De Raedt, R., & Koster, E. H.W. (2010). Understanding vulnerability for depression from a cognitive neuroscience perspective: A reappraisal of attentional factors and a new conceptual framework. *Cognitive, Affective, and Behavioral Neuroscience, 10,* 50-70.

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

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Abstract

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 is under control of the HPA axis, 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 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.

Keywords: prefrontal cortex, attention, cognitive control, depression, vulnerability

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Major depressive disorder is one of the most common psychiatric disorders and is for many people a recurrent problem (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 for relapse or recurrence because successive depressive episodes are triggered by progressively milder stressors (Monroe & Harkness, 2005). The number of previous episodes revealed to be amongst the strongest predictors of relapse or recurrence in several studies (Kessing, Hansen, Andersen & Angst, 2004). All these data are in line with the idea that depressive episodes leave a "scar", which increases vulnerability for new episodes. Understanding underlying mechanisms of this increasing vulnerability for depression is of crucial importance to improve treatment.

To date most vulnerability models focus either on biological or psychological/cognitive processes, although recent research increasingly focuses on the interplay between cognitive and biological processes in depression. We aimed at developing a framework to understand the increasing vulnerability for 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 as attention is directly related to biological processes (e.g., prefrontal functioning) affected by recurrent depression, as well cognitive (i.e., rumination) and affective processes (e.g., emotion regulation) that are 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 cingulate 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 for depression, providing an outline of the different building blocks of our framework. Finally, we will summarize the basic ideas putting them together in one framework. Although several of the cognitive and biological markes we will address have already been described separately in other reviews, our aim is to to integrate these findings to understand the mechanisms underlying the kindling effect based on these mechanisms. We will outline cognitive and neurobiological evidence showing the mechanism of increasing vulnerability for the development of new depressive episodes.

Cognitive framework on increasing vulnerability for depression

Research on information-processing in emotional disorders has predominantly been guided by the cognitive schema theory proposed by Beck (Beck, 1967; Clark, Beck & Alford, 1999) and Bower's associative network theory (Bower, 1981). Beck and colleagues argued that information-processing is guided by schemas, defined as memory structures which, based on 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 in 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 others. The reason why 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, re-

activates 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 already 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 experienced depression in the past, as compared to 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 if cognitive reactivity could predict relapse in a group of formerly depressed patients. Patients underwent a 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 relapsers and non-relapsers. 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 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 mood 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 as reduced metacognitive monitoring. They found evidence that depressed patients show both increased schema accessibility and decreased metacognitive monitoring compared with healthy controls. Importantly, remission is accompanied by improved metacognitive abilities but the accessibility of schemas remains heightened in comparison to 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 sad mood and 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, Kandris, Williams, Lang, Yap & Hoffmeister, 2008) found evidence for 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 schema's and continued elaboration on 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 is considered to be a characteristic symptom of depressive episodes (DSM-IV-TR, APA), which has been related to reduced attentional control (Ellis & Ashbrook, 1988; Hertel & Rude, 1991). 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 non-depressed 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 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 processing mood congruent, negative information. This phenomenon is typically referred to as *attentional bias*, where depressed individuals, relative to non-depressed controls show enhanced attention towards negative material compared with neutral material. Initial research failed to show clear evidence for attentional bias (for a recent review, see Mogg & Bradley, 2005). In the influential theory of Williams and colleagues (1996) on information processing bias in anxiety and depression it was even concluded that depression is not associated with mood-congruent attentional bias, but instead is related to strategic elaboration of negative material, which causes improved explicit memory for this type of information (Williams et al., 1997). However in recent neuropsychological and behavioral studies it has consistently been found that, under specific conditions, attentional bias can be demonstrated (for an overview, see below). These conditions include a relatively long stimulus presentation (> 1000 ms) 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. The majority of 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, MacLeod, and Mathews (1996). Moreover, to date the emotional Stroop task is not considered a valid measure of visual attention because of interpretational difficulties; in the emotional Stroop task, 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 subclinically depressed individuals (refered to as dysphoric). These are individuals, often undergraduates, who indicate subclinical symptoms of depression on depression inventories. Although dysphoric individuals are not fully comparable to 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 only included studies where a clear distinction can be made between dysphoric and non-dysphoric individuals (excluding correlations and median-split procedures without any pre-selection). A comprehensive overview of all separate studies (from 1986 to 2008) is provided in Appendix A. 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 towards emotional compared with 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 a second. However, when a presentation duration of a second or longer was used, 6 out of 7 studies provided some evidence for an attentional bias for negative information, although there is considerable variation in the precise nature of these effects across those studies. This effect is observed in clinically depressed individuals (e.g., Gotlib 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 for the absence of positive bias in depression and dysphoria. In depressed or dysphoric individuals there usually is no bias towards positive material, whereas non-depressed individuals frequently orient more strongly towards positive than to neutral information. However, reduced attention towards positive material in the dot probe task is only found 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, yet is based on a different rationale. In this task, word pairs are presented on two vertically separated locations. Two different 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) attentional bias for positive words that is present in non-depressed individuals ("positive bias"; Gotlib et al., 1988); or (2) attentional avoidance of negative information that is present in non-depressed 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 a-motivational 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 the dot probe task, thus there is little information on the precise attentional processes and experimental parameters in this task. Moreover, this task has been used only with emotional words instead of more potent stimulus material such as emotional facial expressions.

