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Risk Factors for Depression: An Autobiographical Review

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Abstract

I have been given a priceless opportunity to reflect on my career in the remarkably productive field of risk factors for depression. Psychological research on depression exploded in the early years of my work. I try to give an account of the choices and challenges, and reflect on the influences, some calculated and some serendipitous, that determined the paths I have followed. I focus mostly on the robust depression risk factors that have influenced my research, including dysfunctional cognitions, stressful life events and circumstances, parental depression, interpersonal dysfunction, and being female, and I cover some of what I did but also the influential work of others. This is a selective review of depression research in the past 40 or so years, noting some of the big developments that set the stage for the remarkable activity that continues today. In the conclusion, there is a brief statement of aspirations for future developments in our field.

Contents

INTRODUCTION

An invitation to write an autobiographically themed review of risk factors for depression is both an exceptional opportunity for reflection and a joyful trip down memory lane. I am well poised for this task not only because I have a lot of mileage in this field, but also because I have pursued a fairly broad and integrative perspective influenced by research in psychiatry and psychology, in unipolar

and bipolar disorders, and in adult and child populations, conducted in the lab and in the clinic and the community. I have also had the great good fortune to benefit from extraordinary teachers, colleagues, and role models who made singular contributions to clinical science. Reflecting on the more than 45 years of my scholarly training and research activities in this context, it is striking to think of the developments that have produced major changes in our knowledge of depression—but daunting to realize that some earlier challenges remain, even if in different forms. In this article, I hope to credit some of the key ideas, findings, and methods that most influenced me and that helped guide my interests and choices. My aim is to tell the story of research on risk factors for depression then and now and to try to illuminate what I see as key goals for future research on this topic.

A general orientation to some of the major accomplishments of the field of depression research in the time span of my career is warranted. There is no doubt that several big developments occurred in the 1960s, 1970s, and 1980s that stimulated the greatest wave of research on mood disorders that the field had ever known, overtaking, in those years, the popularity of topics in psychopathology such as schizophrenia and anxiety disorders. The vitality, excitement, and promise that came from those early efforts propelled me to join in and push on. I make some assertions that colleagues may disagree with, but my perspective is part of my story. Like siblings in the same family, we were all there, but we likely saw and lived events somewhat differently. In the sections below, I discuss what are, from my viewpoint, some of the big developments and singular achievements of those early years in the 1960s through the 1980s that set the stage for contemporary research on risk factors for depression.

Diagnostic Reliability

The development of the Research Diagnostic Criteria (Spitzer 1978), followed by that of the Diagnostic and Statistical Manual, Third Edition (DSM III; Am. Psychiatr. Assoc. 1980), changed our ways of diagnosing disorders. These changes moved the field of depression research toward greater focus on phenomenology and enabled the unipolar–bipolar distinction to be made more systematically (e.g., Depue & Monroe 1978), and the increased reliability of diagnoses permitted distinctions in clinical studies among schizophrenia, unipolar depression, and bipolar depression, as well as greater confidence in conclusions.

Epidemiology and the Discovery of High Rates of Depression and Evidence of Sex Differences

Diagnostic reliability also enabled the increased push to conduct large representative studies of adult disorders in the community, such as the Epidemiological Catchment Area studies (e.g., Regier et al. 1984), and also, over the years, enabled more sophisticated and larger US epidemiological and World Health Organization cross-national studies. Among the many contributions of these studies was the undeniable and thought-provoking evidence of major sex differences in depressive disorders. Furthermore, depression, which had once been seen in hospitals as a disorder of middle-aged women, was now seen as a huge and broad public health issue affecting those of all ages and socioeconomic backgrounds.

Rise of Antidepressants and Effective Psychotherapy

Although use of antidepressants started in the 1950s, the tricyclic drugs had numerous side effects. Both the development of greater diagnostic reliability and the discovery of the huge potential

market for drugs to treat depression contributed to the development and US Food and Drug Administration approval of the first selective serotonin reuptake inhibitor drug, fluoxetine, in 1987. Compared to earlier decades, when depression was seen as difficult to treat and having few available treatment options and depressed patients were seen as resistant and tedious, there was emerging enthusiasm for the use of pharmacotherapy and also for psychotherapy procedures that actually worked (e.g., cognitive therapy, interpersonal psychotherapy).

Discovery of Depression in Children and Emergence of the Developmental Psychopathology Perspective

Although a number of factors contributed to the "unmasking of masked depression" (Carlson & Cantwell 1980), the use of reliable diagnostic criteria for adults helped investigators to see that children could and did have depressive reactions. Increasingly, also, what had been termed adolescent turmoil was seen to include the symptoms of many teens with clinically significant depression. As more observers paid attention to youth depression, more and more investigators turned to the study of the onset of depression—in younger samples—which in turn helped promote the orientation of developmental psychopathology, the emergence of multiple risk factor models, and the integration of relevant variables across multiple levels of analysis (e.g., Cicchetti 1984).

Beck's Introduction of New Ways of Understanding Depression

I was personally galvanized by a book I read in graduate school, Aaron Beck's (1967) *Depression: Clinical, Experimental, and Theoretical Aspects*. Needless to say, his description of the phenomenology of depression—and particularly the ways in which depressed people thought about themselves, the world, and the future and how those interpretations influenced their mood, physiology, and behavior—presaged the beginning of a new way of viewing depression and of treating it (e.g., Beck 1967, Beck et al. 1979). The approach in the 1967 book, which was subsequently elaborated in later writings, proposed alternatives to the then-currently dominant models of depression—the medical model of depression as a disease and the psychodynamic and personality perspective, in which depression is simply a symptom of an underlying intrapsychic conflict or two. The cognitive emphasis in depression, in its various manifestations, has continued to be one of the most robust areas of research on risk factors for depression, as discussed below.

Early Studies of the Natural Course of Depression

A small handful of research studies helped to characterize the natural course of depression and its impact, illuminating a number of patterns that captured the interest and curiosity of young investigators such as myself. These studies included the Zurich studies (Angst 1986), the Collaborative Depression Study (Katz & Klerman 1979), and the early high-risk studies of effects of parental depression on children (e.g., Weissman et al. 1972, 1987) and the effects of depression on the lives of women (Weissman & Paykel 1974). These and similar studies taught us that adult depression is extremely debilitating and impairing across many adult roles, predicts depression and dysfunction in offspring, and is for many a recurrent or chronic disorder.

In the following sections, I trace the course of research on risk factors for depression in my own lab and in others' research over the past 40 or so years, principally focusing on cognitive vulnerability, stressors, parental depression, interpersonal dysfunction, and female gender as major risk factors.

RISK FACTORS FOR DEPRESSION: QUALIFYING COMMENTS

This article is a very abbreviated and limited review of major risk factors for depression. Most of the focus is on samples with major depression, and the intention is to acknowledge developments and trends in the field as seen from the vantage point of my own efforts. Because of the broad scope and limited space, many important findings, certain risk factors, and critical analyses of individual studies are not included. The article ends with a short commentary on issues of concern and, I hope, future development.

