Understanding vulnerability for depression from a cognitive neuroscience perspective: A reappraisal of attentional factors and a new conceptual framework

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We propose a framework to understand increases in vulnerability for depression after recurrent episodes that links attention processes and schema activation to negative mood states, by integrating cognitive and neurobiological findings. Depression is characterized by a mood-congruent attentional bias at later stages of information processing. The basic idea of our framework is that decreased activity in prefrontal areas, mediated by the serotonin metabolism which the HPA axis controls, is associated with an impaired attenuation of subcortical regions, resulting in prolonged activation of the amygdala in response to stressors in the environment. Reduced prefrontal control in interaction with depressogenic schemas leads to impaired ability to exert attentional inhibitory control over negative elaborative processes such as rumination, leading in turn to sustained negative affect. These elaborative processes are triggered by the activation of negative schemas after confrontation with stressors. In our framework, attentional impairments are postulated as a crucial process in explaining the increasing vulnerability after depressive episodes, linking cognitive and biological vulnerability factors. We review the empirical data on the biological factors associated with the attentional impairments and detail how they are associated with rumination and mood regulation. The aim of our framework is to stimulate translational research.

Major depressive disorder, one of the most common psychiatric disorders, is a recurrent problem for many people (Goodwin, Jacobi, Bittner, & Wittchen, 2006). Although there are currently well-established cognitive/behavioral (Hollon & Dimidjian, 2009) and somatic (Gitlin, 2009) treatment options for depression, relapse or recurrence rate after remission or recovery remains very high. This indicates that current treatment options are insufficiently successful in identifying and diminishing underlying vulnerability.

Vulnerability can be conceptualized as a trait-like latent endogenous process reactive to the effects of stress, residing in genetic, biological, and psychological variables (Ingram & Siegle, 2009). There is accumulating evidence for a kindling effect in depression, which means that after each episode people become more vulnerable to relapse or recurrence, because successive depressive episodes are triggered by progressively milder stressors (Monroe & Harkness, 2005). The number of previous episodes is revealed in several studies (e.g., Kessing, Hansen, Andersen, & Angst, 2004) to be among the strongest predictors of relapse or recurrence. All these data are in line with the idea that depressive episodes leave a "scar," which increases vulnerability to new episodes. Understanding underlying mechanisms of this increasing vulnerability to depression is of crucial importance to improving treatment.

To date, most vulnerability models have focused on either biological or psychological/cognitive processes, although recent research increasingly focuses on the interplay between cognitive and biological processes in depression. We aimed to develop a framework to understand the increasing vulnerability to depression, focusing on the interplay between cognitive and biological processes. Although many other cognitive processes, such as motivation and memory, may also be relevant to depression vulnerability, we propose a new conceptual framework, with mood-congruent attentional biases as the central process. In contrast to previously held ideas (Williams, Watts, MacLeod, & Mathews, 1997), but in line with recent research, we argue that attentional factors are of crucial importance in understanding increasing vulnerability for depression. Attention is considered a central process, being directly related to biological processes (e.g., prefrontal functioning) affected by recurrent depression, as well as cognitive (i.e., rumination) and affective (e.g., emotion regulation) processes linked to the development of (recurrent) episodes of depression. Interestingly, although many affective disorders share similar neurobiological and cognitive features related to general emotion regulation, depression is characterized by a specific attentional bias at later stages of information processing, which fits with depression-specific biological (e.g., anterior cingu-

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late cortex hypoactivation) and cognitive (e.g., rumination) markers of vulnerability.

This review builds on the extant knowledge of cognitive and biological factors to explain how attentional processes provide a link between cognitive processes and biological factors. We will start from a cognitive perspective on depression vulnerability, followed by a review of the existing behavioral data on mood-congruent attentional bias in depression. Thereafter, we will situate these attention processes within a neurobiological view on increasing vulnerability to depression, providing an outline of the different building blocks of our framework. Finally, we will summarize the basic ideas in one framework. Although several of the cognitive and biological markers we will address have already been described separately in other reviews, our aim is to integrate these findings to understand the mechanisms underlying the kindling effect. We will outline cognitive and neurobiological evidence showing the mechanism of increasing vulnerability to the development of new depressive episodes.

Cognitive Framework on Increasing Vulnerability to Depression

Research on information processing in emotional disorders has predominantly been guided by the *cognitive schema theory* proposed by Beck (1967; Clark, Beck, & Alford, 1999) and Bower's (1981) *associative network theory*. Beck and colleagues argued that information processing is guided by schemas, defined as memory structures that, on the basis of previous experiences, contain and organize information about the self, the world, and the future. Depression would be characterized by negative schemas involving loss and failure. These schemas are thought to bias encoding of information. Specific information-processing biases at the level of attention, interpretation, and memory mediate incoming information processing and subjective (emotional) experience. A fundamental aspect of Beck's cognitive model of depression is that cognitive structures or schemas remain latent until activated by relevant stimuli.

Although this model is very broad and general, the concept of *cognitive reactivity* is crucial to our understanding of how the cognitive model links to increasing vulnerability. Cognitive reactivity relates to fluctuations in negative self-attitudes in response to daily (stressful) events (Butler, Hokanson, & Flynn, 1994). The crucial question is why certain individuals are or become more reactive to stressors than do others. The reason people become more sensitive to stressors after each depressive episode relates directly to our question of increasing vulnerability or to the "scar" hypothesis. Teasdale (1988) proposed the *differential activation hypothesis* (DAH) to account for this phenomenon. This framework assumes that depression becomes ever more severe or persistent because negative thinking patterns become more readily accessible and reactive on stressors and negative mood after each successive depressive episode. More specifically, the DAH assumes that during each episode the association between depressed mood and negative thinking patterns is strengthened. Therefore, a depressive mood, which can be evoked by daily stressors, reactivates the negative thinking patterns more easily with increasing depressive episodes. This associative network account can elegantly explain why, after multiple episodes, minor daily hassles leading to minor mood changes can result in a downward spiral of negative thinking patterns.

Many studies found supportive evidence for core predictions from the DAH. It has been shown that people who have experienced depression in the past—compared with never-depressed controls—report more dysfunctional attitudes, negative cognitive biases, and decreased positive biases after negative mood priming such as sad music, imaging of sad autobiographical memories, social rejection, sad film clips, or induced failure experiences (for a review, see Scher, Ingram, & Segal, 2005). Importantly, longitudinal studies have shown that the existence of cognitive reactivity before a stressful life event predicts the onset of depressive episodes (e.g., Hankin, Abramson, Miller, & Haeffel, 2004). For instance, a study by Segal, Gemar, and Williams (1999) investigated whether cognitive reactivity could predict relapse in a group of formerly depressed patients. Patients underwent negative mood induction, in which changes in dysfunctional attitudes were examined during both euthimic and induced transient dysphoric moods. The analyses showed that the magnitude of mood-induced cognitive reactivity significantly predicted relapse over a 4-year interval, with 70% of participants correctly classified as either relapsers or nonrelapsers. Such findings are indicative of a latent cognitive vulnerability for depression. In a recent study, it could be demonstrated that negative cognitions mediated the relationship between the number of past depressive episodes and poorer treatment response, which is in line with the idea that the threshold to react with negative cognitions decreases with accumulating episodes (Beevers, Wells, & Miller, 2007). These data, in combination with the observation that the probability of relapse or recurrence increases 16% with each episode (Solomon et al., 2000), are in line with the DAH conceptualization of increasing cognitive vulnerability.

However, an increased reactivity to sad moods after depressive episodes does not explain why vulnerable people are unable to stop negative thinking patterns and end up in enduring elaborative thinking patterns. Sheppard and Teasdale (2000) proposed two sources of dysfunctional thoughts in depression: (1) increased access to dysfunctional schemas, which refers to the process of schema activation, and (2) decreased monitoring of the thoughts and feelings that are the products of this schema activation, which they refer to as *reduced metacognitive monitoring*. They found evidence that depressed patients, compared with healthy controls, show both increased schema accessibility and decreased metacognitive monitoring. Importantly, remission is accompanied by improved metacognitive abilities, but the accessibility of schemas remains heightened compared with never-depressed controls (Sheppard & Teasdale, 2004). This suggests that remission is mainly characterized by an increased ability to control negative thoughts, a mechanism that we will discuss in detail.

Related to cognitive strategies in response to negative thoughts and mood, the *response styles theory of depression*, proposed by Nolen-Hoeksema (1991), states that the course of depression is strongly influenced by how one responds to depressive symptoms. People who respond to a sad mood and to depressive symptoms by engaging in uncontrollable ruminative thinking about the causes and consequences of their depression are more likely to remain longer in a depressed episode (Nolen-Hoeksema, Morrow, & Fredrickson, 1993). Importantly, prospective studies have shown that rumination plays a role in both the onset and maintenance of depression (Nolen-Hoeksema, 2000). Cognitive reactivity and uncontrollable rumination are both of importance in increasing vulnerability for depression. A recent questionnaire study (Moulds et al., 2008) found evidence of a relationship between cognitive reactivity and a ruminative response style (response style questionnaire: Nolen-Hoeksema, 1991). This correlation between cognitive reactivity and rumination was significant even after controlling for current depressive symptoms. The latter finding warrants further consideration of the underlying mechanisms relevant to both processes.

