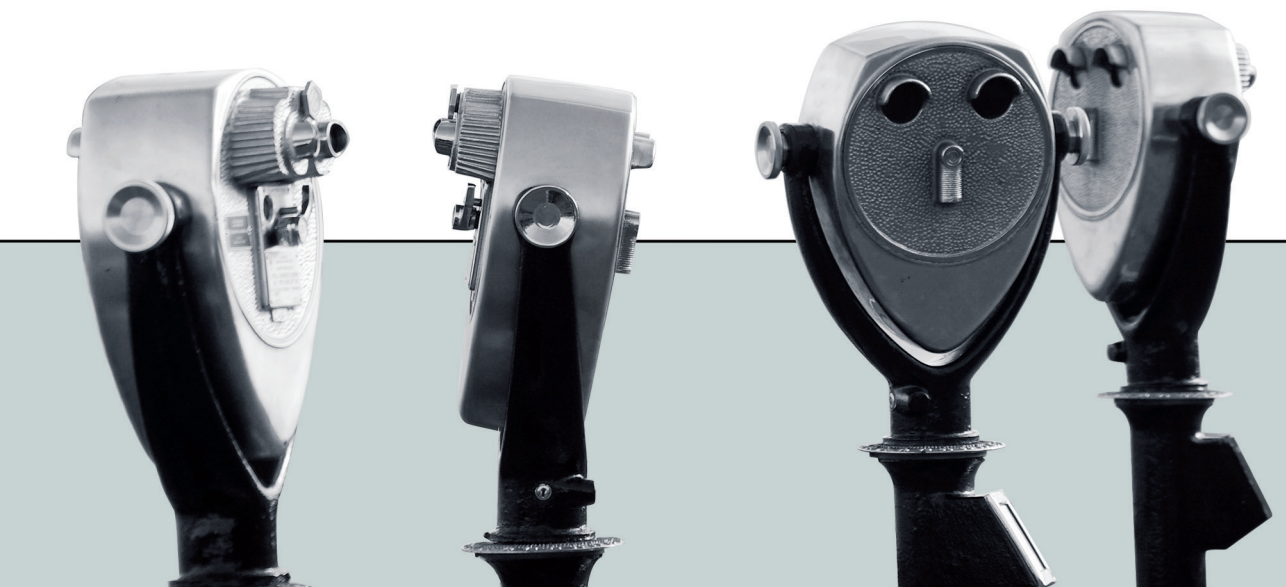
Depression vulnerability

studying components of cognitive models

Anne-Wil Kruijt



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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).

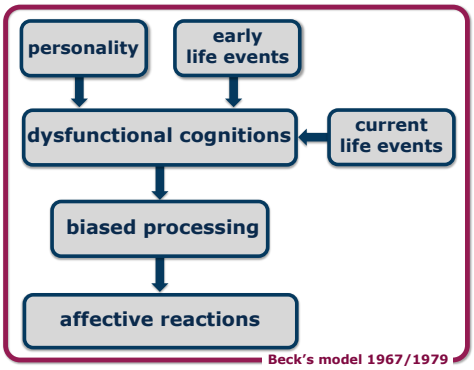
The key symptoms of depression are persistent sadness or low mood, and a loss of pleasure or interest in daily activities. Additional symptoms are fatigue or loss of energy, feelings of worthlessness or excessive guilt, recurrent thoughts of death or suicidal ideation, reduced concentration or decisiveness, 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.

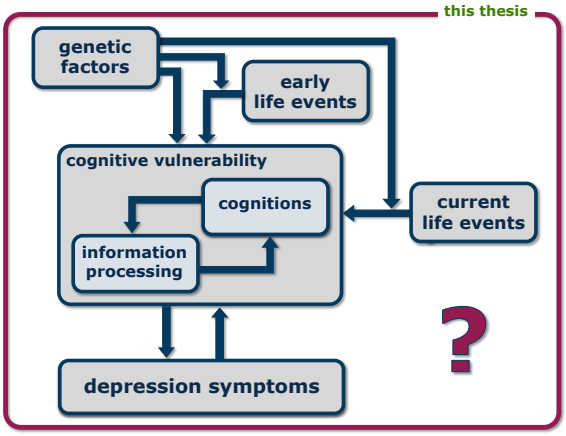
Nearly all cognitive models of depression can be characterized as diathesis-stress models. Diathesis-stress, or vulnerability-stress, models state that individuals can be predisposed to a disease, either cognitively or biologically, and that this vulnerability may evolve into the disease under influence 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.

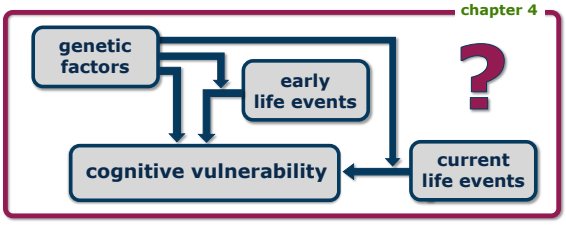
Evidence for the information-processing component of cognitive vulnerability comes mostly from association studies. An extensive review of the empirical evidence relating various types of biased information processing in affected and at-risk samples to various types of psychopathology shows that a relation 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.