Visual search task. The visual search task is a well-established paradigm in experimental psychology to investigate the automatic versus 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 comprised of schematic faces on 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 that was in remission. It is important to note 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 4 categories of target words embedded in 4 categories of distracting words. In this task either neutral or valenced targets were presented within an array of either neutral or valenced distracters. 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 exogenous cueing paradigm is a commonly used task in cognitive-experimental psychology and has been used to distinguish between specific attentional operations (Posner, 1980). The emotional modification of this spatial cueing task allows investigating two attentional operations: (1) attentional engagement with a new stimulus; (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 et al. (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 at the left or right side of a fixation cross. On a proportion of the trials, a peripheral cue precedes the target at the same spatial location ("valid" trials). On the remaining trials, the target is presented at the opposite spatial location of the cue ("invalid" trials). In the emotional modification of this paradigm, the emotional value of the cue is systematically varied (e.g., negative/neutral). This allows investigating attentional engagement by emotional cues through examination of reaction time (and/or accuracy) benefits on valid trials cued by emotional vs. neutral information. Attentional disengagement from emotional cues can be studied through examination of reaction time costs on invalid trials cued by emotional vs. neutral information.

At short intervals between cue onset and target onset (Stimulus Onset Asynchrony; SOA < 300 ms), participants are typically faster to respond to the valid compared with 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. Firstly, with short stimulus onset asynchronies (SOA) 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 is extended with emotional stimuli (hereafter referred to as the "enhanced cue validity effect").

Using the spatial cueing 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 away from negative information, whereas those with low attentional control still showed an attentional bias for such information.

The emotional modification of cueing task was applied in a study on attention for negative and positive words in dysphoric and non-dysphoric individuals (Koster et al., 2005). In two experiments using long cue presentations it was observed that dysphoric individuals showed an enhanced cue validity effect for negative words compared with than non-dysphoric 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 compared to the non-dysphoric individuals. In a study with dysphoric and non-dysphoric participants (Ellenbogen, Schwartzman, Stewart, & Walker, 2002), it was found that under stress, dysphoric individuals had difficulty to disengage from cues. However, this effect occurred regardless of cue valence (Ellenbogen et al., 2002). In sum, spatial cueing 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 under conditions where 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 as emotional information often is important to the individual's goal and task-relevant. Moreover, it is noteworthy that the behavioral paradigms discussed all depend on reaction time 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 non-dysphorics both fixated more and longer to happy material than sad material. However, the dysphorics did fixate more on the sad regions than the non-dysphorics. 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 to 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 fixation), 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 larger fixation time and longer glance duration for dysphoric pictures than controls. These data are similar to the findings in the dot probe and the spatial cueing task. Recent studies where individuals were viewing emotional information provide further evidence for the impaired disengagement hypothesis (Caseras, Garner, Bradley, & Mogg, 2007; Kellough, Beevers, Ellis, & Wells, 2008; Leyman, De Raedt, Vaeyens, & Phillipaerts, submitted).

