models that have proven exceptionally successful at prospectively predicting significant variance in depression can only explain a moderate amount of why individuals become depressed. Thus, continuing to exclusively focus on any singular level aspect of vulnerability will not suffice to advance knowledge on the etiological influences contributing to the development of depression.

After this review, I illustrate one example of a multiple levels of analysis model of vulnerabilities to depression. A brief review of the conceptual underpinnings and evidence in support of each of these select vulnerabilities is provided, followed by some empirical examples of studies that have demonstrated cross-level integrations and connections among the different levels of analysis. Next, I discuss some methodological and conceptual considerations that are especially critical for conducting research that integrates multiple levels of depression vulnerability. Finally, translational implications for how a multiple levels of analysis perspective may confer additional leverage to reduce the burden of depression and improve care are considered.

COGNITIVE VULNERABILITIES TO DEPRESSION AMONG YOUTH: THEORIES AND EVIDENCE

Cognitive theories of depression describe characteristic cognitive vulnerabilities that are hypothesized to causally contribute to depression. These models, like many other vulnerability theories, operationalize vulnerability as an internal and stable feature of an individual that predisposes to develop depression following negative events (Ingram, Miranda, & Segal, 1998). Most of the theories include vulnerability-stress components that posit that depression is produced by the *interaction* between an individual's cognitive vulnerability and certain environmental adversities that serve to activate this vulnerability, thus leading to depression. In contrast, individuals low in cognitive vulnerability are hypothesized to react to similar adversities with an appropriate level of distress and depressive affect to the event but to not spiral into depression.

A multitude of cognitive vulnerability factors have been posited. This brief review focuses on the most extensively studied vulnerability factors across child, early adolescent, and adolescent populations: (1) depressogenic inferential styles about causes, consequences, and the self from hopelessness theory (HT; Abramson, Metalsky, & Alloy, 1989), (2) dysfunctional attitudes from Beck's Cognitive Theory (BCT; Beck, 1967, 1983), and (3) the tendency to ruminate in response to depressed mood from Response Styles Theory (RST; Nolen-Hoeksema, 1991).

These main cognitive vulnerability theories have been studied for several decades, and a large corpus of research has accumulated that largely supports their hypothesized propositions in adults (for reviews see Abramson et al., 2002; Joormann, 2009; Ingram, Miranda, & Segal, 1998; Nolen-Hoeksema, Wisco, & Lyubomirsky, 2008). Similarly, many prospective studies have evaluated whether these vulnerabilities can be extended downward and are equally applicable in the prediction of depressive symptoms and clinical depression

among children and adolescents. A quantitative review of this literature with youth (Lakdawalla, Hankin, & Mermelstein, 2007) showed that each vulnerability significantly predicts prospective increases in depressive symptoms, with generally medium effect sizes (ES) among adolescents and small ES for children (see Abela & Hankin, 2008b; Jacobs, Reinecke, Gollan, & Kane, 2008, for qualitative reviews).

Overall, the preponderance of studies, especially the more recent and exacting multi-wave designs, provide strong support for negative cognitive style (e.g., Abela et al., 2011; Carter et al., 2011; Hankin, 2008a), dysfunctional attitudes (e.g., Abela et al., 2011; Abela & Skitch, 2007; Hankin, Wetter, Cheely, & Oppenheimer, 2008), and rumination (e.g., Abela & Hankin, 2011; Hankin, 2008b; Skitch & Abela, 2008) as vulnerabilities that interact with stress to predict depressive symptoms and disorder among children and adolescents. Support for cognitive vulnerability-stress components has been obtained in samples across different ages (children as young as 5, Conley et al., 2001, to late adolescents, Hankin, Abramson, Miller, & Haeffel, 2004) and cultures (e.g., Chinese adolescents, Abela et al., 2011, and Spanish youth, Calvete et al., 2008). Also, studies using diagnostic interviews to assess clinical depression have demonstrated that cognitive vulnerabilities interact with stressors to predict the prospective onset of depressive episodes (Abela & Hankin, 2011; Bohon, Stice, Burton, Fudell, & Nolen-Hoeksema, 2008; Carter & Garber, 2011; Hankin et al., 2004; Lewinshohn, Joiner, & Rhode, 2001).

Thus, cognitive vulnerabilities prospectively predict depression (symptoms and disorder) across youth of varying ages and cultures. Still, despite clear success with very conceptually rich theoretical models, and when tested with the most recent research using more empirically rigorous methods and designs, the field has not been able to completely explain why and when individuals become depressed. Here, I illustrated this point with cognitive theories, but the point holds with other single-focus vulnerability models. That only a moderate amount of variance can be explained by a conceptual model focused largely on a sole vulnerability can be understood clearly from a developmental psychopathology perspective (Cicchetti, 2006). Concepts of multiple pathways, especially equifinality (multiple processes can contribute to one outcome) and multifinality (multiple outcomes can result from one starting, initial point) can help solve this problem. As noted next, depression is a heterogeneous, multifactorial disorder, and it is unlikely that any one level of analysis vulnerability model can fully explain its etiology. Overall, more needs to be done.

A MULTIPLE LEVELS OF ANALYSIS MODEL INTEGRATING VULNERABILITIES TO DEPRESSION

One of the primary arguments of this paper is that future research can more significantly advance understanding of the development of depression among youth when a multiple levels of analysis approach is utilized. In this section I will first explicate the advantages of studying multiple vulnerabilities to depression. Then I will present one concrete example of a multiple levels of analysis perspective to depression vulnerability (see Figure 1). This is not intended to represent a full, coherent theory; nor does this example comprehensively include all conceptually possible and empirically supported processes. A comprehensive review of the evidence for the aspects of vulnerability included in this integrative model is

beyond the scope of this article; thus, only select, illustrative studies along with reviews are provided.

Why Adopt a Multiple Levels of Analysis Perspective?

First, there are many potential vulnerabilities to depression among youth, including genetic, biological, temperament, cognitive, interpersonal, and emotion regulation (see Abela & Hankin, 2008a, for reviews of each). Depression is a prototypical multifactorial disorder, like heart disease, in that one single cause or underlying vulnerability has not been demonstrated. Unlike some other medical diseases (e.g., cystic fibrosis), it is unlikely that a single cause will ever be found to be necessary or sufficient and completely predict who will develop depression. In light of the etiological heterogeneity of depression, future research would benefit from focusing on cross-level mechanisms that more realistically capture the multifactorial nature of depression and many other psychiatric disorders (Kendler, 2012). So, from a scientific perspective (including nosological classification and etiological understanding), it is necessary to consider multiple factors and processes that contribute to onset, maintenance, and recurrence over time. Second, when envisioning future directions that hold promise in scientific inquiry into the study of youth depression, taking a multiple levels of analysis perspective appears paramount. The National Academy of Science (NAS) has called for creation of new nosology based on multiple levels of analysis across medicine (National Research Council, 2011). NIMH has encouraged future investigations based on Research Domain Criteria (RDoC; Insel, 2008) to integrate across areas of genetics, neurobiology, and behavioral science to understand core mechanisms, such as cognitive systems, social processes, executive functioning, positive and negative valence systems, that may be implicated in depression and other psychopathologies. The NAS and NIMH both emphasize multiple levels of analysis, from genes to neural circuits to observable behavior, emotion, and symptoms.

Multiple Levels: From Individual Difference Vulnerabilities to Environmental Contexts

The multiple levels of analysis approach to depression advocated in this article explicitly considers and articulates a conceptual model in which different levels are represented both within the individual (e.g., genetic risks to intermediate traits/endophenotypes to accessible cognition, mood, and behavior) as well as within the environment (e.g., Bronfenbrenner, 1979). This approach, in which individuals transact and are nested within and across different ecological contexts (e.g., micro-, meso-, macro-, and exo-systems), is consonant with developmental systems (e.g., Bertalanffy, 1950; Hollenstein, 2011; Thelen & Smith, 1994; Waddington, 1957) and developmental psychopathology (Cicchetti, 2006) theories.

Applying such a perspective holds considerable promise for future research aimed at addressing some of the “big facts” of depression (Hankin & Abramson, 2001). For example, the emergence of the sex difference during early adolescence, the overall dramatic surge in rates of depression and first onsets throughout adolescence, as well as cultural and ethnic influences on the development of depression (e.g., Ryder et al., 2012; this issue), could potentially be addressed from a multiple levels of analysis integration that explicitly considers the transactions among the multiple individual differences and various ecological contexts.