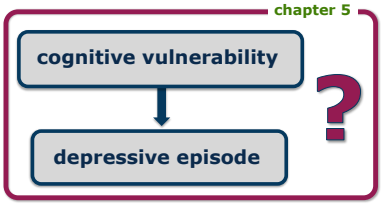
summary

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.

chapter 2

A multiple case series analysis of six variants of attentional bias modification for depression

Kruijt, A.-W., Putman, P., & Van der Does, A. J. W. (2013).
ISRN Psychiatry, 2013.
doi: 10.1155/2013/414170

Background: Attention Bias Modification (ABM) is a new treatment for affective disorders. A meta-analysis of ABM for anxiety disorders showed that the effect size may be large but the number of studies is low. The working mechanism is still unclear and little is known about the optimal treatment parameters. ABM for depression is much less studied. A few studies claimed positive effects but the sample sizes are low. Furthermore, the treatment parameters varied widely and differed from the anxiety literature.
Aim: To select the most promising version of ABM for depression for further evaluation in clinical trials.
Methods: Multiple case series design. We tested six versions of ABM that varied on stimulus duration and training direction. Thirty students with mild to moderate symptoms of depression underwent four sessions of ABM. Change of attentional bias was measured during each session. Generalization of treatment effects and the role of awareness of receiving training were also investigated.
Results: None of the investigated versions of ABM had a consistent effect on attentional bias. Changes of attentional bias in individual participants did not generalize to untrained stimuli.
Conclusion: It is unlikely that any of these ABM versions will have a specific effect on symptoms in controlled studies.

A growing body of literature reports that computerized attention training programs are successful in reducing symptoms of anxiety and depression. These Attentional Bias Modification (ABM) procedures intend to reduce or even reverse patients' habitual tendency to direct their attention towards negative information. Most of these studies use variants of the dot-probe task (Colin MacLeod, Mathews, & Tata, 1986). In ABM variants of this task, participants are implicitly taught to direct their attention away from negative information (a picture or word). This is accomplished by administering several hundreds of trials that involve brief simultaneous presentations of negative and neutral information, followed by a target. This target is systematically presented at the location of the neutral information (Colin MacLeod, Rutherford, Campbell, Ebsworthy, & Holker, 2002). In a recent meta-analysis, an effect-size of .61 was reported for ABM for anxiety over placebo-training (Hakamata et al., 2010). The authors concluded that these training programs show promise as a new treatment but also qualify the research on ABM as immature. Nine of the twelve studies were conducted in non-clinical samples (anxious students or adults) while only three studies concerned patients with an anxiety disorder. The effect sizes across trials also varied substantially and an asymmetrical funnel plot was found, indicating a possible publication bias. Furthermore, it remains unclear whether the treatment actually exerts an effect on attentional bias to threat, the presumed mechanism of action. Actual bias chances are not always reported. Mediation analyses, if performed, give equivocal results and in one study participants who were trained to direct attention towards and away from threat showed comparable reduction of emotional reactivity (Klumpp & Amir, 2009). Several other unresolved questions remain regarding the optimal ABM design. Studies are needed that systematically vary variables such as stimulus durations, stimulus content and sessions durations to establish the optimal training parameters (Bar-Haim, 2010).

Currently and remitted depressed patients show attentional bias for sad words and faces (reviews: Peckham, McHugh, & Otto, 2010; Yiend, 2010) and, compared to healthy controls, lack a bias towards positive information (Fritzsche et al., 2009; Joormann & Gotlib, 2007). Such biased information processing is theorized to play a role in the aetiology and maintenance of major depressive disorder (De Raedt & Koster, 2010). Two studies to date, therefore, have tested ABM procedures in depression. Four sessions of ABM over the course of two weeks had no immediate effect on depression scores of 34 dysphoric students, however a significant difference was observed between the ABM-treated and control group at two weeks follow-up (Wells & Beevers, 2010). A mediation analysis supported the proposed working mechanism, the reduction of attentional bias for negative information, over the course of treatment, was associated with eventual reduction in symptomatology. Attentional bias at follow-up, however, was not reported. Moreover, attrition was very high

at 47%, rendering the conclusion that the treatment had the intended effect premature. In another paper (Baert, De Raedt, Schacht, & Koster, 2010) two studies were presented that tested the effects of an ABM procedure based on the emotional spatial cueing task, which is closely related to the dot probe task. The treatment did not affect attentional bias in depressed patients nor did it affect their symptom severity. In a dysphoric student sample, treatment also had no effect. In a post-hoc analysis, however, symptom severity was decreased in a mildly dysphoric subgroup, whereas increased symptoms were observed in those with moderate to severe symptoms at baseline.