Summary. Despite initial mixed findings on attentional bias, there is now converging evidence from dot probe, spatial cueing, 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 for a bias at later stages of processing. Moreover, this bias reveals to be specific for negative self-relevant material, although the absence of a positivity bias observed in non depressed people has also been observed. Noteworthy is that, although the corpus of empirical data on attention in depression mainly relies on visuo-spatial 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 abovementioned studies 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 that are 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 as a valid index of attentional bias, the results of this study are interesting. It was found that a bias for 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 bias as measured with a dot probe task interacted with intervening life stress to predict higher scores on depression seven weeks later. Furthermore, another study using a dot probe task has been able to demonstrate a mood-congruent attentional bias after a negative mood induction in never depressed offspring at risk for the development of depression (Joormann & Gotlib, 2008).

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 pre-testing differed from the individuals who did not demonstrate an attentional bias on variables that were 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 towards 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 et al. (MacLeod, Rutherford, Campbell, Ebsworthy, & 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 prompts the participant to orient towards 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 away from negative information.

Several studies investigating this type of attentional training procedure have been able to successfully modify attentional bias and found significant effects on emotional reactivity to induced or to real life stressors in normal volunteers (e.g. MacLeod et al., 2002; Dandeneau & Baldwin, 2004; Dandeneau, Baldwin, Baccus, Sakellaropoulo, & Pruessner, 2007). 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 4 sessions of attentional training. Compared to a no training condition, the participants in the training condition reported significantly less depressive symptoms immediately after training (effect size: d = .52) as well as at follow-up 2 weeks later (effect size: d = 1.04). 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 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 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" (Nolen-Hoeksema et al, 1993, p.20). This relation has been confirmed in a dot probe study in depressed patients where trait rumination was associated with an attentional bias for negative words, even when depressive symptoms were statistically controlled for (Donaldson, Lam, & Mathews, 2007). This also provides a 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, attention plays a role in ignoring irrelevant emotional material from entering working memory and attention is important in the updating of working memory, with both concepts being crucial in emotion regulation (see Joormann et al., 2007). 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 also is some research linking attention and memory bias in depression. Depression has been robustly related to biased recall of information on explicit memory tests, with enhanced recall of negative information compared with neutral and positive material, whereas healthy controls show enhanced memory for positive material compared with 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 et al., 2004a). 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 cueing task, examining recall of the words (negative, positive, and neutral words) that were presented during the attention task. In dysphoric individuals it was found that attentional bias for 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, Delissnyder, & Leyman, submitted).

Summary. In the preceding sections we have discussed research indicating that attentional bias for negative information may be causally related to emotional reactivity and depressive symptoms. Moreover, there is emerging research linking attentional bias to 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 that are 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 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 Hypothalamic Pituitary Adrenocortical axis

Many studies show that stressors induce biological changes over time, both at hormonal and neurochemical level (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 that are immediately activated following stress exposure are located in the limbic system, such as the the thalamus, amygdala, and hippocampus (Sergerie, Chochol, Armony, 2008).

Neuronal input from these and other related brain regions reaches the hypotothalamus, 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, 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). Many studies show that feedback inhibition is impaired in major depression, 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). 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, de Kloet, & van Os, 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 show enhanced ACTH and heart rate responses when exposed

to a standardized psychosocial stressor, even if not currently depressed. 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 non-suppression 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 & Cohen, 2003), which means that it is not only an epiphenomenon of a depressed state.

The relationship between the HPA-axis and neurotransmittor systems

A large number of studies show a relationship between HPA-axis functioning and monoaminergic neurotransmission, more specific the serotonin metabolism. For example, studies by Mizoguchi and coworkers illustrate 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, Yuzurihara, Ishige, Sasaki, Chui, & Tabira, 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 (Lopez, Liberzon, Vasquez, 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 former paragraph: the feedback mechanism). Clinical improvement after antidepressant treatment with selective serotonin reuptake inhibitors (SSRI's), 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 (Keck & Holsboer, 2001; Barden, 2004). 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 SSRI's.

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 (see Uher & McGuffin, 2008 for a review). This has first been shown for the genes encoding the 5-HT transporter (5-HTT), 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-HTTLPR polymorphism (allelic variation in the promotor region of the 5-HT transporter gene: S/S genotype) were more likely to develop depressive symptoms upon encounter of stressful life-events. Although a recent meta-analysis (Risch et al., 2009) has failed to replicate the original Caspi et al study, the 5-HTTLPR polymorphism has been linked to biological as well as cognitive factors involved in stress reactivity. For example by Gotlib, Joormann, Minor and Hallmayer (2008), who found that adolescent girls with the specific 5-HTTLPR polymorphism showed an increased cortisol response to experimentally induces 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 that are relevant for depression include, among others, tryptophan hydroxylase (TPH1 and TPH2, enzymes related to serotonin synthesis), and the genes encoding the 5-HT2A 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} en 5-HT_{2A}, are mainly important for the pathophysiology of depression and are targeted by antidepressant medication (SSRI's) (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, a large amount of 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 a review, see Cools, Roberts & Robbins, 2007; Hariri & Holmes, 2006). Moreover, the amygdala response to negative stimuli reveals to be associated with the abovementioned 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 and collegues also