Multiple Levels of Analysis for Depression Vulnerability: An Example

Approaches to characterizing depression vulnerability across multiple levels have been proposed previously (e.g., for outstanding examples, see Beck, 2008; Davey, Yucel, & Allen, 2008; DeRaedt & Koster, 2010; Disner, Beevers, Haigh, & Beck, 2011; Goodyer, 2007; Ingram, Atchley, & Segal, 2011; Nelson, Leibenluft, McClure, & Pine, 2005). Here I provide one concrete example of how genetic factors, neural processes, biological stress reactivity, information processing of socially imbued affective cues, and temperament dimensions can be combined with the explicit cognitive vulnerabilities (see Figure 1 for a schematic illustration). In this Figure, different levels of individuals' environment and context are represented by the circles, consistent with Bronfenbrenner's classic ecological model, and the different levels of individuals' vulnerabilities are represented in the arrow to more explicitly articulate that there are multiple levels of both individual vulnerabilities and environmental ecology and that multiple levels of co-action are likely. Such perspective offers potential for new questions to be asked and addressed in future research inquiries. In the following sections, some of the essential conceptual and empirical points relevant to this multiple levels of analysis model are illustrated followed by initial evidence.

Individual differences in temperament as vulnerabilities to depression—

Temperament typically has been broadly defined as individual differences in emotional and behavioral style that appear early in life, are stable across time and situations, and presumably have some biological and/or genetic underpinnings, although temperament characteristics can be modified by experience (Rothbart & Bates, 1998; Shiner, 1998). The basic child developmental literature (Rothbart & Bates, 1998) suggests three higher-order temperament dimensions: negative emotionality (NE), positive emotionality (PE), and effortful control (EC). NE involves a tendency toward negative emotions (e.g., discomfort, fear, anger, sadness) and stress, and PE characterizes the extent to which an individual is outgoing, sociable, and receptive to reward (Rothbart & Bates, 1998). Both NE and PE represent affective reactive dimensions of temperament. Finally, EC taps into self-regulatory, executive functioning (EF), and control processes (e.g., task persistence, attentional control, planfulness, inhibitory control) that can modulate the more affective/reactive dimensions of NE and PE. As a regulatory dimension of temperament, EC permits and can promote flexible modulation of individuals' reactive responses to aid pursuit of longer-term goals.

Considerable research has examined vulnerability models¹ of these temperament dimensions as predicting prospective elevations of depressive symptoms over time among children and adolescents (for reviews, see Compas, Connor-Smith, & Jaser, 2004; Harbaugh et al., 2012; Tackett & Krueger, 2005). The preponderance of studies show that the reactive dimensions of temperament, especially NE, are associated with and prospectively predict later depression. The evidence for NE x PE interactions is relatively supportive but still mixed, especially among longitudinal investigations (see Harbaugh et al., 2012 for review). With respect to higher-order interactions involving EC as a self-regulatory dimension capable of

¹I quickly note here that theorists have postulated several conceptual models that may characterize associations among temperament and psychopathology, including: (a) vulnerability, (b) pathoplasty, (c), scar, and (d) spectrum or continuity (see Clark, Watson, & Mineka, 1994; Klein, Kotov & Bufferd, 2011 for discussion).

reducing risk conferred by reactive temperament dimensions, most cross-sectional studies have demonstrated that the interactions of low EC with high NE, or low EC with low PE, show significant associations with elevated internalizing symptoms (see Harbaugh et al., 2012 for review). Finally, initial research has begun to suggest that the 3-way interaction (high NE, low PE, and low EC) may constitute the highest temperament risk to depression (Dinovo & Vasey, 2011; Vasey, Harbaugh, Lonigan, Phillips, Hankin, Bijttebeir, & Willem, 2012). In essence, reactive temperament risk is a function of high NE x low PE, but this synergistic affective reactivity would likely only manifest itself and contribute to depression among individuals with low EC who do not have the resources or skills to inhibit or interrupt the more toxic combination of high NE and low PE.

Overall, relatively less research has focused on the role of EC in depression compared to NE and PE. Future research would benefit from expanding the scope of inquiry to include EC as an important regulatory temperament dimension for depression vulnerability. This could be accomplished via typical temperament approaches (e.g., child or parent report or observational methods and tasks of EC) as well as through the use of measures of executive functioning (EF). EFs are higher-level cognitive processes that control and regulate lower-level processes to effortfully guide behavior toward a goal (Banich, 2009). EF is impaired among depressed adults (Snyder, 2012) and adolescents (Matthews & Coghill, 2008; Wilkinson & Goodyer, 2006, but see Favre et al., 2008; Halari et al., 2009; Pan et al., 2011 for null findings).

Information processing biases as vulnerabilities to depression—The cognitive vulnerability theories introduced earlier propose that explicit, accessible negative cognitions, such as negative cognitive styles, dysfunctional attitudes, and rumination, predict depression and that implicit, less accessible cognitive processes, such as attention and memory, are also related to depression. These more automatic, implicit models of biased information processing have been studied among adults (see Joormann, 2009; Matthews & MacLeod, 2005 for reviews) relatively more so than with youth. Research with at-risk (Gibb, Benas, Grassia, & McGeary, 2009; Joormann, Talbot, & Gotlib, 2007) and clinically depressed (Hankin et al., 2010) youth have demonstrated attention biases specifically to sad faces. Other research examining overgeneral autobiographic memory biases has shown significant effects among clinically depressed youth (Kuyken & Howell, 2006; Kuyken, Howell, & Dagleish, 2006; Park, Goodyer, & Teasdale, 2004) and at-risk youth (Kuyken & Dagleish, 2011).

These information processing biases can also be placed within modern cognitive science, especially EF, models. For example, impairments in cognitive inhibition or updating, which have been hypothesized as deficits that may underlie information processing biases (Joormann, 2010), may involve difficulties in overriding prepotent responses, removing negative material from working memory, and reducing the influence of task-irrelevant material that captures attention. Thus, one intriguing hypothesis that can be examined in future research is the possibility that youth who exhibit high levels of NE may be at greater risk for depression, especially when they also possess poor EF, because they have more negative emotional material that resides in their working memory, and, they have greater

difficulty eliminating negatively toned information. This may be one cross-level interactive process to characterize some risks to depression, such as rumination.

HPA axis dysregulation and biological stress reactivity—Stressful life events are one of the strongest predictors of depression among children and adolescents (Grant et al., 2006 for review), and major stressors have been demonstrated to be a significantly important predictor for first onsets of depressive disorder among adolescents (Lewinsohn, Allen, Seeley, & Gotlib, 1999; Stroud, Davila, & Moyer, 2008). Accessible individual differences, such as cognitive vulnerabilities, have been shown to potentiate the association between stressors and depression. But, how does “stress get under the skin,” and what are biological/physiological processes of stress reactivity?

The association between stress and hypothalamic pituitary adrenal (HPA) – axis activation has been extensively investigated in both animals and humans at all developmental periods and as part of both normative and maladaptive processes (see Gunnar & Quevedo, 2007; Lupien, McEwen, Gunnar, & Heim, 2009, for reviews). Cortisol is the primary hormonal product of the HPA-axis. However, more extended exposure to elevated steroid hormones is physiologically damaging and may contribute to disease (McEwen, 1998). In the concept of allostatic load, or the “wear and tear” on the body that can occur with repeated activation of the adaptive physiological systems as a result of repeated stress over time, there can be both over- and under-activation of the HPA axis (McEwen, 1998). While both too much and too little cortisol can contribute to disease states (Miller, Chen, & Zhou, 2007), hypercortisolism has overwhelmingly received the preponderance of research attention in most investigations of the HPA axis in developmental psychopathology (Gunnar & Vazquez, 2006) and depression (Burke, Davis, Otte, & Mohr, 2005).