In summary, ABM treatment for anxiety disorders has been called promising but a close look at the individual clinical trials reveals many open questions, while ABM for depression is even less studied. Two studies have claimed small effects in non-clinical samples including an adverse effect in some participants. The ABM parameters used in both studies differ substantially from each other and from those typically used in anxiety disorder studies. Instead of carrying out another randomized controlled trial with one of these treatments, we propose that intensive case studies are needed to select the most promising approaches for evaluation in clinical trials. The current study is such an case study in which the effect of two parameters of the dot probe ABM paradigm, stimulus duration and aiming at inducing towards positive information versus reducing bias towards negative information, will be evaluated in a dysphoric student sample.

The depression ABM procedure designed by Wells and Beevers (2010) differs from ABM procedures for anxiety disorders. Sad (depression-relevant) pictures were used rather than threatening stimuli, as well as exceptionally long stimulus durations (3000 ms for faces and 4500 ms for scenic pictures). The spatial cueing ABM procedure introduced by Baert and colleagues also used a relatively long cue duration of 1500 ms (Baert, et al., 2010). The rationale is that, compared to anxiety, attentional biases in depression may be more pronounced at longer stimulus durations, after more elaborated processing and greater activation of relevant schemata (Mogg & Bradley, 2005). A recent meta-analysis, however, found similar effect sizes for studies assessing attentional bias in depression, dysphoria or induced dysphoria at 500 ms stimulus duration (d=0.54, 7 studies) and at 1000 ms or higher (d=0.59, 9 studies) (Peckham, et al., 2010).

In addition to bias towards sad information, remitted and currently depressed patients also show a reduction in bias towards happy faces compared to healthy controls (Fritzsche, et al., 2009; Joormann & Gotlib, 2007). This combination of biases was also found in dysphoric students (Shane & Peterson, 2007) and girls at risk for depression (Joormann, Talbot, & Gotlib, 2007). The spatial cueing ABM procedure tested by Baert and colleagues was designed to induce bias towards positive information as well as reduce bias towards negative information (Baert, et al., 2010). One other study, that did not explicitly target nor measure depression symptomatology, successfully modified attentional bias using a dot probe ABM procedure to induce bias towards positive word stimuli in healthy students at a stimulus duration of 500 ms (Wadlinger & Isaacowitz, 2008). In a post-training eye-tracking procedure participants trained to attend towards happy words were found to spend less time gazing at negative portions of images than before the training.

In the present study, 30 students with mild to moderate symptoms of depression engaged in one of six variants of the ABM paradigm for four sessions within a week. Each condition was defined by a combination of one of two training directions, away from neutral towards happy information or away from sad towards neutral information, and either a long, a short, or a variable stimulus duration. To our knowledge such a variable duration has not been used before. The rationale is that, instead of training participants to direct their attention at a specific point in time, a variable stimulus duration will train participants at several stages of attention orienting simultaneously. We used an 85% congruency contingency, i.e. 85% of the trials where congruent or incongruent trials, dependent of the training direction. This allowed monitoring attentional bias per session and also obscured the rationale of the study from the participants (Wells & Beevers, 2010). Attentional bias was assessed throughout the four training sessions and at pre- and post-training using a separate stimulus set. Upon completion of the training procedure, participants were interviewed regarding their awareness of the task mechanics, as unpublished data suggest that training may only have an effect on symptoms if participants remain unaware of the congruency contingency (C MacLeod, Mackintosh, & Vujic, 2009).

In summary, we tested the effects of six variants of an ABM procedure in dysphoric students. Four treatment sessions were conducted over the course of one week. The main outcome measure was the change of attentional bias, assessed during the training as well as post training on a separate set of stimuli. Symptom changes were not expected within this time frame. We hypothesized that attentional bias would change in the intended direction during the course of treatment, and that this change would generalize to untrained stimuli. The effect of participants' awareness of receiving training was also explored.

Methods

Participants

Participants were students recruited through posters and handouts. Potential participants filled out the depression subscale of the Hospital Anxiety and Depression Scale (HADS: Zigmond & Snaith, 1983). Participants who scored between 4 and 8 and had not previously participated in ABM studies were eligible.

Self-report measures

The (HADS: Zigmond & Snaith, 1983) has a score range of 0-21. A Dutch general population sample had a mean HADS-D score of 3.4, whereas psychiatric outpatients had a mean score of 9.3 (Spinhoven et al., 1997). Depressive symptoms were assessed with the Beck Depression Inventory-II (BDI-II). Fourteen is the cut-off score for a mild depression (Beck, Steer, & Brown, 1996). Anxiety symptoms were measured with the Beck Anxiety Inventory (Beck, Epstein, Brown, & Steer, 1988).

