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A Unified Model of Depression: Integrating Clinical, Cognitive, Biological, and Evolutionary Perspectives

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Abstract

We propose that depression can be viewed as an adaptation to conserve energy after the *perceived loss of an investment in a vital resource* such as a relationship, group identity, or personal asset. Tendencies to process information negatively and experience strong biological reactions to stress (resulting from genes, trauma, or both) can lead to depressogenic beliefs about the self, world, and future. These tendencies are mediated by alterations in brain areas/networks involved in cognition and emotion regulation. Depressogenic beliefs predispose individuals to make cognitive appraisals that amplify perceptions of loss, typically in response to stressors that impact available resources. Clinical features of severe depression (e.g., anhedonia, anergia) result from these appraisals and biological reactions that they trigger (e.g., autonomic, immune, neurochemical). These symptoms were presumably adaptive in our evolutionary history, but are maladaptive in contemporary times. Thus, severe depression can be considered an anachronistic manifestation of an evolutionarily based "program."

Keywords

depression, unified model, cognitive theory, biological, evolutionary

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A substantial body of research has provided strong support for the cognitive model of depression (Clark & Beck, 1999). Nevertheless, key contributions from a number of novel biological investigations since the most recent update of this model (Beck, 2008) have helped expand our understanding of the links between cognitive and biological processes involved in depression and in turn justified the proposal of a unified model of depression within a cognitive framework. More important, there is a need for a comprehensive theoretical model that brings together relatively disparate literatures and accounts and in doing so highlights emerging consistencies across findings and perspectives while generating novel insights. Such an endeavor should help promote integration and collaboration within the field and in turn the development of more integrative approaches to clinical care (both of which are still lacking).

A unified model of depression should fulfill a number of requisites. First and foremost, it should integrate findings from various levels of analysis (e.g., genetic, psychological) into a coherent account. Second, it should fully account for symptomatology, including those aspects of depression that appear to violate the basic canons of human nature (e.g., the sexual instinct and pleasure principle). Many theoretical models attempt to account for only particular symptoms or cases and do not explicitly address potential adaptive functions. Third, it should provide a framework to explain the natural history of depression: predisposition, precipitation, and recovery from the disorder.[1] For example, the model must be able to account for documented variability in precipitating circumstances across individuals (e.g., cases of "endogenous depression") and across time (e.g., sensitization to stressors following initial recovery, also known as "the kindling effect").

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From Adaptation to Depression

Personality is organized to satisfy biologically determined needs and to utilize vital human resources to help meet those needs. These resources consist of close kinships, peer groups, romantic partners, and identity groups, which provide access to the necessities of life, including nurturance, support, prospects for pair bonding, and elemental nutritional needs.[2] Depression represents an adaptation to the perceived loss of a vital resource investment that exceeds the individual's competencies and capacities (e.g., resourcefulness, problem-solving, support) to mitigate the impact of the loss.

An important corollary of this adaptationist view of depression, in contrast to the traditional disease model, is that the symptoms are viewed on a continuum of severity (see Nettle, 2004). In support of this view, most evidence suggests that depression is dimensional (e.g., Beck, 1967; Haslam & Beck, 1994; Haslam, Holland, & Kuppens, 2012; but for an alternative view, see Ruscio, Brown, & Ruscio, 2009). Also, and particularly pertinent to our model, evidence suggests that cognitive vulnerability to depression is dimensional (e.g., Gibb, Alloy, Abramson, Beevers, & Miller, 2004). For practical purposes, we use the phrase *severe depression* in reference to any case that is above the threshold of clinical significance, acknowledging that such thresholds are difficult to determine (e.g., Wakefield & Schmitz, 2013; see Horowitz & Wakefield, 2007). We also address the potential functions and adaptive value of milder (i.e., "subclinical") symptoms, as these are key to an understanding of when and how a given level of depression is dysfunctional or maladaptive (see Wakefield, 1999). To this end, we begin with a brief review of the core aspects of the cognitive model of depression, presented within an adaptationist framework and in the context of our working model of personality (derived from research, theorizing, and clinical observations).

The structure of personality

Three systems of personality—cognitive, motivational/behavioral, and affective (see Beck, 1996; Hilgard, 1980)—implement evolutionarily derived goals. We propose that the cognitive system operates as a "master program" that coordinates the other personality systems, as well as the biological processes that support those systems (see also Cantor, 1990; Denson, Spanovic, & Miller, 2009; Dweck & Leggett, 1988; Lazarus, 1966, 1991; Ortony, Clore, & Collins, 1990; Weiner, 1985). This system's key functions are to perceive, interpret, synthesize, and evaluate. Primal needs are experienced subjectively as urges and cravings, and these needs are met through the use of behavioral strategies that increase the likelihood they will be satisfied. Affective states provide positive and negative reinforcement in support of the satisfaction of these basic cravings and drives, as well as feedback on our progress toward goals.

We propose that the beliefs most relevant to an individual's well-being involve domains of vital resources (interpersonal relations and internal assets) and expectations of success or failure exploiting these resources. For additional details about our conceptualization of the cognitive system and the general cognitive model (not specific to depression), please see Beck and Haigh (2014). The affective and motivational/behavioral systems have been described elsewhere (e.g., Beck, 1996; Ortony et al., 1990; Weiner, 1985).

The cognitive triad

Beliefs are embedded in schemas. The cognitive triad (Beck, 1967) consists of three schemas that simultaneously operate to determine the meaning/value of life events (i.e., make appraisals) and generate appropriate responses. These include the self-image (lovable vs. unlovable), image of the world (friendly vs. unfriendly, accepting vs. rejecting), and expectations of the future (hopeful vs. hopeless).

Given the inherent constraints on how much information we can process at once, *how* we prioritize this information has important implications for our perceptions and beliefs (and in turn, our well-being). When not depressed, individuals generally show a positive bias in attending to and recalling data from the flow of constant information they receive from external and internal stimuli (e.g., Pool, Brosch, Delplanque, & Sander, in press; Walker, Skowronski, & Thompson, 2003). This positive bias has several adaptive consequences. For example, if one overestimates the probability of a successful outcome from an endeavor, one may try harder and thereby increase the probability of a positive result. Conversely, beliefs and perceptions that produce mild sadness or frustration can also be adaptive insofar as they motivate an individual to take stock after a devaluing experience, assess his or her role evenhandedly, and then problem-solve, withdraw, or adopt a new strategy (e.g., Alloy & Abramson, 1979; Storbeck & Clore, 2005). We revisit and further discuss this progression later, after detailing the predisposition to and precipitation of severe depression within the unified model.

Self-image and self-esteem. Individuals' views of themselves are represented in their self-image. The image is colored by evaluative processing, generally referred to as self-esteem. Horney (1937) first described the despised self-image and idealized image. The idealized image is an exaggerated form observed in manic states (accompanied

by extreme positive beliefs, such as "I am superior"), whereas the despised image is seen in severe depression. Although an individual's self-image is relatively stable, the evaluative component may fluctuate, depending on his or her life experiences. These evaluations are tied to the pleasure/pain system so that losses or gains may stimulate pleasant and unpleasant emotions.

Although self-evaluations may include a pejorative element, the kind of harsh self-criticism observed in perfectionistic or severely depressed individuals emanates from the imperative system. Notably, these injunctions and prohibitions can be useful in everyday life, as can the self-criticism that they may lead to. Like criticism from others, self-criticism fosters learning that can guide future behavior to head off unfavorable outcomes or to overcome inertia standing in the way of "doing what is right." For example, if an individual is caught cheating on an exam, he or she is subjected to external criticism like "you are a cheat" (actually an overgeneralization) and incorporates this experience into memory. Thinking of the experience elicits (emotional) pain, which motivates him or her not to cheat in the future. The individual may help to anchor this by thinking "I am stupid to take a chance like that." Notably, the extent to which the individual is personally invested in a particular life goal or situation (e.g., a job) determines the extent to which perceived success or failure in that domain influences self-esteem.

In severe depression, self-criticism tends to be magnified and inappropriate (and thus often becomes maladaptive). These self-criticisms are actually self-devaluations (e.g., you are stupid, you are dumb, you are useless), and begin to dominate consciousness in the form of ruminations about past mistakes and excessive/inappropriate guilt. They become generalized to a negative self-concept (e.g., viewing oneself as lazy, weak, or a burden), and ultimately individuals may come to believe that their life has no worth at all because they are also suffering. They see that life itself has only a negative value (for themselves and others)—therefore, the logical thing to do (in their minds) is to get rid of this useless object (suicide; see Bi et al., 2012; Joiner, Horn, Hagan, & Silva, in press; see also Wenzel, Brown, & Beck, 2009, for details about the cognitive model of suicidal acts).