The term risk factor has been variously used to describe risk mechanisms as well as risk triggers, moderators as well as mediators, and causal risk factors as well as noncausal risk markers. This conceptual fog is pervasive, and while precision of terminology is vitally important (e.g., Kraemer et al. 1997, 2001), I proceed with the discussion to broadly characterize the emerging themes in risk research.

The past 40 years of research have identified most consistently the following depression risk factors: cognitions and cognitive processes; stressors; certain sociodemographic factors, such as being female; parental depression; and certain traits, behavior patterns, and dispositions. I note that each of these risk factors has biological and genetic correlates, as well as research goals and developments, beyond my expertise; these are only briefly mentioned. Finally, with permission generously granted by the editors in their invitation, I cheerfully acknowledge that this list largely maps onto my own research preferences and output and is therefore highly selective.

COGNITIVE RISK FACTORS FOR DEPRESSION

One of the most venerable topics in the modern history of depression research in psychology is cognitive vulnerability, stimulated largely by Aaron Beck's (1967; Beck et al. 1979) views of depression. While most individuals react to adversities without significant depression, Beck observed that some individuals are characteristically prone to preferentially focus on and exaggerate the negative, especially around themes of loss and depletion. Beck hypothesized that depression is a disorder of biased thinking as well as of mood, with emotional, cognitive, behavioral, and biological symptoms of the depression syndrome arising from viewing the self, the world, and the future in excessively negative ways.

My college years at Stanford had been highly influenced by the growing cognitive revolution in psychology (represented at Stanford by Bower, Festinger, Bandura, Mischel, and others) and its emphasis in memory, social, personality, and clinical psychology on humans' emotions, perceptions, and constructions of the self, the world, and the future. The fact that human information processing was often demonstrated to be biased and illogical (but predictable) had crucial implications for emotions and behaviors, including those relevant to psychopathology and psychotherapy. Aaron Beck's ground-breaking observations specifically about depressed patients' negatively biased thinking stimulated some of my earliest clinically relevant research. I attempted to operationalize negative thinking in laboratory analog studies, naturalistic studies, and the development of a cognitive bias questionnaire (Krantz & Hammen 1979) and conducted studies testing or critiquing various concerns about different cognitive models, eventually publishing more than 20 empirical articles on depressive cognition.

I characterize the abundant research in the field on depressive cognition as evolving in three overlapping epochs, as described below.

Depressive Cognitive Bias in Content

In the 1970s and 1980s, especially, a newish breed of depression researchers in psychology began to operationalize and test cognitive models of depression, examining dysphoric affect associated

with negative memories, interpretations, response to feedback, predictions, and expectations (for reviews, see, e.g., Blaney 1986, Gotlib & Hammen 1992, Mathews & MacLeod 2005). In addition to Beck, Seligman (1972) had expanded his animal model of learned helplessness to apply to human depression, with many analog studies exploring motivational, cognitive, and emotional reactions to uncontrollable situations (e.g., Hiroto & Seligman 1975). The learned helplessness model was later reformulated as the explanatory (attributional) style model of depression (Abramson et al. 1978; for a review, see Sweeney et al. 1986) and then revised as the hopelessness theory of depression (Abramson et al. 1989).

Whether using questionnaire methods or more experimentally measuring facets of information processing such as memory, prediction, and decision-making tasks in the laboratory, the great majority of studies found that people who were currently depressed endorsed or displayed more negative content and patterns of cognition than those not currently depressed. However, concerns began to emerge. One concern was about aspects of the cognitive models, noting gaps and limitations in theoretical frameworks and how cognitive vulnerabilities operated. Another concern was growing awareness that many of the emerging methods of assessing depressive cognition were reflecting the state of depression rather than underlying vulnerabilities and risk factors (e.g., Hammen et al. 1986). Improved research methods, such as priming of sad mood by mood induction processes, were deployed (e.g., Scher et al. 2005), but there was comparatively little evidence that what was being measured was a stable vulnerability capable of predicting risk for future depression.

Depressive Information Processing

Motivated by the need for measures of vulnerabilities that were not largely measures of current mood, there was a growing interest in the use of methods, many derived from experimental cognitive psychology, to assess more automatic rather than controlled functioning involving depressive content and processes (e.g., Stroop tasks, dot probe tasks, self-reference encoding, and tasks of memory bias; Gotlib & Neubauer 2000). Gotlib & Joormann (2010) present a detailed review of information processing studies and conclude that depressed individuals, relative to nondepressed individuals, show increased elaboration of negative information, difficulties disengaging from negative material, and deficits in cognitive control when processing negative information (for further reviews, see Bistricky et al. 2011, Blaney 1986, Mathews & MacLeod 2005).

An aspect of depressive cognition that has emerged as a research topic in recent years is the processing of facial affect. Depressed individuals, relative to nondepressed individuals, generally maintain attention preferentially for sad faces and appear to have greater difficulties disengaging from such material (Bistricky et al. 2011, Bourke et al. 2010).

The great majority of research on this topic has been based on cross-sectional case-control designs, with relatively sparse use made of designs for testing whether cognitions are a causal risk factor. Promising exceptions are studies of children at risk for depression due to parental depression, where the cognitive patterns are evident when the children have not yet become depressed; these studies are described in the section titled Intergenerational Transmission of Depression.

Unfortunately, the challenge of testing the predictive association of cognitive biases and depressive information processing with depression outcomes in these high-risk samples has yet to be fully resolved, and more longitudinal studies are needed (for an exception, see Alloy et al. 2006). Conceptually, also, further research is needed to attempt to validate different models of cognitive bias and its functional association with depressive mood. For example, are neural and cognitive vulnerabilities stable, and do they trigger depressive reactions in the face of perceived stress, or does depressed mood in response to negative stimuli trigger neural processes that intensify the

symptoms of the depressive syndrome such that cognitive and neural patterns associated with depression would be observed only in the depressed state? These and related questions concerning mechanisms remain to be fully addressed.

Neural Correlates of Cognitive and Emotional Processes in Depression

Evidence of impairment of executive functioning in depression has long been noted, and a recent meta-analysis of over 100 studies confirmed significant differences in performance on various neuropsychological tasks between depressed cases and controls (Snyder 2013). In their review and meta-analysis of patients tested during depression and during symptom remission, Rock et al. (2014) found that significant decrements remained during remission, suggesting that cognitive performance is not directly related to mood state in patients. A review and meta-analysis by Foland-Ross & Gotlib (2012) concluded that cognitive deficits are not general, but rather are specifically consistent with negative bias and difficulty with cognitive control and disengaging from negative material.