Dot probe task (DPT)

Stimuli

Stimulus pictures were selected from the Karolinska Directed Emotional Faces set (Lundqvist, Flykt, & Ohman, 1998). Four separate stimulus sets were created, two containing pictures of happy and neutral expressions and two containing pictures of neutral and sad expressions. Each sets consisted of ten male and ten female actors. The facial expressions were correctly identified at least 60% of the time in ratings obtained from a female student population (Goeleven, De Raedt, Leyman, & Verschuere, 2008). The two sets for each emotion (happy, sad) contained different actors and were matched on hitrates, valence, and arousal ratings. Mean hit rates, valence, and arousal ratings for each set are presented in table 2.1. A third set of pictures for both emotions was used in the practice trials. All pictures were converted to greyscale and shown against a light grey background. The probe was a small black square (15 x 15 pixels) that was shown either upright (square) or rotated 45 degrees (diamond). Participants were seated circa 60 cm from the display resulting in a horizontal distance of 16.0° of visual angle between the midlines of the two stimulus pictures and the two possible probe locations. The horizontal width of the stimulus pictures and the probe were 8° and 0.4° respectively.

Table 2.1. *hit rates, intensity, and arousal ratings for each of the four stimulus sets.*

	emotional pictures			neutral pictures		
Set	hit rate	intensity	arousal	hit rate	intensity	arousal
happy A	78.8 (10.8)	6.1 (.9)	3.8 (.4)	78.8 (10.8)	5.0 (.5)	2.5 (.2)
happy B	78.6 (10.9)	6.2 (.6)	3.7 (.4)	78.6 (10.9)	4.9 (.5)	2.6 (.2)
sad A	84.6 (10.1)	5.5 (.7)	3.5 (.4)	72.5 (12.8)	4.9 (.5)	2.6 (.2)
sad B	84.8 (10.3)	5.2 (.9)	3.3 (.5)	80.9 (11.3)	5.0 (.5)	2.5 (.2)

[a] *All measures are reported as M (sd).*
[b] *Based on ratings provided by Goeleven, De Raedt, Leyman, & Verschuere (2008).*

Single trial

Throughout the procedure a single trial started with a 750 ms fixation cross followed by the stimulus images in a horizontal arrangement. Upon offset of stimulus pictures the probe appeared at the location previously taken by either stimulus. The probe remained on the screen until the participant responded by pressing one of two mouse buttons, corresponding to the two possible probe identities (square/diamond). The mouse was fixated to the desk in front of the participant. Upon response a 750 ms intertrial interval preceded the next fixation cross.

Congruency contingencies

During the pre- and post-training bias assessment tasks the probe appeared on the location previously occupied by the neutral (incongruent trial) or the emotional stimulus (congruent trial) with equal probability (congruency contingency: 50%). Emotional stimulus location, probe identity and stimulus identities were randomized

and counterbalanced within the congruent and incongruent trials. Within each training session of 200 trials, 170 trials (85%) were either happy congruent (neutral-towards-happy conditions) or sad incongruent (sad-towards-neutral conditions). The congruency of 140 of these 170 trials was predetermined. The remaining 30 trials were half of 60 trials with a 50% congruency contingency. These 60 trials were used for the 'on-line' assessment of attentional bias within each training session.

Conditions
Six versions of the dot probe task all differed on two dimensions: direction of training (sad-towards-neutral or neutral-towards-happy) and stimulus duration (500 ms, 3000 ms, or variable). Within each block of 40 trials in the variable stimulus duration conditions, the stimulus durations 500, 1125, 1750, 2375, and 3000 ms were randomized and counterbalanced within each combination of trial congruency (for the 50% congruency trials), location of the emotional stimulus and probe identity.

Procedure
Participants were scheduled to visit the laboratory on a Monday, Tuesday, Thursday, and Friday within one week. The appointments were scheduled at the same time each day with a maximum deviation of 1.5 hours. Upon completion of the procedure participants were compensated with a small financial reward or course credit. Participants were randomly assigned to one of the six conditions. The Ethics Committee of the Institute of Psychology at Leiden University approved the study and informed consent was obtained.

The first session started with filling out the questionnaires, followed by 100 trials of a dot probe bias assessment task (congruency contingency of 50%) and 200 trials of the training (congruency contingency of 85%). The second and third session consisted of 200 training trials only. The fourth session started with 200 training trials, followed by 100 assessment trials, filling out questionnaires and the debriefing procedure.

At the first session participants were required to take as many practice trials as needed for six consecutive correct answers with a minimum of 10 trials. For sessions 2, 3 and 4 only six practice trials with four consecutive correct trials were required. Throughout the experimental sessions short breaks were given every 40 trials; participants could take a few seconds rest and continue the task with a mouse click. After 200 trials in the first and the fourth session participants were required to take a 5 minutes break. In sessions 1 and 4 the program switched between the pre- and post-training assessment trials and the training trials without notice.