Expectations for others and the future. Individuals' views of other people have important implications for how they relate to others. These views also have an evaluative component, helping to differentiate kin from nonkin. However, more generalized views of groups and people in general are also maintained, which has functional value (e.g., fostering expectations when encountering strangers). These generalized views of others interact with the self-image to create expectations for both the present and the future. Thus, strong negative views of the self or others, but particularly their combination, lead to the high expectations for negative outcomes and low expectations for positive outcomes seen in severe depression. In turn, the depressed individual begins to divest from previously valued interests and attachments.

In the next section, we discuss in detail key factors and processes that can lead to these extreme negative evaluations of the self, others, and the future and, thus, predispose individuals to experience severe depression. Given the ambitiousness of this undertaking and the scope of our article, we focus on general conclusions that have emerged from various literatures, and refer readers to key studies/reviews detailing the methodologies and findings from those literatures. For a comprehensive review of the depression literature, please see Gotlib and Hammen (2014).

Predisposition

Most individuals by and large adapt reasonably well to life stressors.[3] They draw on their own resilience strategies and problem-solving techniques and can lean on their social support systems to soften the impact of adverse life events. However, these strategies are undermined in individuals who have had early traumatic experiences, are vulnerable because of genetic factors, or both. Consequently, they are at risk for severe depression and other psychological disorders.[4] A critical element in the development of vulnerability to depression is the formation of depressogenic beliefs about the self, the world, and the future (i.e., "negative cognitive triad"; Beck, 1967).

Distal vulnerability factors

There is growing evidence that traumatic experiences can sensitize individuals to later interpersonal losses, such that they increase risk for depression. An early study, for example, showed that the loss of a parent in childhood was associated with severe depression later in life (Beck, 1963). In fact, adults who experienced early parental loss may be sensitized to later experiences, such that they require less stress to develop depression in adulthood (see Slavich, Monroe, & Gotlib, 2011). Abuse or adversity during childhood also appears to have a particularly formative effect (see, e.g., Gibb, Butler, & Beck, 2003; Hammen, Henry, & Daley, 2000). For example, the impact of negative interactions with parents is illustrated in elegantly designed observational studies demonstrating that higher levels of negative emotional (e.g., aggressive) expressions and behaviors by parents appear to prospectively predict depression in adolescence (e.g., Schwartz et al., 2012; Schwartz et al., 2014).

Beyond their influence on cognitive development (e.g., information processing, belief formation; both discussed more later), there is evidence that these sorts of formative early experiences may disrupt neural development. For example, early life adversity has been linked with reduced volume of the hippocampus (Rao et al., 2010), a brain structure that plays a critical role in learning and memory formation (see Squire, 1992) and is implicated in the neuropathology of depression (see Campbell & MacQueen, 2004). It is important to note that this reduction predicts later symptoms of depression (Rao et al., 2010), and has also been observed in adults who experienced emotional neglect during childhood but have not (yet) suffered from severe depression (Frodl, Reinhold, Koutsouleris, Reiser, & Meisenzahl, 2010).

It is clear, however, that not everyone who experiences adversity in childhood later becomes severely depressed. One clue to this puzzle came from the landmark finding by Caspi and colleagues (2003) suggesting that individuals possessing either one or two copies of the short genetic variant of the serotonin transporter-linked polymorphic region (*5-HTTLPR*) experience higher levels of depression and suicidality following a life stressor. Furthermore, those who experienced maltreatment in childhood and also carried the *5-HTTLPR* short variant were more likely to become depressed as adults. This finding was replicated by Kendler, Kuhn, Vittum, Prescott, and Riley (2005), who demonstrated increased sensitivity to severe depression in these individuals. Since then, a number of other studies examining this genetic polymorphism have yielded consistent findings. In a sample of adolescents and young adults, the interaction of *5-HTTLPR* genotypes and major interpersonal stress predicted the onset of severe depression (Vrshek-Schallhorn et al., 2014). Yet another study showed that these genotypes were associated with more negative appraisals of stressful life events, which in turn predicted future depressive symptoms (Conway et al., 2012). The moderating effect of this genetic polymorphism on the link between stress and depression was confirmed in a recent meta-analysis (Karg, Burmeister, Shedden, & Sen, 2011; for a broader review of supporting evidence, see Caspi, Hariri, Holmes, Uher, & Moffitt, 2010; but for an alternative view, see Risch et al., 2009).

It is important that vulnerability to depression is almost certainly polygenic (see Flint & Kendler, 2014, for a detailed discussion and review), and other candidate polymorphisms have been identified that may play a role as well. For example, several studies (e.g., Kaufman et al., 2006; Kudinova, McGeary, Knopik, & Gibb, 2015) have found that the association between *5-HTTLPR* genotypes and depression is moderated by variants of the brain-derived neurotrophic factor (BDNF) gene (a key neurochemical in neural development and known resilience factor). Of note, BDNF gene variants have also been linked with structural and functional abnormalities in the hippocampus (e.g., Egan et al., 2003). Furthermore, the "minor" variant of the FKBP5 gene (which modulates glucocorticoid receptors) has been shown to interact with adverse life events to predict the onset of severe depression (e.g., Zimmerman et al., 2011). Notably, this polymorphism also predicts symptom course and prognosis (e.g., Binder et al., 2004; Lekman et al., 2008). Also, pro-inflammatory genetic polymorphisms have been shown to predict depression following chronic interpersonal (but not other) stress (e.g., Tartter, Hammen, Bower, Brennan, & Cole, 2015; see Raison & Miller, 2013, for broader evidence linking genes involved in immune functioning with depression). Finally, in line with other evidence for a parallel between physical and emotional pain (e.g., Eisenberger & Lieberman, 2004), genes that regulate endogenous opioid production have been found to moderate depressive reactions to targeted rejection (Slavich & Irwin, 2014).

Critics of candidate gene research (e.g., Duncan & Keller, 2011) point out that the effects in these studies are small (particularly in relation to heritability estimates) and have proven difficult to replicate. Although the importance of confirming positive findings in genome-wide association studies (GWAS) has been argued, unfortunately few reliable and consistent findings have emerged from research using that rigorous methodological approach (see Cohen-Woods, Craig, & McGuffin, 2003; Flint & Kendler, 2014). Notably, a large GWAS study by the Psychiatric Genomics Consortium (Cai et al., 2015) did identify several locations on the genome associated with shared risk for various forms of psychopathology, including severe depression. More recently, the CONVERGE Consortium (Musliner et al., 2015) identified and replicated a genetic signal near the *SIRT1* gene (which is involved in mitochondrial biogenesis) associated with melancholic depression. We believe that both candidate gene and genome-wide methodologies have important merits (as well as limitations) for exploring genetic predisposition to depression, and are encouraged by emerging efforts to combine them (e.g., developing polygenic risk scores and examining their interaction with environmental risk factors; Musliner et al., 2015).

Although there is not yet a clear consensus about the specific genes that predispose an individual to depression, it is firmly established that depression risk has a heritable component, based on both behavior genetic research (e.g., family, twin studies; see Sullivan, Neale, & Kendler, 2000) and molecular work (e.g., genome-wide complex trait analysis; Lubke et al., 2012) to date. However, there is also evidence that genetic risk is not necessary for an individual to become predisposed to depression—severe negative experiences such as parental loss may be

sufficient (see, e.g., Kendler et al., 2005; Kendler, Neale, Kessler, Heath, & Eaves, 1992). Furthermore, it is important to note that genetic and environmental risk factors are by no means independent of one another—rather, there is emerging recognition that they mutually influence one another in important ways. For example, our personal experiences can alter the expression of relevant genes (e.g., Klengel et al., 2013; see Nestler, 2014). Conversely, the occurrence of certain stressful life events associated with risk for depression has been shown to have a heritable component (e.g., family conflict; see Kendler, 1998; Kendler & Baker, 2007).

Information processing biases

It is well established that depressed individuals selectively attend to negative information (Peckham, McHugh, & Otto, 2010) and ignore positive information (Winer & Salem, in press). In turn, depressed individuals have been found to be more sensitive to negative feedback (e.g., as evidence by enhanced "error-related negativity" in event-related potential studies; see Olvet & Hajcak, 2008), and also show impaired reward learning (e.g., Kumar et al., 2008). Furthermore, depressed individuals tend to more readily remember negative information (Dalgleish & Watts, 1990) and have difficulty recalling specific autobiographical memories (leading to "overgeneralization"; see Williams et al., 2007). Notably, there is mounting evidence that these information processing "biases" are not simply a by-product of depressed mood, but rather confer vulnerability to depression (e.g., Gibbs & Rude, 2004; Gotlib & Krasnoperova, 1998; Wells & Beevers, 2010). Such biases may (in part) reflect impaired executive control, mediated by dysfunction of the prefrontal cortex and other regions within the brain's "executive network" (e.g., Elliott, Rubinsztein, Sahakian, & Dolan, 2002; Murphy et al., 1999; see Levin, Heller, Mohanty, Herrington, & Miller, 2007). Ultimately, they may contribute to over-interpretation of events and negative evaluations of life experiences (see Joormann & Gotlib, 2006; MacLeod & Hagan, 1992; Minnen, Wessel, Verhaak, & Smeenk, 2005), and in turn shape the individual's views and expectations over time.