In summary, mild dysphoria after a stressor can lead to the activation of negative schemas and continued elaboration on a negative mood, but this process does not explain why depression-prone individuals are unable to stop ruminative processes. We propose that diminished attentional control plays a crucial role in sustained negative cognitions and affect, linking cognitive and neurobiological evidence. We will describe a neurobiological account of attentional processes to gain a deeper understanding of these continued elaborative processes. In this account, we will emphasize the role of attentional processing of mood-congruent information. We start by considering the available data on dysfunctional attentional processes in depression.

Attentional Characteristics of Depression

Difficulty concentrating, which has been related to reduced attentional control (Ellis & Ashbrook, 1988; Hertel & Rude, 1991), is considered to be a characteristic symptom of depressive episodes (American Psychiatric Association, 2000). However, studies examining attentional functioning in general, using cognitive neuropsychological tasks, do not unambiguously support this idea. For instance, studies examining working memory tasks that heavily rely on attentional control have frequently failed to show strong and broad impairments in depressed versus nondepressed individuals (for a review, see Joormann, Yoon, & Zetsche, 2007). Instead, studies indicate that depression is mainly characterized by attentional problems under conditions of set switching and/or dual-task conditions (Murphy et al., 1999; Rokke, Arnell, Koch, & Andrews, 2002). The absence of broad impairments in the processing of neutral information has led investigators to start examining whether attentional impairments are observed under conditions of processing emotion-relevant, mood-congruent information.

Related to the prediction of schema-congruent information processing bias (Clark et al., 1999), a wealth of studies have examined whether attentional problems are observed when mood-congruent negative information is processed. This phenomenon is typically referred to as *attentional bias*, whereby depressed individuals, compared with nondepressed controls, show greater attention toward negative material than toward neutral material. Initial research failed to show clear evidence of attentional bias (for a review, see Mogg & Bradley, 2005). Williams et al. (1997), in their influential theory on information-processing bias in anxiety and depression, even concluded that depression is not associated with mood-congruent attentional bias but is instead related to strategic elaboration of negative material, which causes improved explicit memory for this type of information. However, in recent neuropsychological and behavioral studies, it has consistently been found that, under specific conditions, attentional bias can be demonstrated (see below). These conditions include a relatively long stimulus presentation (>1,000 msec) and self-relevant stimulus material (e.g., depression-relevant words, or emotional facial expressions). In addition, there are indications from behavioral high-risk studies (Beevers & Carver, 2003) and treatment studies (Teasdale, Segal, & Williams, 1995) that attentional factors may play an important role in the etiology and maintenance of depression. Yet, to date, little is known about the conceptual nature of mood-congruent attentional bias in depression and its relation to other processing biases and biological factors in depression. In order to understand the influences of mood-congruent attentional bias on depressive symptomatology, an improved conceptualization of attentional influences on depression is required.

In addressing these issues, we will start by reviewing the empirical data on the association between depression and mood-congruent attentional bias. Most studies have been performed using behavioral tasks and eye-movement registration methodology. We have limited the review of empirical data to tasks that have been used frequently in the study of attentional bias in depression. Note that the data from the emotional Stroop task are not considered in this review. A concise review of these data has been provided by Williams, Mathews, and MacLeod (1996). Moreover, to date, the emotional Stroop task is not considered a valid measure of visual attention because of interpretational difficulties; in it, delayed color-naming of emotional words compared with neutral words has traditionally been taken as evidence for facilitated attentional capture by the emotional meaning of the words. However, it has been argued that delayed responding in this task cannot be unambiguously interpreted as an attentional effect. Alternative causes of delayed responding on emotional stimuli are, among others, general interference effects (Algom, Chajut, & Lev, 2004) and cognitive avoidance (De Ruiter & Brosschot, 1994).

This review draws on findings in clinically depressed individuals as well as in subclinically depressed individuals (referred to as *dysphoric*). These are individuals, often undergraduates, who indicate subclinical symptoms of depression on depression inventories. Although dysphoric individuals are not fully comparable with depressed individuals (see Ingram & Siegle, 2009), many studies have

been conducted with dysphoric individuals, and the inclusion of these data provides a richer database for the present purposes. We included only studies in which a clear distinction can be made between dysphoric and nondysphoric individuals (excluding correlations and median-split procedures without any preselection). A comprehensive overview of all separate studies (from 1986 to 2008) is provided in the Appendix. In the text, we briefly describe the procedure of each task, describe the commonly observed pattern of data, and highlight some of the most relevant findings.

Empirical Data on Mood-Congruent Attentional Bias in Depression

Visual dot probe task. In response to the interpretational problems of the emotional Stroop task, the dot probe paradigm was developed by MacLeod, Mathews, and Tata (1986) to examine selective visual attention. In their initial study, word pairs (one emotional, one neutral) were presented at two spatially separated locations (one upper, one lower location) of a screen, followed by a dot probe. The main assumption of this task is that individuals will respond faster to probes presented at the spatial location that is previously attended, typically in function of selective attention toward emotional rather than neutral information. Careful inspection of data generated by dot probe studies reveals an interesting pattern of results. There is no evidence for attentional bias at presentation durations of less than 1 sec. However, when a presentation duration of 1 sec or longer was used, six out of seven studies provided some evidence for an attentional bias for negative information, although there is considerable variation in the precise nature of these effects across the studies. This effect is observed in clinically depressed individuals (e.g., Gotlib, Kasch, et al., 2004; Gotlib, Krasnoperova, Yue, & Joormann, 2004; Joormann & Gotlib, 2007), as well as dysphoric individuals (Bradley, Mogg, & Lee, 1997; Shane & Peterson, 2007).

There is also some evidence of absence of positive bias in depression and dysphoria. In depressed or dysphoric individuals, there is usually no bias toward positive material, whereas nondepressed individuals frequently orient more strongly toward positive than toward neutral information. However, reduced attention toward positive material in the dot probe task is found only in some studies, and is not unambiguously supported across studies.

Deployment of attention task. This task was developed by Gotlib, McLachlan, and Katz (1988). It bears a number of similarities to the dot probe task, but is based on a different rationale. In this task, word pairs are presented on two vertically separated locations. Two differently colored bars subsequently replace these words. Participants are misinformed that one of the colored bars will temporally precede the other bar and are required to determine which bar was presented first. Based on the idea that bars presented at attended locations will be detected more rapidly (cf. the *law of prior entry*; Titchener, 1908), this paradigm allows investigating whether attention is systematically drawn to certain classes of information.

In contrast to the dot probe task, only a couple of studies have been performed using this methodology, and it has generated consistent but surprising data. This set of studies found that depressed individuals are characterized by a lack of (1) the attentional bias for positive words present in nondepressed individuals (*positive bias*; Gotlib et al., 1988); or (2) the attentional avoidance of negative information present in nondepressed individuals (*protective bias*; McCabe & Gotlib, 1995). The absence of attentional bias has been related to the concept of "even-handedness" by depressed individuals, referring to an absence of attentional preferences for either positive or negative material due to their amotivational state. These findings in clinically depressed individuals have also been replicated in dysphoric individuals.

Clearly, data from the deployment-of-attention task differ from the findings in the dot probe task. It must be noted that this task has been used less frequently than has the dot probe task, so there is little information on the precise attentional processes and experimental parameters in it. Moreover, this task has been used only with emotional words instead of with more potent stimulus material, such as emotional facial expressions.

Visual search task. The visual search task is a well-established paradigm in experimental psychology. It investigates the automatic versus the controlled detection of stimuli (Treisman & Souther, 1985). In a typical version of this task, individuals are asked to indicate the presence of a target stimulus within an array of distracting stimuli. Hansen and Hansen (1988) were the first to develop an emotional face-in-the-crowd variant of this task. Recently, this task has also been used to examine attentional bias for emotional material in depression.

In a first study (Suslow, Junghanns, & Arolt, 2001), individuals had to examine displays of schematic faces in the presence of a negative or positive target stimulus. These displays were presented for a relatively short duration, and the data showed that depressed individuals were slower to detect the positive faces. In a second study (Suslow et al., 2004), the same effect was found in a depressed population in remission. It is important to note that the two studies by Suslow and colleagues were specifically aimed at the initial detection of emotional information in depression.

Using a different approach, Rinck and Becker (2005) had individuals search for four categories of target words embedded in four categories of distracting words. In this task, either neutral or valenced targets were presented within an array of either neutral or valenced distractors. With this approach, a differentiation could be made between detection and distraction of certain classes of valenced information. The outcome of that study was that depression was associated with increased distraction by negative words. However, these findings were not replicated by a recent study presenting schematic faces (Karparova, Kersting, & Suslow, 2007). One important issue in explaining this mixed pattern of findings is that, in the visual search paradigm, participants tend to base their search strategy on lower level visual features instead of the emotional meaning of stimuli (see Cave & Batty, 2006). Search strategies based on lower level features may

reduce the amount of attention to more holistic, emotionally relevant material.

Exogenous cuing paradigm. Posner's (1980) exogenous cuing paradigm is a commonly used task in cognitive experimental psychology, and has been used to distinguish between specific attentional operations. The emotional modification of this spatial cuing task allows the investigation of two attentional operations: (1) attentional engagement with a new stimulus, and (2) attentional disengagement from a previously attended stimulus. Recently, it has been argued that the assessment of these two different components is important in determining the nature of attentional bias (Fox, Russo, Bowles, & Dutton, 2001; Koster, De Raedt, Goeleven, Franck, & Crombez, 2005). In fact, Bradley, Mogg, and Lee (1997) already suggested that this distinction might map onto the differentiation between processing biases at initial versus later stages of information processing, with depression being more strongly associated with the bias at later stages.