Following Wells and Beevers (2009), we did not mention the word "training" to the participants, nor any other phrase that implied that their mood might change. Participants were informed that we were interested in the effects of repeated engagement in a task. The debriefing at the end of the last session consisted of a funnelled interview in which participants were first asked to guess the purpose of the study followed by a series of open questions informing whether they noticed anything specific regarding the faces, the location of the faces, the probes, the location of the probes, and whether anything else had changed when the images changed (the switch from the training to the post assessment

in the fourth session). Afterwards, the experimenter explained the concept of attentional bias, the dot probe task and the rationale of the dot probe training. Participants were then told that they could have been in either a training or a control condition (congruency contingency 85% or 50%). All participants had to guess which condition they had been in and rate how certain they were of their answer on a scale ranging from 50 to 100%. This percentage, reversed for those who believed to have been in the control condition, was used as an index of awareness. Finally, participants were fully debriefed and were given the opportunity to ask questions.

Results

Participants

Two hundred students filled out the HADS-D. Fifty-two of these scored between 4 and 8 points and were subsequently invited. Thirty-three participants were scheduled and engaged in the experimental procedure. Data of three participants had to be discarded due to technical problems. These three participants were replaced to obtain a total of 30 participants.

Data preparation and calculation of bias indices

The pre- and post-training assessment trials as well as the 60 trials with a 50% congruency contingency within each of the four training sessions were included in the analyses. Inspection of the error rates per participant and session showed that none of the participants made more than 10% errors within a single session. Erroneous responses (3% of the dot probe data) were eliminated. Inspection of the remaining data showed that their distribution was skewed and we therefore used median instead of mean response times to calculate the bias indices (Colin MacLeod, et al., 2002). Bias indices were calculated separately for each participant and each of the six phases (pre-training, training sessions 1 to 4, and post-training) by subtracting the median response time for congruent trials from the median response time for incongruent trials.

Group characteristics

Baseline group characteristics are presented in table 2.2. Non-parametric tests showed no differences between the groups at baseline (Kruskal-Wallis tests, all $p > .5$)

Table 2.2. *characteristics at baseline, per condition*

	sad-towards-neutral			neutral-towards-happy		
	500 ms	3000 ms	variable	500 ms	3000 ms	variable
age	24.0 (7.9)	19.4 (1.5)	20.2 (1.5)	20.0 (1.4)	20.6 (5.3)	21.0 (3.3)
BDI-II	11.4 (4.7)	13.8 (7.7)	12.6 (6.4)	14.8 (4.7)	11.8 (6.3)	15.2 (5.5)
BAI	13.4 (5.9)	11.0 (5.6)	9.2 (5.8)	11.4 (5.5)	10.0 (4.5)	13.2 (4.8)

All measures are reported as M (sd).
BDI-II = Beck Depression Inventory II; BAI = Beck Anxiety Inventory.

Change in bias index over the course of training

The bias indices obtained during each of the four sessions for each individual participant are shown in figure 2.1. Note that for the upper three rows (neutral-to-happy conditions) an increase in bias index was the intended effect of training, while for the lower three rows (sad-to-neutral conditions) bias index was intended to decrease.