Biases in information processing appear to mediate the effects of genetic and environmental risk factors. Although the relationship between serotonergic functioning and depression is still not fully understood, mounting evidence suggests that the *5-HTTLPR* short variant is directly associated with negative processing biases (e.g., Beevers, Gibb, McGeary, & Miller, 2007; Beevers, Scott, McGeary, & McGeary, 2009; Hayden et al., 2008; see Canli & Lesch, 2007; Pergamin-Hight, Bakermans-Kranenburg, Van Ijzendoorn, & Bar-Haim, 2012). Similarly, childhood trauma and abuse predict information processing biases later in life (e.g., Gibb, Schofield, & Coles, 2009; Pine et al., 2005).

Stress reactivity

Biological reactivity to stress also seems to play a critical role in the pathway from genetic and cognitive predisposition to depression. Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis is one of the most consistent biological correlates of severe depression (see Pariante & Lightman, 2008; Stetler & Miller, 2011) and may be linked to serotonergic or noradrenergic dysfunction (given the important role of these neurotransmitters in HPA activation/regulation; see Dinan, 1996; Tsigos & Chrousos, 2002). Also, numerous studies have found elevated levels of cortisol in response to stress in depressed individuals (e.g., Burke, Davis, Otte, & Mohr, 2005; Knorr, Vinberg, Kessing, & Wetterslev, 2010; Stetler & Miller, 2011). Notably, cortisol reactivity has also been observed in healthy individuals with the FKBP5 gene minor variant (e.g., Ising et al., 2008), carriers of the *5-HTTLPR* short variant (see Miller et al., 2013), and individuals who lost a parent during childhood (e.g., Tyrka et al., 2008). Over time, elevated cortisol can lead to neural atrophy (mediated by glutamate, and particularly in the hippocampus;[5] see McEwen, 2003; Sapolsky, 2000) that could further exacerbate HPA dysregulation (as the hippocampus plays a key role in HPA feedback inhibition; see Mahar, Bambico, Mechawar, & Nobrega, 2014) and memory biases (e.g., Gerritsen et al., 2012; Young et al., 2012; see Gradin & Pomi, 2008).

The amygdala, a brain region strongly implicated in salience detection, emotional processing, and activation of the HPA axis (Adolphs, 2010; Herman & Cullinan, 1997), seems to play an important role in this stress reactivity and its apparent link with information processing (see also Disner, Beevers, Haigh, & Beck, 2011). The extent to which the amygdala is activated by negative stimuli is directly associated with *5-HTTLPR* genotypes (see Munafò, Brown, & Hariri, 2008), and carriers of the short variant have been found to show elevated amygdala activation and cortisol responses when attempting to "repair" their mood (Gotlib, Joormann, Minor, & Hallmayer, 2008). Likewise, enhanced amygdala reactivity is associated with childhood maltreatment, independent of psychiatric status (e.g., Van Harmelen et al., 2013). In turn, amygdala activation predicts biased recall of negative information in individuals with a history of depression (e.g., Ramel et al., 2007), as does functional connectivity between the amygdala and hippocampus (e.g., Hamilton & Gotlib, 2008). In short, this biological reactivity to environmental input/stress may foster greater affective instability (see, e.g., Thompson, Berenbaum, & Bredemeier, 2011) and in turn strengthen learning.

Belief formation

In simplified terms, the developmental sequence to predisposition follows the genetic or environmental risk to negative memories of devaluation as well as negative evaluations of the self and future. Resulting negative views coalesce into the negative cognitive triad.

Support for this formulation is provided by the large number of publications detailing the role of negative self-esteem as a predictor of future depression (see Sowislo & Orth, 2013), and more recent evidence that the tendency to experience a decline in self-esteem (shown using ecological momentary assessment) in response to negative events does as well (e.g., Clasen, Fisher, & Beevers, 2015). Research using the Dysfunctional Attitude Scale (DAS; Weissman & Beck, 1978) lends further support to this model. This scale includes items such as "if I don't do well all the time, it means I am a failure." Numerous studies have shown that these attitudes moderate the impact of stressful life events on depression (e.g., Abela & Skitch, 2007; Abela & Sullivan, 2003; Hankin, Abramson, Miller, & Haeffel, 2004; Lewinsohn, Joiner, & Rohde, 2001).

These negative attitudes and beliefs seem to result in important and predictable learned patterns of appraising life experiences/events. For example, using the Attributional Style Questionnaire, Alloy, Abramson, and colleagues (e.g., Alloy, Abramson, & Francis, 1999; Alloy, Abramson, Whitehouse, et al., 1999) have demonstrated that depression-prone people have a tendency to view negative events as caused by themselves and anticipate enduring negative consequences. This attributional "style" prospectively predicts depressive symptoms (e.g., Hankin et al., 2004; Nolen-Hoeksema, Girguis, & Seligman, 1986) and has been linked with maltreatment in childhood (e.g., Gibb, Alloy, Abramson, & Marx, 2003). In turn, these individuals become more pessimistic about the future (e.g., Alloy & Ahrens, 1987; Metalsky & Joiner, 1992).

Our general model of depression proneness or predisposition is portrayed in Figure 1. As shown in this figure, we propose that genetic and experiential risk factors contribute to the development of information processing biases and biological reactivity to stress. Over time, these processes can lead to the development of depressogenic beliefs (i.e., negative views of the self, world, and future), which in turn further exacerbate processing biases and stress reactivity. Early negative experiences are also hypothesized to contribute directly to depressogenic belief formation.

Pinpointing person-specific vulnerabilities

In addition to the general vulnerabilities we have described earlier, depression-prone individuals often have specific vulnerabilities that are triggered by specific types of stressors/events (e.g., Hammen & Goodman-Brown, 1990; Robins, 1990; Segal, Shaw, Vella, & Katz, 1992). For example, there is evidence that individuals who place greater value on independence or autonomy are relatively more sensitive to events that impinge on or undermine their sense of achievement, mastery, and control (e.g., Clark, Steer, Haslam, Beck, & Brown, 1997; Hammen, Ellicott, Gitlin, & Jamison, 1989; see Beck, 1982; but for an alternative view, see Clark, Beck, & Brown, 1992). Conversely, those with higher levels of dependency (i.e., "sociotropy") seem to be more sensitive to interpersonal stress, particular events that involve feeling rejected or abandoned. These personality factors may also influence symptom expression—for example, dependent individuals may be more likely to cry, whereas autonomous individuals may be more likely to withdrawal (see, e.g., Clark et al., 1997).

Some of these vulnerabilities are salient during particular development periods and are represented by conditional beliefs. For example, adolescents tend to develop acute sensitivity to criticism and rejection by other people (Chango, McElhaney, Allen, Schad, & Marston, 2012). In turn, they may be prone to develop beliefs such as "if somebody rejects me, it means I am undesirable."

Individuals often attempt to create circumstances in their lives that will counteract or compensate for these specific vulnerabilities. An individual, for example, might develop skills as an entertainer as a way of connecting to compensate for inner loneliness or fear of group rejection. When such an individual fails to entertain a relevant group, the perceived bond with other people is broken, increasing susceptibility to depression. It is important that such compensatory behaviors may serve to reinforce key beliefs. For example, an individual might come to believe that he or she will be liked or accepted by others only if he or she entertains them. Also, compensatory behaviors such as these can elicit negative reactions from others, presenting yet more stress to the individual (see Hammen, 2006; Lewinsohn, Mischel, Chaplin, & Barton, 1980).

Precipitation

Predisposition is not sufficient to cause depression—rather, something must trigger the onset of symptoms. We propose that the critical element in the precipitation of depression is the *perceived loss of the investment in a vital resource.*

Stress as a common precursor

In line with the traditional diathesis-stress model, various adverse life experiences predict the onset of severe depression (see Hammen, 2005; Kendler, Karkowski, &

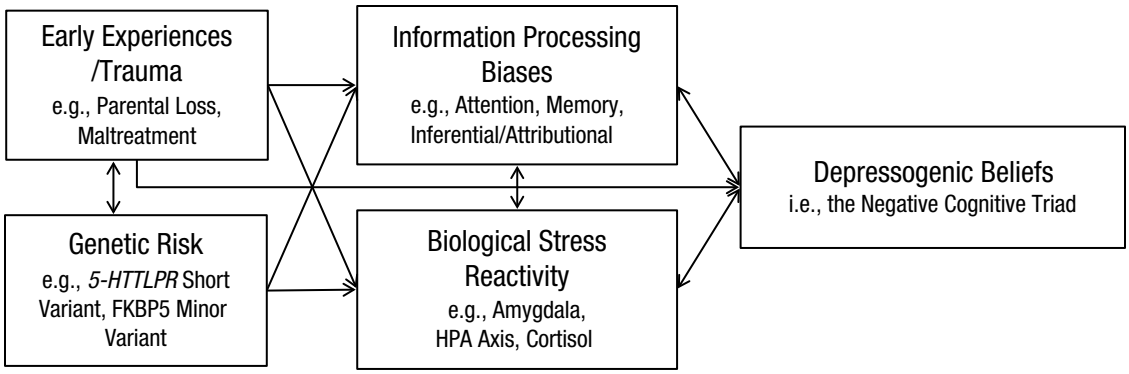

Fig. 1. Predisposition to depression. According to our unified model, genetic risk and early experiences/trauma both contribute to the development of information processing biases and biological reactivity to stress. Over time, these tendencies can lead to the development of the "negative cognitive triad" (i.e., depressogenic beliefs about the self, world, and future). In turn, the formation and activation of these beliefs further exacerbate cognitive biases and stress reactivity. Early experiences/trauma are also considered to play a direct role in the formation of depressogenic beliefs.