In this task, participants are asked to detect a visual target presented on the left or right side of a fixation cross. On a proportion of the trials ("valid" trials), a peripheral cue precedes the target at the same spatial location. On the remaining trials ("invalid" trials), the target is presented at the opposite spatial location from the cue. In the emotional modification of this paradigm, the emotional value of the cue is systematically varied (e.g., negative/neutral). This allows the investigation of attentional engagement by emotional cues through examination of reaction time (RT), and/or accuracy, benefits on valid trials cued by emotional versus neutral information. Attentional disengagement from emotional cues can be studied through examination of RT costs on invalid trials cued by emotional versus neutral information.

At short intervals between cue onset and target onset (stimulus onset asynchrony [SOA] < 300 msec), participants are typically faster to respond to the valid than to the invalid trials. This is called the *cue validity effect*. At longer SOAs, the cue validity effect disappears and even reverses, because attention to the location of a previously attended stimulus is inhibited in favor of new locations. This is the *inhibition of return effect* (IOR; Posner & Cohen, 1984). Two strategies have been applied to investigate attentional bias in psychopathology in this paradigm. First, with short SOAs between cue and target, attentional engagement and disengagement have been investigated. Second, with longer cue presentations or SOAs, one can examine the emotional modification of the IOR as well. It may be expected that, in the case of emotionally relevant stimulus material, the IOR will not emerge as easily as with neutral information, because of impaired attentional disengagement. This would mean that the time course of the cue validity effect was extended with emotional stimuli (hereafter referred to as "the enhanced cue validity effect"). Using the spatial cuing task, Derryberry and Reed (2002) showed that the temporal processing of negative information in high-trait-anxious individuals was modulated by their level of attentional control. At later stages of information processing, anxious individuals who score high on attentional control avert attention from negative information, whereas those with low attentional control still show an attentional bias for such information.

The emotional modification of a cuing task was applied in a study on attention for negative and positive words in dysphoric and nondysphoric individuals (Koster et al., 2005). In two experiments using long cue presentations, it was observed that dysphoric individuals showed a greater cue validity effect for negative words than did nondysphoric individuals. This effect was positively correlated with impaired disengagement from negative material in the dysphoric individuals. These effects were replicated in a clinically depressed sample using emotional facial expressions as cues (Leyman, De Raedt, Schacht, & Koster, 2007). In addition, the dysphoric individuals oriented less to positive words than did the nondysphoric individuals. In a study with dysphoric and nondysphoric participants (Ellenbogen, Schwartzman, Stewart, & Walker, 2002), it was found that, under stress, dysphoric individuals had difficulty disengaging from cues. However, this effect occurred regardless of cue valence (Ellenbogen et al., 2002). In sum, spatial cuing studies have been successful in isolating the components of attentional bias in depression, suggesting that attentional disengagement of negative information is impaired.

Eye-movement methodology. One important problem of the aforementioned tasks is that attention is investigated in conditions under which individuals are performing a primary task, and emotional material is presented as distracting, task-irrelevant information. Arguably, it could be that these specific task conditions lead to an underestimation of attentional bias, since emotional information is often task relevant and important to the individual's goal. Moreover, it is noteworthy that the behavioral paradigms discussed all depend on RT data, with depression being associated with response slowing that may hamper the interpretation of such data.

Therefore, researchers have argued that eye-movement recording allows a more valid measure of attention in depression. In studies using eye registration, various methodologies have been applied to examine attentional bias. A first study by Matthews and Antes (1992) examined eye fixations to sad, happy, and neutral regions of pictures, mean gaze time for each of these regions, and mean number of first fixations. Dysphorics and nondysphorics both fixated more and longer on happy material than on sad material. However, the dysphorics did fixate more on the sad regions than did the nondysphorics. In a study by Mogg, Millar, and Bradley (2000), initial orienting biases were examined by combining a dot probe task with eye-registration methodology. They specifically examined direction and latency of the first eye movement in response to emotional faces. This study revealed no differential attentional effects for emotional faces in the depressed individuals compared with the controls. Given the findings presented earlier, it is not surprising that depressed individuals did not display initial attentional bias.

In a naturalistic viewing study, fixation time (total time looked at a picture), fixation frequency (number of fixations), and glance duration (average duration of fixation for emotional versus neutral photographs) were examined

in depressed individuals (Eizenman et al., 2003). Using these indices, it was found that depressed individuals had a longer fixation time and longer glance duration for dysphoric pictures than did controls. These data are similar to the findings in the dot probe and the spatial cuing task. Recent studies in which individuals were viewing emotional information provide further evidence of the impaired disengagement hypothesis (Caseras, Garner, Bradley, & Mogg, 2007; Kellough, Beevers, Ellis, & Wells, 2008; Leyman, De Raedt, Vaeyens, & Phillipaerts, in press).

Summary. Despite initial mixed findings on attentional bias, there is now converging evidence from dot probe, spatial cuing, and eye-registration studies that depression is associated with impaired attentional disengagement. This effect is mainly found when longer stimulus presentations are used, which is indicative of a bias at later stages of processing. Moreover, this bias reveals itself to be specific to negative self-relevant material, although the absence of a positivity bias observed in nondepressed people has also been observed. It is noteworthy that, although the corpus of empirical data on attention in depression mainly relies on visuospatial tasks, the finding of impaired disengagement from negative material has also been corroborated in a recent study using a modified attentional blink task that did not rely on spatial attention processes (Koster, De Raedt, Tibboel, De Jong, & Verschuere, 2009).

Attentional Bias, Attentional Control, and Depression Vulnerability

Although many researchers start from the assumption that attentional bias is a vulnerability factor for the development of depression, the studies mentioned above are all cross-sectional, which means that it is impossible to make inferences about causality. In this section, we will discuss prospective and experimental studies investigating the causal relationship between attentional bias, emotional reactivity, and depressive symptoms. Thereafter, we will explore the link between attentional bias and depression-relevant cognitive processes related to emotion regulation.

Causal influence of attentional bias on depression. In cognitive theories, information processing biases are considered to be a vulnerabiliy factor for the etiology, maintenance, and recurrence of depressive episodes (Clark et al., 1999). However, assumptions on a causal relationship between attentional biases and depression can only be confirmed by research that goes beyond cross-sectional designs. A number of prospective studies suggest that attentional bias is associated with emotional reactivity and precedes the development of anxiety and depression. In a seminal study by MacLeod and Hagan (1992), an emotional Stroop task was administered to a group of women before they underwent a gynecological examination. Although, as mentioned before, Stroop effects cannot unequivocally be considered a valid index of attentional bias, the results of this study are interesting. It was found that a bias toward subliminally presented negative information was the best predictor of enhanced emotional reactivity to a stressful outcome. In the context of depression, Beevers and Carver (2003) demonstrated

that attentional biases, as measured with a dot probe task, interacted with intervening life stress to predict higher scores on depression 7 weeks later. Furthermore, another study using a dot probe task has demonstrated a mood-congruent attentional biases after a negative mood induction in never-depressed offspring at risk for the development of depression (Joormann, Talbot, & Gotlib, 2007).

Importantly, no strict conclusions concerning causal hypotheses can be drawn from prospective studies, because the influence of a potential third factor that could account for the established associations cannot be ruled out. It could be that participants demonstrating an attentional bias at pretesting differed from the individuals who did not demonstrate an attentional bias on variables not controlled for. The only way to adequately address causal hypotheses is by experimentally manipulating attentional bias in order to test whether variations in the bias influence the emotional reactivity or depressive symptoms.

To experimentally manipulate attentional bias, cognitive bias modification (CBM) procedures have been developed (MacLeod, Koster, & Fox, 2009). These procedures intend to train the participant in orienting toward or away from specific emotional stimuli through systematic manipulation of contingencies between the valence of the stimulus and the location of a target to which the participant has to respond. Using a modified dot probe task, MacLeod, Rutherford, Campbell, Ebsworthy, and Holker (2002) created a task in which the dot probe appeared at the same location of the negative cue in every trial to induce attentional bias. This prompted the participant to orient toward the negative information. To reduce attentional bias, the dot probe was set to always appear on the opposite side of a negative stimulus, prompting participants to divert their attention from negative information.

Several studies investigating this type of attentional training procedure have been able to successfully modify attentional bias, and they found significant effects on emotional reactivity to induced or to real-life stressors in normal volunteers (e.g., Dandeneau & Baldwin, 2004; Dandeneau, Baldwin, Baccus, Sakellaropoulo, & Pruessner, 2007; MacLeod et al., 2002). These results confirm the hypothesized causal relationship between attentional bias and vulnerability factors associated with the development of emotional disorders. Moreover, a recent study investigated attentional retraining in dysphoria (Wells & Beevers, in press). During a period of 2 weeks, 16 dysphoric students completed four sessions of attentional training. The participants in the training condition reported significantly fewer depressive symptoms immediately after training (effect size: $d = 0.52$), as well as at a follow-up 2 weeks later (effect size: $d = 1.04$), than in a no-training condition. Interestingly, improvement in the training condition was mediated by change in attentional bias. These preliminary results are in need of replication, but they are in line with the assumption of causality ascribed to biased attention in the course of depressive symptoms.