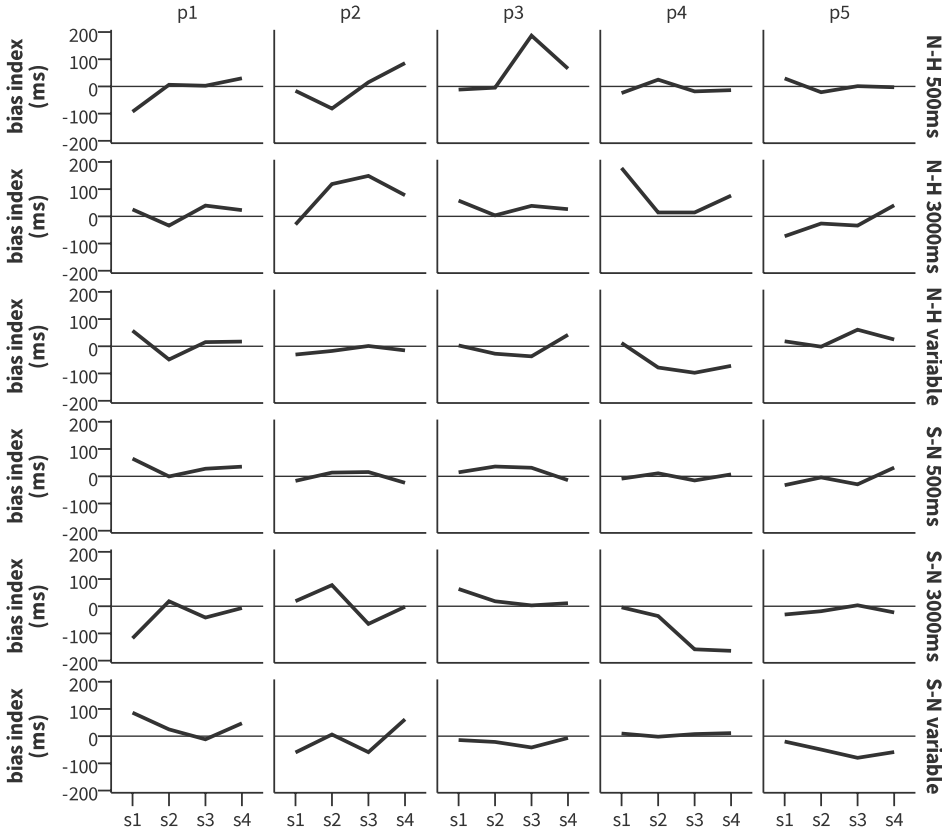


Figure 2.1. bias index during the four training sessions for each individual participant. Each row shows the five participants within a condition. Note that for the neutral-towards-happy conditions (top three rows) training should induce an increase in bias index whereas for the sad-towards-neutral conditions (bottom three rows) training is intended to reduce bias index. N-H = neutral-towards-happy, S-N = sad-towards-neutral, s1 = session 1 etc., p1 = participant 1 etc.

Visual inspection of each row of panels in figure 2.1 learns that none of the training conditions had a consistent effect on the participant's bias indices. The neutral-towards-happy 500 ms condition (top row) had the most consistent effect: relatively large increases in bias indices in three out of five participants while the other two participant's bias indices remained relatively stable. During the post-training interview, participant 3 in this condition reported to have noticed at some point that the location of the probe and the happy face may have been associated. The participant then tested and rejected this idea, probably due to the 85% contingency. This may explain this person's peak in

bias obtained during the third session. Both 3000 ms conditions (rows 2 and 5) as well as the sad-towards-neutral variable condition (bottom row) showed a change in the intended direction in two participants and a change in the opposing direction in another. The neutral-towards-happy variable condition (row 3) had only one participant who showed the expected change in bias index while two participants showed a change in the non-intended direction. The neutral-towards-sad 500 ms condition (row 4) had one participant whose bias changed slightly in the non-intended direction while the other four participant's bias indices remained largely stable.

Transfer of training effects

In order to assess whether a change in bias during the training transferred to a changed bias for the untrained stimulus pictures used in the pre- and post-training assessment, we calculated two new variables:

SCT (Successful Change Trained stimuli) = bias index s4 – bias index s1
SCU (Successful Change Untrained stimuli) = bias index post – bias index pre

SCT and SCU are multiplied by -1 for the sad-towards-neutral conditions so that a positive value of SCT and SCU represents a change in the intended direction while a negative value represents a change in the non-intended direction. A larger value represents a larger change in bias index at session 4 (SCT) or post-training (SCU), as compared to session 1 and pre-training respectively.

Figure 2.2 illustrates that changes in bias during the training did not systematically transfer to the untrained stimuli used in the pre- and post-assessment. Bias indices of 16 participants changed in opposing directions while five participants had negative values for both SCT and SCU. Bias index changed in the intended direction for both trained and untrained stimulus pictures in nine participants, as indicated by positive values of SCT and SCU. For one of these participants (p2 in the sad-towards-neutral 500 ms condition) the values of SCT and SCU were 7 and 9 ms respectively. These values are so small that they likely fall within the range of measurement error. The remaining eight participants whose bias changed in the intended direction for both trained and untrained stimulus pictures were scattered over the six conditions. Three conditions (sad-towards-neutral 500 ms and the two variable ms conditions) each contained two such participants, the neutral-towards-happy 500 and 3000 ms conditions each had one such participant, whereas the sad-towards-neutral 3000 ms condition had no such participants.

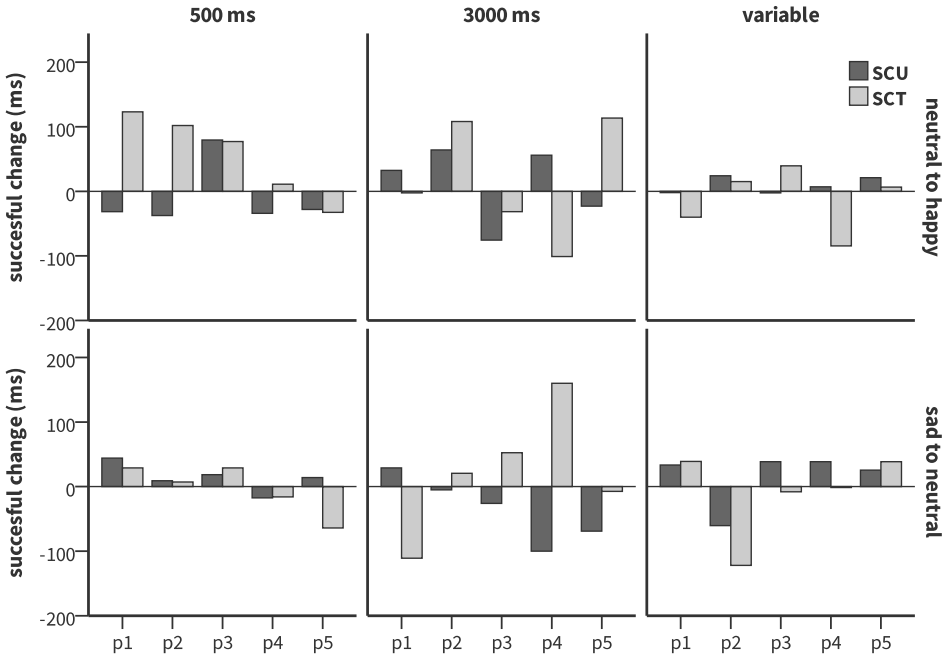


Figure 2.2. successful change in bias index for trained (SCT) and untrained (SCU) stimulus pictures per participant ordered by condition. p1 = participant 1, etc.