With the advent of increasingly sophisticated neuroimaging techniques, many investigators have examined neural correlates of cognitive and emotional processing tasks among depressed patients. The results are difficult to characterize from study to study, with considerable variability in findings, imaging strategies, and analytic procedures. One recent large meta-analysis concluded that there was a lack of spatial convergence of results comparing patients and controls during cognitive and emotional processing tasks (Müller et al. 2017; but for commentary, see Barch & Pagliaccio 2017). Notably, however, the ENIGMA work group reanalyzed magnetic resonance imaging (MRI) scans from 20 research sites around the world according to a standardized protocol and found significant evidence of regional cortical thickness differences between adult depression patients (especially those with adult onset and first episodes occurring over age 21) and controls in the orbitofrontal cortex, anterior and posterior cingulate cortices, insula, and temporal lobes (Müller et al. 2017). These results are largely consistent with the difficulties in cognitively controlling and disengaging from negative material often found to be associated with dysfunctions in frontal areas such as the anterior cingulate cortex and dorsolateral prefrontal cortex (for a review, see, e.g., Disner et al. 2011).

Many groups have also reported subcortical abnormalities, such that negative cognitive biases are associated with prolonged amygdala activation in functional MRI studies (for a review, see Disner et al. 2011). Additionally, smaller hippocampal volumes have commonly been reported in MRI studies of brain structure in depressed patients, a pattern confirmed by the ENIGMA work group in its meta-analysis of subcortical brain volumes across many studies, finding significantly lower hippocampal volumes in the depressed group than among nondepressed controls. This finding was strongest among those with histories of recurrent depression and those with a young age of onset (i.e., under 21 years of age) (Muller et al. 2017). Reviews and discussions of interconnected structures and circuits and their bidirectional interactions have emerged frequently as the field and imaging methodologies have evolved (e.g., Davidson et al. 2002, Hamilton et al. 2012, Treadway & Pizzagalli 2014).

It is important to at least briefly acknowledge examples of emerging research strategies based on cognitive intermediate phenotypes of depression. One such phenotype is abnormal reward processing, signifying impaired behavioral and motivational indicators of reward learning and reward responsiveness in depression (e.g., Whitton et al. 2015). Another example is ruminative response style, a coping strategy that could also be characterized in part as a dysfunctional and depression-inducing style of repetitive thinking about one's low mood and problems; Disner et al. (2011) summarizes the features and neural correlates of this response style.

STRESS AND DEPRESSION

Although I began my career in depression research studying cognitive bias, that interest was diverted very early, in part because I received a request to review a new book that became a landmark study on stress and depression. George Brown & Tirril Harris's (1978) *The Social Origins of Depression* had the effect of affirming my growing interest in the stressors occurring in individuals' lives and the prospect that, in many cases, the negative events themselves, perceived realistically—and not simply distorted cognitions about the events—were triggering depression. In the late 1970s and early 1980s, I began to include measures of life stress in my studies of depressive cognition, looking to learn about how individuals construed their real-life negative events and how those events and the cognitions about them predicted the course of their depression (e.g., Gong-Guy & Hammen 1980, Hammen 1978, Hammen & Cochran 1981, Hammen & DeMayo 1982). I was increasingly aware of the limitations of lab and questionnaire measures of depressive cognitive content and comparatively less interested in the interior workings of the depressive mind than in the challenging life situations addressed with ineffective coping skills and resources. Cognitive factors are critical, to be sure. There is no doubt that it is the environment as construed that is the proximal trigger of depression, and individuals will view some negative experiences as having more personal significance than other events. In terms of focus, however, I fixed my attention on the life and social interactions of the depression-prone person and the extent to which and ways in which certain vulnerabilities and risk factors led, in the face of stressors, to depression in some people but not others. Stress as a variable in depression research has led my program in many new directions, some of which I discuss briefly below. My personal opinion is that understanding the role of stress and how it eventuates in depression is the central challenge in understanding the etiology of most forms of depression (Hammen 2015).

Assessment of Stressors

Stress measurement is a central challenge that, unfortunately, has been met by most depression investigators (who nominally operate in a diathesis–stress conceptual framework) by simply omitting stress assessment from their protocols or inferring it (if they think of it at all). Despite the fact that checklists are inexpensive, their use, with subjective ratings of the severity of recent stressors, has been called worse than nothing at all (Harkness & Monroe 2016) because they provide misleading information by confounding self-rated severity with symptoms, obscuring critical differences between respondents in the meaning of the same item, and having limited coverage of and omission of items of unique personal significance. We can simply ask people to report on how much stress they perceive they are experiencing, but this will be highly confounded with depression. Thus, subjective perceptions tell us little about what actually occurred or whether timing of onset of depression can validly be tied to the triggering effect of a negative event, and they fail to address relevant issues such as the differential impact of stressor content and magnitude and the relevance of the stressor to the course of the disorder.

Inspired by interview methods reported by Brown & Harris (1978), I devised the UCLA Life Stress Interview to assess the context in which each stressful event occurred for an individual; this contextual information provides a basis for independent judges to make objective and reliable ratings of the impact for the typical person in the same circumstances (e.g., Hammen et al. 1985, Hammen et al. 1989b). We eventually expanded the procedure to include children and adolescents (Daley et al. 1997, Hammen et al. 1988, Rudolph & Hammen 1999), and also elaborated interview methods of assessing chronic stress, as operationalized by ongoing conditions in the key roles of individuals (e.g., Hammen et al. 1987a, Hammen et al. 1992).

Stress as a Risk Factor for Depression

In community samples, more than 80% of individuals who meet criteria for clinically significant depression have experienced a recent major life event or ongoing stressor (Brown & Harris 1989); these rates are also high for clinical samples (e.g., Brown & Harris 1989, Kendler et al. 1999, Mazure 1998). Importantly, although, according to cognitive models, subjective but biased perceptions of stress can theoretically trigger depression following even a minor or imagined event, these studies clearly demonstrate that the great majority of clinically significant depressive episodes are triggered by objectively severe stressors.

Two additional forms of stressors are critically important in depression. Although chronic stress is an important variable in many animal analogs of distress, it has been relatively neglected in depression. I argue that it is present and exerting its influence even if it is not measured, and often, studies of acute life stress are actually confounded by unmeasured chronically stressful conditions in various roles, such as marital, parental, financial, and occupational functioning (see Hammen 2016, Hammen et al. 2009). Also, there has been extensive interest in assessment of exposure to stress in early childhood, as typically assessed retrospectively across multiple items (such as emotional, physical, or sexual abuse; exposure to family violence; parental criminality; and parental substance abuse or mental illness) or in relation to more specific events, such as maltreatment, and the relationship of these events to depression (e.g., Green et al. 2010, Kessler et al. 2010, Lindert et al. 2014).

Most stress research in the past few decades has turned from replicating the impact of stress to tests of diatheses that promote vulnerability and therefore serve as moderators or mediators of the stress–depression association. This research is far too voluminous to cover in this review, but some of these vulnerability factors are major risks for depression and are briefly covered in this article, including parental depression; cognitive factors, as discussed above; sociodemographic factors, such as female sex; and certain traits and interpersonal styles, such as neuroticism, ruminative response style, and insecure attachment.