Dysregulation of the HPA axis is a potentially robust biomarker for depression among many adults (Burke et al., 2005; Parker, Schatzberg, & Lyons, 2003), who show cortisol hyperreactivity in response to a psychosocial stressor. While most studies of depressed adults demonstrate cortisol hyperreactivity in response to challenge, fewer studies have investigated the role of cortisol, and the direction of effects, among depressed youth (for reviews, see Guerry & Hastings, 2011, and Lopez-Duran, Kovacs, & George, 2009). Indeed, HPA axis dysregulation among youth may be more complex and nuanced than the standard hypercortisolism to challenge pattern found in depressed adults. While research with postpubertal adolescents (e.g., Hankin et al., 2010; Rao, Hammen, Ortiz, Chen, & Poland, 2009) shows that depressed adolescents exhibit cortisol hyperreactivity in response to challenge in a similar manner as do adults, younger prepubertal children tend to demonstrate cortisol hyporesponsivity to laboratory stressors (e.g., Hankin et al., 2010; Luby et al., 2003). Such research suggests a developmental switch in HPA axis dysregulation around puberty (see Gunnar, Wewerka, Frenn, Long, & Griggs, 2009; Stroud et al., 2009 with healthy youth). Finally, the few longitudinal studies suggest that HPA axis dysregulation predicts later symptoms and the course of depression (Adam, 2010; Rao, Hammen, & Poland, 2010). For example, youths’ lower levels of cortisol, as a physiological indicator of allostatic load, interacted with prospectively assessed increases in stressful life events to predict elevations of depressive symptoms over one year (Badanes, Watamura, & Hankin, 2011).

Neural activity and connectivity—Considerable research, including neuroimaging work from basic cognitive and affective neuroscience as well as more clinically oriented research with at-risk or patient populations, suggests a generally consistent picture of how particular brain regions and neural circuits operate and are connected in such a way as to confer risk to depression (for reviews, see Davidson, Pizzagalli, & Nitschke, 2009; Disner, Beevers, Haigh, & Beck, 2011; Gotlib & Hamilton, 2008; Mayberg, 2007). In short, this corpus of research converges to suggest that limbic areas (e.g., the amygdala), which are frequently found to be associated with high negative emotion and affectivity, tend to be overactive, whereas various interconnected prefrontal cortex (PFC) areas (e.g., dorsolateral, ventromedial, orbitofrontal), which commonly are found to be associated with EF and cognitive control, are underactivated. Moreover, some empirical evidence shows strong functional connectivity (inverse association) between PFC and limbic areas. The PFC, as a broad area linked with higher order planning, EF, and cognitive control, can moderate more affective, limbic-driven activity.

In addition, several neural circuitry models of depression include other prominent brain regions hypothesized to be dysregulated in depression. These include the anterior cingulate, which has been associated with emotion processing, attention, and more general cognitive control (e.g., Hamani et al., 2011; Hamilton, Chen, Thomason, Schwartz, & Gotlib, 2011; Wagner et al., 2008), and reward processing areas (e.g., nucleus accumbens and ventral striatum; Forbes et al., 2006; Pizzagalli et al., 2009).

Despite studies showing significant patterns of association consistent with these neural circuitry models, the vast majority of research continues to employ cross-sectional designs. There are relatively few longitudinal studies, especially with children or adolescents, in which baseline neural activity and connectivity are used to predict later increases in depression and retesting of these neural circuits is conducted after depressive episode (Kessler, Traue, & Wiswede, 2011).

Genetic influences—There are genetic influences to the development of depression across the lifespan as demonstrated by significant, moderate heritability estimates from behavioral genetic research conducted with children, adolescents, and adults (e.g., see Lau & Eley, 2008; Levinson, 2009 for reviews). More recent molecular genetic research has produced significant advances in knowledge of how measured, specific genes relate to depression, from either direct main effects associations or through gene-environment interplay (i.e., Gene x Environment interaction, GxE; or Gene-Environment correlation, rGE).

Probably the most investigated candidate gene associated with depression is the serotonin transporter promoter polymorphism (5-HTTLPR). Although there is no consistent direct association between depression and 5-HTTLPR (e.g., Anguelova, Benkelfat, & Turecki, 2003), most evidence shows a significant interaction between 5-HTTLPR and stressful life events (GxE) predicting prospective increases in depression in adults (Karg, Burmeister, Shedden, & Sen, 2011), especially when more reliable and sophisticated assessments of life events are used (Monroe & Reid, 2008; Uher & McGuffin, 2010). The majority of youth GxE studies show significant interactions between 5-HTTLPR and environmental stress,

such as maltreatment (Cicchetti, Rogosch, & Sturge-Apple, 2007; Kaufman et al., 2006), family environment (Hammen, Brennan, Keenan-Miller, Hazel, & Najman, 2010; Jenness, Hankin, Abela, Young, & Smolen, 2011; Nobile et al., 2009; Sjöberg et al., 2006), and general stressors (Eley et al., 2004; Hankin et al., 2011). In addition to 5-HTTLPR, other well-investigated candidate genes include catechol-o-methyltransferase (COMT), brain-derived neurotrophic factor (BDNF), other broad monoamine-(e.g., MAOA) and serotonin-(e.g., TPH) system related genes, and other physiological stress-system related genes (e.g., glucocorticoid receptor genes—FKBP5, NR3C1; corticotropin releasing hormone genes—CRHR1 and 2).

Another way in which genetic influences work with the environment is through gene-environment correlations (rGE; Plomin, DeFries, & Loehlin, 1977; Scarr & McCartney, 1983). With rGE processes, individuals' genes influence the likelihood of exposure to particular environments through three mechanisms: (1) passive rGE, in which genetic factors that are common to both a parent and the child influence parenting behaviors or the environment the parent provides, (2) evocative rGE, in which individuals' genetically influenced behaviors elicit reactions from others, and (3) active rGE, in which individuals' genetic factors influence their selection of environments. The majority of evidence in support of rGE derives from behavioral genetic studies (Plomin & Daniels, 1987); such research shows that many "environmental" experiences, including negative life events, divorce, marital quality, parental warmth and discipline, and social support are moderately heritable. In contrast to considerable and consistent evidence for rGE from behavioral genetic research, the current evidence for rGE with measured, specific candidate genes is thin (Jaffee & Price, 2007). There is good reason to believe that future research will unearth rGEs with candidate genes, as recent studies have demonstrated rGEs between parenting quality and variation of the dopamine D2 receptor gene (e.g., Hayden et al., 2010; Lucht et al., 2006; Mills-Koonce et al., 2007; Propper et al., 2008).

Taking together both GxE and rGE as forms of gene-environment interplay, future research can investigate which particular genes affect individuals' exposure to environmental contexts (positive and negative) through rGE processes as well examine which specific candidate genes potentiate reactivity to those positive and negative environmental contexts through GxE processes.

In addition to allelic variation in structural DNA sequences, epigenetics and gene expression are important, as more dynamic sources of genetic influence can also contribute risk to depression. Epigenetics involves biochemical modifications of DNA, without alterations of the base-pair sequence itself, that affect gene expression, such as through the process of methylation, or the silencing of genes. The epigenome is more dynamic and interacts with the environment, which can have a significant impact on gene expression across the lifespan (Meaney, 2010). Epigenetic processes are important because they affect gene expression through dynamic interplay with individuals' environment, and such epigenetic modifications of genes can result in enduring changes in other biological, cognitive, emotional, and behavioral changes at other levels of analysis (Zhang & Meaney, 2010).

Much of the empirical research on epigenetics, and the demonstration that environmental influence can have profound effects on DNA methylation, and in turn, phenotypical characteristics, has been conducted with animal models (e.g., Weaver et al., 2004; see also Petronis & Mill, 2011; Zhang & Meaney, 2010). For example, Meaney and colleagues (Weaver et al., 2004) have elegantly demonstrated intergenerational transmission of behavioral change through epigenetic processes with their experimental and cross-fostering studies of rats. The quality of maternal care (e.g., licking and grooming behavior), which is associated with the offspring's stress response, physiology, and brain morphology, can be altered over multiple generations in the glucocorticoid (GR) receptor gene and have ensuing effects for the next generation's parenting behavior and stress regulation.

In addition to these animal studies, recent research with human development reinforces the importance of incorporating epigenetic processes and gene expression into a multiple levels of analysis perspective to understand how the environment can affect genetic, biological, and psychosocial processes leading to depression. In one groundbreaking study (McGowan et al., 2009), the brains of humans who completed suicide, some of whom had documented cases of maltreatment and others did not, were shown to have different gene expression in the hippocampus that was reduced through methylation. Importantly, this epigenetic effect was observed only in the adults who completed suicide and had been maltreated (i.e., GxE), not in those who committed suicide without abuse or in controls.