Effects on symptoms

Wilcoxon signed ranks tests comparing the BDI and BAI scores pre- and post-training for the entire sample indicated no effects of training (Z =-1.54, p = .12 and Z =-1.44, p =.15 respectively), as was expected. However, mean BAI scores decreased significantly within the sad-towards-neutral conditions (Z = -2.35, p = .02) but not within the neutral-towards-happy conditions (Z = -.52, p = .61). Mean BDI scores did not change significantly within either the sad-towards-neutral or the neutral-towards-happy conditions (Z = -1.16, p = .24 and Z = -1.03, p = .30 respectively).

Awareness of receiving training

At the start of the post-training funnelled interview, none of the participants accurately guessed the purpose of the experiment. Sixteen participants believed to have been in a (nonexistent) control condition whereas 14 participants thought to have received training. The confidence with which participants believed to have received training correlated significantly with the change in bias for untrained stimuli (SCU; r_s = .57, p = .001) but not with change in bias index for the trained stimuli (SCT; r_s =-.02, p = .93) nor with the absolute bias indices obtained during session 4 and the post-training assessment (p = .47 and p = .27 respectively). From the scatterplot showing the relation between SCU and the confidence rating (figure 2.3) it was observed that this effect was restricted to participants who believed to have received training (confidence ratings > 50%). Indeed, within the group that indicated to have received training, confidence ratings correlated significantly with SCU (r_s = .82, p < .001) while the correlation was non-significant within the group

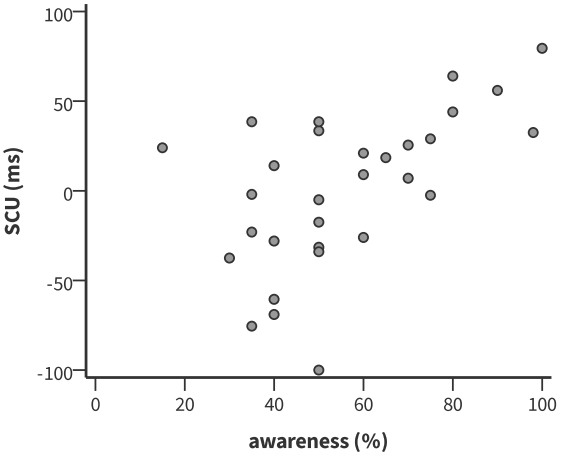


Figure 2.3. scatterplot of the correlation between Successful Change in bias index for Untrained stimuli (SCU) and awareness confidence ratings.

that believed not to have received training (r_s = -.04, p = .89). These correlations differ significantly (test of Fisher z-transformed correlation coefficients: Z = 2.92, p = .004).

Discussion

We studied six variants of an ABM procedure in a multiple case series design, in order to select the most promising variant for further testing in future controlled clinical trials. No consistent effects on attentional bias were observed for any version of ABM. Changes of attentional bias in individual participants did not generalize to untrained stimuli. This makes it very unlikely that any of these ABM versions will have a specific effect on symptoms in controlled studies.

During the training, the bias index changed in the intended direction in 17 out of 30 participants. For nine of these 17 participants the bias index for untrained stimulus pictures also changed in the intended direction. This lack of generalization is problematic as generalization of a modified bias is theoretically the key mechanism of ABM. In the study by Wells and Beevers (2010) (testing an ABM variant comparable to the current studies' sad-to- neutral 3000ms condition) for instance, depressive symptoms were unaffected during the training but did improve in the two weeks between training and follow-up. This is consistent with a model that cognitive changes only lead to symptomatic changes after interaction with the environment, as has also been proposed for pharmacologically induced cognitive changes (Booij & van der Does, 2011; Harmer, Goodwin, & Cowen, 2009). We did not measure longer-term effects, but since the effects of training on attentional bias, if any, did not generalize, a delayed effect on symptoms is quite unlikely. Furthermore, 14 of our 30 participants showed a change of bias in the wrong direction.

As expected, depressive symptom levels did not change during the training. Self-reported anxiety symptoms did decrease significantly within the sad-towards-neutral conditions, however. Although the lack of a control treatment makes this finding hard to interpret, we argue that this is a chance finding: an effect on symptoms was not expected, the training

was designed to target depression rather than anxiety, and our data do not support the working mechanism that would theoretically mediate such an effect. ABM studies reporting effects on self-reported anxiety measures often do not relate effects to changes in attentional bias, however.