demontrated that variations in the 5HT polymorphism are associated with attentional processing of emotional information in a non-clinical population. It was found that short allele carriers show impaired disengement from emotional material (Beevers, Wells, Ellis, & McGeary, 2009).

Based on an extensive literature review (Carver et al., 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 (Seminowicz et al., 2004; Johnstone, Van Reekum, Urry, Kalin, & Davidson, 2007; Ochsner & Gross, 2008). Emotional arousing stimuli activate the amygdala (Zald, 2003), which is highly connected to the 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) and the latter being implicated in the facilitation of task-appropriate response selection and conflict monitoring (Macdonald, Cohen, Stenger,

& Carter, 2000). The ACC signals to 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, é Ochsner, 2008), via connections with other frontal regions such as the orbitofrontal (OFC) cortex (Taylor & Fragopaganos, 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 mechanisms 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., submitted), 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 of the left DLPFC (rTMS: a technique to safely depolarize the underlying neurons of particular areas in the human brain cortex), it was observed that, compared to 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 treatment correlated positively with 5-HT_{2A} receptor BI in the DLPFC. Moreover, it was found 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 for 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 depressed people, a 10-day treatment period with rTMS over the left DLPFC, which is thought to induce a lateralized frontal brain activity

pattern characteristic for non-depressed people, was administered. Using this procedure, nine out of fourteen patients demonstrated significant mood improvements, as indexed by a reduction of more than 50 % on the Hamilton depression rating scale (Leyman, De Raedt, Vanderhasselt and Baeken, in press). Of particular relevance to the present purposes, compared to non-responders, 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 abovementioned studies using attention and inhibition tasks that are 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 5HT metabolism to dysregulated information processing and depression has also been obtained by 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 and colleagues (2001) observed that tryptophan depletion decreased 5-HT_{2A} receptor binding index (BI) in the DLFPC, which indicates that receptors in this area are particularly sensitive to serotonergic variation. These results fully concur with the abovementioned SPECT study of Baeken and collegues (submitted) study, 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 for 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 toghether, these findings are also in line with the abovementioned 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 for 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 SSRI's. Harmer and colleagues administered citalopram (20 mg/day) over 7 days, which facilitated recall of positive information and impaired detection of facial expressions of anger and fear in healthy volunteers (Harmer, Mackay, Reid, Cowen, & Goodwin, 2006; Harmer, Shelley, Cowen, & Goodwin, 2004). 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 compose the building blocks for our framework. A basic outline of our framework is provided in Figure 1.

The framework can explain the kindling effect of an increased vulnerability for depression after each episode in genetically vulnerable people from a biological stance. 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 as activity in this structure is mediated by the serotonin metabolism, which is under control of a 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 thus 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 for negative information is, in contrast to anxiety, specifically related to depression. The ruminative process is caused by the activation of negative schemas. Because after each episode the association between depressed mood and

negative thinking patterns is strengthened, negative thinking patterns become more reactive upon negative mood 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, as compared to 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 and colleagues (Ingram, Miranda & Segal, 1998). Attentional control, as measured by experimental tasks, is considered a process influencing products such as rumination, measured by 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.

Insert Figure 1 about here

Based on 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., a remembering a distressing event or external, e.g., social rejection), where individuals have difficulty to disengage 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 upon the findings that (a) prospective research shows that the presence of attentional

bias for negative information can, in interaction with stress, magnify depressive symptoms; (b) research has shown that interrupting prefrontal control, causing a lateralized frontal brain activity pattern characteristic for depressed people using rTMS, causes similar mood congruent attentional impairments in normal individuals as observed in depressed individuals; (c) 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 in the ability 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 impairments observed in depression acts as a gateway, related to impaired inhibition of negative material and thus increased negative material in working memory which, in the long run, fuels negative beliefs and schemas (see the arrow from elaboration/rumination to negative schemata in our framework). 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 Potentials 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 on

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 compared to healthy controls. The fact the recruitment of cognitive control remains deficient after full recovery further confirms that abnormalities in cortico-limbic activation that are independent of mood state are a vulnerability factor for depression.