Stress Generation

It turns out that the diathesis–stress model of depression is woefully inadequate because it is unidirectional, with stress predicting depression in those with the diathesis. It seemed apparent that the reverse is also true: Depressive people cause stressful life events. Stressors may occur to an individual for random reasons, but many life events are not random. I first tested this hunch in samples of unipolar depressed, bipolar, medically ill, and well women in a longitudinal study of risk to children and found that the women with histories of unipolar depression had significantly higher levels of negative events to which they had at least partly contributed (dependent events), especially dependent events with interpersonal content, compared to women in the other groups (Hammen 1991b). The groups did not differ in rates of independent life events. I further found that these events commonly occurred when the women were not in a depressive episode; event occurrence was not simply a consequence of being in a depressive state. I called the phenomenon stress generation (Hammen 1991b), and my findings have now been replicated extensively in depressed or at-risk adults, children, and adolescents (for reviews, see Hammen 2006, 2018; Liu 2013; Liu & Alloy 2010). More recently, I expanded the concept of stress generation to include the creation of or selection into adverse environments that heighten the probability of continuing acute and chronic stress. For example, teens with histories of depression, compared to nondepressed youth, more frequently select romantic partnerships in which severe interpersonal violence occurs or elect to give birth before age 20, typically without a job or partner (Hammen et al. 2011, Keenan-Miller et al. 2007)—both situations that may promote further depression and dysfunction.

Is stress generation specific to depression? Conway et al. (2012a) used latent variable modeling in a large community sample containing both youth at risk for depression and those not at risk to explore the contributions of transdiagnostic internalizing and externalizing factors, as well as syndromes specific to stress occurrence. Once variance due to the broadband factors and to each diagnosis were partialled out, only unipolar depression contributed incrementally to the generation of interpersonal stress (but not noninterpersonal stress, such as achievement failures). Thus, history of depression uniquely predicts interpersonal stress generation.

What are the predictors of stress generation? Hammen (2018) provides a review of these predictors. In brief, cognitive vulnerability, such as negative cognitive style, predicts generation of interpersonal life events (e.g., Safford et al. 2007). Formative environmental experiences such as child abuse (e.g., Harkness et al. 2008) or attachment insecurity (Hankin et al. 2005) also predict stress generation, as do dispositions and relational styles such as excessive reassurance seeking (e.g., Shih & Auerbach 2010) and neuroticism (high negative emotionality) (e.g., Stroud et al. 2015). It should be noted that stress generation also involves genetic factors (e.g., Kendler et al. 1999) and gene–environment interactions (e.g., Harkness et al. 2015; Starr et al. 2012, 2014). Moreover, many of the predisposing vulnerability factors, such as rumination, neuroticism, and stress reactivity, also involve genetic factors with links to complex neural circuits relevant to emotional reactivity and cognitive control that are relevant to depression (e.g., Caspi et al. 2010, Conway et al. 2012b, Pezawas et al. 2005).

How does stress generation work? In a daily diary study of nondepressed women in committed romantic relationships (Eberhart & Hammen 2009), behavioral instances of maladaptive relational styles, such as insecure attachment (e.g., "I worried that my partner will not want to stay with me") and excessive reassurance seeking ("I found myself asking my romantic partner how they truly feel about me") were recorded daily for 2 weeks. Also, romantic conflict events were recorded daily. As predicted, maladaptive relationship style behaviors predicted daily romantic strains and romantic life events 4 weeks later. The link between interpersonal style and depression level after 4 weeks was mediated by romantic conflict stress generation (Eberhart & Hammen 2010).

There are three main reasons why the phenomenon of stress generation is important. First, it predicts a continuing cycle of depression–stress–depression that largely ensures chronic or recurrent depression (Davila et al. 1995; Hammen et al. 2004b, 2012; Rudolph et al. 2009; Shapero et al. 2013). Second, continuing patterns of depression predicting stress lead to long-term continuity of stress exposure and accumulated stress burden or allostatic load (e.g., McEwen 1998, McEwen & Morrison 2013), which has long-term physical as well as mental health consequences. We demonstrated continuity of stress exposure from birth to age 15 (Hazel et al. 2008), to age 20 (Hammen et al. 2012), and to age 30 (Hammen & Brennan 2016).

Third, stress generation exposes others in the family to high levels of stressors—such as marital conflict and instability and problems in parent–child relationships—as well as to fallout from the depressed parent's frequent financial, work, and health events. An example is the intergenerational transmission of depression, discussed in the section titled Intergenerational Transmission of Depression.

Stress Sensitization

The study of childhood and adult patterns of stress also contributed to the questioning of another limitation of the diathesis stress model of depression: It is too static, implying an invariant association of the effect of stress on depression over time and course. In fact, increasingly, research has shown a dynamic, changing relationship between stress and depression over the course of the disorder. Post (1992), the first to discuss this kindling or sensitization process, noted that patients

with mood disorders tend to have stronger associations between a stressor and their first episode than between the stressor and their later episodes. This pattern has largely been confirmed for unipolar depression (Kendler et al. 2000, Monroe & Harkness 2005, Stroud et al. 2011). We found that early exposure to adverse conditions in childhood lowers the threshold of stress magnitude required to trigger a major depressive episode (e.g., Hammen et al. 2000). Exposure to adverse conditions in childhood sensitizes individuals to be more likely to experience major depression following past-year stressful life events (e.g., McLaughlin et al. 2010). Research continues on mechanisms of stress sensitization, which presumably occur through complex neurobiological, genetic, cognitive, and psychosocial processes.

Mechanisms of Stress Effects

The when, why, and how questions of stress triggering depression are vitally important to understand (e.g., Hammen 2015). I credit Gold et al. (1988, part 2) for encouraging this important line of research and for promoting an integrative research agenda. I acknowledge the massive amounts of conceptualization and research on dysfunctions of the hypothalamic–pituitary–adrenal axis and their neural consequences; genetic aspects of stress sensitivity, forms of gene–environment relationships, and epigenetic processes; and the developmental psychopathology of stress effects on brain, endocrine, and hormonal development. Others are much better equipped to discuss and pursue these important topics than I am.

INTERGENERATIONAL TRANSMISSION OF DEPRESSION

An important aspect of my pursuit of risk factors for depression has been the study of children of depressed mothers, which illustrates several choice points in my research career: the shift in emphasis from adult depression to children and adolescents and the use of a high-risk longitudinal design to further probe causal risk factors. It became clear in my early work and that of others that to understand the origins of depression, models of adult depression needed to be adapted for and tested in childhood and adolescence, when it is likely that risk and vulnerability experiences are taking place. It had long been noted that depression runs in families. To better address etiological factors and mechanisms, I was inspired by the high-risk research model, especially as represented in the field of schizophrenia research at that time, and also by the opportunity to meet Myrna Weissman, who encouraged my efforts to develop our first high-risk depression project in the 1980s. Weissman's landmark offspring study spanned many years, including a recent 30-year follow-up (Weissman et al. 1987, 1997, 2006, 2016). Weissman was also known for pioneering work on depression in women and its devastating effect on performance of typical roles, including those of parent and spouse (Weissman & Paykel 1974).

