# Depression vulnerability: Studying components of cognitive models

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# chapter 1

## general introduction

Every year, one in twenty Dutch experiences a depressive episode, nearly one in five suffers depression at least once in their lifetime. Depression is estimated to affect 350 million people globally. Although these estimation methods have been criticized (Moffitt et al., 2010), it is clear that depression is a highly prevalent disorder, with a high risk of recurrence following a first episode (Hardeveld, Spijker, De Graaf, Nolen, & Beekman, 2013; Mueller et al., 1999). Depression is associated with increased mortality, through suicidality and unhealthy lifestyle choices, but also through association with for instance diabetes and cardiovascular disease (Cuijpers & Smit, 2002; Seymour & Benning, 2009). Depression has substantial economic consequences (Sobocki, Jönsson, Angst, & Rehnberg, 2006). Most importantly: depression severely impacts the daily life experience of patients as well as their relatives and friends (Burke, 2003; van Wijngaarden, Schene, & Koeter, 2004). It is estimated that in 2004, unipolar depression was the third leading cause of disability worldwide (Mathers, Fat, & Boerma, 2008; part 4). Future projections estimate that unipolar depression will be the highest ranking cause of burden of disease worldwide by 2030 (Mathers, et al., 2008, p. 51).

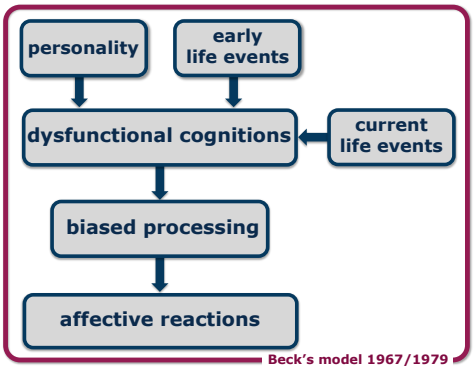
The key symptoms of depression are persistent sadness or low mood, and a loss of pleasure or interest in daily activities. Additional symptoms are fatigue or loss of energy, feelings of worthlessness or excessive guilt, recurrent thoughts of death or suicidal ideation, reduced concentration or decisiveness, noticeable agitation or psychomotor retardation, and unintentional changes in weight and sleeping patterns (American Psychiatric Assocation, 2000; World Health Organization, 1993). The diagnosis major depressive episode is defined by the occurrence of at least one key symptom and five total symptoms, almost daily for a period of at least two weeks.

In this thesis, studies informed by cognitive models of depression are presented and discussed. Cognitive models of depression focus on the cognitive symptoms: excessive feelings of worthlessness or guilt, recurrent thoughts of death and suicidal ideation, loss of pleasure and interest, and how they relate to persistent sad or low mood. In the cognitive tradition these symptoms are termed dysfunctional cognitions or dysfunctional attitudes.

Cognitive models have influenced research on depression since almost five decades. In a recent review, Beck (2008) relays what observations gave rise to the development of the first cognitive model of depression, published in 1967 (Beck). Studying the then leading, psychodynamic, theory of depression at the ‘deepest level’, he noticed that the dreams of depressed patients commonly dealt with themes of loss, rejection, defeat, and that it was often the dreamer himself who was represented as being defected or affected by

disease. This was different from the hypothesized hostile themes in depressed patients' dreams, although it could indicate 'masochism', a need to punish oneself. Yet, it appeared that encouraging patients to express their hostility made them become more depressed, which did not quite fit the theory of inverted hostility. Moreover, and again opposing expectations, patients appeared to benefit from positive reinforcement. That cognitions represented in dreams had a similar content to cognitions consciously expressed by depressed patients was an important notion. That their cognitions represented distorted interpretations of reality, was another. Importantly, modifying these (mis)interpretations trough reappraisal led to reduction of depressive symptoms. This observation is at the core of cognitive behavioral therapy (CBT), which nowadays is a preferred treatment modality for depression and several other psychopathologies.

Throughout this thesis the term cognitive vulnerability is used to refer to dysfunctional cognitions, biased information processing, and their interplay. Beck's model asserts that stressful life events may activate latent depression related cognitions which in turn bias information processing. Depression related dysfunctional cognitions are often classified as negative views or expectations of the world, the self, and the future. For biased information processing three different modalities are often discerned: attention allocation, interpretation, and memory. Together, these cover almost all information that an individual perceives from his or her environment. Thus, an individual experiencing negative cognitions regarding oneself, the world, and the future is expected to allocate attention more towards negative than positive information, to interpret information as more negative, and to have a better memory for negative than positive information.