Summary—This section has briefly introduced various vulnerabilities to depression at multiple levels of analysis, ranging from those most easily accessed and measured (e.g., cognitive vulnerabilities, temperament), to the intermediate process/endophenotype level (e.g., information processing biases, biological stress reactivity, and neural activation and connectivity), and finally to various genetic influences (e.g., candidate genes, epigenetics and gene expression). Evidence was reviewed showing that each of these vulnerabilities is associated with depression, either as a main effect or through interplay with the environment. The following section provides some empirical examples of how these different vulnerabilities are related to each other based on research that has crossed these typically disparate levels of analysis.

Genetic influences and neural activity: Several exciting, innovative studies have examined connections between candidate genes and neural activity. Indeed, genomic imaging is a burgeoning new area (e.g., for review, see Hariri, 2009) that has emerged to explore these fertile relations (e.g. see Hyde, Bogdan, & Hariri, 2011, for an excellent review of GxE and neural imaging with implications for psychopathology). For example, research with adults has shown that 5-HTTLPR is associated with greater amygdala activity to negative emotional faces (see Munafo, Brown, & Hariri, 2007 for review) as well as reduced functional connectivity in the amygdala-cingulate feedback circuit that is important for regulation of negative emotion (Pezawas et al., 2005) and in frontal-limbic pathway connections (Pacheco et al., 2009). The available research with youth likewise suggests significant associations between amygdala activation to negative affective stimuli and commonly investigated candidate genes, including 5-HTTLPR (e.g., Fortier et al., 2010; Lau

et al., 2009) and BDNF (e.g., Lau et al., 2010). 5-HTTLPR correlates with regions of association cortex that underlie attentional control, an aspect of EF (Thomason et al., 2010).

Genetic influences and biological stress reactivity: A variety of studies show that the short allele of 5-HTTLPR is linked to heightened sensitivity and stress reactivity, as operationalized in various ways (Caspi, Hariri, Holmes, Uher, & Moffitt, 2010; McGuffin, Alsabban, & Uher, 2011; Thase, 2009). For example, girls carrying the S allele of 5HTTLPR exhibit elevated cortisol in response to a laboratory stressor (Gotlib, Joormann, Minor, & Hallmayer, 2008) and higher waking diurnal cortisol levels (Chen, Joormann, Hallmayer, & Gotlib, 2009). Other studies have shown that MAOA in interaction with COMT is associated with cortisol stress response differentially for boys versus girls (Bouma, Riese, Doornbos, Ormel, & Oldehinkel, 2012; Jabbi et al., 2007). Last, short allele carriers of 5-HTTLPR with high morning cortisol levels were most likely to experience a depressive episode (Goodyer, Bacon, Ban, Croudace, & Herbert, 2009; see also Goodyer, Croudace, Dubridge, Ban, & Herbert, 2010, with 5-HTTLPR and BDNF).

Genetic influences and biased information processing: Several studies suggest that 5-HTTLPR is associated with attentional bias to negative emotional stimuli (Beevers, Gibb, McGeary, & Miller, 2007; Beevers, Wells, Ellis, & McGeary, 2009; Perez-Edgar et al., 2010) and memory biases among children (Hayden et al., 2012). Other research suggests that BDNF is associated with rumination in healthy adults (Beevers, Wells et al., 2010), although the pattern of association may be complex and vary by age (Hilt, Sander, Nolen-Hoeksema, & Simen, 2007). Other research suggests that rumination is linked with BDNF only in the context of stress (Clasen, Wells, Knopik, McGeary, & Beevers, 2011) or maternal depression history (Hayden et al., 2012).

Neural activity and biased information processing: Various studies with adults have examined associations between information processing (attention and memory) tasks and different patterns of neural circuitry. Attentional bias was associated inversely with activation in lateral PFC, and interestingly, this effect was observed only among those carrying the short allele of 5-HTTLPR (Beevers, Pacheco, Clasen, McGeary, & Schnyer, 2010). Other research suggests interesting potential neural links to rumination and difficulties with perseverating on negative emotional material (e.g., Berman et al., 2011; Cooney, Joormann, Eugene, Dennis, & Gotlib, 2011; Eugene, Joormann, Cooney, Atlas, & Gotlib, 2009). Last, a handful of other studies have investigated neural activation in relation to depression-related categorization and memory biases (Chan, Harmer, Goodwin, & Norbury, 2008; Ramel et al., 2007; Wolfensberger et al., 2008) as well as selective attention (Mannie et al., 2008).

Biological stress reactivity and cognitive vulnerabilities: A few studies suggest that cortisol is associated with explicit self-reported cognitive vulnerabilities. Rudolph and colleagues (2011) found that anticipatory cortisol during a social challenge task predicted rumination and depressive symptoms 1 year later among children who experienced peer victimization. Kuehner and colleagues showed that rumination is associated with basal

cortisol among adults (2007) and with cortisol response after mood induction only among vulnerable adults (2009).

Other possible links in this hierarchical, multiple levels of analysis model (Figure 1) have not been thoroughly investigated. For example, neither the degree to which information processing tasks relate to biological stress reactivity nor neural activity associates with biological stress reactivity has been investigated. These, and other underinvestigated, links offer promising areas for future research to flesh out the degree to which the different factors and processes outlined in this multiple levels of analysis model cohere and connect. Finally, although many cross-level connections in this emerging model have been examined, fewer studies have investigated how these cross-level associations contribute risk to the development of depression or function differently in depressed relatively to non-depressed individuals.

METHODOLOGICAL AND CONCEPTUAL RECOMMENDATIONS AND CONSIDERATIONS WHEN CONDUCTING MULTIPLE LEVELS OF ANALYSIS VULNERABILITY RESEARCH

Up to now, I have advocated that future research adopt a multiple levels of vulnerability perspective, have conceptually discussed some of these risks, and reviewed some evidence in support of each vulnerability and their potential integration. This section introduces some methodological and conceptual issues and questions to consider when conducting multiple levels of analysis research. Several of these require additional attention beyond those typical methodological recommended approaches (e.g., multiple methods and informants) used in the standard single level-of-analysis vulnerability investigation.

Conceptualizing multiple vulnerabilities: Articulating and testing clear models

It is essential that future research endeavors consider how putatively different vulnerabilities, across different levels of analysis, relate to each other and determine what are the most appropriate conceptual models for these vulnerabilities. There is a strong need for multivariate research on a host of different risks and processes across multiple levels of analysis to chart and place these multiple influences into the relevant multivariate nomological network space for depression vulnerabilities across development.

A primary question when using a multiple levels of analysis perspective is determining whether the different risks and processes are redundant with one another and merely mark the same vulnerability, or whether these different factors represent relatively distinct risks and processes. After all, if the architecture and structure of depression vulnerability reveals the former (different labels marking the same latent vulnerability), then it would seem most efficient, economical, and clinically practical to simply measure the easiest and cheapest marker of this single risk. Moreover, as noted by Cronbach and Meehl (1955), “confidence in a theory is increased as more relevant evidence confirms it, but it is always possible that tomorrow’s investigation will render the theory obsolete.” Future research may reveal that certain risks are redundant with other risks, at varying levels of analysis, and if so, such data would importantly advance a more parsimonious theoretical and empirical knowledge base.

While not much empirical research has systematically investigated the multi-level structure of various vulnerabilities, most evidence suggests that the different vulnerabilities articulated in the multiple levels of analysis vulnerability model (Figure 1) are, in fact, factorially independent and do not entirely overlap. First, as the evidence reviewed earlier on the correspondence between different vulnerabilities across levels shows, many of these various factors and processes (e.g., genetics, neural activity, information processing, etc.) are moderately correlated, but not so strongly to suggest that one influence is entirely redundant with another. Second, factor analytic research examining the structure of cognitive and personality vulnerabilities with young adults (e.g., Hankin, Lakdwalla, Carter, Abela, & Adams, 2007; Joiner & Rudd, 1996) and youth (Adams, Abela, & Hankin, 2007; Gotlib, Lewinsohn, Seeley, Rhode, & Redner, 1993, but see Garber, Weiss, & Shanley, 1993 for exception) suggests that the core cognitive risks are factorially separable, albeit moderately intercorrelated, from each other and from NE. Finally, other research demonstrates the independence between explicit, self-reported cognitive vulnerabilities and implicit information processing biases (e.g., Gotlib et al., 2004), and theoretical models have been articulated to illustrate how explicit and implicit cognitive vulnerabilities at different levels of analysis can culminate in depression (e.g., dual-process models; Beevers, 2005).