Our framework provides a useful theoretical explanation for several innovative clinical interventions that deem successful to reduce 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 that is currently widely under investigation is mindfulness-based cognitive therapy (MBCT). MBCT can be conceived as an attentional control training (Baer, 2003) with an influence on DLPFC activity (for a review, see Cahn & Polich, 2006), an effect on attentional control (Jha, Krompinger, &, Baime, 2007) and on ruminative thinking (Ramel, Goldin, Carmona, & McQuaid, 2004). Second over the last years, rTMS over the DLPFC has emerged as a promising treatment procedure for Major Depressive Disorder (Avery et al., 2006; Bortolomasi et al., 2007). Research is indicative of the effectiveness of multi-session rTMS in reducing depressive symptoms, by influencing brain activity and increasing attentional control (Vanderhasselt, De Raedt, Leyman, & Baeken, 2009). Finally, there also is emerging research suggesting that the therapeutic effects of antidepressant medication is related to changes in cognitive processing of emotional information (see Browning et al., 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 beneficiary to combine biological and psychological treatment options. Based on our framework, an important therapeutical aim

would be to restore stress reactivity. Interventions should be tailored to facilitate emotion regulation allowing 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 vulnerabilies might also be treated, which might lead to decreased relapse rates.

Clearly, there are several limitations in our present knowledge 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 that is 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 and therefore 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 on 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 mood. Again, this seems a fruitful area for further research.

Another important issue is to consider the specificity of our framework for depression. Although our framework is based on depression specific research, there clearly is an overlap

between depression and anxiety related vulnerability factors, both at the cognitive and the biological level. This is not surprising considering the high comorbidity rates between depression and anxiety. Although anxiety is also characterized by attentional bias for 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 < 1000 ms). After this initial attentional response, anxious individuals are able to disengage attention from threat and sometimes even show attentional avoidance from 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 is anxiety and depression. In anxiety, initial attentional bias may contribute to the initial stress reactivity upon encounter of 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 in 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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Acknowledgements

We would like to thank Jan De Houwer and Gilles Pourtois for their thoughtful comments on an earlier version of this manuscript.

Figure caption

Figure 1 A schematic outline of the link between biological and cognitive vulnerability for recurrent depression.

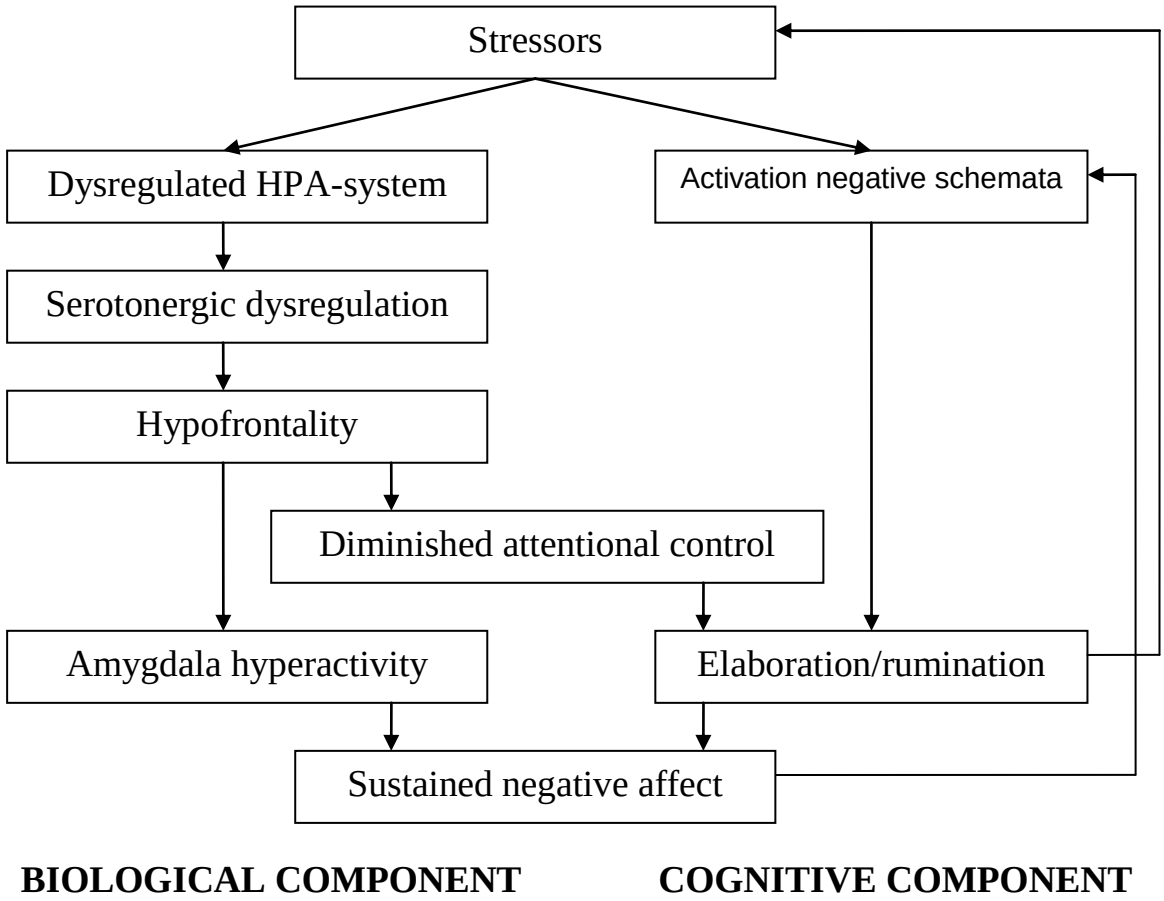
Stressors
Dysregulated HPA-system
Activation negative schemata
Serotonergic dysregulation
Hypofrontality
Diminished attentional control
Amygdala hyperactivity
Elaboration/rumination
Sustained negative affect
BIOLOGICAL COMPONENT
COGNITIVE COMPONENT