This combination of negative cognitions and negative information processing is believed to initiate and perpetuate a persistent sad mood. Although Beck in 1967 mentioned the possibility of a feedback loop, such that depressive affect influences cognitions, he also qualified this idea as "highly speculative" (1967, p. 289). In modern day cognitive models (see below) it often is assumed that both affect and biased information processing reinforce negative cognitions, in turn again affecting information processing biases and affect.

Additional and alternative hypotheses to the cognitive model have been formulated over the years, to the extent that the literature may seem riddled by different theories, models, and hypotheses. These are, however, often not mutually exclusive but rather emphasize specific processes related to cognitive vulnerability or alternative definitions of cognitive vulnerability. I will briefly discuss some of these theories and reformulations, focusing on those that influenced the studies in this thesis.

In many of the studies cited and presented in this thesis negative cognitions and biased processing, and their interplay, are considered components of cognitive vulnerability.

Yet, alternative formulations of the nature of cognitive vulnerability exist as well. Hopelessness theory for instance, defines cognitive vulnerability as a tendency to engage in specific beliefs, termed attributions, in response to negative events. Perceiving negative events as important and consequential, as revealing negative characteristics about oneself, or as indicative that negative events may occur at any time and in any area of one's life, is theorized to predispose to a specific subtype of depression: hopelessness depression (Abramson, Metalsky, & Alloy, 1989). More recently, a dual processing model of depression was formulated (Beevers, 2005), adding a more detailed mechanism to cognitive vulnerability. Dual processing models state that a balance exists between automatic and effortful cognitive processing. The dual processing model of depression offers an explanation why the presence of (latent) dysfunctional cognitions should not necessarily result in depression and specifies circumstances under which it would, namely when effortful reflective processing falls short in correcting biased automatic processing (Beevers, 2005). The mood state hypothesis is another addition to the cognitive model, offering an explanation for the observed lack of empirical evidence supporting the existence of heightened dysfunctional cognitions in depression vulnerable and remitted individuals (Miranda & Persons, 1988; Persons & Miranda, 1992). It states that dysfunctional cognitions are only active and observable when an individual is in dysphoric mood. Experimental studies informed by the mood-state hypothesis aim to assess changes in activation of dysfunctional cognitions induced by mood induction or priming manipulations.

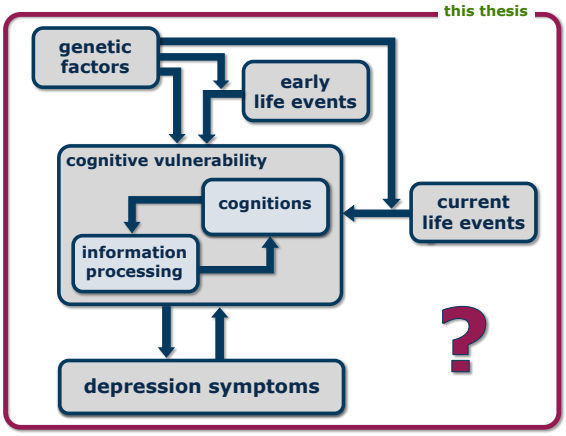
Nearly all cognitive models of depression can be characterized as diathesis-stress models. Diathesis-stress, or vulnerability-stress, models state that individuals can be predisposed to a disease, either cognitively or biologically, and that this vulnerability may evolve into the disease under influence of environmental stress (Monroe & Simons, 1991). The more recently formulated model of differential vulnerability offers an alternative characterization of the dynamics between vulnerability factors and environmental stress, and is gaining attention, especially in studies on genetic influences on the etiology of depression. It states that the same factors that predispose to depression may also protect an individual against depression under positive environmental circumstances or even in the mere absence of environmental stressors (Belsky & Pluess, 2009).

Lastly, an explanation of the 'scar hypothesis' is warranted. This term appears to be coined in 1981, as a third possible characterization of the relationship between dysfunctional cognitions and depression incidence (Lewinsohn, Steinmetz, Larson, & Franklin, 1981). Steinmetz and colleagues aimed to test the competing hypotheses that increased dysfunctional cognitions precede depression (antecedent hypothesis), or emerge and disappear with depressive episodes (consequence hypothesis). Nowadays, the term cognitive scarring is commonly used to classify observations of increased cognitive vulnerability following a depressive episode, which would increase predisposition to a subsequent episode.

A modern cognitive model of depression is given in the figure 'this thesis'. This representation depicts all components assessed in the studies in this thesis. Central to this model is the assumption that a causal relation exists between cognitive vulnerability

and the occurrence of depressive episodes.