Additionally, future research can address the intriguing, but unanswered question, of whether the underlying factor structure of depression vulnerabilities changes substantially across development. It is conceivable that the hierarchical organization and factor structure among different vulnerabilities changes and manifests differently across time and development. For example, the orthogenetic principle of development (Werner, 1957) states that organisms progress from a relatively undifferentiated state to a relatively more complex, distinguishable organization over time. This would predict that younger individuals may not exhibit as many empirically distinct and theoretically separable vulnerabilities as may be identified among adults and as theoretically specified in originally adult-based vulnerability models. Rather, children may be more likely to exhibit an undifferentiated “lump” of fewer, simpler vulnerabilities (e.g., a single broad vulnerability) earlier in childhood, and these vulnerabilities then become more differentiated risks that emerge and stabilize later in adolescence. Future research examining these core questions can importantly advance basic knowledge necessary for a taxonomy of depression vulnerabilities across multiple levels of analysis. Such answers can have important translational implications for what factors and processes to target and when in developmentally sensitive interventions.

Different Conceptual Models of Depression Vulnerabilities—Presuming that the fundamental, prerequisite research has established a taxonomy of depression vulnerabilities that exhibits some degree of factorial independence, then explicit articulation and consideration of different conceptual models that may provide the most accurate representation of the multiple levels of analysis combination of these risks is needed. While there are likely many potential conceptualizations that could characterize different combinations of risks, three meaningfully different conceptual approaches toward conceptualizing the relation among various vulnerabilities across different levels of analysis are articulated here: additive, multiplicative, and weakest link (see Abela & Hankin, 2008b, for greater discussion).

The *additive approach* assumes that an individual's degree of vulnerability to depression depends upon the ultimate *balance* among his/her vulnerability and protective factors. Vulnerability factors exhibit a cumulative effect with the presence of each additional risk leading to a greater degree of risk, whereas, protective factors do the opposite (presence of each additional protective influence subtracts risk). This approach assumes the factors work independently of one another (this is another reason for demonstrating factorial independence among vulnerabilities) and are weighted relatively equally. Thus, an individual with three vulnerabilities (e.g., high negative cognitive style, high NE, and attentional bias to sad faces) should exhibit greater risk than an individual with two vulnerabilities (e.g., average negative cognitive style, high NE, and HPA axis dysfunction). Moreover, protective factors can counterbalance against vulnerability factors, so the additive approach would predict that an individual with two vulnerabilities (e.g., high rumination, memory bias, and average neural activation) is equally at risk as someone with three vulnerabilities and one protective factor (e.g., genetic risk, HPA axis dysregulation, high rumination, and high PE as protection). Note that the additive approach is highly similar to Rutter's (1977) classic research on indicators of adversity (e.g., family conflict, social class, maternal psychopathology) in which the additive summation best predicted risk to psychopathology.

Next, the *multiplicative approach* posits that the vulnerability factors will interact synergistically to potentiate the stress-depression relation such that the greatest increases in depressive symptoms following increases in stress will be observed in individuals possessing both (or more) vulnerability factors. For example, in the temperament vulnerabilities reviewed earlier, individuals with high NE, low PE, and low EC may be expected to experience the highest levels of depressive symptoms. Although the multiplicative approach has proven useful in examining the integration and cross-level connection of any given *two* or *three* models of vulnerability to depression, such an approach can become increasingly cumbersome, both theoretically and methodologically, when attempting to integrate across a more extensive range of vulnerabilities. As the pool of vulnerabilities across levels increases, the precision of the hypotheses can become so exact that only individuals possessing the complete "depressogenic profile" would be expected to exhibit increases in depressive symptoms. Considerable sample sizes would be needed to have sufficient statistical power to meaningfully test such increasingly higher-order interactions (e.g., high NE x low PE x low EC x high stress x HPA axis dysregulation x genetic risk).

Finally, the *weakest link approach* (Abela & Sarin, 2002) posits that when multiple vulnerability factors and processes are expected to predict depression through a *similar mediating pathway* (e.g., overall cognitive vulnerability, including explicit cognitive risks and biased information processing), then an individual's most depressogenic vulnerability is the best marker of his/her true propensity for developing depression. Thus, when considering similar vulnerabilities (and this can be construed and postulated to be as narrow, e.g., explicit cognitive risks, or as broad, e.g., individual differences in reactivity to environment), this approach predicts that an individual will be as vulnerable to depression as his/her most depressogenic vulnerability makes him/her.

Conceptualization of interdependence with environment: Vulnerability or Susceptibility/Plasticity?

—It is essential to evaluate whether each particular hypothesized factor or process across the different levels of analysis operates best according to a traditional vulnerability concept (e.g., Zubin & Spring, 1977; Zuckerman, 1999) or a susceptibility/plasticity perspective (Belsky & Pluess, 2009). According to a pure vulnerability model, heightened level of risk is associated with only negative outcomes. In contrast, the differential susceptibility hypothesis (DSH) suggests the possibility that some individual difference factors and processes may confer increased sensitivity to the relevant environmental context, and outcomes can result “for better and for worse” depending on that environment. Under negative environmental contexts and high risk (or susceptibility) status, the vulnerability and DSH models make the same prediction that maladaptive outcomes may occur. Yet the DSH makes the novel prediction that positive outcomes can be attained when high susceptibility individuals experience positive environments. Thus, careful consideration of the meaning, definition, and operationalization of vulnerabilities (or susceptibilities) at different levels of analysis can yield important new insights into pathways leading to the development of depression, especially dependent on particular environments across different ecological contexts. These points are illustrated with respect to 5-HTTLPR as a genetic influence interacting with different environments, how such GxE processes may enhance risk to depression, and how these vulnerability conceptualizations can suggest very different underlying processes depending on the particular form of the conceptual model.

In Caspi and colleagues’ original, seminal investigation (2003) showing that 5-HTTLPR interacted with negative events to predict depression, this GxE was initially interpreted from the traditional vulnerability-stress perspective (e.g., Hankin & Abela, 2005; Zuckerman, 1999). More recently, this specific GxE, and 5-HTTLPR as a candidate gene, has been reframed and reconceptualized from a susceptibility/plasticity model (see Belsky & Pluess, 2009; see Caspi et al. 2010 for a related environment sensitivity model). Overall, there has been considerable controversy and mixed evidence surrounding GxE processes in depression, especially with respect to 5-HTTLPR and negative events (e.g., Karg et al., 2010; Risch et al., 2009). Unfortunately, many prior studies examining 5-HTTLPR x stress used cross-sectional designs with poor environment measures (Monroe & Reid, 2008; Uher & McGuffin, 2010), and this contributed to the mixed GxE literature. With inadequate measures and designs, misleading conclusions can be reached. To enable proper empirical tests of these different underlying conceptual models (e.g., DSH or vulnerability), rigorous and appropriate methodological approaches are necessary.

Guided by theory and evidence suggesting that 5-HTTLPR enhances susceptibility and sensitivity to one’s environment (Caspi et al. 2010), rather than only vulnerability to depression per se, Hankin and colleagues (2010) reasoned that youth carrying short 5-HTTLPR alleles would be more reactive to increases in stressful life events relative to their own typical stress level, consistent with an idiographic perspective (see Abela & Hankin, 2008b for greater discussion). From an idiographic conceptual and analytic model, it is within-person fluctuations and changes in the environment from the individual’s perspective (i.e., individual is experiencing high levels of stress relative to his/her own individual average level) that are most important. In contrast, from a nomothetic perspective it is

between-subjects differences in environment (i.e., individual is experiencing high levels of stress in comparison to the sample's, or population's, average stress level) that are most salient. A design with multiple waves of data is necessary to disentangle more precisely within-subjects from between-subjects effects (Curran & Bauer, 2011) and to investigate whether a GxE (or other vulnerability-stress processes) best conforms to an idiographic or nomothetic model (see Carter & Garber, 2011, for another illustration of these points with cognitive vulnerabilities to depression). However, all of the prior GxE studies used either cross-sectional or two-time point designs that only allowed for a test of GxE from a nomothetic approach; thus, an exacting test of DSH or vulnerability models could not be achieved. To remedy this gap, Hankin, Jenness and colleagues (2011) collected multiple waves of stress and symptom data to evaluate whether 5-HTTLPR interacts with stressors from an idiographic or nomothetic approach and evaluate whether the expected GxE best conforms to DSH or vulnerability. Consistent with the DSH model, multilevel modeling showed that there was a significant GxE effect for 5-HTTLPR when interacting with idiographic, but not nomothetic, stressors in the prospective prediction of depressive symptoms.