Thus, in the mid-1980s, my group and I undertook our first high-risk depression study, a 3-year longitudinal study of 8–16-year-old children of depressed, bipolar, medically ill, and well mothers in which we investigated the roles played by stress, parenting quality, and negative cognitions. A second study in the 1990s came about because of a serendipitous phone call from noted schizophrenia researcher Sarnoff Mednick, then at the University of Southern California. He had an opportunity for collaboration in Australia, and a postdoctoral researcher who was interested in studying children at risk for depression. Thus began my stimulating and fruitful second high-risk study, in collaboration with Patricia Brennan (Emory University), in which we joined the faculty of the University of Queensland and embedded an intensive direct interview substudy into their ongoing birth cohort study of health and development that they started in the early 1980s.

Another formative factor for me was the shift away from disease models of depression. Although some biological psychiatrists and geneticists were confident into the 1980s that someone would find a gene for depression or bipolar disorder, the groundbreaking biometric analyses of twin studies soon made it clear that, for depression, genetic effects are only moderate, with substantial contributions from the construct individual-specific environment (for a review, see, e.g., Sullivan et al. 2000). Eventually, such findings, along with the significant and extensive flood of research in psychology and psychiatry in the 1980s and 1990s, shifted views of depression. Depressive disease is not, in itself, inherited; instead, it was generally thought that individuals are born with, are exposed to, and acquire causal risk factors and mechanisms, such as temperament, cognitive and coping styles, reactivity to stress, and relational styles, that eventuate, through both environmental and biological processes, in depression.

MATERNAL DEPRESSION AS A RISK FACTOR FOR DEPRESSION

Being the offspring of a depressed parent, particularly a depressed mother, is a strong risk factor for depression. Beardslee et al. (1998) published a review of studies of children of depressed parents and estimated that, by age 20, the children had a 40% chance of a major depressive episode, a rate very similar to outcomes at age 20 in our longitudinal high-risk study of over 800 families (e.g., Hammen et al. 2008a). Goodman et al. (2011) meta-analyzed results from 193 studies of children of depressed mothers up to age 20 and concluded that about 68% of children of depressed mothers were worse off in terms of internalizing problems than the average child of a nondepressed mother. Studies also demonstrated that children of depressed parents had significantly higher rates of externalizing and other disorders and more cognitive, social-interpersonal, academic, and health difficulties (e.g., Hammen et al. 2008b, Lampard et al. 2014, Weissman et al. 2006; for a review, see Stein et al. 2014). Both sons and daughters of depressed mothers are affected, and larger effects are generally associated with younger ages of exposure to maternal depression and with more severe and chronic or intermittent depression (Goodman et al. 2011, Stein et al. 2014).

How Does Parental Depression Predict Offspring Depression?

Children of depressed mothers inherit not only genetic predispositions for depression but also risk factors typically correlated with depression: exposure to stressful conditions throughout their development; marital conflict and instability; maladaptive parenting; parents who modeled (and whose behaviors elicited in children) beliefs and cognitions expressing negative views of the self, world, and future; and dysfunctional coping strategies. Our first high-risk study hypothesized and found evidence for stress, parenting quality, and negative cognitions as predictors of youth depression (e.g., Gordon et al. 1989; Hammen et al. 1987a,b, 1990).

In our second high-risk study in Queensland, Australia, we collected a large array of variables through interviews and questionnaires with offspring, mothers, and fathers. We collected intensive direct interview data from the youth and parents, supplemented by questionnaire information from the mothers from pregnancy through early childhood and collection of offspring DNA in their early 20s. We explored topics such as long-term course of youth disorders, psychosocial predictors from birth, clinical and functional outcomes of youth and mothers, different aspects of associations between stress and depression, and predictors of resilient outcomes; tested complex models; and evaluated several gene–environment interactions. Some of the key themes in our research or that of others on offspring of depressed parents are discussed below.

Perinatal Depression Effects

Particularly in recent years, there has been an enormous focus on maternal depression occurring prenatally or postnatally, suspected to be especially disruptive of healthy development in the infant. Longitudinal studies, conducted mostly in high-income countries, reported higher levels of emotional, behavioral, and social difficulties in children of prenatally depressed women and women with postnatal depression (for a review, see Stein et al. 2014), especially those with chronically elevated symptoms (e.g., Cents et al. 2013). Perinatal depression is highly correlated with later and continuing depression in the mother.

Parenting Difficulties and Family Discord as Risk Factors for Depression

Considerable evidence of the effects of maternal perinatal depression on attachment insecurity in children suggest dysfunctional parenting as a key mechanism of children's adverse outcomes (Atkinson et al. 2000, Hayes et al. 2013, Martins & Gaffan 2000). This association between maternal depression and insecure attachment in children underscores the effects of depressive symptoms on impairment of parental sensitive and consistent nurturing. Such symptoms, as well as parents' underlying emotional, cognitive, and social vulnerabilities, impede parental warmth, responsiveness, monitoring, and discipline, which undermines children's well-being and effectiveness (Goodman 2007). Importantly, a depressed mother is typically a stressed mother, further eroding her attention, motivation, and organization. For infants and young children especially, environmental stress is funneled through the mother, and the quality of her care has an enormous impact on the child's development (e.g., Tang et al. 2014).

Depression associated with maternal withdrawal or harsh parenting has been a consistent theme in depression. Observational studies of depressed women with their infants and children, adult depressives' retrospective reporting of their relationships with parents, and studies of depressed children and their parents have all reported evidence of maladaptive parenting (e.g., Burbach & Borduin 1986, Chiariello & Orvaschel 1995, Lovejoy et al. 2000, Wang & Dix 2013).

Marital difficulties are strongly associated with parental depression (for a review, see, e.g., Cummings & Davies 2002) and are a contributor to family discord and children's disorders. For example, Hanington et al. (2012) found that marital discord partially mediated the association between parental depression and child outcomes, defined as emotional and conduct problems. Hammen et al. (2004a) found high levels of marital and child–parent conflict in families with a depressed mother; youth depression was especially likely under those conditions, but if conflict was low, then the youth were no more likely to be depressed than children of nondepressed mothers.