Prescott, 1999). Rejection by a loved one, social exclusion or degradation, loss of a child, and loss of productivity are among the most potent precipitants of depression (see Kendler, Hettema, Butera, Gardner, & Prescott, 2003; Slavich, Thornton, Torres, Monroe, & Gotlib, 2009). The common thread among these stressors is that they appear to negatively impact key evolutionary goals such as having close interpersonal relationships, reproductive success, acceptance by the identity group, and effective internal resources. However, the precipitant does not need to be a discrete event—chronic stressors (e.g., marital discord, financial difficulties) can lead to depression as well (Hammen, 2005). The body responds to stressors through activation of the HPA axis and the release of cortisol (Selye, 1973), both of which are typically amplified in those prone to depression (as discussed earlier).

The precipitating stressor impacts one or more vital resources, depending on the stage of life and the unique vulnerabilities of the individual. In infancy, the loss of nurturance from a parental figure can lead to "anaclitic" depression (Spitz & Wolf, 1946). Adolescents seek acceptance and are particularly sensitive to exclusion by their peer group. For example, in a longitudinal study of late-adolescent women, nonsevere interpersonal stressors were nearly two times more likely to be followed by severe depressive episodes than noninterpersonal ones (Stroud, Davila, Hammen, & Vrshek-Schallhorn, 2011). Adults, on the other hand, are especially likely to react to rejection by an intimate partner or exclusion by the larger community (e.g., Slavich et al., 2009). Finally, we have observed that older adults who have been productive most of their lives may slip into severe depression after they recognize that they have lost some competencies or experienced failure in their occupations.

Of note, recurrent bipolar and endogenous depressions can occur without obvious precipitating events or stressors. Severe depressive episodes, whether or not they occur in reaction to external events/circumstances, are characterized by a catastrophic loss of self-esteem and dominant negative bias in perceiving ongoing experiences and anticipating the future. Nevertheless, depressed individuals who experience a severe life event prior to the onset of their symptoms have been found to exhibit greater variability in negative attitudes over the course of the episode than depressed individuals without a severe precipitating event (Monroe, Slavich, Torres, & Gotlib, 2007).

The role of appraisals

Of course, adverse events/stressors do not always lead to depression. Everyone experiences painful events that lead to sadness or anger, but we propose that these do not culminate in full-blown depression unless there is a perceived loss of what they believe to be a *vital investment*. Furthermore, it is critical that this loss be perceived as beyond the individual's control (Brown & Siegel, 1988), and thus irreversible. In essence, the impact of a depressogenic event depends on its personal meaning. In turn, an event's meaning is contingent on the value that the individual places on the investment, reflected in the perceived importance of the resource in question.

The magnitude of perceived loss is proportional to individuals' degree of investment. When individuals allocate their cravings, expectancies, energy, and even well-being to their investment, the loss will be intense. For example, an individual who invests heavily in a romantic relationship would be particularly vulnerable to depression if that relationship ends. When the individual utilizes this investment to compensate for beliefs of undesirability, inferiority, or inadequacy, his or her loss is further compounded.

Negative thinking about and interpretations of experiences can be considered proximal cognitive causes of depression (Hammen & Watkins, 2008). In line with this formulation, it has been demonstrated that cortisol changes in response to stressors are closely tied to cognitive appraisals of those events (e.g., Gaab, Rohleder, Nater, & Ehlert, 2005; see Denson et al., 2009, for a review).

The role of schemas

The link between stress and severe depression appears to change over multiple episodes, such that an individual's "threshold" of stress necessary to precipitate onset may decrease over recurrences (referred to as "the kindling effect"; e.g., Post, 1992; Stroud et al., 2011; see Monroe & Harkness, 2005). And as previously mentioned, depressive episodes can certainly occur without any apparent precipitant, and yet are still characterized by profound depressive thinking. Schema theory can help to explain both of these phenomena.

The predispositional schemas (negative cognitive triad) become activated as a result of a stressor that is congruent with the schematic belief, which in turn influences subsequent information processing. The levels of depression (mild, moderate, or severe) depend on the degree of activation. The content of negative beliefs is graded and fluctuates with the degree of activation (e.g., "I am clumsy and inept" vs. "I am a total loser"). In turn, this activation and subsequent biasing of information processing and interpretations/appraisals further reinforces and strengthens the schema, causing it to become increasingly more dominant, essentially preempting other more adaptive schemas. Through this continuous cycle of reinforcement, these schemas become denser, more robust, and less permeable. At a biological level, this is likely reflected in the strengthening of relevant synaptic connections (and, in turn, neural networks). These cognitive and biological changes reflect learning processes that promote adaptation, all things equal. Yet in recurrent depressions, the schemas become consolidated through this cycle of increasingly negative perceptions and interpretations. Under these conditions, negative schemas begin to have a continuous low level of activation even during asymptomatic periods, and in turn are more easily raised to maximum activation (the "kindling effect"). Similarly, these schemas become "frozen" and are therefore relatively impermeable to positive life events. In endogenous depression, these schemas are consolidated to a degree that very minimal (if any) additional activation is required. For further elaboration, see Beck and Haigh (2014).

Support for this formulation comes from work by Lewinsohn, Allen, Seeley, and Gotlib (1999), which showed that stressful events are more predictive of initial onset of severe depression, whereas depressogenic attitudes (measured by the DAS) are more predictive of recurrence. Furthermore, research suggests that experiencing depression leads to greater "cognitive reactivity" (e.g., depressogenic attitudes when in a sad mood), which in turn predicts risk of recurrence (Lau, Segal, & Williams, 2004; Teasdale, 1988). Finally, experiencing severe depression leads to a decreased sense of mastery over time (Nolen-Hoeksema, Larson, & Grayson, 1999). We propose that these findings reflect the consolidation of depressogenic schemas. Along with the enhanced reactivity and diminished cognitive control that may result from neural atrophy (discussed earlier), this consolidation increases risk.

But why does the perceived loss of a vital investment produce such a profound effect? We suggest that the internal representation of the self and the vital resources in question constitute a prominent part of the cognitive organization (i.e., "core beliefs") and are embedded in schemas that include various beliefs and the meaning associated with both the self and the resource. More specifically, internal representations of the self and these vital resources overlap and become assimilated into the self-schema. Thus, the disruption of this integration following precipitating events leads to the profound sense of loss. For example, the self-image of those who invest heavily in romantic relationships may come to center on feeling lovable. As a result, relationship difficulties (e.g., a breakup) may make them feel not only unlovable, but worthless and hopeless.

The Evolutionary-Based "Depression Program"

Negative thoughts/beliefs can directly account for many cardinal depressive symptoms (e.g., sadness, self-criticism, difficulty sleeping, suicidal behavior; see Beck, 1976; Lewinsohn, Hoberman, & Rosenbaum, 1988). They reflect extreme deactivations of positive schemas (resulting in decreased "investments") as well as activations of negative schemas (promoting withdrawal). The apparent dysfunctionality of severe depression, represented by symptoms such as profound anergia and anorexia, is best understood by carefully considering the potential evolutionary value of such symptoms. In doing so, we expand on a previous cognitive-evolutionary formulation (Beck, 1993), incorporating more clinical features as well as new scientific findings (for discussions of other evolutionary accounts, see Durisko, Mulsant, & Andrews, 2015; Rottenberg, 2014). Initial clues about the evolutionary origins and functions of depression come from work examining depression-like behaviors/syndromes in other species.

Nonhuman animal studies

Making extrapolations from the present to the past ("what may have happened") and back to the present again ("what could be happening") is a risky undertaking, beset with anthropomorphism, zoomorphism, and circular reasoning. Still, animal models can provide an interesting heuristic approach to the task of unraveling the mystery of depression.