Figure 1

Appendix A

Overview of attentional bias studies in depression and dysphoria

Study	Participants	Stimulusmaterial	Presentation Duration	Between-group effects (depressed vs. controls)	Within-group effects (for the depressed)
Dot Probe Task					
Macleod et al. (1986)	depression (*n* = 16, *M*BDI =28) generalized anxiety (*n* = 16, *M*BDI = 14) controls (*n* = 16, *M*BDI = 7)	words social threat-neutral physical threat-neutral neutral-neutral	500 ms	No differential effects between depressed and controls	No differential effects between word categories
Hill & Dutton (1989)	dysphoric (*n* = 16, *M*BDI = 21) non-dysphoric (*n* = 16, *M*BDI = 2)	words self-esteem threatening neutral	750 ms	No differential effects between depressed and controls	No differential effects between word categories
Mogg et al. (1995)	depressed (*n* = 17) anxious (*n* = 17) controls (*n* = 15)	Words -anxiety-relevant -depression-relevant -positive	-14 ms (mask 14 ms) -1000 ms	-Depressed individuals showed more attention towards negative words than controls (most pronounced at supraliminal conditions -No differences for positive words	Attentional bias for negative compared with neutral words
Mathews et al. (1996)	depressed (*n* = 20; dysthymic, (*n* = 13; major depression, (*n* = 7) anxious (*n* = 25)	words -socially threatening -physically threatening -neutral	-50 ms (masked) -500 ms	-Depressed showed larger attentional bias for socially threatening words compared to the anxious and controls -Anxious showed larger	-attentional bias for socially threatening words at the 500 ms word presentation

	controls (*n* = 22)			atentional bias for physically threatening words than depressed	
Bradley, Mogg, and Lee (1997)	*Exp 2* dysphorics (*n* = 25, *M*BDI =14) non-dysphorics (*n* = 16, *M*BDI =5)	*Exp 2* words depression-related-neutral anxiety-related-neutral filler pairs (negative & positive words)	*Exp 2* -14 ms (mask 186 ms) -500 ms -1000 ms	*Exp 2* The ANOVA with dysphoria as between-subjects variable revealed no significant interactions	*Exp 2* Attentional bias for negative words correlated with (1) BDI (2) proneness to depression (3) severity of past depressive episodes
Bradley et al. (1997)	*Exp 1* Pp. preselected on fear of negative evaluation dysphorics (*n* = 20, *M*BDI = 14) non-dysphorics (*n* = 20, *M*BDI = 3) *Exp 2* Pp. preselected on depression (POMS-D & BDI) dysphorics (*n* = 9, *M*BDI = 15) non-dysphorics (*n* = 15, *M*BDI = 4)	*Exp 1 & 2* facial expression (photos) -angry-neutral -happy-neutral -neutral-neutral	*Exp 1 & 2* 500 ms	*Exp 1* -non-dysphoric avoided attention to the threat pictures and were more vigilant for the happy faces (all effects are trends) *Exp 2* -non-dysphoric avoided attention to the threat pictures (trend)	*Exp 1 & 2* -no significant effects