While this multi-wave study with idiographic analysis was consistent with a DSH, rather than traditional vulnerability, model, only half of the DSH conceptualization was examined. Recall that both vulnerability and DSH posit that negative outcomes (e.g., depression) would result when susceptible (e.g., short carriers of 5-HTTLPR) individuals experience negative environments (e.g., stress), yet DSH uniquely predicts that enhanced outcomes would be observed among susceptible individuals who have experienced positive outcomes. Only one study has tested the full DSH conceptualization and prediction. Hankin, Nederhoff and colleagues (2011) examined whether 5-HTTLPR functioned as a vulnerability or susceptibility gene in three independent studies of youth with measures of the environment (parenting) and an outcome (positive emotion) that fully ranged from positive to negative. Consistent with DSH, youth carrying the short allele of 5-HTTLPR experienced lower positive emotion under negative environment conditions (unsupportive, less warm parenting), and higher positive emotion was reported under positive environments (supportive, warm parenting).

Given this differential susceptibility GxE pattern, how might S carriers who experience negative parenting (and, likely, other negative environmental experiences) be at enhanced risk for depression? Establishing which youth are more likely to experience low positive emotion can inform mechanisms contributing to depression. Affective neuroscience and reward-processing models that implicate low positive affect and difficulties upregulating positive emotion act as potent risks to depression, including at the most observable, accessible (e.g., temperament [PE], emotion regulation) and neural levels (e.g., Davey et al., 2008; Davidson et al., 2009; Forbes & Dahl, 2005; Sheeber et al., 2009).

While this evidence suggests that 5-HTTLPR may conform best to a DSH perspective, the data reviewed earlier show that explicit cognitive risks correspond to a traditional vulnerability model (e.g., Abela et al., 2011; Carter & Garber, 2011). Thus, investigators need to evaluate carefully whether particular factors and processes function solely as

vulnerabilities or more subtle, differential susceptibilities, and examine which do so across the multiple levels of analysis².

In sum, future research is needed to examine how different potential individual difference risks at each level of analysis operate, what conceptual model best applies to that particular risk (e.g., susceptibility, traditional vulnerability), at what developmental stage (e.g., pre vs post puberty; cognitive, social, emotional level), and how these different individual difference factors may transact across levels—both within individual vulnerabilities and across environment contexts (e.g., parents, peers, romantic partners). Thus, examining individual difference factors and processes across multiple levels of analysis from fresh conceptual, theoretical perspectives promises to yield exciting new advances.

Methodological considerations to enable rigorous empirical tests of vulnerabilities

To allow for clear, thoughtful articulation of the conceptualization of vulnerability, it is necessary that methodologically sophisticated and developmentally appropriate measures, designs, and analyses are used (e.g., Rutter, 2005). Here I focus on using longitudinal designs, prospective follow-ups with systematically varied time courses, multiple measures of different aspects of psychopathology, and precise assessment of key phenomenological features of depression.

First, longitudinal designs should be used to more accurately and rigorously test developmental processes and establish temporal ordering among key variables. Unfortunately, the preponderance of research investigating many depression vulnerabilities (e.g., information processing biases, biological stress reactivity, neural activation and connectivity) has used cross-sectional designs. As a result, differentiating among basic alternative models relating putative risk factors to depression, including predisposition, concomitant, or consequence, cannot be accomplished. Thus, future research should collect at least two time points at a minimum, as a second assessment does not require substantially more resources relative to the significant advances in knowledge obtained. Still, while two-time point panel designs can provide the most basic demonstration that a vulnerability precedes later depression, such designs are not much more informative than simple cross-sectional designs (Curran & Willoughby, 2003). With designs involving multiple time points, various conceptual models with importantly different underlying processes involved can be rigorously tested and compared. These include: (1) idiographic versus nomothetic approaches to vulnerability-stress processes (Abela & Hankin, 2008b), (2) within versus between subjects effects (Curran & Bauer, 2011), (3) dynamic, bi-directional and transactional models (Sameroff & MacKenzie, 2003), and (4) developmental cascade models (e.g., Hankin et al., 2010; Masten et al., 2005). Finally, with multiple waves of data, the temporal ordering and time course of depressive symptoms and the covariation between vulnerabilities and environmental influences can be more rigorously investigated using modern data analytic approaches, such as growth curve modeling, trajectory analyses/ growth mixture modeling, and multi-level modeling (e.g., Collins & Horn, 2003; Singer & Willet, 2003).

²For this paper, I will continue to use the term “vulnerability,” although it should be clear that care needs to be taken to determine whether results are best understood from the traditional vulnerability model or a susceptibility model.

Second, by using longitudinal designs, especially multiple time points, future research can investigate developmental origins of different depression vulnerabilities. This topic remains an important, but relatively understudied goal and can be advanced by consideration of the interplay among vulnerabilities at different levels of analysis and a developmental systems theoretical perspective within an ecological framework. Prior research has examined some predictors of vulnerabilities and shown that negative environmental experiences, ranging from peer rejection and victimization to negative parenting styles and behaviors to frank child maltreatment, are associated with and predict the emergence of psychosocial risks, such as explicit cognitive vulnerabilities (e.g., Alloy, Abramson, Smith, Gibb & Neeren, 2006; Gibb, 2002; Hankin et al., 2009) and biased information processing (e.g., Gibb, Schofield, & Coles, 2009; Pollak & Tolley-Schell, 2003), as well as biological stress reactivity (e.g., Badanes et al., 2011; Cicchetti, Rogosch, Gunnar, & Toth, 2010; Heim, 2007; Lupien et al., 2009) and methylation of candidate genes (McGowan et al., 2009).

Related, future research would benefit from investigating the degree of stability and change in different vulnerabilities across the multiple levels of analysis along with factors and processes that contribute to the stabilization and crystallization of these vulnerabilities at different points across development. A fundamental assumption of most vulnerability theories of depression, whether psychosocial (Ingram & Luxton, 2005) or possible biomarkers and endophenotypes (Gottessman & Gould, 2003), is that the risk factors and/or processes are relatively stable, trait-like, and enduring. To exactly investigate degree of stability and change, several time points are required as a two-time point design is inadequate (Fraleigh & Roberts, 2005).

Some rigorous, multi-wave research has supported these hypothesized tenets of stability for cognitive vulnerabilities with adolescents (Hankin, 2008c) and young adults (Hankin, Fraley, & Abela, 2005) and for temperament dimensions (Caspi, Roberts, & Shiner, 2005). Basic test-retest reliability research has been conducted with methylation status for some commonly investigated candidate genes (Wong et al., 2010). Yet, no research has examined such fundamental properties, especially degree of trait-like stability, which is necessary for demonstrating that a hypothesized factor or process is in fact an enduring vulnerability, including biased information processing, cortisol indices for biological stress reactivity to challenge, or neural activation patterns.

The extant research suggests that explicit cognitive vulnerabilities (e.g., negative cognitive style, dysfunctional attitudes, and rumination) are already relatively stable and trait-like by early adolescence (e.g., Cole et al., 2008; Hankin, 2008c). Even for temperament and personality traits, which are constructs that are typically believed to exhibit strong continuity, it has been demonstrated that the degree of stability changes across development, including in the first few years of life (Lemery, Goldsmith, Klinnert, & Mrazek, 1999) and over decades in adulthood (Roberts & DelVecchio, 2000). Significant continuity co-exists alongside change (Caspi et al., 2005). Other than DNA allelic variation, all of the vulnerabilities across a multiple levels of analysis model likely exhibit both continuity and change across the lifespan. Future research is needed to continue to investigate when vulnerabilities across levels of analysis begin to coalesce and crystallize into enduring, trait-like risks to depression. Knowing when during development various

vulnerabilities begin to stabilize can provide important clues that can inform future research investigating the developmental origins of these risk factors and processes as well as offer essential information regarding developmentally sensitive periods that may be optimal for delivering preventions to forestall the crystallization of these risks into enduring vulnerabilities so that individuals' likelihood of developing depression later in the lifespan (e.g., during middle to late adolescence) is significantly diminished.