Animal observations and experiments suggest that, following social deprivation, primates manifest behavioral characteristics that resemble human depression (McKinney, Suomi, & Harlow, 1971), such as crying, decreased activity, and social interaction, decreased appetite, and sleep disturbances. It has been speculated that a key function of this "deprivation depression" is to attract the attention of significant others. Other experimental work with primates has shown a hypersensitivity to the loss of an intimate relationship, as well as losses in competitive struggles that result in a lowering of group status ("defeat depression"). By adopting a submissive role, the individual no longer invites attacks from competitors (Gilbert, 1989; Price & Sloman, 1987).

Of note, depressive reactions have been observed in nonprimate species as well (see McKinney & Bunney, 1969). For example, rats develop a depression-like state following maternal separation (Hall, 1998), characterized by a significant decline in motor activity. Similarly, depression can occur in dogs when separated from their owner (Aisa, Tordera, Lasheras, Del Rio, & Ramirez, 2008). And it has been shown that these same species can exhibit "helplessness" in response to uncontrollable stressors (e.g., inescapable shock; Seligman & Maier, 1967), which extinguishes instrumental learning as well as interest in food, sex, and play.

These findings reinforce the idea that depression may have evolutionary origins (derived through nature selection because of its adaptive value), and point to some potential functions it may serve (e.g., protection). Even more interesting, other species seem to exhibit depressive reactions in response to the same types of events that precipitate depression in humans (e.g., loss of a caregiver or group status). Finally, these reactions seem to consistently involve a profound *damping down* of activities.

Conservation of energy

As noted earlier, vital resources such as social relationships play an important role in helping us meet evolutionarily derived goals/needs. Thus, following the perceived loss of a vital investment, we are naturally drawn to compensate for this loss by limiting all activity not necessary for survival. To implement this conservation strategy/"program," sexual drive, hunger, and parenting are largely extinguished. Under the condition of an expectation of exhaustion of residual energy, an enforced conservation of energy would permit the individual to survive until the circumstances become more favorable. Of note, similar energy conservation strategies are observed in other species, under certain environmental conditions (e.g., amphibians in cold weather). In fact, the increased incidence of depressive symptoms/episodes during the fall and winter months (see, e.g., Magnusson, 2000) could be considered in line with this formulation (see also Davis & Levitan, 2005),[6] perhaps suggesting an evolutionarily derived sensitivity of the "depression program" to environmental cues signaling scarcity of various sources of sustenance (e.g., reduced sunlight). With the development of social behavior at a later stage of evolution, other members of the social group assumed a key role in promoting survival. Thus, the same strategy that conserved energy during food scarcity was later displaced onto the loss of "human resources" (see also Allen & Badcock, 2003).

To the extent that objective circumstances warrant energy conservation, such behavioral strategies can be considered adaptive. Similarly, factors that predispose individuals to depression (e.g., information processing biases, stress reactivity) can be considered adaptive in particular environmental situations (e.g., persistent danger or persecution). However, these symptoms and factors likely were more often warranted (and therefore adaptive) in our evolutionary history than they are in the contemporary context. Also, we propose that, like other evolutionarily based "programs" derived through nature selection (e.g., the fight-or flight response), the degree of activation of the depression program varies (concomitant with the extent of the perceived loss and resulting schema activation), accounting for symptoms that range from mild (i.e., dysphoria) to the most severe (i.e., melancholia). As previously noted, mild symptoms may generally be adaptive even today, in that they can motivate us to take stock after a devaluing experience (see, e.g., Alloy & Abramson, 1979; Wakefield & Schmitz, 2013). Conversely, in their most extreme forms, some symptoms inherently undermine the individual's prospects for survival and procreation (e.g., suicidal acts).

Support for the conservation of energy hypothesis comes from the noted parallel between "sickness behaviors" of individuals experiencing infection and symptoms of severe depression (see, e.g., Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008; Durisko et al., 2015). Evidence for the mobilization of the immune system in depression is indicated by the presence of proinflammatory immune bodies (cytokines; see Dowlati et al., 2010; Slavich & Irwin, 2014),[7] as well as experimental research showing that inducing inflammation in humans can cause severe depressive symptoms (e.g., Capuron & Miller,

2004; Harrison et al., 2009). Recent findings suggest that this immune activation may be driven by stress-induced endogenous opioids (e.g., Prossin et al., in press). The physiological components of both infection and depression can be viewed as consequences of the limitation of the expenditure of energy. Because the immune response to infections consumes an inordinate amount of energy, the body is programmed to reduce energy output not essential for immediate survival (see also Segerstrom, 2007). Thus, loss of appetite, loss of sexual drive, and generalized fatigue tend to restrict energy-demanding activities such as foraging for food and engaging in sex. Activation of the parasympathetic nervous system (which generally promotes "rest and digest") may also play an important mediating role in these symptoms/behaviors, as evidenced by research showing that depression is associated with respiratory sinus arrhythmia (e.g., Yaroslavsky, Rottenberg, & Kovacs, 2013), vagal tone (e.g., Kogan, Gruber, Shallcross, Ford, & Mauss, 2013), and other biomarkers of parasympathetic activation (see Lin, Lin, Lin, & Huang, 2011). Finally, emerging evidence shows that the serotonin system plays a key role in energy regulation (see Andrews, Bharwani, Lee, Fox, & Thomson, 2015), suggesting that serotonergic dysregulation may contribute as well.

Although others have highlighted that these "sickness behaviors" promote energy conservation, we propose that common cognitive and emotional symptoms of depression can be conceptualized within this same functional framework. Perhaps most notably, depressed mood (and the negative thoughts that accompany it) promotes withdrawal from people and activities. Also, the broad cognitive deficits (see McDermott & Ebmeier, 2009) and psychomotor retardation seen in severe depression may be viewed as a consequence of energy conservation mechanisms within the brain (typically a large consumer of the body's energy). In line with this proposal, depressed individuals show decreased neural/metabolic activity in several areas of the brain (e.g., prefrontal regions; see Drevets, 2000; Mayberg, 1997). Furthermore, there is evidence that depressed individuals often fail to deactivate the brain's "default-mode network" (which includes the hippocampus) when asked to perform a task (e.g., Sheline et al., 2009; see Hamilton, Chen, & Gotlib, 2013), which may also have a net effect of conserving energy. Diminished communicative behavior observed in depression (e.g., blunted affect; see Berenbaum & Oltmanns, 1992; Rottenberg, Gross, Wilhelm, Najmi, & Gotlib, 2002) might be seen as a strategy that prevents unnecessary energy expenditure as well, in light of concomitant social withdrawal. Finally, another key factor contributing to inactivity is diminished pleasure in previously valued goals and activities, as evidenced by research showing muted responses to pleasurable stimuli in depression (e.g., Pizzagalli et al., 2009) as well as after experimentally induced inflammation (e.g., Eisenberger et al., 2010). Dopaminergic dysfunction is thought to play a key role in this phenomenon, and perhaps cognitive and motor disturbances as well (Nestler & Carlezon, 2006; Willner, 1995), which may be a biological mechanism for discouraging appetitive behavior (and thus energy consumption) during stress or illness. Of note, loss of libido, decreased investment in progeny, and withdrawal from close relationships (all vital evolutionary demands) parallel the common precipitating factors of rejection by a lover, loss of an offspring, and public humiliation.

The initial cognitive evolutionary formulation (Beck, 1993) did not attempt to account for "atypical" symptoms of depression, such as hypersomnia and increased appetite (American Psychiatric Association [APA], 2013). Nevertheless, if conceptualized as behavioral strategies to *replenish* energy, these symptoms can be considered in line with the broader function of energy conservation as well. Specifically, sleeping more than usual undoubtedly promotes energy restoration beyond mere inactivity, and notably is common in response to infection. Similarly, increased caloric intake should increase energy reserves, overcoming the fact that some energy is used in the process of consumption (especially if minimal effort/energy is required to obtain the food). It is interesting that increased appetite is common in seasonal depression (APA, 2013; Rosenthal et al., 1984), perhaps reflecting an evolutionarily derived strategy to compensate for decreased food availability during winter. Biologically, some recent evidence suggests that the likelihood of depression being manifest in traditional versus atypical forms (e.g., decreased vs. increased sleep and appetite) reflects the relative balance of the stress and immune responses within an individual (e.g., Lamers et al., 2013), but this requires further testing/replication. From a cognitive perspective, we hypothesize that atypical depressive symptoms may be more common in the absence of prominent hopelessness (leading to perceptions that current resource scarcity is *temporary*). We are not aware of any research that has tested this directly. But notably, in a recent, large-scale factor analytic study of clinical symptom ratings, hopelessness and atypical symptoms did load on separate factors (Li et al., 2014). This prediction is also consistent with lower levels of hopelessness observed in seasonal depression (Michalak et al., 2002), which is commonly characterized by certain atypical symptoms (e.g., hypersomnia; APA, 2013).