Westra & Kuiper (1997)	*Exp 2* dysphoric (*n* = 9) non-dysphoric (*n* = 9)	*Exp 2* words dysphoric-neutral threatening-neutral performance-neutral food/weight-neutral	*Exp 2* 750 ms	*Exp 2* between-group differences were not tested	*Exp 2* attentional bias for dysphoric compared to neutral information (revealed by error rates)
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	1000 ms	No differential findings between depressed and the other groups	No differential findings for emotional categories
Gotlib, Kasch et al. (2004)	depressed (*n* = 88, SI DSM-IV) social phobics (*n* =35) controls (*n* = 55)	facial expression (photos) -angry-neutral -sad-neutral -happy-neutral	1000 ms	depressed individuals had a stronger attentional bias for sad faces than the controls	attentional bias was stronger for sad faces compared with angry or happy faces
Gotlib, Krasnoperova, et al. (2004)	depressed (*n* = 19, SI DSM-IV) generalised anxiety (*n* =18) controls (*n* = 16)	facial expression (photos) -angry-neutral -sad-neutral -happy-neutral	1000 ms	depressed individuals had a stronger attentional bias for sad faces than the controls	attentional bias was stronger for sad faces compared with angry or happy faces
Joormann & Gotlib (2007)	depressed (*n* = 26, SI DSM-IV) formerly depressed (*n* = 23) never depressed (*n* = 19)	facial expression (photos) -sad-neutral -happy-neutral	-16 ms (mask 984 ms) -1000 ms -3000 ms	-1000 ms: depressed and formerly depressed indiviuals had a stronger attentional bias for sad faces than controls Controls showed a stronger attentional bias towards	-1000 ms: specific attentional bias for sad faces in depressed and formerly depressed -16 ms & 3000 ms: no valence specific

				happy faces than depressed (sign.) and formerly depressed (marg. sign.) -16 ms & 3000 ms: no specific group differences	attentional bias
Shane & Peterson (2007)	*Exp 1* dysphoric (*n* = 29, *M*BDI = 14) non-dysphoric (*n* = 42) *Exp 2* dysphoric (*n* = 27, *M*BDI = 19) non-dysphoric (*n* = 39)	*Exp 1* pictures (IAPS) -negative-neutral -positive-neutral -neutral-neutral *Exp 2* words -negative-neutral -positive-neutral -neutral-neutral	*Exp 1* -500 ms -1500 ms *Exp 2* -200 ms -1500 ms	*Exp 1* (collapsed over presentation duration) -Nondysphoric individuals attended more towards positive information than dysphoric individuals -No differential effects for negative information *Exp 2* (collapsed over presentation duration) -Nondysphoric individuals attended more towards positive information than dysphoric individuals -Dysphoric individuals showed an attentional bias for negative words compared with non-dysphoric individuals	*Exp 1* No significant within group effects *Exp 2* -Dysphoric individuals avoided attention towards positive words -Dysphoric individuals showed an attentional bias for negative words

Donaldson et al. (2007)	depressed (*n* = 36, SI) non-depressed (*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 ms -1000 ms	-No interactions were observed at the 500 ms presentation duration -There was a valence x group interaction at the 1000 ms condition (no independent t-tests were reported)	-No effects at the 500 ms word presentation -At the 1000 ms 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) non-depressed (*n* = 20) women only	words negative-neutral positive-neutral positive-negative)	750 ms	-depressed individuals showed an attentional bias for negative information (on neg-neut and pos-neg word pairs) -no differences were found on pos-neut pairs	in contrast to the non-depressed participants, depressed individuals did not attend more to the emotional (pos nor neg) words
McCabe & Toman (2000)	selection through two (2-6 weeks apart) BDI screenings: dysphoric (n = 19, *M*BDI = 17) unstable non-dysphorics (n = 20, *M*BDI = 6) stable non-dysphorics (n = 20, *M*BDI = 3)	words trait like-adjectives negative-neutral positive-neutral negative-positive	-750 ms -1000 ms -1250 ms -1500 ms	non-dysphoric individuals displayed a “protective bias” with reduced attention for negative words, whereas the dysphorics did not. The protective bias was strongest in the unstable non-dysphoric group	no differential effects for word category