Third, when using longitudinal designs, there is a need for careful consideration of the length of time for the follow-up assessments. Unfortunately, there seems to have been little thoughtful, theoretical consideration to this critical design feature of follow-up length in most depression studies that have employed longitudinal designs. The time course in which different vulnerabilities to depression across levels of analysis relate to changes in depressed mood and symptoms across systematically varying time frames (e.g., minutes, to days, to weeks, to several months) is dramatically understudied. For several of the vulnerabilities reviewed in this paper (e.g., information processing, biological stress reactivity, neural activation, genetic influence), the majority of studies employed cross-sectional designs, so understanding the duration or persistence of depression across different time frames cannot be achieved. Thus, it is unknown whether information processing biases, for example, predict mood and symptom changes over a matter of minutes to hours, days, and/or weeks. Future research can examine the time course (e.g., on a distal to proximal dimension) of various vulnerabilities and how well these risk factors and processes predict depressed mood, symptoms, and episodes across systematically different time frames. This becomes important because evidence consistently shows that almost all individuals, regardless of vulnerability or clinical status, experience increases in negative affect/depressed mood immediately after stressful life events (Rottenberg, 2007; Weiner, 1985).

Future research that systematically examines the strength of associations between vulnerabilities and depression across varying time courses can explicate more carefully how and when various vulnerability factors and processes, at different levels of analysis, predict enduring elevations in depressed mood and symptoms for different youth. Such work promises to be valuable for understanding which etiological factors and processes contribute to the development of clinical depression (i.e., persistent, sustained negative mood and other symptoms) and its associated distress and impairment, in contrast to temporary, short-lived, normative increases in negative affect that would be expected after negative events and challenges. Future research can investigate the association between different vulnerability factors and the varying time course (from minutes to days to weeks to months) using different approaches, such as Ecological Momentary Analysis (EMA) for minutes to hours, to daily diaries for days, to prospective multi-wave follow-ups of symptoms and episodes for weeks to months. For example, prior research shows that cognitive vulnerabilities predict depressive mood and symptoms after stress exposure after a few days (e.g., daily diaries, Hankin et al., 2005; naturalistic stressors, Hankin et al., 2004; Metalsky, Joiner, Hardin, & Abramson, 1993), several weeks (e.g., Abela & Skitch, 2007; Hankin, 2008a, b), and over several years (e.g., Abela & Hankin, 2011; Carter & Garber, 2011; Hankin et al., 2004). While some research has investigated these critical questions from cognitive vulnerability and affective neuroscience (Davidson, Jackson, & Kalin, 2000) perspectives, future research can and should be extended to investigate different time courses and the maintenance and

intensification of negative affect into enduring, persistent clinical depression for multiple vulnerabilities.

Fourth, future research on depression vulnerability needs to routinely incorporate multiple measures of psychopathology. Comorbidity of depression with commonly occurring emotional and behavioral problems, especially anxiety, conduct problems, and ADHD, has been well-established (Angold, Costello, & Erkanli, 1999). However, the degree to which supposedly depression-specific vulnerability factors and processes predict prospective increases in depression, as opposed to these and other frequently co-occurring, symptoms, has been understudied. Some research has demonstrated that particular vulnerabilities, such as HT's negative cognitive style (e.g., Hankin, 2008a) or 5-HTTLPR (Hankin et al., 2010) interacting with stressors, predict depressive symptoms specifically relative to anxious or behavioral problems, whereas other cognitive vulnerabilities, such as RST's ruminative response style, more generally predict depressive symptoms along with other general emotional forms of distress, including eating pathology (Holm-Denoma & Hankin, 2010; Nolen-Hoeksema, Stice, Wade, & Bohon, 2007) and anxiety symptoms (e.g., Abela & Hankin, 2011; Hankin, 2008b).

The degree to which various vulnerabilities across multiple levels of analysis operate as relatively specific predictors of depression versus more general psychopathology (i.e., "transdiagnostic" factors; Nolen-Hoeksema & Watkins, 2011) can be informed by recent hierarchical, structural models of psychopathology among youth (e.g., Lahey et al., 2004; Lahey, D'Onofrio, & Waldman, 2009) and adults (e.g., Krueger & Markon, 2006). Future research is needed to examine how vulnerabilities across the multiple levels of analysis relate to which particular hierarchical level in these structural psychopathological models (e.g. rumination predicting an overarching internalizing distress factor; negative cognitive style predicting depression specifically, etc.). Certain vulnerabilities, across multiple levels of analysis, likely relate to differing levels in the structural hierarchy of common psychopathological symptoms. Knowledge of both transdiagnostic and depression-specific factors and processes can be better advanced by examining at which level of this hierarchical structural model the various vulnerabilities best connect.

Last, it is essential that research properly and fully assess key phenomenological features of depression, such as duration, severity, time to episode onset, and chronicity (e.g., first onset vs. recurrence; single episode versus first lifetime episode, Monroe & Harkness, 2005; 2011). Remarkably little attention has been paid to these critical phenomenological qualities. Indeed, few studies have considered and carefully investigated whether particular factors and processes predict anything beyond variability in depressive symptoms (typically self-reported depression questionnaire) or dichotomous onset of disorder at any point over the lifecourse.

Many of the studies in the depression literature have indiscriminately lumped together all individuals who have experienced a depressive disorder and have not explicitly considered and analyzed critical depression features (e.g. separating first onsets vs recurrent episodes). There are likely important differences in the processes and factors that may contribute to a first depressive onset (e.g., major stressful event; Lewinsohn et al., 1999; Stroud et al.,

2008), a recurrent episode (e.g., kindling or neural sensitization; Post, 1992), or potentially to both (e.g., cognitive vulnerabilities; Abela & Hankin, 2011).

This becomes especially salient depending on the age and developmental status of participants (e.g., child, adolescent, or adult) that depression investigators select, and such choices can have important implications and affect conclusions. With younger samples, especially children or early adolescents, it is most likely that first-onsets of depression are being measured, and thus, the factors and processes associated with risk to first onsets are under investigation. With middle to late adolescent samples, the preponderance of the sample is likely experiencing a first episode (given that most individuals experience their first depressive episode between ages 14–18; Hankin et al., 1998), although there will be an admixture of recurrences of those who had early-onset episodes in childhood or early adolescence. In contrast, with adult samples, it is most likely that investigators are studying an even more complex mixture of first-episodes, single recurrences, or multiple recurrences. Unfortunately, many investigations do not clearly report such essential facts and do not analyze their data accordingly. As a result, it is unknown precisely which aspects of depression phenomenology (e.g., first onset vs recurrence; single vs. first lifetime episode) the set of risk factors and processes under investigation relate to.

Future research on depression vulnerability across the lifespan requires an explicit developmental rationale for the age of participants, and investigators should provide descriptive statistics, and conduct moderator analyses, for the phenomenological features of depression in the sample. Just as any investigator should carefully select the measures and methods to rigorously test underlying hypotheses based on the theoretical model, thoughtful selection *a priori* of the appropriate developmental nature of the sample (e.g., pubertal status; cognitive, social, and emotional level), including other salient demographic characteristics (e.g., gender, race, ethnicity, culture, SES) is necessary so that the field can more accurately understand and have an accumulating knowledge base of which vulnerability factors and processes, across the different levels of analysis, relate best to first onsets, single recurrences, or multiple recurrent episodes (cf., Monroe & Harkness, 2005; 2011) as well as other features (e.g., severity, duration, etc.).

As one example, we (Technow, Hankin, Hazel, & Abela, 2012) have recently completed a 2-year multi-wave prospective study. We purposefully selected a group of early adolescents (ages 11–14 at baseline) and followed them every 3 months for two years into middle adolescence in order to examine the beginning of the surge of depression across the adolescent transition. Multilevel modeling analyses showed that baseline negative cognitive style interacted with idiographic increases in dependent stressors over the 2-year follow-up to predict elevations of depressive symptoms, consistent with prior cognitive vulnerability-stress studies. But this effect was particularly pronounced among the sub-group of youth with a prior history of clinical depression. Those youth who were previously depressed, had a negative cognitive style, and experienced more dependent stressors exhibited chronically high levels of depressive symptoms across the two years. By explicating considering important phenomenological depression features (i.e., depression history) into the design and analysis, we unearthed potentially important new knowledge that may inform which particular factors and processes predict and differentiate those youth on a chronic, recurrent

depression pathway versus those youth who may be on a more resilient path and recover from an initial depressive episode. Several longitudinal investigations using trajectory analyses (Costello, Swendsen, Rose, & Dierker, 2008; Galambos, Leadbeater, & Barker, 2004; Wickrama, Wickrama, & Lott, 2009) have now demonstrated different depression trajectories, including a high-stable/chronic, a low-stable, and often an initially high then decreasing group. Our results suggest that cognitive risk processes and ongoing dependent stressful environments are two, likely of many, processes that can predict which youth are more likely to constitute the high-stable/chronic group of youth. Prior research has shown there is a sub-set of depressed individuals who constitute the highly recurrent depressed group over the lifecourse (cf., Monroe & Harkness, 2011). Clearly, being able to identify which youth are at maximal risk for a chronic, recurrent trajectory of depression over their lifetime is important for informing basic etiological theories and enhancing translational knowledge.