The necessity of maintaining vigilance

Still, some symptoms of depression, including a few that are more commonly seen in atypical presentations (e.g., psychomotor agitation), seem difficult to reconcile with the conservation of energy hypothesis. Specifically, it

would appear that these symptoms deplete, rather than conserve or restore, energy. To understand the function of these symptoms and how they might fit within the depression "program," we argue that it is essential to consider the evolutionary significance of ongoing vigilance for threat.

Even when energy conservation is a salient goal, monitoring the environment for potential danger remains crucial to survival. In fact, one could argue that vigilance is even more important when energy is being conserved, as inactivity/immobility would make one an easy prey. So, it is understandable that depressed individuals would exhibit vigilance (Lebano, 2015), as suggested by neuroimaging findings that reveal *increased* activity in some brain regions involved in attention and vigilance (i.e., "the salience network"), such as the amygdala (discussed earlier) and areas of the anterior cingulate cortex and insula (see Drevets, 2000; Hamilton et al., 2013). This vigilance, particularly in combination with a preexisting tendency to attend to negative stimuli, should promote the rapid detection of any dangers that arise. Consistent with this account, it has been shown that attentional biases in depression-prone individuals are accentuated during negative mood states (e.g., McCabe, Gotlib, & Martin, 2000), as is error monitoring (e.g., Olvet & Hajcak, 2008). We hypothesize that several common depressive symptoms (e.g., psychomotor agitation, difficulty concentrating, insomnia) serve to promote this vigilance (or, alternatively, are a consequence of it). The same may be true for anxiety and irritability, which commonly cooccur with depression. Finally, social withdrawal and inactivity could be seen as also serving this overarching protective function (in addition to conserving energy), by limiting numerous risks. Arguably, this is consonant with the apparent functions of some depressive-like syndromes in other species (e.g., "defeat depression").

The immune response may play a mediating role in this vigilance as well, as evidenced by neuroimaging studies examining the cognitive effects of induced inflammation (see Miller, Maletic, & Raison, 2009), perhaps as an important evolutionary safeguard during times of sickness. Also, inflammation further activates the HPA axis (see Leonard, 2005). When considered along with bidirectional links between negative thinking and beliefs, one can see how the depression program can become self-perpetuating (and even self-enhancing) once activated.

From adaptation to depression, revisited

The evolutionary-based depression program involves coordinated activations and deactivations of the cognitive, affective, and motivational/behavioral systems of personality. Negative life events do not inherently activate this program, although they do routinely activate parts of it (e.g., sadness, elimination of the positivity bias) that are functionally relevant to the situation at hand (e.g., promoting accurate memory; Storbeck & Clore, 2005). Rather, we propose that such events do not fully activate the depression program unless there is a *perceived loss of a vital investment*. Even when this occurs, the degree of activation varies (and in turn, so does the severity of negative thinking, biased information processing, HPA/immune activation, and resulting symptoms) based on the magnitude of the perceived loss. At lower levels of activation, the dampening of energy consumption may be relatively mild, and can even stimulate or help foster adaptive responses (e.g., problem-solving; see Andrews & Thomson, 2009). However, at the highest levels, the pull to conserve energy overcomes the individual (based on our evolutionary heritage, given the adaptive value this would have had for our ancestors). This shift in balance might explain why depressive symptomatology can appear categorical in certain respects (e.g., Ruscio et al., 2009), as there is often marked behavioral changes when this occurs (e.g., from support seeking to withdrawal). From a cognitive perspective, this shift would likely occur when the individual develops perceptions of helplessness or hopelessness. The point at which these symptoms become maladaptive (and thus "clinically significant") is subject to debate, but likely varies across individuals (based on their unique life circumstances) and depends a great deal on their duration/frequency. Nevertheless, we are hopeful that our model can inform diagnostic decision making, based on our proposal that the energy conservation functions of depression are unlikely to be adaptive in contemporary times—thus, significant impairment should be more likely when they predominate. Furthermore, it is important to consider the accuracy of the individual's perceptions about the precipitating loss, as marked distortions in these perceptions are more likely to promote maladaptive responses.

Predisposition plays an important role in this progression. Specifically, individuals who are predisposed to depression exhibit greater sensitivity to stress (see, e.g., Hammen et al., 2000; Kendler, Thornton, & Gardner, 2001), and in turn have lower "thresholds" along this continuum (based on exaggeration of loss due to their beliefs about the importance of certain resources or their ability to cope). Again, such heightened sensitivity can have adaptive value in certain circumstances. Conversely, those with key resilience factors (discussed briefly later) would exhibit the opposite tendency. That is, resilient individuals are more capable of responding adaptively when the depression program is activated, and thus less likely to progress to severe depression. Furthermore, if these individuals ever do become severely depressed (e.g., as the result of a severe stressor), they would be better able to reverse the program. In some respects,

clinical decision making (about diagnosis and treatment) hinges on determining who is at risk and then how to intervene to reduce risk and promote resilience.

The proposed links between precipitating factors and symptoms of depression described earlier are portrayed in Figure 2. As shown in this figure, depressogenic beliefs interact with the precipitating stressor(s) to generate negative cognitive appraisals. It is important that both stress and predisposing beliefs may not be necessary to precipitate such appraisals, and yet can be sufficient. When there is a *perceived loss of a vital investment*, cognitive, emotional, and biological processes are initiated in service of energy conservation. In this sense, the conservation of energy is under cognitive control, and will in turn be abandoned when the cognitive appraisal changes from a worldview of scarcity to one of availability of vital resources. In line with this idea, cognitive appraisals also play a critical and direct role in mediating the effect of stress on immune functioning (see Denson et al., 2009).

Controlled by areas of the brain that evolved relatively later (e.g., prefrontal cortex; see Ochsner & Gross, 2005), this capacity for cognitive flexibility is generally quite adaptive for responding to complex or novel situational demands. And yet, the presence of depressogenic beliefs can undermine the utilization of this capacity (and more broadly, strategies for terminating the "program"). In this sense, the capacity to develop such beliefs (which may be unique to humans) creates the potential for chronic difficulties that can persist even after a stressful situation has resolved (see Sapolsky, 2004), and in turn bouts of depression that are prolonged or endogenous. Furthermore, these beliefs (and the schemas in which they are embedded) are reinforced/strengthened by negative appraisals, which can promote cognitive and behavioral rigidity (e.g., reflected in diminished activity within the brain's executive network; see Hamilton et al., 2013). We return to these topics later when (briefly) discussing ways to alleviate depression.

Summary and Integration

There is a continuity of cognitive structure and function across all domains pertinent to depression. Starting at the earliest stage of cognition, negative perceptions and appraisals lead in sequence to negative thoughts and beliefs. The beliefs, embedded in schemas, further influence information processing and interpretations in the predisposition to and precipitation of severe depression.

There is also continuity from the evolutionary prototype to the current experience of depression. From both perspectives, the appraisal of the loss of a vital investment/resource leads to a profound damping down of energy consuming functions. In this sense, severe depression can be considered an extension of normal/adaptive functions, which fully manifests when it is perceived that the loss of the resource exceeds capacities/competencies, and typically becomes maladaptive only when the perceptions driving them are distorted.

Biological and evolutionary approaches to depression have been investigated utilizing genotyping, neuroimaging, hormone assays, examinations of immune and autonomic responses, and nonhuman animal observations and experiments. Investigations at each of these levels have contributed greatly to our understanding of depression, and in turn, the proposed unified model.

Genetic level: Genetic polymorphisms associated with risk (e.g., *5-HTTLPR*, FKBP5) and resilience (e.g., BDNF) appear to contribute to cognitive biases or reactivity to stress (e.g., Miller et al., 2013; Pergamin-Hight et al., 2012), which promote the development of negative beliefs. These beliefs (and the schemas in which they are embedded) constitute predisposition to depression.

Neuroanatomical level: Links between genetic and environmental risk, cognitive biases, and stress reactivity are mediated by structural and functional alterations in several brain regions/networks, most notably the amygdala (salience network), hippocampus (default-mode network), and prefrontal cortex (executive network) (Beck, 2008; Disner et al., 2011; Drevets, 2000; Hamilton et al., 2013; Mayberg, 1997). These can be exacerbated over time due to neural atrophy resulting from the impact of stress on the brain.

Personality level: The cluster of depressogenic beliefs produce negative cognitive appraisals, and in turn hypersensitivity to negative events/stressors. The interaction of these schemas with stress results in the catastrophic loss of self-esteem and negative expectations (Beck, 1967, 1976).

Neurochemical level: Negative cognitive appraisals result in hypercortisol secretion (Denson et al., 2009; Gaab et al., 2005). These appraisals can also lead to immune or parasympathetic activation (Denson et al., 2009; Lin et al., 2011), which contribute to anorexia, anergia, and anhedonia ("sickness behavior") that promote energy conservation (Durisko et al., 2015). Dysregulation of several neurotransmitters systems, in particular monoamines (e.g., serotonin, dopamine), likely play a mediating role in these processes as well.