Influence of attentional bias on cognitive processes. Depression is generally considered to be associated with a wide range of affective and somatic symptoms, as well as

with cognitive deficits. One could argue that attentional bias will have a proximal relationship to cognitive processes implicated in depression. In emerging research, attentional bias has been investigated in relation to rumination and memory.

As we discussed earlier, a ruminative thinking style is considered an important cognitive risk factor in depression, as shown by prospective studies (e.g., Nolen-Hoeksema, 2000). Attentional bias may contribute to the continuous elaborated processing of negative information observed in depressed individuals. In fact, rumination has sometimes even been defined in relation to attention, with, for instance, Nolen-Hoeksema et al. (1993) stating that ruminative responses are "behaviors or thoughts that focus an individual's attention on his or her depressed mood, and [on] the possible causes and consequences of that mood" (p. 20). This relation has been confirmed in a dot probe study in depressed patients, in which trait rumination was associated with an attentional bias toward negative words even when depressive symptoms were statistically controlled for (Donaldson, Lam, & Mathews, 2007). This also provides crucial confirmation that data from behavioral measures of attention can be related to internal attentional processes.

Attention is also considered to be related to inhibitory control and working memory; that is, it plays a role in preventing irrelevant emotional material from entering working memory, and it is important in the updating of working memory, with both concepts being crucial in emotion regulation (see Joormann & Gotlib, 2008). To our knowledge, there is no empirical research directly linking the concepts of impaired disengagement, inhibition, and working memory in depression. Nevertheless, it is worth mentioning that depression was found to be associated with impaired inhibition of negative material (Goeleven, De Raedt, Baert, & Koster, 2006; Joormann, 2004) and impaired abilities to remove negative material from working memory (Joormann & Gotlib, 2008).

Finally, there is also some research linking attention and memory bias in depression. Depression has been robustly related to biased recall of information on explicit memory tests, with greater recall of negative information than of neutral and positive material, whereas healthy controls show greater memory for positive material than for negative and neutral material (e.g., Bradley, Mogg, & Williams, 1995; Denny & Hunt, 1992). In a first study, it has been found in clinically depressed individuals that incidental recall of emotional words did not correlate with attentional bias (Gotlib, Kasch, et al., 2004). However, in that study, stimuli from the attentional tasks (pictures) were different from those in the recall task (words), reducing the probability of finding strong correlations. In a recent study, an incidental free-recall test was administered immediately after a spatial cuing task, examining recall of the words (negative, positive, and neutral words) presented during the attention task. In dysphoric individuals, it was found that attentional bias toward negative words was associated with enhanced recall of these negative words relative to neutral words. This effect remained significant even when depression severity was controlled for (Koster, De Raedt, Leyman, & De Lissnyder, 2010).

Summary. In the preceding sections, we have discussed research indicating that attentional bias toward negative information may be causally related to emotional reactivity and depressive symptoms. Moreover, there is emerging research linking attentional bias with other depression-relevant cognitive processes and products, such as rumination and memory. In addition, there are interesting links between attentional bias, attentional inhibition, and working memory, all processes heavily involved in emotion regulation.

In the next section, the attention deficiencies observed in depression will be framed within a neurobiological account, starting from stressors in the environment that activate the hypothalamic pituitary adrenocortical (HPA) axis with a specific influence on the serotonin metabolism, leading to decreased activity in prefrontal areas. This decreased activity in prefrontal areas is associated with attenuated inhibition of subcortical regions, resulting in prolonged activation of the amygdala and an impaired ability to exert attentional inhibitory control over negative elaborative processes such as rumination. These elaborative processes are caused by the activation of negative schemas after confrontation with stressors. Impaired attentional control can explain the cascade of depressive symptoms in relation to enhanced elaboration of negative information: problems in emotion regulation and persistent negative affect.

Neurobiological Underpinnings of Impaired Attentional Control and Depression Vulnerability

The HPA axis. Many studies show that stressors induce biological changes over time, at both hormonal and neurochemical levels (Thase, 2009). The HPA axis is the hallmark of the stress response, stimulating the release of corticosteroids. The HPA axis is stimulated in reaction to the perception of stressors, which takes place in different subcortical areas, depending on the nature of the stressor. Subcorticol areas immediately activated following stress exposure are located in the limbic system, such as the thalamus, amygdala, and hippocampus (Sergerie, Chochol, & Armony, 2008).

Neuronal input from these and other related brain regions reaches the hypothalamus, and this activating input provokes the release of adrenocorticotrophic hormone-releasing factor (CRF), which in turn activates the secretion of adrenocorticotrophic hormone (ACTH) in the pituitary. ACTH travels via the bloodstream to the adrenal cortex in the periphery of the body, where it targets receptors in the adrenal cortex to release glucocorticoid hormones (cortisol). An important aspect of the HPA system is the inhibitory feedback regulation after the stressor has disappeared, inhibiting CRF in the hypothalamus as well as the secretion of ACTH in the pituitary. This feedback mechanism is regulated by the glucocorticoids interacting with their receptors in multiple target tissues related to the HPA axis (Pariante & Lightman, 2008).

The activated HPA axis regulates bodily functions such as glucose and lipid metabolism and immunity, which promotes survival in life-threatening situations. Moreover, the HPA axis also has important effects on the brain. For

example, glucocorticoids regulate neuronal survival and neurogenesis, influence the size of the hippocampus, and are related to the acquisition of new memories and emotional appraisal processes (Herbert et al., 2006). However, sustained cortisol hyperdrive over time has detrimental effects because it increases the risk for hypertension, obesity, heart disease, and several autoimmune diseases (McEwen, 2000).

Many studies over the last decades have demonstrated that hyperactivity of the HPA axis is one of the most consistent biological findings in depression (van Praag, de Kloet, & van Os, 2004). Sustained hypercortisolism can result from dysfunctional glucocorticoid-mediated feedback inhibition (Holsboer, 1995) and there is accumulating evidence that prolonged hypercortisolism can impair the HPA axis permanently (Sapolsky, 1996). By demonstrating that the HPA axis is not suppressed by pharmacological stimulation with an oral dose of the synthetic glucocorticoid dexamethasone (the dexamethasone suppression test) (Holsboer, 1995), many studies show that feedback inhibition is impaired in major depression. Melancholic depression can be conceptualized as a prolonged and intensified stress response of the HPA axis, which results in a disruption of the homeostatic interplay between prefrontal cortex and amygdala activity (Gold & Chrousos, 2002).

HPA axis dysfunctioning remains a cornerstone of neurobiological depression research, despite open questions on the specificity for depression and the melancholic subtype of depression (van Praag et al., 2004). In a recent review, Pariante and Lightman (2008) concentrated on the most recent advances in this research area. They present data supporting the hypothesis that HPA axis hyperactivity is not a consequence or an epiphenomenon of depression but is a risk factor predisposing to the development of depression, influenced by early stressful life experiences programming molecular changes, as well as by genetic liability. In an exemplary study, women who have been sexually or physically abused in childhood, even if they are not currently depressed, show enhanced ACTH and heart rate responses when exposed to a standardized psychosocial stressor. Moreover, during a depressed episode, they show the largest increase in ACTH secretion and heart rate, as well as a large increase in cortisol secretion (Heim & Nemeroff, 2001). In clinical studies, indications have been found that normalization of HPA axis functioning following treatment with antidepressive drugs might be a prerequisite for stable remission of depression, showing that persistent cortisol nonsuppression in the DST after recovery is predictive for relapse (e.g., O'Toole, Sekula, & Rubin, 1997). Such findings indicate that dysregulation of the HPA system is associated with relapse and persistency of depression (Mizoguchi, Shoji, Ikeda, Tanaka, & Tabira, 2008). Importantly, it has been demonstrated that recovered depressed patients continue to show a disturbed HPA axis functioning (Bhagwagar, Hafizi, & Cowen, 2003), which means that it is not only an epiphenomenon of a depressed state.

The relationship between the HPA axis and neurotransmitter systems. A large number of studies show a relationship between HPA axis functioning and monoaminergic neurotransmission, more specifically the serotonin metabolism. For example, research by Mizoguchi and coworkers illustrates this interaction in animal studies. In line with many other studies, chronically stressed rats show a dysregulation of the HPA system, characterized by dexamethasone negative feedback resistance (Mizoguchi et al., 2001). Moreover, chronic stress also reduces serotonergic transmission in the PFC (Mizoguchi, Yuzurihara, Ishige, Sasaki, & Tabira, 2002), and there are indications that serotonin (5-HT$_{1A}$) receptors are downregulated as a consequence of chronic stress exposure (López, Liberzon, Vázquez, Young, & Watson, 1999). Importantly, it has been demonstrated that there are reciprocal causal interactions between the HPA axis and the 5-HT system (Lanfumey, Mongeau, Cohen-Salmon, & Hamon, 2008).

In line with these results and HPA axis studies, it has been demonstrated that the serotonin (5-hydroxytryptamine or 5-HT) system is influenced by animal maternal deprivation (Gardner, Thrivikraman, Lightman, Plotsky, & Lowry, 2005). Importantly, the HPA axis is also under tonic 5-HT (inhibitory) neurotransmission (see previous paragraph on the feedback mechanism). Clinical improvement after antidepressant treatment with selective serotonin reuptake inhibitors (SSRIs), which temporarily normalizes 5-HT functioning, has been associated with a normalization of HPA system function, and other antidepressants may act in the same way in attenuating the HPA axis (Barden, 2004; Keck & Holsboer, 2001). However, it has also been shown that recovered depressed patients continue to show overall decreased 5-HT$_{1A}$ receptor availability (Bhagwagar, Rabiner, Sargent, Grasby, & Cowen, 2004), which means that disruption in the serotonin metabolisms may be a scar of past depressive episodes, increasing vulnerability for future episodes. Of course, it remains an intriguing question whether this diminished receptor availability might also be related to the use of SSRIs.