Multiple Risk Factor Models of Outcomes of Children of Depressed Parents

In view of substantial evidence of risk factors correlated with maternal depression, investigators have long espoused the consideration of and integration across multiple variables in longitudinal studies (e.g., Goodman & Gotlib 1999). Such complex models are, of course, enormously difficult to test due to the need for large samples, large costs, participant burden, and difficulty of retention. In recent years, there have been more and more such complex studies, and several have particularly emphasized parental depression, along with environmental and psychosocial factors such as family conflict and dysfunction and stressful conditions. A few examples are the studies conducted by Abela et al. (2005), Barker et al. (2012), Côté et al. (2009), Fergusson et al. (1995), Jaffee et al. (2002), Luby et al. (2006), Seifer et al. (1996), and Reising et al. (2013). For example, Hammen et al. (2004b) found support for a structural equation model in which maternal depression was associated with family and environmental stressors (including marital conflict), with both stress

and depression predicting poorer parenting quality, which in turn predicted less youth social competence, associated with youth stress as the proximal predictor of depression. These risk factors largely mediated the effect of maternal depression on youth depression.

Biological Contributors

In more recent years, high-risk projects have included genetic, neural, and neuroendocrine variables, along with various cognitive and psychosocial factors, although for the most part, complex integrative models have yet to be tested. In their high-risk study of adolescent daughters of depressed mothers, Gotlib and colleagues reported that daughters at risk for depression (but not yet depressed) showed cognitive information-processing vulnerabilities (e.g., Dearing & Gotlib 2009, Joormann et al. 2007) and neural patterns similar to those of their mothers (Chen et al. 2010, Gotlib et al. 2010). Other high-risk studies of children of different ages have also shown information-processing biases similar to those of depressed adults: selective attention to sad faces (Kujawa et al. 2011), reactivity to emotional stimuli (Burkhouse et al. 2014), and cognitive engagement and emotion regulation (Silk et al. 2006). Investigators have also observed abnormal cortisol activity in children of depressed mothers (e.g., Gotlib et al. 2015, Halligan et al. 2004). Badanes et al. (2011) reported that maternal depression, recent stressful conditions, and abnormal cortisol levels predicted internalizing symptoms in samples of preschoolers and school-age children.

In additional studies of neural activity, Dawson and her colleagues (2003; see also Forbes et al. 2006, Jones et al. 2000) found lower frontal activation in children of depressed mothers, and such brain activity, along with family stress and marital discord, mediated the association between maternal depression and children's behavior problems at age 3. Kujawa and colleagues have also found blunted reactivity to rewards in children of depressed (but not anxious) mothers in 9-year-old offspring (Kujawa et al. 2014), and the effect was moderated by maternal low levels of authoritative parenting (Kujawa et al. 2015).

INTERPERSONAL ASPECTS OF DEPRESSION

One theme woven through my research on risk factors for depression has been interpersonal predictors and consequences. Initially influenced by the work of Coyne (1976) on the negative impact of depression on others, potentially leading to rejection (e.g., Hammen & Peters 1978), I was also interested in Brown & Harris' (1978) theory of social origins of depression, in which depression in women is typically a response to negative interpersonal events, commonly compounded by low support from spouse or partner and often by childhood loss experiences. In the 1980s, I published a set of studies on specific vulnerability to interpersonal life events, notably the tendency of individuals, especially women, who endorse high levels of sociotropy (attaching great importance to maintenance of close bonds with others) to become depressed specifically as a consequence of relational loss or rejection (e.g., Hammen & Goodman-Brown 1990, Hammen et al. 1989a). My early high-risk research affirmed the likely influence of parent–child and marital difficulties as factors in children's development of disorder and impairment in families with depressed mothers (e.g., Hammen 1991a), and that study also led to the stress generation hypothesis and its emphasis on depressed individuals' contributions to interpersonal stressors and conflicts (Hammen 1991b). Ian Gotlib and I coauthored a book on depression, subtitled *Toward Cognitive and Interpersonal Integration* (Gotlib & Hammen 1992).

Based on empirical observations and conceptual developments, I came to hypothesize that depression in some of its forms is a disorder of interpersonal vulnerability and that impaired intimate relationships are stressors triggering depression (Hammen 1992, Hammen & Shih 2014, Rudolph

et al. 2000; see also Joiner & Timmons 2009, Slavich & Irwin 2014). Interpersonal difficulties are robust predictors and consequences of depression, and many other forms of vulnerability to depression (e.g., cognitive, emotional) are expressed in interpersonal contexts. In the sections below, I briefly and selectively review five types of research potentially supporting the social element of depression vulnerability and evidence of a potential interpersonal pathway to depression.

Dysfunctional Family Functioning

There is significant evidence that depressed adults, children, and adolescents—and those at risk due to parental depression—experience difficult family lives with marital discord and disruption and harsh and/or disengaged parenting. Whether gathered using direct observation of children and families or using retrospective recall, the evidence of family discord is strong (e.g., Burbach & Borduin 1986, Epkins & Heckler 2011, Goodman 2007, Keitner & Miller 1990, Parker 1983, Parker et al. 1995, Rapee 1997, Stein et al. 2014). Family dysfunction in relationships between parents and children and between spouses in families of depressed adults tends to continue even when the depressed individual is in remission (e.g., Hammen & Brennan 2002, Keitner & Miller 1990). Importantly, this dysfunction contributes to disorders in the offspring and to continuing recurrence or chronicity in depression (Hammen et al. 2004a, Keitner & Miller 1990, Silk et al. 2009). There is substantial evidence of the association between parental depression and insecure attachment in children (Brumariu & Kerns 2010). Notably, family dysfunction is a highly nonspecific predictor of psychopathology, but it is likely that particular elements of negative parenting behavior (e.g., affectionless control) portend internalizing disorders in part by promoting low self-worth and other depressive cognitive styles (Garber & Flynn 2001, Mezulis et al. 2006, Parker 1983).

Social Impairments in Depressed Youth and Children at Risk

Social difficulties in children have particular salience because of the developmental consequences of poor functioning. Depressed and high-risk children commonly have conflict in their relationships with parents and family members (e.g., Kim et al. 2003) and with peers (for reviews, see, e.g., Epkins & Heckler 2011, Rudolph & Clark 2001). Interpersonal difficulties across several social roles (family member, close friend, romantic partner, peer) were evident in depressed adolescents, especially among offspring of depressed mothers (Hammen & Brennan 2001), and such difficulties were predictors of recurrent depression before age 20 (Hammen et al. 2008a) and contributed to intimate partner violence in romantic relationships (Keenan-Miller et al. 2007), as well as lower relationship satisfaction in committed relationships at age 20 (Katz et al. 2013). In general, research supports bidirectional effects between social difficulties and depression (e.g., Hammen et al. 2014).

Stress Sensitization and Stress Generation in Relation to Interpersonal Content

As noted above, the research on stress generation confirms the specific link between depression and occurrence of negative life events with interpersonal content (e.g., Conway et al. 2012a). Stress generation is not just commonly associated with impairment due to states of depression, but also predicted by certain dispositions and interpersonal styles.