Evolutionary framework: The perceived loss of a vital resource triggers a drastic energy conservation strategy in effort to promote survival (Beck, 1993). Other mammal species exhibit similar symptoms/reactions when exposed to the kinds of event that precipitate depression in humans (events that simulate loss of a close relationship, loss of status, or exclusion from the group).

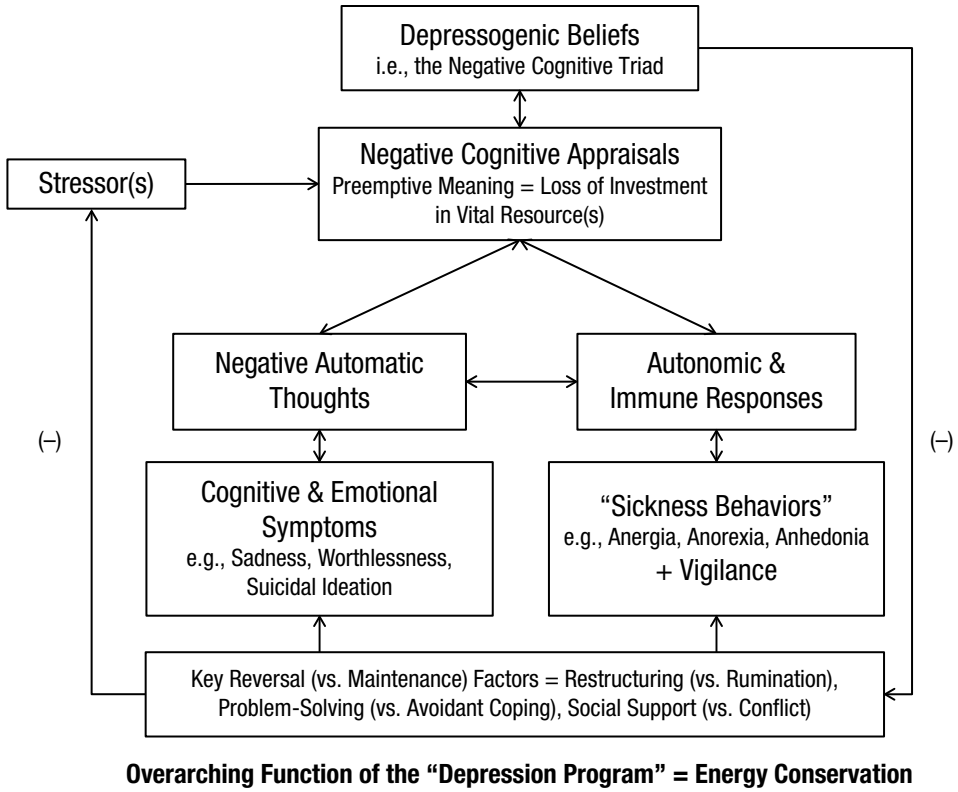

Fig. 2. Precipitation, manifestation, and maintenance of the "depression program." According to the model, precipitating stressors and depressogenic beliefs interact to generate negative cognitive appraisals. If the individual perceives that he or she has *lost a vital investment*, various processes are initiated in service of energy conservation to compensate for this loss. Specifically, these processes consist of (a) negative automatic thoughts that generate cognitive and emotional symptoms (e.g., sadness, feelings of worthlessness) and (b) autonomic and immune responses resulting in "sickness behaviors" (e.g., anorexia, anhedonia) coupled with vigilance. Furthermore, depressogenic beliefs are reinforced/strengthened. Once this program is activated, a number of factors can determine if/when it is terminated, including the individual's available support as well as engagement in cognitive restructuring or problem-solving. However, these processes are undermined by depressogenic beliefs. The converse processes that serve to maintain the depression program (e.g., ruminative thinking, social conflict) can generate additional stress for the individual. (–) indicates proposed negative relationships/effects.

Clinical framework: The clinical features of severe depression result from extreme deactivations of positive schemas and activations of negative ones. If and when these (de)activations reach a certain level (often due to cognitive distortions), the pull to conserve energy can overcome the individual, which undermines adaptive coping and results in clinically significant impairment.

This article is intended to show the synchrony between the psychological and biological findings in normal adaptation and in the predisposition to and precipitation of severe depression. All of the findings related to depression can be joined together to provide a comprehensive model of the disorder that explains its puzzling features.

The unified model is summarized in Figures 1 and 2. The progression or sequence begins with genetic risk/protective factors and childhood trauma, which (alone, or in combination) lead to stress reactivity and negative cognitive biases, reflected in structural and functional brain alterations. Ultimately, this can lead to the development of negative beliefs about the self, world, and future (the negative cognitive triad). In turn, these beliefs accentuate the impact of the negative life experiences or stressors by shaping individual's appraisal of their meaning. When a perceived loss of an investment in a vital resource (often in response to an event or stressor), the "depression program" is initiated. Specifically, negative thoughts trigger consistent emotions (e.g., sadness, guilt) as well as behavioral responses (e.g., withdrawal, inactivity, vigilance). Furthermore, activations of the immune and autonomic nervous systems promote "sickness behaviors" (e.g., loss of appetite, anhedonia). The overarching function of this program is to promote the conservation of

energy, in response to the perceived loss. Prolonged activation of this program can result in consolidation/reinforcement of depressogenic beliefs coupled with neural atrophy in key cognitive brain structures, thus exacerbating future risk.

Figure 2 also highlights several factors that seem to play a key role in symptom course and prognosis, and thus we argue are important in determining whether the depression program is maintained or terminated. These factors are reviewed in the next section, which briefly discusses recovery or "reversal" processes.

Reversing the Depression Program

The depression program can be terminated through the restoration of resources, resulting from situational changes or active problem-solving by the individual. But evolutionary programs can be reversed when corrective interpretations occur. For example, in the fight/flight response, the individual may learn that what seemed like a threat is actually innocuous. Similarly, the depression program is flexible, and can be terminated if the cognitive appraisal turns out to be inaccurate. This can occur when the individual spontaneously makes a correction based on new information. To facilitate this, behavioral flexibility is often crucial, as coping responses motivated by the depressive program (e.g., social withdrawal) generally interfere with exposure to corrective information. Similarly, reversal can occur through reflective/elaborative processing by the individual that fosters cognitive reappraisal (see Beevers, 2005; Troy, Wilhelm, Shallcross, & Mauss, 2010). To facilitate these reversal processes, support from others is beneficial, as evidenced by the buffering effects of social support (see Cohen & Willis, 1985; Kaufman et al., 2004) and, conversely, elevated risk of recurrence associated with criticism by loved ones (e.g., Hooley & Teasdale, 1989). However, depressogenic beliefs (and the other predisposing factors discussed earlier) can potentially undermine these processes. For example, the individual may ignore or discount information provided by others that it inconsistent with his or her beliefs. Thus, these beliefs not only play a key role in the initiation of the depression program, but also can serve to maintain it. Alternatively, beliefs that support processes such as problem-solving (e.g., D'Zurilla, Chang, Nottingham, & Faccini, 1998; Nezu, 1986), restructuring (e.g., Beevers & Meyer, 2004; Papageorgiou & Wells, 2009), and support seeking/utilization (e.g., Collins & Feeney, 2000; DeFronzo, Panzarella, & Butler, 2001) will promote resilience/recovery. More generally, the belief that people have the potential to change/develop seems to promote adaptive coping and may buffer against depression (e.g., Miu & Yeager, 2015; see Dweck & Elliott-Moskwa, 2010).

It is important that these same termination processes can be facilitated through psychotherapy. The engagement with the therapist may be very powerful and in itself help to modify thoughts of worthlessness, helplessness, and hopelessness that keep the depressive program going. In line with this idea, psychotherapy research suggests that these "nonspecific factors" account for about half of the change observed in treatment (Cuijpers et al., 2012). Of course, specific psychotherapy techniques have been shown to be important as well (particularly for those with more severe symptoms; see Driessen, Cuijpers, Hollon, & Dekker, 2010). For example, cognitive restructuring can help change distorted appraisals to more realistic ones. Of note, this can often occur as a result of effective *action* (as opposed to, for example, Socratic questioning) that contradicts the belief of being incapable (Beck, Rush, Shaw, & Emery, 1979). For example, depressed individuals who want to stay in bed because of the evolutionarily mandate to rest generally feel better when they return to engaging in important activities (e.g., work). There is now compelling evidence from extensive clinical trials that these sorts of cognitive and behavioral strategies can have strong and lasting effects on depressogenic thoughts and beliefs (e.g., Cristea et al., 2015; Lorenzo-Luaces, German, & DeRubeis, 2015).