One of the most important research findings over the last decade is that genetic polymorphisms in serotonin-related genes can modify susceptibility to developing depression following stressful life events (for a review, see Uher & McGuffin, 2008). This has first been shown for the genes encoding the 5-HT transporter, affecting the reuptake of serotonin back into the presynaptic cell, where a gene by environment interaction was clearly observed (Caspi et al., 2003). That is, individuals with a specific 5-HT transporter gene promoter region (5-HTTLPR) polymorphism (allelic variation in this region: S/S genotype) were more likely to develop depressive symptoms after stressful life events. Although a recent meta-analysis (Risch et al., 2009) failed to replicate the original Caspi et al. study, the 5-HTTLPR polymorphism has been linked to biological as well as to cognitive factors involved in stress reactivity; for example, a study by Gotlib, Joormann, Minor, and Hallmayer (2008) found that adolescent girls with the specific 5-HTTLPR polymorphism showed an increased cortisol response to experimentally induced stress. Recently, a variant of the L-form for the serotonin transporter has also been found to be associated with melancholic depression (Firk & Markus, 2007). Other genes

involved in serotonergic neurotransmission relevant for depression include, among others, tryptophan hydroxylase (TPH1 and TPH2, enzymes related to serotonin synthesis) and the genes encoding the 5-HT$_{2A}$ receptor (5HTR2A; Levinson, 2009).

The observation that some polymorphisms can modify susceptibility to developing depression upon stressors may suggest that the mutual relationship between HPA axis functioning and the serotonin metabolism is also dependent on genetic vulnerability factors (Firk & Markus, 2007).

The 5-HT neurotransmitter system and its relationship with prefrontal cortex and attention. Serotonin is mainly synthesized in the midbrain raphé nuclei. These 5-HT neurons project to virtually all brain regions, cortical as well as subcortical areas (Kingsley, 2000). Although there are ±15 different types of serotonin receptors, two specific receptors, 5-HT$_{1A}$ and 5-HT$_{2A}$, are mainly important for the pathophysiology of depression and are targeted by antidepressant medication (SSRIs; Mann, Brent, & Arango, 2001).

Serotonin plays an important role in cognition and emotion, with implications for affective disorders such as depression and anxiety. Interestingly, the serotonin system is related to emotion regulation, most likely through its effects on attentional control over negative stimuli; that is, many experimental studies show that 5-HT is implicated in enhanced sensitivity to negative stimuli and modulates the responsiveness of the amygdala via connected frontal regions (for reviews, see Cools, Roberts, & Robbins, 2007; Hariri & Holmes, 2006). Moreover, the amygdala response to negative stimuli is revealed to be associated with the above-mentioned polymorphism of 5-HT (e.g., Dannlowski et al., 2008). It has been proposed that the short allele variant, associated with a reduced 5-HT function, causes increased brain responses to negative stimuli (Bethea et al., 2004). Beevers, Wells, Ellis, and McGeary (2009) also demontrated that variations in the 5-HT polymorphism are associated with attentional processing of emotional information in a nonclinical population. It was found that short allele carriers show impaired disengagement from emotional material.

On the basis of an extensive literature review (Carver, Johnson, & Joormann, 2008), it has been proposed that the relationship between low serotonergic function and decreased reduced inhibition of negative affective states can be linked to emotion–attention networks in the brain. One of the key structures in this network is the dorsolateral prefrontal cortex (DLPFC). It has been proposed that the DLPFC initiates emotion regulation, causing inhibition of the amygdala (Davidson, Pizzagalli, Nitschke, & Putnam, 2002; Mayberg, 1997, 2002, 2003; Ochsner, Bunge, Gross, & Gabrieli, 2002). The amygdala is the foremost brain region implicated in emotion processing, involved in detecting, generating, and maintaining emotions (Phan, Wager, Taylor, & Liberzon, 2004). Depression has been conceptualized as a failure of dorsal areas, related to cognitive control, to regulate ventral emotion producing systems (Phillips, Drevets, Rauch, & Lane, 2003), based on evidence of abnormalities in these pathways in

depressed patients that change after treatment (Mayberg, 1997). Moreover, recent research shows that a functional balance between ventral and dorsal regions in the brain is important for maintaining homeostatic emotional control. A widely distributed and functionally interactive network of cortical-limbic pathways plays an important role in cognitive regulation of mood (Johnstone, Van Reekum, Urry, Kalin, & Davidson, 2007; Ochsner & Gross, 2008; Seminowicz et al., 2004). Emotion-arousing stimuli activate the amygdala (Zald, 2003), which is closely connected to the anterior cingulate cortex (ACC). The ACC integrates signals from the ventral ACC and the dorsal ACC (Bush, Luu, & Posner, 2000), the former related to emotion processing (e.g., Yücel et al., 2003), the latter being implicated in the facilitation of task-appropriate response selection and conflict monitoring (MacDonald, Cohen, Stenger, & Carter, 2000). The ACC signals to the DLPFC to alter the direction of attention or to modify the distribution of processing resources (Hopfinger, Buonocore, & Mangun, 2000), which in turn sends feedback signals to the subcortical system in order to suppress emotion processing in the amygdala (Wager, Davidson, Hughes, Lindquist, & Ochsner, 2008), via connections with other frontal regions such as the orbitofrontal cortex (OFC; Taylor & Fragopanagos, 2005). Abnormalities in DLPFC and ACC activity have been commonly observed in depression, specifically during tasks related to emotion processing (Fales et al., 2008) and cognitive control (Holmes & Pizzagalli, 2008). This reciprocal mechanism can elegantly explain the specific mood-congruent nature of attentional control problems in depression.

In relation to this emotion-processing network, emerging research has modeled the depressogenic effects of reduced frontal functioning related to the serotonin metabolism. In a recent study investigating postsynaptic 5-HT$_{2A}$ receptor binding in a sample of severely depressed patients (Baeken et al., 2010), as measured with ^{123}I-5-I-R91150 single photon emission computed tomography (SPECT) before and after 10 daily sessions of treatment with repetitive transcranial magnetic stimulation (rTMS: a technique to safely depolarize the underlying neurons of particular areas in the human brain cortex) of the left DLPFC, it was observed that, compared with a control group, patients displayed significantly less baseline 5-HT$_{2A}$ receptor binding index (BI) in the frontal cortex, and the antidepressant effect of high-frequency rTMS (HF-rTMS) treatment correlated positively with 5-HT$_{2A}$ receptor BI in the DLPFC. Moreover, it was found that one session of HF-rTMS over the right DLPFC in healthy volunteers, which is thought to induce a lateralized frontal brain activity pattern characteristic of depressed people (Davidson et al., 2002), produced instant impairments in the ability to inhibit negative information (Leyman, De Raedt, Vanderhasselt, & Baeken, 2009). Moreover, in severely depressed treatment-resistant people, a 10-day treatment period with rTMS over the left DLPFC, which is thought to induce a lateralized frontal brain activity pattern characteristic of nondepressed people, was administered. Using this procedure, 9 out of 14 patients demonstrated significant mood improvements, as indexed by a reduc-

tion of more than 50% on the Hamilton depression rating scale (Leyman, De Raedt, Vanderhasselt, & Baeken, in press). Of particular relevance to the present purposes is the fact that, compared with nonresponders, responders demonstrated improvements in the inhibitory processing of negative information.

Although regions of the dorsal PFC are activated when people engage in reflective top-down processing, as in reappraising emotional stimuli in order to regulate emotional responses (e.g., Ochsner et al., 2002), or in effortful suppressing emotion on demand (e.g., Beauregard, Lévesque, & Bourgouin, 2001), the studies mentioned above that use attention and inhibition tasks unrelated to effortful regulatory processing suggest that the DLPFC is also involved in a more automatic mode of attentional control.

Taken together, these observations suggest that the 5-HT metabolism could be related to attentional inhibition for negative stimuli in a specific circuitry of emotion regulation, in which the DLPFC cortex has an important role. Empirical evidence linking the 5-HT metabolism to dysregulated information processing and depression has also been obtained in studies using an elegant and well-studied procedure to temporarily decrease levels of serotonin experimentally, by artificially depleting people of L-tryptophan (dietary manipulation), a precursor to serotonin. Yatham et al. (2001) observed that tryptophan depletion decreased $5-HT_{2A}$ receptor BI in the DLFPC, which indicates that receptors in this area are particularly sensitive to serotonergic variation. These results fully concur with the above-mentioned SPECT study of Baeken et al. (2010), which showed that increased $5-HT_{2A}$ receptor binding is related to the antidepressant effect of rTMS in depressed people. Importantly, in a recent study, tryptophan depletion also reduced the normal attentional bias toward positive stimuli in healthy people, which was accompanied by increased hemodynamic responses (fMRI) during the processing of emotional words in several subcortical structures (Roiser et al., 2008). In a review including 25 studies (Merens, Van der Does, & Spinhoven, 2007), serotonin manipulations were found to affect facial emotion recognition, attentional bias, emotional memory, dysfunctional attitudes, and decision making. Taken together, these findings are also in line with the previously mentioned study showing a decreased attentional control for negative stimuli after rTMS of the DLPFC (Leyman et al., 2009). Interestingly, tryptophan depletion causes a temporary increase in depressive symptoms among formerly depressed persons (e.g., Booij & Van der Does, 2007; but see Leyton et al., 1997). This effect is not observed in people who show no history of depressive episodes or other risk factors (Ruhé, Mason, & Schene, 2007). Moreover, the finding that only people with the short variant of the 5-HTTLPR gene show depressive symptoms after tryptophan depletion is also indicative of a relation between genetic and neurochemical vulnerability for depression.