Translational implications

What are some of the more applied, clinical applications of these future directions, especially as the majority of this paper has focused on the etiology of depression and vulnerabilities from a multiple levels of analysis perspective? Especially with respect to depression, the scope, burden, and pain of the syndrome are enormous. The National Comorbidity Study (1992; Kessler et al., 1994) and its Replication (2002; Kessler et al., 2008), spanning a 10 year period, showed overall no change in the prevalence of overall mental illness, an increase in the rates of treatment, but no improvement in decreasing disability (Kessler et al., 2008). While more adults are getting treatment, especially for depression, many receive non-evidence based interventions. Specifically for depression, while it may be positively viewed that 50% of adults receive treatment, it is disheartening that only 20% receive care that is deemed minimally adequate (Kessler et al., 2003). Moreover, when appropriate care is delivered with real-world adult patients as typically seen in clinical practice, the results are relatively disappointing: only 31% of patients remit (Warden, Rush, Trivedi, Fava, & Wisniewski, 2007). Overall, this indicates that many individuals receive sub-optimal care even when seeking treatment, and for those receiving appropriate care, many do not recover. Moreover, effect sizes in most evidence-based psychosocial interventions for adults (e.g., CBT, IPT) seem to have hit a ceiling in that ~65% in the intervention arm improve relative to ~40–50% response rate in placebo/control conditions (Kirsch, Moore, Scoboria, & Nicholls, 2002).

What are some possible solutions to the enormous need to improve evidence-based interventions? How can a basic child clinical scientific understanding of the etiological pathways leading to depression inform and advance progress in depression interventions? Here, I comment on two. These can be broadly construed as need for enhancing knowledge on mechanisms (i.e., mediation) as well as personalized treatment and prevention (i.e., moderation).

First, we know very little about the actual processes of successful treatment and mechanisms of action, especially in the best and most tested treatments for child and adolescent depression (e.g., CBT; see Webb et al., 2012, this issue). Of interest, there are recent reviews

in the adult psychotherapy literature indicating some of the cognitive and neural changes underlying successful treatment (e.g., DeRubeis, Siegle, & Hollon, 2008; Roiser, Elliott, & Sahakian, 2012), and these adult-based models and mechanisms could be applied downward to youth for relevant, developmentally appropriate examination of process. So, while CBT works for many youth, although clearly not sufficient numbers, as a field we do not know why CBT may work or what else could be done to improve various CBT treatments, whether by adding on elements or refining CBT processes (or other evidence-based treatments, such as IPT, Young & Mufson, 2008; or Behavioral Activation, Martell, Dimidjian, & Herman-Dunn 2010), to improve overall care. Such modifications could be accomplished through either (or both) reducing individuals' deficits (i.e. vulnerabilities) or enhancing their strengths (i.e., resilience). Knowing better the causal chain and etiological processes leading to depression, or those influences that enhance resilience, would surely inform the next generation of treatment development, including what treatment elements to include, whether from a deficit reducing or strength building perspective, and for whom.

Second, personalizing interventions (i.e., "what works for whom"; Insel, 2008; Shoham & Insel, 2011) is essentially a question of moderation and individual differences. Enhancing the basic knowledge on individual difference moderators from multiple levels, including genetic, neural, biological stress reactivity, information processing, interpersonal, temperament, cognitive control, etc., holds great promise for improving individualized treatment and prevention. The field of personalized psychological interventions is in its relative infancy, so there are presently few empirical examples available to demonstrate the strong potential of enhanced effect sizes when treatments and preventions are matched to the particular individuals' strengths and/or risks. One example comes from Gillham and colleagues (2012; this issue) who demonstrated substantially larger effect sizes for their CBT-based prevention approach for reducing adolescent depression when delivered to youth with high levels of initial hopelessness.

SUMMARY

This is an exciting time to investigate vulnerabilities to the development of depression among children and adolescents. Child clinical science and developmental psychopathology have produced many significant, impressive foundational theories and knowledge sets. Inquiry into vulnerability to depression among youth is on a very strong, firm footing based on considerable progress examining descriptive features, epidemiology, course, etiology, and intervention options over the past several decades. Building on this solid foundation, future research holds great potential to continue to yield important, significant, and innovative contributions to understand the different developmental etiological pathways that ultimately contribute to the first onset, maintenance, recurrence, and resolution, of depression over the lifespan and to translate this basic knowledge into new and refined clinical interventions that can reduce the significant global burden and distress of the syndrome of clinical depression (cf., Collins et al., 2011). Through future research efforts that seek to integrate knowledge on etiological risks and processes, across multiple levels of analysis, that contribute to the ontogeny of depression among children and adolescents, we, as developmentally informed clinical scientists, will hopefully have improved the degree to which we can metaphorically slay the ogre of clinical depression.

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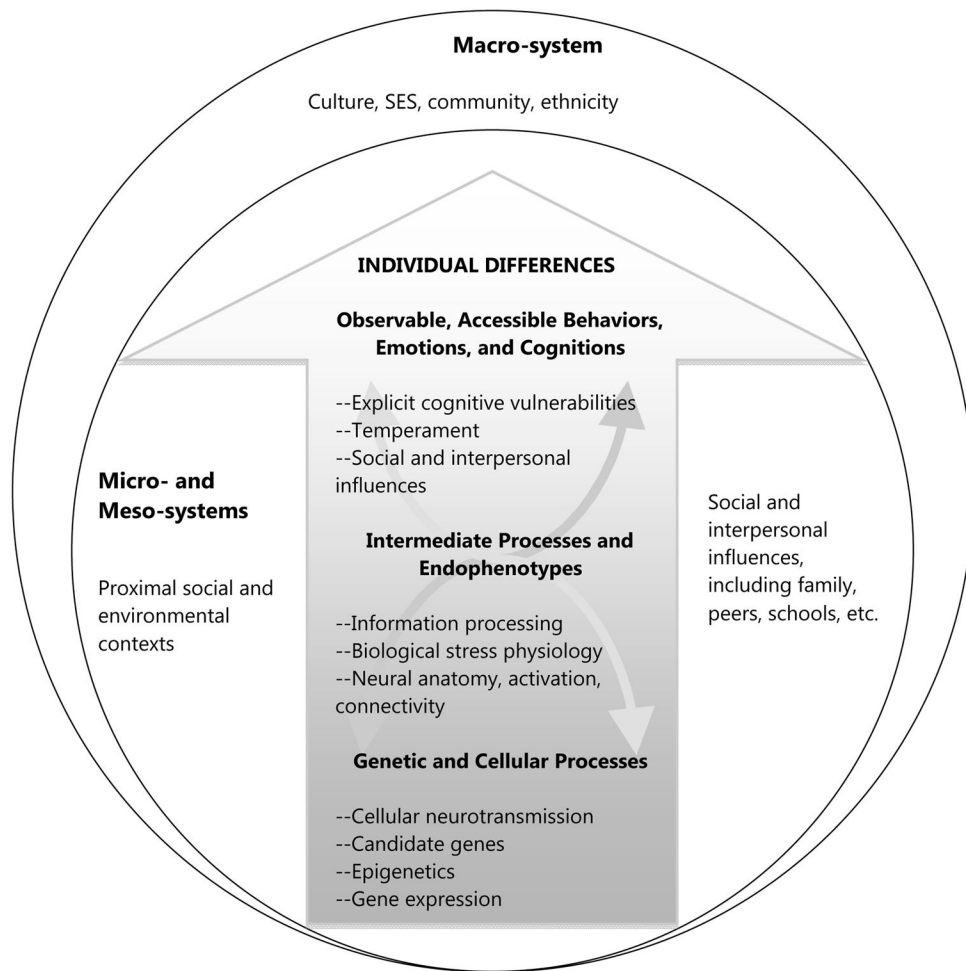


Figure 1. This conceptual example of a multi-level analysis model of depression is structured and organized from the NAS and NIMH perspective emphasizing multiple levels of analysis ranging from genes, to intermediate traits, to observable and accessible features.