Of course, biological treatments can also help alleviate the symptoms of depression. Most notably, antidepressant medications can be effective (again, particularly in more severe cases; see Fournier et al., 2010). In line with our unified model, there is evidence that a primary mechanism of action for some antidepressant medications may be the promotion of neurogenesis in brain areas such as the hippocampus (see, e.g., Tanis, Newton, & Duman, 2007), which in turn quells HPA dysregulation (see Barden, Reul, & Holsboer, 1995) and possibly negative information processing biases (see Harmer, Goodwin, & Cowen, 2009). These changes seem to precede symptom improvement, and we hypothesize that they may help promote the processing of corrective information. Of course, like psychotherapy, positive expectations may play a key role in the therapeutic effects of these medications, as evidenced by robust placebo effects in antidepressant medication trials (particularly for those with *less* severe symptoms; see Kirsch et al., 2008).

More generally, a number of promising treatment/prevention approaches for depression exist (a full discussion of which is beyond the scope of this article), and our model suggests that *any* intervention that targets key predisposing, precipitating, or resilience factors can reduce risk or alleviate symptoms. These include a variety of psychotherapeutic approaches, such as problem-solving therapy (Nezu, Nezu, & Perri, 1989), acceptance and commitment therapy (Hayes, 2004), and mindfulness-based interventions (Segal, Williams, & Teasdale, 2012). It

is important that current evidence supports the notion that interventions that directly target proximal cognitive factors have the most reliable prophylactic effect (e.g., Hollon, Stewart, & Strunk, 2006; Rohan, Roecklein, Lacy, & Vacek, 2009; Segal et al., 2006). In further support of our integration across levels of analysis, changes that result from such treatments can also be observed in altered functioning in relevant brain regions (e.g., hippocampus, prefrontal cortex; Beevers, Clasen, Enock, & Schnyer et al., 2015; Goldapple et al., 2004; see DeRubeis, Siegle, & Hollon, 2008) as well as endocrine/immune responses (e.g., cortisol levels—Antoni et al., 2000; Gaab et al., 2003; inflammation—Gazal et al., 2013; Moreira et al., 2015). In turn, some promising efforts are under way to develop novel interventions for depression that capitalize on recent advances in our understanding of specific cognitive and neurobiological mechanisms discussed earlier (e.g., Beevers et al., 2015; De Raedt, Vanderhasselt, & Baeken, 2015; Siegle et al., 2014).

Conclusions and Future Directions

In this article, we have presented a unified model of depression, integrating the clinical features with cognitive theory, recent advances in the neurobiology of this phenomenon, and evolutionary perspectives. Our motivation for doing this was to incorporate new findings that have emerged since previous models were published (e.g., Beck, 2008), but more important, present an account that would integrate seemingly disparate work across different frameworks and levels of analysis in a cohesive, coherent, and novel fashion. We also briefly reviewed some approaches to alleviating depression and how they fit within our model. In turn, we hope that this model will motivate further development of new (and more integrative) approaches for treating or preventing depression (see, e.g., De Raedt et al., 2015; Siegle et al., 2014).

Of course, like any theoretical model, the proposed model should be viewed as tentative, to be systematically evaluated and refined/expanded based on new research findings. In fact, given the ambitious goals of this undertaking, it is not surprising that some aspects of the model are relatively speculative. For example, direct evidence for the central mediating role of depressogenic beliefs/schemas in links between information processing, stress reactivity, and depression has proven difficult to obtain, in part because these beliefs/schemas are considered to remain dormant until activated along with symptoms. This could be addressed in future research with priming procedures (e.g., mood inductions; see Gotlib & Krasnoperova, 1998; Lau et al., 2004) or using psychophysiological measures that might be sensitive to these vulnerabilities (e.g., neuroimaging—Zhong et al., 2011; eye tracking—Sears, Newman, Ference, & Thomas, 2011). In turn, such methods of assessing cognitive vulnerability could be examined in studies to determine their predictive power, and ultimately could be used as selection and outcome measures when developing and testing new *preventive* interventions. This work not only would have clear and significant clinical implications, but also would provide important confirmation for key aspects of the model.

More generally, despite major advances in our understanding of the nature and etiology of depression over the past five decades, many important questions remain unanswered. Although it would be unfeasible to discuss them all here, we highlight a few general directions that we consider important to pursue in future research, motivated by our unified model.

1. First and foremost, we hope this model will stimulate more integrative research examining multiple levels of analysis (e.g., cognitive, genetic, neural, hormonal) within the same study (see, e.g., Gotlib et al., 2008). Such work would also fit nicely with the National Institute of Mental Health's Research Domain Criteria initiative, several aspects of which have clear and strong relevance to depression and our model (e.g., loss, reward responsivity).
2. Largely for practical reasons, a bulk of research exploring the neurobiology of depression has been cross-sectional. As biological methodologies continue to become more affordable, we hope that more longitudinal work will be done to explore how neurobiological aspects of depression unfold over time (e.g., structural abnormalities in the hippocampus), and how this relates to cognitive changes/risk.
3. Additional research is needed to determine whether a single model of depression will ever suffice to account for all clinical cases, or instead whether there are distinct subtypes with meaningfully divergent etiological pathways (e.g., Gold, Machado-Vieira, & Pavlatou, 2015). If such heterogeneity were confirmed, it would be critical for future (basic and applied) research to account for this.
4. Although we provided some brief speculations about how treatments for depression might work within the context of our model, the fact remains that our understanding of the key change mechanism(s) in treatments for severe depression is largely speculative. Although this has been explored for a few more established treatment approaches (e.g., cognitive therapy, antidepressant medication; see DeRubeis et al., 2008), it will be particularly important to carefully test putative mechanisms (both psychological and biological) for more recently established ones (e.g., mindfulness-based interventions, transcranial magnetic stimulation).

Ultimately, a better understanding of the mechanisms involved in these treatments not only would help us refine them, but also could help foster the optimization of individual treatment plans (in service of "precision medicine").

5. Perhaps due to the dominance of the disease model, we feel that the topic of resilience has been relatively understudied. For example, it would be interesting to carefully study the cognitive and biological characteristics of individuals who experience significant losses yet due *not* become severely depressed, as well as those who recover quickly without formal treatment (see, e.g., Charney, 2014). Such work would have important implications for validating/refining our unified model, and also direct clinical implications (see, e.g., Waugh & Koster, 2015).

Author Contributions

A. T. Beck developed the framework of the model and wrote the initial draft of the manuscript. K. Bredemeier assisted in reviewing key literatures and updating the model/manuscript. The authors worked closely together to complete final revisions and edits, as well as incorporate feedback from colleagues.

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Notes

1. It is well established that depressive disorders are more common in females (APA, 2013). Nevertheless, the model does explicitly not address these gender differences, based on evidence suggesting that the same factors are involved in the etiology of depression for both genders, but some are simply more common in females (e.g., Hamilton, Stange, Abramson, & Alloy, 2015; Nolen-Hoeksema, Larson, & Grayson, 1999; see Nolen-Hoeksema & Girgus, 1994). Thus, we propose that our model is applicable to depression in both males and females.

2. From this point on, discussions of "resources" or "vital resources" reference these.

3. We define "stressors" broadly, as any significant change that an individual must adjust to. This includes life situations as well as biological insults (e.g., an infection; see Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008; Yirmiya et al., 2000).

4. As we allude to here, there is evidence that many of the predisposing factors discussed in the model are not unique to depression, but rather are common across multiple (if not most) forms of psychopathology (e.g., MacMillan et al., 2001; Psychiatric Genomics Consortium, 2013). Although there is evidence for specificity regarding the proximal cognitive precipitants (e.g., of depression vs. anxiety; see Beck & Clark, 1988; Hankin, Abramson, Miller, & Haeffel, 2004), a discussion of this work is beyond the scope of our article.

5. The prominence of this neural atrophy within the hippocampus is evidenced by a documented negative association between hippocampal volume and depression duration (e.g., Sheline, Wang, Gado, Csernansky, & Vannier, 1996), and may be due to the high concentration of glucocorticoid receptors in this brain region (possibly to promote specific enhancements in cognition during acute stress; see McEwen & Sapolsky, 1995).

6. Seasonal depression appears to be linked with the same distal risk factors (e.g., the *5-HTTLPR* short variant; Rosenthal et al., 1998) and proximal risk factors (e.g., negative automatic thoughts; Rohan, Sigmon, & Dorhofer, 2003) as nonseasonal depression. Thus, we propose that our unified model is also applicable to cases/episodes with a seasonal pattern (but see Rohan, Roecklein, & Haaga, 2009, for an integrative review/model focused on seasonal depression). In fact, seasonal depression could be consider a prototypical manifestation of the evolutionarily derived depression "program" that we propose, given the notable connections with energy conservation and access to vital resources (e.g., supporting reproduction) that have been discussed (e.g., Davis & Levitan, 2005).

7. It is important to note that there is also evidence for immune *suppression* in depression (Blume, Douglas, & Evans, 2011), in line with established links among stress, cortisol, and immune functioning (see, e.g., Selye, 1973). However, immune activation and suppression are not mutually exclusive, and may even be interrelated in important ways (see, e.g., Blume et al., 2011; Segerstrom, 2007).

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