Finally, another way to investigate the relationship of 5-HT and emotional processing is to improve 5-HT function with SSRIs. Harmer and colleagues (Harmer, Mackay, Reid, Cowen, & Goodwin, 2006; Harmer, Shelley, Cowen, & Goodwin, 2004) administered citalopram (20 mg/day) over 7 days, facilitating recall of positive information and impairing detection of facial expressions of anger and fear in healthy volunteers. Finally, a single intravenous dose of citalopram attenuated the increased sensitivity for fearful expressions of formerly depressed patients (Bhagwagar, Cowen, Goodwin, & Harmer, 2004). All these data are consistent with the idea that the serotonin metabolism mediates attentional bias for emotional material in a specific neurocircuitry of attentional control.

Summary: An Integrative Framework

In the preceding sections, we have reviewed the empirical evidence that composes the building blocks of our framework. A basic outline of our framework is provided in Figure 1.

The framework can explain from a biological stance the kindling effect of an increased vulnerability to depression after each episode in genetically vulnerable people. Importantly, each of the building blocks of our framework shows characteristics that remain disturbed in recovered patients.

The HPA axis becomes increasingly impaired after periods of hypercortisolism during depressive episodes, which means that it becomes more reactive to stressors. This can lead to decreased activity in DLPFC areas, since activity in this structure is mediated by the serotonin metabolism, which is under control of an HPA axis. In our conceptualization, decreased activity in DLPFC areas is linked with prolonged activation of the amygdala in response to stressors in the environment. Impaired attenuation of amygdala activity through reduced frontal control leads to sustained negative affect. Decreased DLPFC activity also causes attentional impairment at the cognitive level, mediating sustained emotional responding to stress. We thus conceive the increasing vulnerability as an interaction between cognitive and biological factors in which the vulnerability relates to a dysfunctional reaction on stressors. We propose that the crucial link between cognitive and biological vulnerability is attentional control, because decreased inhibitory control and maintained attention for negative material leads to impaired ability to stop negative elaborative processes, such as rumination, and consequent sustained negative affect. The mood-congruent nature of attention impairment is related to the fact that emotional processing in the amygdala no longer causes increased cognitive control in the DLPFC, mediated by the ACC. Although this does not rule out the existence of general impaired cognitive control, maintained attention to negative information is, in contrast to anxiety, specifically related to depression. The ruminative process is caused by the activation of negative schemas. Because the association between depressed mood and negative thinking patterns is strengthened after each episode, negative thinking patterns become more reactive to negative moods and stressors, with increasing depressive episodes. Moreover, the elaborative process can act as an internal stressor, activating the stress system. The relationship between our biological and cognitive conceptualization is compatible with the finding that people who have a tendency to ruminate show,
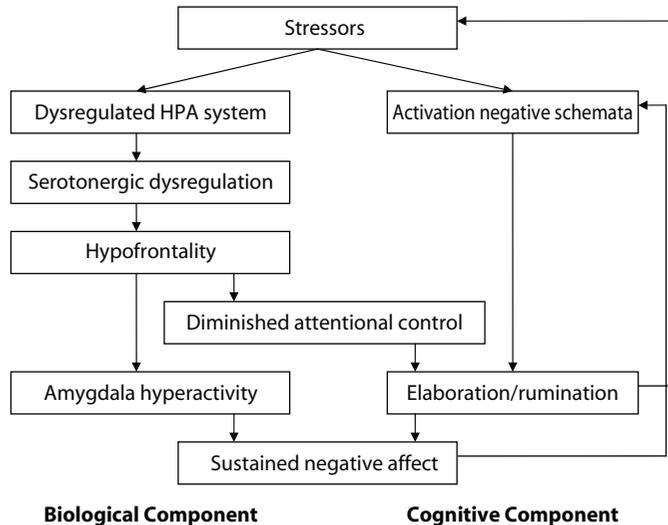
Figure 1. A schematic outline of the link between biological and cognitive vulnerability for recurrent depression.

compared with controls, higher and prolonged amygdala activation when asked to temporarily increase their negative affect (Ray et al., 2005). It is important to mention that we make a clear distinction between processes and products, as proposed by Ingram, Miranda, and Segal (1998). Attentional control, as measured by experimental tasks, is considered a process influencing products such as rumination, measured by responses in questionnaires. Although the definition of rumination refers to a process, we differentiate between underlying information processing related to neurobiological functioning and the content and style of thinking, which is the end product of these processes.

On the basis of this framework, we make the following specific assumptions: Episodes of depression are associated with increasing attentional impairments that remain present after remission. These attentional impairments are most pronounced in the processing of negative information after confrontation with stressors (these can be internal—e.g., remembering a distressing event—or external—e.g., social rejection), where individuals have difficulty disengaging their attention from negative emotional material once this has entered the focus of attention. We posit that attentional bias for negative information is not merely an epiphenomenon of depression but an important etiological and maintaining factor. This idea is based on the findings that (1) prospective research shows that the presence of attentional bias for negative information can, in interaction with stress, magnify depressive symptoms; (2) research has shown that interrupting prefrontal control, causing a lateralized frontal brain activity pattern characteristic for depressed people using rTMS, causes mood-congruent attentional impairments in normal individuals similar to those observed in depressed individuals; and (3) experimental manipulation of attentional bias influences depressive symptoms.

There are several testable predictions that can be derived from our account. First, in our view, attentional control under conditions of negative mood or in the presence of stress is crucial to being able to inhibit emotional responding and reorient attention to task-relevant or more positive information. Note that cognitive reappraisal is also crucially dependent on these aspects of attentional control (Ochsner et al., 2002). The attentional impairment observed in depression acts as a gateway, related to impaired inhibition of negative material and thus increased negative material in working memory, that in the long run fuels negative beliefs and schemas (see the arrows leading from elaboration/rumination back to negative schemata in Figure 1). Second, because experimental studies in at-risk individuals and dysphoric individuals fail to show an attentional bias in all individuals, we do not posit that attentional factors are necessarily implicated in the etiology of all individuals who develop depressive episodes. However, with increasing depressive episodes, attentional processes will become increasingly important as regulatory control diminishes. In a recent event-related potential study, it was indeed found that electrophysiological brain activity markers of deficits in cognitive control increase with each depressive episode and persist after symptom remission, suggesting that successive depressive episodes leave a "scar" on cognitive control processes (Vanderhasselt & De Raedt, 2009). The detrimental effect of these deficient control processes on real life stressors is nicely illustrated in a study by Hooley et al. (2009). Recovered individuals with a history of major depression were scanned while they heard praising, critical, and neutral comments from their own mothers. The groups showed no differences in self-reported mood and showed similar mood changes after being praised or criticized. However, formerly depressed participants responded to criticism with greater amygdala activation, and less activation in the DLPFC and ACC, than did healthy controls. The fact that the recruitment of cognitive control remains deficient after full recovery is further confirmation that abnormalities in corticolimbic activation independent of mood state are a vulnerability factor for depression.

Our framework provides a useful theoretical explanation for several innovative clinical interventions deemed successful in reducing relapse in formerly depressed patients. Given the dynamic interplay of risk factors, interventions can be successful by targeting one or more of the mechanisms that we have postulated because of reciprocal interactions with other risk factors. One clinical intervention currently widely under investigation is mindfulness-based cognitive therapy (MBCT). MBCT can be conceived as attentional control training (Baer, 2003) with an influence on DLPFC activity (for a review, see Cahn & Polich, 2006), attentional control (Jha, Krompinger, & Baime, 2007), and ruminative thinking (Ramel, Goldin, Carmona, & McQuaid, 2004). Second, over the last years, rTMS over the DLPFC has emerged as a promising treatment procedure for MDD (Avery et al., 2006; Bortolomasi et al., 2007). Research is indicative of the effectiveness of multisession rTMS in reducing depressive symptoms, by influencing brain activity and increasing attentional control (Vanderhasselt, De Raedt, Leyman, & Baeken, 2009). Finally, emerging research suggests that the therapeutic effect of antidepressant medication is related to changes in cognitive processing of emotional information (see Browning, Holmes, & Harmer, 2010, in this issue). These findings are also in line with the causal relation between attention and depressive symptoms suggested in our framework.

However, to optimize treatments it could be beneficial to combine biological and psychological treatment options. On the basis of our framework, an important therapeutic aim would be to restore stress reactivity. Interventions should be tailored to facilitate emotion regulation, making it possible to adaptively cope by down-regulating negative, distressing emotions after confrontation with emotion-arousing situations. Whereas nowadays cognitive interventions are aimed at altering dysfunctional cognitions, these therapies could be supplemented by techniques to influence deficient processing of these cognitions. In this way, trait vulnerabilities might also be treated, which might lead to decreased relapse rates.