Dispositions and Interpersonal Styles

Considerable research has supported predictive associations both between temperament neuroticism and negative emotionality (NE) and depression and between low positive emotionality (PE) and depression (for reviews, see, e.g., Klein et al. 2011, Lahey 2009, Ormel et al. 2013). Although

these associations are not specific to depressive disorders, there are several ways in which NE and neuroticism (and low PE) may be vulnerability factors for interpersonally relevant depression. One is the link between NE and neuroticism and stress generation, with evidence that high NE is predictive of marital difficulties, conflicted relationships, and low social support (e.g., Lahey 2009), and low PE likely reflects depression-relevant reward-processing patterns (e.g., Hankin 2015). Ormel et al. (2013) concluded after their extensive review of the literature that neuroticism has a predictive relationship with disorders and may be linked to depression through genetic negative information-processing biases, heightened NE in the face of stress, stress generation, and ineffective coping styles (such as passive emotion-focused coping).

Insecure attachment cognitions and experiences commonly promote relationship distrust and dissatisfaction and demanding behaviors that likely annoy partners and create conflicts (e.g., Eberhart & Hammen 2009). Similarly, interpersonal styles reflecting excessive reassurance seeking and rejection sensitivity are substantially related to depression (Downey & Feldman 1996, Joiner & Metalsky 2001, Joiner et al. 2006, Starr & Davila 2008). Stewart & Harkness (2015) found that excessive reassurance seeking in women predicted a shorter time to boyfriend-initiated breakups in a 1-year follow-up. In general, targeted rejection life events, such as being spurned in a close relationship, are especially likely to provoke depressive responses (Slavich et al. 2010); some individuals may be genetically more liable to rejection-related depression (Slavich et al. 2014).

Neural Aspects of Social Functioning in Depression

Social cognitive neuroscience and related fields have seen enormous increases in research on neural contributions to psychopathology. Kupferberg et al. (2016) reviewed elements of the research that applies to depression within the framework of the Research Domain Criteria (RDoC), including some 10 subcategories of the systems for social processes. Essentially all indicate some decrements in functioning and comparative differences between depressed and nondepressed participants—largely affecting the reward and cognitive control systems, as indicated by neural differences in particular regions of the brain during imaging. Examples of these decrements include social anhedonia, increased sensitivity to social rejection, mood-congruent bias in processing of emotional expression, and heightened reactivity to negative emotional faces. Kupferberg et al. (2016) concluded that social disturbances are pervasive in patients with major depression.

It might be argued that some of the features noted above could be developed into interpersonally relevant intermediate phenotypes with some specificity for depression, including rejection sensitivity (Downey & Feldman 1996, Slavich et al. 2010), social stressor reactivity, and stress generation (Harkness et al. 2015). Other models are also possible. For instance, Epkins & Heckler (2011) reviewed evidence of family and peer difficulties in children and argued for a cumulative social risk model of depression.

GENDER DIFFERENCES IN DEPRESSION

Most pathways to the study of depression point to sex differences, and the issue has influenced my research in countless ways since the beginning of my career (e.g., Hammen & Padesky 1977). Because sex differences emerge in adolescence (Nolen-Hoeksema & Girgus 1994) and largely affect women in their child-bearing years, the potentially unique predictors and experiences of depression in women have permeated my research efforts. I use the terms sex differences and gender differences interchangeably, per Kuehner (2017).

Any comprehensive model of depression needs to account for female sex as a major risk factor for depression. Adolescent and adult women have a 2:1 greater likelihood of major depression

than men, a ratio representative of virtually all countries that have been surveyed. The difference occurs throughout the adult age range (e.g., Seedat et al. 2009, Weissman et al. 1996). The lifetime risk for major depression in the United States is 21.3% for women and 12.7% for men, according to the National Comorbidity Survey (Kessler et al. 1993), and 17.1% for women versus 9% for men in the larger National Epidemiologic Survey on Alcohol and Related Conditions (Grant et al. 2005).

Why Gender Differences?

For the most part, research has explored whether the sex differences are artifacts of measurement and differential expression of symptoms, whether women have more risk factors, whether women are more sensitive than men to the same risk factors, and whether women's resources and coping strategies for dealing with stressors are less optimal than those of men. These issues overlap, and the research on the topic is enormous. I selectively mention some key findings and contemporary perspectives, and refer readers to excellent reviews such as those of our late colleague Susan Nolen-Hoeksema (e.g., 1990, 2001) and Kuehner (2017).

Biological factors such as sex hormones have been assumed to be contributory factors given the link between depression and certain phases of women's reproductive life: the emergence of the gender difference around the time of puberty, premenstrual dysphoric disorder and mood shifts during the premenstrual phase, postpartum depression, and depression during menopause and perimenopause. In general, however, complex associations among sex hormones, neurotransmitter systems, and neuroendocrine mechanisms, as well as contributing factors that are likely due to genetic, developmental, and environmental effects working together, defy simple conclusions. There are likely some women who are highly sensitive to hormonal fluctuations, and possibly some types of depression that are particularly related to hormonal processes, but the vast majority of women who experience typical reproductive phase–related changes in hormones do not experience significant depression (e.g., Martel 2013, Steiner et al. 2003). Recent research has shed light on the potential effects of female hormones and stress experiences on the emergence of depression in adolescence. Early maturing girls, for example, have higher rates of depression (e.g., Graber 2013), with hormonal effects interacting with adverse environmental experiences such as abuse and family discord (conditions that also predict early maturation), as well as issues of negative body image and changes in peer relationships (e.g., Rudolph 2014).

There is some evidence that adolescent girls and women experience more exposure to stressors and adverse conditions than males, contributing to higher rates of depression. There are several facets of adversity. Women have greater exposure to child sexual abuse, domestic violence, and sexual victimization (e.g., Barth et al. 2013, Stoltenborgh et al. 2015). Women also have stress in the form of disadvantaged status; they are poorer, have less power to control their own destinies, have lower-status jobs or roles and lower pay, and have less access to sources of acclaim and reward than men do. Women also tend to be more burdened with chronically stressful roles as caregivers, including dual roles that cause strain, such as those of worker and parent, spouse and worker, or single working parent. Furthermore, adolescent and adult women may be more likely to experience and have greater depressive reactions to interpersonal life events than males (e.g., Hankin et al. 2007, 2015; Harkness et al. 2010; Kendler & Gardner 2014; Rose & Rudolph 2006; Shih et al. 2006). Females' greater susceptibility to distress in the face of interpersonal failure and loss has long been speculated to result in part from culturally and biologically programmed tendencies to be more oriented than men to affiliative, nurturing roles with others; more likely to base their sense of self-worth on close connections with others; and more strongly affected by misfortunes in the lives of loved ones (e.g., Cyranowski et al. 2000).

Finally, a fairly recent emphasis in depression risk research is ruminative response style, a form of passive coping defined by repetitive efforts to think about emotional distress and its causes and consequences instead of taking active steps to solve the problems causing the distress. It is a response style that promotes, intensifies, and prolongs depression and is more common in females than males (Nolen-Hoeksema 1991, 2001; Nolen-Hoeksema et al. 2008). There is extensive interest in the neural correlates of rumination and its link to maladaptive cognitive style (e.g., Cooney et al. 2010).