McCabe et al. (2000)	currently non-depressed, comprised 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 ms	-previous depressed and never depressed attended attention away from negative information in neutral moodl -in a sad mood, never depressed individuals avoided attention to the negative words (in the neg-neut pairings), whereas previously depressed did not	-previously depressed avoided negative information in neutral mood. In a sad mood this protective bias disappeared
Karparova et al. (2007)	depressed (*n* = 15, SI DSM-IV) controls (*n* = 15) tested before and after treatment	words adjectives -negative-neutral -positive-neutral -negative-positive	750 ms	Before treatment: -depressed individuals attended more to the negative targets than controls (on the negative-neutral and negative-positive trials) After treatment -no differences between groups	No effects
Visual Search task					
Suslow et al. (2001)		schematic faces 1 negative among 8 neutral 1 positive among 8 neutral	500 ms display		

		all neutral			
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 ms display	-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 type of target words embedded in 4 type of distracter words	irrelevant	-depressed individuals were distracted more by depression-related words than social phobics and controls	-stronger distraction bij depression-related words compared to the word types -no facilitated search for any word types
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 ms display	-overall slower responding in depressed individuals -no differential attentive processing between depressed and controls	-no differences in attention for specific facial expressions

Spatial Cueing Task

Koster et al. (2005)	*Exp 1* dysphorics (*n* = 15, *M*BDI = 16) nondysphorics (*n* = 15, *M*BDI = 4) *Exp 2* dysphorics (*n* = 20, *M*BDI = 15) nondysphorics (*n* = 20, *M*BDI = 2)	*Exp 1 & 2* words -negative, self-refering -positive, self-refering -neutral	*Exp 1* 1500 ms *Exp 2* -250 -500 -1500 ms	*Exp 1* -dysphoric individuals showed maintained attention for negative words compared with non-dysphoric individuals -dysphoric individuals had a stronger difficulty to disengage attention from negative words compared to non-dysphorics *Exp 2* -250 ms: no differential effects -500 ms: trend towards maintained attention for negative words in dyshorics but not in non-dysphorics. Non-dysphoric individuals showed maintained attention for positive words, whereas dysphorics did not -1500 ms: maintained attention for negative words in dysphorics compared to non-dysphorics. Reduced attention for	*Exp 1* -dysphoric individuals had difficulty to disengage attention from negative words *Exp 2* -250 ms: no effects -500 ms: difficulty to disengage from negative words (trend) -1500 ms: maintained attention to and impaired disengagement from negative words

				positive words in dysphoric compared to non-dysphoric	
Leyman et al. (2007)	depressed (*n* = 20, SI DSM-IV) controls (*n* = 20)	facial expression (photos) -angry -neutral	1000 ms	-There was an interaction of group x 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, *M*BDI = 18) non-dysphorics (*n* = 20, *M*BDI = 3)	pictures with sad, happy, and neutral regions to be rated on aestethic vale	20 sec.	*Number of fixations* -dysphorics and dysphorics fixated happy regions more than sad regions -dysphorics fixated the sad regions more than the non-dysphorics -no differences were found between dysphorics and non-dysphorics in fixation happy regions *Duration of fixations* -dysphorics and dysphorics fixated happy regions more than sad regions *First fixations*	*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 to happy than to sad regions

				-dysphorics and non-dysphorics first fixations were more frequently to sad than to happy regions	
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	1000 ms	-no differential findings for sad faces between groups -anxious participants attended more to the angry faces compared to depressed and 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 glance longer at dysphoric pictures	No within-group analyses were conducted visual inspection of table 2 & 3 indicates longer fixation time and glance duration for dysphoric pictures compared with threatening and neutral pictures (but not social pictures)
Cazeras et al. (2007)	dysphorics (*n* = 23, *M*BDI = 16) non-dysphorics (*n* = 20, *M*BDI = 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 non-dysphorics	*First fixations* -more fixations on positive compared with neutral pictures -less 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 et al. (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

* This study reports behavioral as well as eye-registration data which are discussed in each section