Clearly, in our present knowledge there are several limitations that provide important new avenues for investigation. It is noteworthy that the effect size of attentional impairments in depression is often small to moderate. This could lead one to doubt whether attentional bias can be considered a process involved in important ways in the etiology and maintenance of depression. However, we think that attentional impairments can have quite substantial effects on depression, through its interaction with other cognitive processes (rumination, inhibition, memory) and life stress, causing effects on emotional reactivity. Moreover, we mainly consider the influence of attentional control on rumination. However, we cannot exclude the possibility that the reverse effect is present as well, with ruminative responding directly causing attentional bias. At present, there is no research on the latter possibility, so we decided not to include it in our framework. Finally, general attention deficits and valence-specific attentional impairments have been investigated in separate studies. Therefore, the available data does not

allow us to be highly specific about the exact role that each of these factors plays in depression. Moreover, the influence of processing positive stimuli might also be an important factor related to vulnerability, because it might be a resilience factor related to the way people can recover from negative moods. Again, this seems a fruitful area for further research.

Another important issue to consider is the specificity of our framework for depression. Although our framework is based on depression-specific research, there is clearly an overlap between depression and anxiety-related vulnerability factors, at both the cognitive and biological levels. This is not surprising, considering the high comorbidity rates between depression and anxiety. Although anxiety is also characterized by attentional bias toward negative information, the nature of the attentional bias between anxiety and depression seems different in several ways; that is, attentional bias in anxiety is typically relatively automatic in nature and short-lived (stimulus presentation durations $< 1,000$ msec). After this initial attentional response, anxious individuals are able to disengage attention from threat and sometimes even show attentional avoidance of threat. Depression is clearly associated with an attentional bias at later stages of information processing with more sustained attentional control impairments. These differences in the nature of attentional bias are presumably related to a different influence of attentional bias in anxiety and depression. In anxiety, initial attentional bias may contribute to the initial stress reactivity to threatening information, whereas attentional bias in depression is related to prolonged processing of negative material and impaired emotion regulation. Empirical research is required to examine the shared and differential effects of attentional bias in depression versus anxiety.

An important aim of our framework is to stimulate further integrative hypothesis-driven research efforts to gain a deeper understanding of the working mechanisms of the development of depression. The ultimate goal is to stimulate translational research to improve the effectiveness of interventions by tailoring them to account for individual differences in underlying processes.

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APPENDIX

Overview of Attentional Bias Studies in Depression and Dysphoria

Study	Participants	Stimulus Material	Presentation Duration	Between-Group Effects (Depressed vs. Controls)	Within-Group Effects (for the Depressed)
			Dot Probe Task		
MacLeod, Mathews, & Tata (1986)	Depression ($n = 16$, MBDI = 28) Generalized anxiety ($n = 16$, MBDI = 14) Controls ($n = 16$, MBDI = 7)	Words • Social threat–neutral • Physical threat–neutral • Neutral–neutral	500 msec	No differential effects between depressed and controls	No differential effects between word categories
Hill & Dutton (1989)	Dysphoric ($n = 16$, MBDI = 21) Nondysphoric ($n = 16$, MBDI = 2)	Words • Self-esteem-threatening • Neutral	750 msec	No differential effects between depressed and controls	No differential effects between word categories
Mogg, Bradley, & Williams (1995)	Depressed ($n = 17$) Anxious ($n = 17$) Controls ($n = 15$)	Words • Anxiety-relevant • Depression-relevant • Positive	14 msec (mask 14 msec) 1,000 msec	Depressed individuals showed more attention toward negative words than did controls (most pronounced at supraliminal conditions) No differences for positive words	Attentional bias for negative compared with neutral words
Mathews, Ridgeway, & Williamson (1996)	Depressed ($n = 20$) Dysthymic ($n = 13$) Major depression ($n = 7$) Anxious ($n = 25$) Controls ($n = 22$)	Words • Socially threatening • Physically threatening • Neutral	50 msec (masked) 500 msec	Depressed individuals showed larger attentional bias for socially threatening words than did the anxious or controls Anxious individuals showed larger attentional bias for physically threatening words than did depressed	Attentional bias for socially threatening words at the 500-msec word presentation
Bradley, Mogg, & Lee (1997), Experiment 2	Dysphorics ($n = 25$, MBDI = 14) Nondysphorics ($n = 16$, MBDI = 5)	Words • Depression-related–neutral • Anxiety-related–neutral • Filler pairs (negative and positive words)	14 msec (mask 186 msec) 500 msec 1,000 msec	The ANOVA with dysphoria as between-subjects variable revealed no significant interactions	Attentional bias for negative words correlated with (1) BDI (2) proneness to depression (3) severity of past depressive episodes
Bradley, Mogg, Millar, et al. (1997), Experiments 1 and 2	Experiment 1: Participants pre-selected on fear of negative evaluation • Dysphorics ($n = 20$, MBDI = 14) • Nondysphorics ($n = 20$, MBDI = 3) Experiment 2: Participants prese-lected on depression (POMS-D and BDI) • Dysphorics ($n = 9$, MBDI = 15) • Nondysphorics ($n = 15$, MBDI = 4)	Facial expressions (photos) • Angry–neutral • Happy–neutral • Neutral–neutral	500 msec	Experiment 1: Nondysphoric individuals avoided attention to the threat pictures and were more vigilant for the happy faces (all effects are trends) Experiment 2: Nondysphoric individuals avoided attention to the threat pictures (trend)	No significant effects
Westra & Kuiper (1997), Experiment 2	Dysphoric ($n = 9$) Nondysphoric ($n = 9$)	Words • Dysphoric–neutral • Threatening–neutral • Performance–neutral • Food/weight–neutral	750 msec	Between-group differences were not tested	Attentional bias for dysphoric compared to neutral information (re-vealed by error rates)
Mogg, Millar, & Bradley (2000)*	Depressed ($n = 15$, SI) Generalized anxiety without depres-sion ($n = 14$) Controls ($n = 16$)	Facial expressions (photos) • Angry–neutral • Sad–neutral • Happy–neutral	1,000 msec	No differential findings between depressed and the other groups	No differential findings for emo-tional categories

APPENDIX (Continued)

Study	Participants	Stimulus Material	Presentation Duration	Between-Group Effects (Depressed vs. Controls)	Within-Group Effects (for the Depressed)
Gotlib, Kasch, et al. (2004)	Depressed ($n = 88$, SI DSM-IV) Social phobics ($n = 35$) Controls ($n = 55$)	Facial expressions (photos) • Angry–neutral • Sad–neutral • Happy–neutral	1,000 msec	Depressed individuals had a stronger attentional bias for sad faces than did controls	Attentional bias was stronger for sad faces than for angry or happy faces
Gotlib, Krasnoperova, Yue, & Joormann (2004)	Depressed ($n = 19$, SI DSM-IV) Generalized anxiety ($n =18$) Controls ($n = 16$)	Facial expressions (photos) • Angry–neutral • Sad–neutral • Happy–neutral	1,000 msec	Depressed individuals had a stronger attentional bias for sad faces than did controls	Attentional bias was stronger for sad faces than for angry or happy faces
Joormann & Gotlib (2007)	Depressed ($n = 26$, SI DSM-IV) Formerly depressed ($n = 23$) Never depressed ($n = 19$)	Facial expressions (photos) • Sad–neutral • Happy–neutral	16 msec (mask 984 msec) 1,000 msec 3,000 msec	1,000 msec: Depressed and formerly depressed individuals had a stronger attentional bias for sad faces than did controls, who had a stronger attentional bias toward happy faces than did depressed (sign.) and formerly depressed (marg. sign.) individuals 16 msec and 3,000 msec: No specific group differences	1,000 msec: Specific attentional bias for sad faces in depressed and formerly depressed individuals 16 msec and 3,000 msec: No valence-specific attentional bias
Shane & Peterson (2007)	Experiment 1 • Dysphoric ($n = 29$, MBDI = 14) • Nondysphoric ($n = 42$) Experiment 2 • Dysphoric ($n = 27$, MBDI = 19) • Nondysphoric ($n = 39$)	Experiment 1: Pictures (IAPS) • Negative–neutral • Positive–neutral • Neutral–neutral Experiment 2: Words • Negative–neutral • Positive–neutral • Neutral–neutral	Experiment 1 • 500 msec • 1,500 msec Experiment 2 • 200 msec • 1,500 msec	Experiment 1 (collapsed over presentation duration) • Nondysphoric individuals attended more toward positive information than did dysphoric individuals • No differential effects for negative information Experiment 2 (collapsed over presentation duration) • Nondysphoric individuals attended more toward positive information than did dysphoric individuals • Dysphoric individuals showed an attentional bias for negative words compared with nondysphoric individuals	Experiment 1 No significant within-group effects Experiment 2 • Dysphoric individuals avoided attention toward positive words • Dysphoric individuals showed an attentional bias for negative words
Donaldson, Lam, & Mathews (2007)	Depressed ($n = 36$, SI) Nondepressed ($n = 36$) The attention task was split by a distraction, and rumination induction was administered (did not affect attention)	Words • Negative–neutral • Positive–neutral • Neutral–neutral	500 msec 1,000 msec	No interactions were observed at the 500-msec presentation duration There was a valence × group interaction at the 1,000-msec condition (no independent t tests were reported)	No effects at the 500-msec word presentation At the 1,000-msec condition, there was an attentional bias for negative words compared with neutral and positive words
Deployment of Attention Task					
McCabe & Gotlib (1995)	Depressed ($n = 20$, SCID) Nondepressed ($n = 20$) Women only	Words • Negative–neutral • Positive–neutral • Positive–negative	750 msec	Depressed individuals showed an attentional bias for negative information (on negative–neutral and positive–negative word pairs) No differences were found on positive–neutral pairs	In contrast to the nondepressed participants, depressed individuals did not attend more to the emotional (positive or negative) words