Findings reported by Kendler & Gardner (2014) from a co-twin control design comparing brothers and sisters support the greater role of interpersonal factors in women's depressive disorders than in those of men. The authors examined the predictive effects of 20 lifetime risk factors and found gender differences in 11 of these factors. Women's depression was more strongly predicted by mostly interpersonal events: low parental warmth, neuroticism, divorce, low social support, and low marital satisfaction. Men's depression was more predicted by childhood sexual abuse, conduct disorder, drug abuse, prior major depression, and distal and dependent proximal stressful life events with financial, occupational, or legal content.

RISK FACTORS FOR DEPRESSION: CLOSING THOUGHTS AND FUTURE HOPES

Numerous unanswered questions remain in the specific domains of risk that I have covered, and leaders in each of these domains have frequently noted these questions, often in articles in the *Annual Review of Clinical Psychology* or other significant outlets; I do not specifically catalog them in this review. However, I briefly note some of my general concerns in the field of depression research, many shared and expressed by others, and I regret that this final section is, out of necessity, very brief. I acknowledge the influence on my comments of the voices of experts in recent years, whose wisdom, foresight, and eloquence certainly exceed my own.

Methodologically, depression's heterogeneity and comorbidity with other disorders continue to be great limitations to the consistency, coherence, and, ultimately, validity and utility of research findings. Improvements in methodology ushered in by transdiagnostic, RDoC, and continuous measures and by endophenotype strategies are all well worth trying. However, I argue that depression and the environment interact in a bidirectional and dynamically changing manner. Thus, focus on alternative phenomenological bases of sample selection must not distract from reducing or accounting for potentially crucial underlying heterogeneity in the course of the disorder, such as age of onset, prior episode history, and, possibly, developmentally maladaptive experiences in early life, among other factors that shape the neurobiological, genetic, and clinical features of depressive disorders. Perhaps one day we will have critical markers—genetic, neuroendocrine, neural, or behavioral—to refine groups and distinguish reliably among subtypes or profiles (a kind of RDoC on a different scale). There simply must be more ways to reduce heterogeneity of samples than those that rely on manifest symptom expression.

Methodologically, also, there is considerable recognition of problems due to small sample sizes and to a plethora of imaging protocols and data management strategies that make it difficult to compare studies, much less find consistent patterns and phenomena. I join the many calls for—and am pleased to see some movement toward—neuroinformatic tools and techniques for promoting standard protocols, data sharing, aggregation methods and opportunities, and statistical strategies that promote uniform guidelines and relevant procedures for increasingly complex designs. Such protocols are needed for more than just neuroimaging, neuroendocrine, and genetic assessments. There is also a critical need for further development of impeccably validated and easily disseminated tasks for various facets of the constructs, such as reward processing, emotion

processing, information processing, and stress reactivity—not to mention measures of environmental events and disruptive experiences and the countless psychological constructs intended to capture motives, cognitions, dispositions, and interactional styles. Many of these areas are underdeveloped, but researchers quite understandably reach for off-the-shelf tasks and measures to the point of reification. I personally would like to see much more conceptualization and development of interpersonal motives, traits, and behaviors, but virtually any widely shared scale, performance, or lab-based task should be unquestionably predictive of real-world behaviors, not to mention administered with scrupulous uniformity.

Conceptually, in my view, theories or conceptual frameworks about depression are remarkably sparse. I argue that the stress–depression link is a key to most depression (e.g., Hammen 2015), and yet many approaches to depression do not measure actual environmental stress—or even perceptions of stress—or conceptually and concretely map out how the processing of a negative experience turns into a set of negative emotions, cognitions, behaviors, and bodily symptoms and how the findings that are observed reflect depression rather than just stress reactions. It is true that most clinical scientists subscribe to complex frameworks with multiple levels of analysis [or more aptly, multiple lenses of analysis (Lilienfeld 2017) or integrative explanatory pluralism (Kendler 2005)]. There has been an important conceptual progression in our field moving from aggregations of risk factors to speculations about how the psychosocial and biological factors relate to each other and to the outcome, and there has also been a general acceptance of equifinality (multiple pathways to depression). We can all acknowledge the unlikelihood of a single model to account for most depression, but even a model for a specific phenotype would entail extraordinary complexity in articulating a comprehensive theory and then translating it into research with sufficient power to test many variables, especially over time. Theories that apply even solely to specific phenotypes (or subgroups) would necessarily require research that is not for the faint hearted and underfunded. Such efforts are likely to be limited to the patchy reductionism of building local linkages among different lenses of analysis, rather than understanding the whole ball of wax (see also Kendler 2005, Lilienfeld 2017). Still, for the most part, we do not even have clear conceptual models about whether (or which aspect of) depression results from stable underlying abnormalities, or whether negative emotions trigger abnormal responses. Additionally, with some exceptions, there are not adequate models of risk factors that are specific to depressive disorders. Finally, with apologies for simply repeating the obvious, a conceptual gap of enormous proportions concerns integration of developmental processes and developmentally informed hypotheses as they relate to depression.

Conceptual models are also constrained by research design problems. It would appear that a huge proportion of past and current research on risk factors is cross-sectional in nature, and the extent to which causal language creeps into results that are more likely to illustrate correlates or consequences of depression, rather than causes, is striking. Of course, early stages of new research goals and methods in clinical science typically start with description of current comparisons of cases and controls, but it is essential for maturing paradigms purporting to reveal risk factors for depression to actually make use of designs appropriate for testing causal relationships. Such designs are woefully limited, especially in cognitive and neuroimaging paradigms. I am a great fan of high-risk longitudinal designs, although I acknowledge their limitations. For instance, in our case, we were fortunate to have information collected contemporaneously from birth in our high-risk study, but unfortunately, we lacked the foresight, at the inception of study in the early 1980s, to include variables we would now love to have included. Obviously, prescience and the unlimited funding needed for top-tier risk factor research are in short supply. However, we simply must acknowledge that breakthroughs in understanding causal risk factors and their mechanisms require more deployment of appropriate causally informative research designs.

I end with a note on reductionism, echoing the many concerns expressed by Miller (2010), Lilienfeld (2017), and others about the illogical and harmful ways in which the headlong pursuit of the biology of psychopathology has resulted, at times, in the sloppy language or deep-seated belief in biological bases or underlying causes of disorder, attributed to neural structures and functions or molecular genetic and chemical characteristics. Some of the forms of reductionism (e.g., eliminative reductionism) presume the primacy of explanatory power of lower levels of (biological) description over higher levels, including psychological description (Lilienfeld 2007). Advances in our knowledge of the brain and genetics and their relationships to behavior and emotions are undeniably exciting and vitally important, but they are only part of the causal chain of events, not the end. I look forward to scientific and clinical developments in the years ahead and sincerely wish for all young investigators who study depression to experience the excitement, growth-inducing challenges, and sense of progress that have been my good fortune to witness over the past decades.

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