In this thesis, biases in information processing (attention allocation bias and facial emotion recognition bias), implicit self-depressed associations, and dysfunctional cognitions in response to sad mood are all considered measures of cognitive vulnerability. Cognitive vulnerability itself is expected to be influenced by genetic factors, by early life experiences, current life events, and by having experienced previous episodes of depression.




Empirical evidence for cognitive models of depression comes mainly from treatment and association studies. From its introduction onwards, the most compelling, but indirect, evidence for a causal relation between cognitions and depression has been the observation that reappraisal of negative cognitions, as is done in CBT and related psychotherapies, relieves depressive symptoms and is protective against future episodes of depression. CBT and pharmacotherapy are comparably effective in inducing remission (Roshanaei-Moghaddam et al., 2011). However, studies comparing patients whom achieved remission through pharmacotherapy or through CBT, found that the latter group showed less dysfunctional cognitions (cognitive vulnerability) following remission, and that these levels predict remission duration, i.e. the risk of relapse (Paykel, 2007; Segal, Gemar, & Williams, 1999; Segal et al., 2006).

On the other hand, evidence that cognitive vulnerability precedes depression incidence, the first onset of depression, is rare. Direct evidence could come from studies wherein a measure of cognitive vulnerability is prospectively assessed in large, never depressed samples. A relatively recent review notes that such studies were yet to be presented (Scher, Ingram, & Segal, 2005, p. 504). Instead, from the available empirical studies it appears that most measres of cognitive vulnerability co-occur with active depression state. As mentioned above, the observed lack of evidence that cognitive vulnerability precedes the first episode of depression, led to the mood state hypothesis: simple assessment of cognitive vulnerability does not suffice to determine whether these precede depression incidence because dysfunctional cognitions are only active when an individual experiences sad mood (Persons & Miranda, 1992). The mood state hypothesis is closely associated with the concept of cognitive reactivity to sad mood: the relative ease with which dysfunctional cognitions become active when a drop in mood is experienced. Dual processing theory, on the other hand, suggests that implicit dysfunctional cognitions may be present but, under normal circumstances, are corrected by explicit processing. When explicit processing is challenged, for instance under stressful circumstances, implicit cognitions will manifest more. Thus, it suggests that implicitly, but not explicitly, measured dysfunctional cognitions could predict depression onset. Chapter five presents

a study of the predictive value of two operationalizations of cognitive vulnerability: cognitive reactivity to sad mood and implicit self-depressed associations. Their ability to predict first onset of depression over a two-years period was prospectively assessed in a large and never previously depressed sample.

Evidence for the involvement of environmental and genetic components in the etiology of depression is almost exclusively obtained from association studies. It is beyond doubt that depression can run in families. The odds ratio for developing depression for individuals with and without an affected first degree relative was estimated at 2.84 in a meta-analysis of five family studies (Sullivan, Neale, & Kendler, 2000). A meta-analysis of six twin studies (> 21 000 individuals) arrived at a model estimating that incidence of depression can be explained for 37% from genetic factors (Sullivan, et al., 2000). Associating specific genotypes with depression has proven difficult however. Hugenavigator is a scientific literature database dedicated to genetic studies, deriving its data from pubmed (Yu, Gwinn, Clyne, Yesupriya, & Khoury, 2008). A search for 'depressive disorder' yields more than 1000 studies published since 2001. These assess associations with depression and depression related outcomes for 445 different genetic polymorphisms (accessed: august 3, 2013). Yet, there is no conclusive evidence that any of these candidate genoptypes is involved in depression. By far the most studied genetic factor in relation to depression is 5-HTTLPR, a repeat length polymorphism in the promoter region of the SLC6A4 gene, which encodes the serotonin receptor. 5-HTTLPR has repeatedly been reported to predict depression in interaction with life stress, either recent negative life events or childhood adversity. However, meta-analyses have arrived at opposing conclusions as to whether 5-HTTLPR is truly associated with depression (Karg, Burmeister, Shedden, & Sen, 2011; Munafó, Durrant, Lewis, & Flint, 2009; Risch et al., 2009). Studies associating genetic factors with psychopathology are generally not without controversy, not in the least because of the notoriously small expected effect sizes. This is due to the sheer number of (genetic and environmental) factors that are expected to play a role in the etiology of depression, and the relative distance of the genetic factors to the complex disease of interest. A proposed solution is to assess effects of genotypes on endophenotypes rather than on the phenotype (depression). Endophenotypes are constructs that are related to a disease, which are expected to be more proximally related to the genetic factor of interest. Operationalizations of cognitive vulnerability, such as processing biases, are prime candidates for an endophenotype approach to depression (Gottesman & Gould, 2003; Hasler, Drevets, Manji, & Charney, 2004). Chapter four presents a study wherein two operationalizations of cognitive vulnerability, attention allocation bias and facial emotion recognition bias, are tested as endophenotypes for depression.