APPENDIX (Continued)

Study	Participants	Stimulus Material	Presentation Duration	Between-Group Effects (Depressed vs. Controls)	Within-Group Effects (for the Depressed)
McCabe & Toman (2000)	Selection through two (2–6 weeks apart) BDI screenings: • Dysphoric ($n = 19$, MBDI = 17) • Unstable nondysphorics ($n = 20$, MBDI = 6) • Stable nondysphorics ($n = 20$, MBDI = 3)	Words • Trait like-adjectives • Negative–neutral • Positive–neutral • Negative–positive	750 msec 1,000 msec 1,250 msec 1,500 msec	Nondysphoric individuals displayed a "protective bias" with reduced attention for negative words, whereas the dysphorics did not. The protective bias was strongest in the unstable nondysphoric group	No differential effects for word category
McCabe, Gotlib, & Martin (2000)	Currently nondepressed, composed of • Previously depressed ($n = 40$) • Never depressed ($n = 40$) under conditions of sad and neutral MIP	Words • State and trait words • Negative–neutral • Positive–neutral • Positive–negative	750 msec	Previously depressed and never-depressed individuals attended attention away from negative information in neutral mood In a sad mood, never-depressed individuals avoided attention to the negative words (in the negative–neutral pairings), whereas previously depressed individuals did not	Previously depressed individuals avoided negative information in neutral mood; in a sad mood, this protective bias disappeared
Karparova, Kersting, & Suslow (2007)	Depressed ($n = 15$, SI DSM-IV) Controls ($n = 15$) Tested before and after treatment	Words (adjectives) • Negative–neutral • Positive–neutral • Negative–positive	750 msec	Before treatment: Depressed individuals attended more to the negative targets than did controls (on the negative–neutral and negative–positive trials) After treatment: No differences between groups	No effects

Visual Search Task

Study	Participants	Stimulus Material	Presentation Duration	Between-Group Effects (Depressed vs. Controls)	Within-Group Effects (for the Depressed)
Suslow, Junghanns, & Arolt (2001)	Depressed ($n = 15$, SI DSM-IV) Controls ($n = 15$)	Schematic faces • 1 negative among 8 neutral • 1 positive among 8 neutral • All neutral	500 msec	Depressed individuals showed no performance differences in detection of negative faces and no differences in decision latency for the control condition (all neutral faces) relative to controls Depressed individuals were significantly slower in responding to positive faces than were controls	Not reported
Suslow et al. (2004)	Depressed ($n = 22$, SI DSM-IV) Controls ($n = 22$) Tested twice with 7 weeks between testing, while undergoing treatment	Schematic faces • 1 negative among 8 neutral • 1 positive among 8 neutral • All neutral	500 msec	No time effects and no differences in detecting negative faces Depressed (only those with comorbid anxiety) were slower to detect positive faces	Not reported
Rinck & Becker (2005)	Depression ($n = 27$, SI DSM-IV) Social phobia ($n = 35$) Controls ($n = 55$) All women	Words • Depression-related • Social-phobia-related • Positive • Neutral • 4 types of target words embedded in 4 types of distractor words	Irrelevant	Depressed individuals were distracted more by depression-related words than were social phobics and controls	Stronger distraction by depression-related words compared with the word types No facilitated search for any word types

APPENDIX (Continued)

Study	Participants	Stimulus Material	Presentation Duration	Between-Group Effects (Depressed vs. Controls)	Within-Group Effects (for the Depressed)
Karparova et al. (2007)	Depressed (n = 15, SI DSM-IV) Controls (n = 15)	Schematic faces • All similar faces • 1 negative, 3 neutral • 1 negative, 3 positive • 1 positive, 3 neutral • 1 positive, 3 negative	800 msec	Overall slower responding in depressed individuals. No differential attentive processing between depressed and controls	No differences in attention for specific facial expressions
Spatial Cuing Task					
Koster, De Raedt, Goeleven, Frank, & Crombez (2005), Experiments 1 and 2	Experiment 1 • Dysphorics (n = 15, MBDI = 16) • Nondysphorics (n = 15, MBDI = 4) Experiment 2 • Dysphorics (n = 20, MBDI = 15) • Nondysphorics (n = 20, MBDI = 2)	Words • Negative, self-referring • Positive, self-referring • Neutral	Experiment 1 • 1,500 msec Experiment 2 • 250 msec • 500 msec • 1,500 msec	Experiment 1 • Dysphorics showed maintained attention for negative words compared with nondysphorics • Dysphorics had more difficulty disengaging attention from negative words than did nondysphorics Experiment 2 • 250 msec: No differential effects • 500 msec: Trend toward maintained attention for negative words in dysphorics but not in nondysphorics. Nondysphorics showed maintained attention for positive words, whereas dysphorics did not • 1,500 msec: Maintained attention for negative words in dysphorics compared with nondysphorics. Reduced attention for positive words in dysphorics compared with nondysphorics	Experiment 1 • Dysphorics had difficulty disengaging attention from negative words Experiment 2 • 250 msec: No effects • 500 msec: Difficulty disengaging from negative words (trend) • 1,500 msec: Maintained attention to and impaired disengagement from negative words
Leyman, De Raedt, Schacht, & Koster (2007)	Depressed (n = 20, SI DSM-IV) Controls (n = 20)	Facial expressions (photos) • Angry • Neutral	1,000 msec	There was an interaction of group × emotion on attentional bias for negative information, but independent samples showed no specific differences between both groups on attention for angry faces	Depressed individuals had an attentional bias for angry compared with neutral faces
Eye Registration					
Matthews & Antes (1992)	Dysphorics (n = 20, MBDI = 18) Nondysphorics (n = 20, MBDI = 3)	Pictures with sad, happy, and neutral regions to be rated on aesthetic value	20 sec	Number of fixations • Dysphorics and nondysphorics fixated happy regions more than sad regions • Dysphorics fixated the sad regions more than did nondysphorics • No differences were found between dysphorics and nondysphorics in fixation on happy regions Duration of fixations • Dysphorics and nondysphorics fixated happy regions more than sad regions First fixations • Dysphorics' and nondysphorics' first fixations were more frequently on sad than on happy regions	Number of fixations • Dysphorics fixated happy regions more than sad regions Duration of fixations • Dysphorics fixated happy regions more than sad regions First fixations • Dysphorics' first fixations were more frequently on happy than on sad regions

APPENDIX (Continued)

Study	Participants	Stimulus Material	Presentation Duration	Between-Group Effects (Depressed vs. Controls)	Within-Group Effects (for the Depressed)
Mogg et al. (2000)*	Depressed (n = 15, SI) Generalized anxiety without depression (n = 14) Controls (n = 16)	Facial expression (photos) • Angry–neutral • Sad–neutral • Happy–neutral	1,000 msec	No differential findings for sad faces between groups Anxious participants attended more to the angry faces than did depressed or controls	No differential findings for picture category
Eizenman et al. (2003)	Depressed (n = 8, SI DSM-IV) Controls (n = 9)	Slides composed of 4 pictures (IAPS) depicting • Dysphoric themes • Threatening themes • Social themes • Neutral themes	10.5 sec	Fixation time • Depressed fixated longer on dysphoric pictures Fixation frequency • No effects Glance duration • Depressed glanced longer at dysphoric pictures	No within-group analyses were conducted. Visual inspection of Tables 2 and 3 indicates longer fixation time and glance duration for dysphoric pictures compared with threatening and neutral pictures (but not social pictures).
Caseras, Garner, Bradley, & Mogg (2007)	Dysphorics (n = 23, MBDI = 16) Nondysphorics (n = 20, MBDI = 3)	Pictures (IAPS) • Negative–neutral • Positive–neutral	3 sec	First fixations • No differences Latency of initial fixation • No differences Initial fixation duration • Dysphorics looked longer at negative pictures than did nondysphorics	First fixations • More fixations on positive compared with neutral pictures • Fewer fixations on negative compared with neutral pictures Latency of initial fixation • No differences between negative and neutral pictures • Quicker to look at positive than at neutral pictures Initial fixation duration • Dysphorics looked longer at negative pictures than at neutral pictures
Kellough, Beevers, Ellis, & Wells (2008)	Depressed (n = 15, SI DSM-IV) Controls (n = 45) Young adolescents (18–21 years)	Slides composed of 4 pictures (IAPS) depicting • Dysphoric themes • Threatening themes • Social themes • Neutral themes	30 sec	Fixation time • Depressed fixated longer on dysphoric pictures • Depressed fixated less on positive pictures Fixation frequency • Depressed fixated longer on dysphoric pictures • Depressed fixated less on positive pictures (marg. sign.) Glance duration • No differences Location of first fixation • No differences	Within-group analyses are not reported

Note—BDI, Beck Depression Inventory; POMS-D, Profile of Mood States–Depression subscale; SI, structured interview; IAPS, International Affective Picture System; SCID, structured clinical interview for DSM disorders; MIP, mood induction procedure.   *This study reports behavioral as well as eye-registration data, which are discussed in each section.