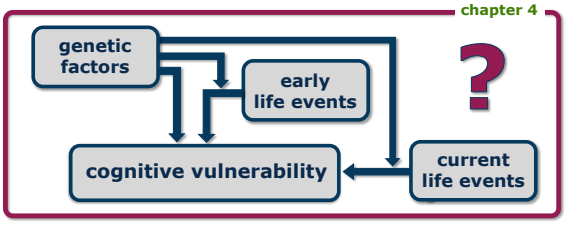
Evidence for the information-processing component of cognitive vulnerability comes mostly from association studies. An extensive review of the empirical evidence relating various types of biased information processing in affected and at-risk samples to various types of psychopathology shows that a relation between biased information processing and belonging to either an affected or at risk sample is often observed (Yiend, 2010). Several studies in the currently presented thesis incorporated the dot probe measure of attention allocation bias (MacLeod, Mathews, & Tata, 1986). A recent meta-analysis concluded that depression is associated with dot probe assessed allocation bias towards negative visual

information (d= .52; Peckham, McHugh, & Otto, 2010). Selective attention allocation away from positive information was also found to be associated with depression status (Fritzsche et al., 2009; Joormann & Gotlib, 2007; Shane & Peterson, 2007), and depression risk (Joormann, Talbot, & Gotlib, 2007). Another type of information processing biases observed as a function of depression status are biases in the identification of facial emotional expression. These may be due to either impaired recognition of (negative) facial expressions, interpretation of expressions as relatively more negative, or a combination of these (reviews: Bourke, Douglas, & Porter, 2010; Demenescu, Kortekaas, den Boer, & Aleman, 2010). In recent years researchers have been seeking to also obtain experimental evidence for the link between biased processing and depression. Experimental manipulation of information processing biases has gained considerable attention with the introduction of cognitive bias modification (CBM) procedures (MacLeod, Rutherford, Campbell, Ebsworthy, & Holker, 2002). If cognitive biases are involved in the etiology or maintenance of depression, then reducing biases may lead to subsequent reduction in symptoms. It is important to note that symptom reduction following bias manipulation would provide only indirect evidence for the assumption that bias also preceded the onset of symptoms. Chapters two and three of this thesis present two studies testing two attention bias mofidication (ABM) procedures for their ability to modify depression related attention allocation bias.

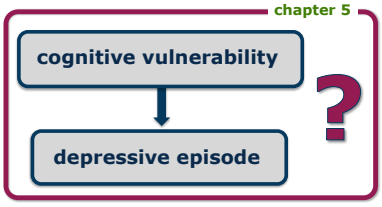
## summary

Introduced nearly fifty years ago, cognitive models of depression have a major influence on current day research on, and treatment of, depression. Central to these models is the concept of cognitive vulnerability, which in many models encompasses two components and their interplay: dysfunctional cognitions and biased information processing. Evidence for the role of dysfunctional cognitions is derived mostly from treatment (experimental) studies, whereas evidence for the role of biased cognitive processing comes mostly from cross-sectional (association) studies. The studies presented in this thesis assess the possibilities to experimentally manipulate information processing bias, to utilize biased information processing as an endophenotype in order to assess the influence of genetic and environmental factors on depression, and whether two measures of dysfunctional cognitions precede the first onset of depression.


Chapters 2 and 3 describe two experimental studies testing two ABM procedures designed to manipulate attentional bias for negative facial expressions in dysphoric student samples. Chapter 2 presents a single case series design testing whether six variants of the, most commonly used, dot probe ABM procedure were able to modify attentional bias towards happy or away from sad facial expressions. In the study presented in chapter 3 an ABM procedure based on the visual search task, adapted from self-esteem literature, was tested for its ability to modify attentional bias away from disgusting and towards happy facial expressions.




The association study in chapter four followed an endophenotype approach. The proposed endophenotypes for depression were attentional allocation bias for positive and negative visual information, and biased recognition of positive and negative mood states from pictures depicting eye regions. Hypothesized interaction effect of the most studied genetic factor in the context of depression, 5-HTTLPR, and early as well as recent life stress on these two measures of biased information processing were assessed.




Chapter five presents a prospective study design testing whether self-reported cognitive reactivity to sad mood and implicit associations between the concepts 'self' and 'depression' yield predictive value for depression incidence. This was assessed in a large, never-depressed, community based sample and the prediction period extended two years.

Finally, in chapter six the preceding chapters will be discussed and synthesized.