In an unpublished study comparing implicit and explicit instructions conditions, it was found that explicit instructions increased the effect of ABM on attentional bias but abolished the effect on emotional reactivity (C MacLeod, et al., 2009). In the current study participants were kept unaware of the study's objectives, but awareness of training contingency was assessed in an funnelled interview following the procedures. One participant reported to have considered the possibility that the probe systematically appeared on the location of one type of stimulus, while 16 out of 30 participants believed to have been in a non-existent control treatment. The more certain participants were that they had received treatment, the more their bias index for untrained stimuli pictures had changed in the intended direction. No correlation existed between certainty of receiving training and the direction and magnitude of change in bias index during the training. This could be a reflection of demand characteristics in participants who were implicitly aware of the training contingency. It cannot be ruled out that such an effect could also influence self-reported measures of symptoms. Further research into the role of awareness in ABM seems warranted.

In summary, this single case series approach enabled us to scrutinize the effects of six variants of ABM for depression at the individual's and at training session level. Since we did not observe any consistent effects on attentional bias, we advice not to proceed yet to RCTs to test DPT-based ABM for depression. Given the large placebo effect in clinical trials of affective disorders, the risk of non-replicable findings would be large.

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chapter 3

The effects of a visual search attentional bias modification paradigm on attentional bias in dysphoric individuals

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Background and Objectives: Attentional Bias Modification (ABM) may constitute a new type of treatment for affective disorders. ABM refers to computerized training programs that have been developed based on laboratory findings in experimental psychology. Meta-analyses have reported moderate effect sizes in anxiety disorders. Two small studies have also claimed an effect in dysphoria. Furthermore, a series of studies in individuals with low self-esteem has shown that they benefit from a single session of an ABM variant based on a visual search task. The current study tested the working mechanism of visual search ABM in dysphoria.
Methods: Forty dysphoric individuals engaged in a single session of ABM training or control training. Attentional bias for positive and negative facial expressions was assessed pre- and posttraining. Positive and negative mood states were assessed throughout the procedure.
Results: Attentional training had no effect on attentional bias. Positive and negative mood states were not differentially affected by training condition.
Limitations: Small treatment effects may have gone undetected and there are some methodological differences with prior research.
Conclusion: We found no evidence that engaging in a single session of a visual search ABM modifies attentional biases for happy, sad or disgusted facial expressions.

Despite the availability of psychotherapies and medications for affective disorders, the search for new treatments continues. Existing treatments have limited efficacy, unwanted side effects, (Cuijpers, van Straten, Bohlmeijer, Hollon, & Andersson, 2010; Turner, Matthews, Linardatos, Tell, & Rosenthal, 2008) or are not easily available (Shapiro, Cavanagh, & Lomas, 2003). It is therefore not surprising that there is much interest in the development of computerized programs for the treatment of affective disorders. These could be relatively cheap, easily available, and more tolerable (Bar-Haim, 2010; Browning, Holmes, & Harmer, 2010).

Computerized treatments in development include the so-called Attention Bias Modification (ABM) paradigms. These training programs aim to modify individuals' automatic tendencies to direct attention towards negative visual information. Cognitive theories predict that such automatic tendencies, called attentional bias, play a role in the aetiology and maintenance of mood and anxiety disorders (Roiser, Elliott, & Sahakian, 2012; Yiend, 2010). Attentional bias is most often assessed with the so-called dot probe task. The ABM version of the dot probe task is designed to reduce attentional bias to negative information (MacLeod, Rutherford, Campbell, Ebsworthy, & Holker, 2002), which is expected to lead to a reduction in symptoms (Bar-Haim, 2010; Browning, et al., 2010; MacLeod & Mathews, 2012). Many studies have now tested ABM for anxiety and anxiety disorders and meta-analyses found small to moderate effect sizes compared with control treatment (Hakamata et al., 2010; Hallion & Ruscio, 2011).

A few small studies have tested ABM for depression. In the first of these, 34 dysphoric students engaged in four sessions of a dot probe ABM treatment (Wells & Beevers, 2010). No effects were observed immediately following training, but depressive symptoms were reduced in the ABM group at a 2-week follow-up assessment. This is consistent with the model that ABM changes information processing, which over time translates into an effect on mood. Attrition over the course of this study was quite high, however. The follow-up assessment was based on only 18 participants, seven of whom were in the ABM condition. In an extensive case series analysis in a similar population, we did not observe any consistent effect of six variants of the dot probe ABM training on attentional bias, the hypothesized mediator of clinical response (Kruijt, Putman, & Van der Does, 2013). An ABM version of the spatial cueing task, which is closely related to the dot probe task, has also been explored (Baert, De Raedt, Schacht, & Koster, 2010). No effects of this training were found in both a dysphoric and a depressed patient sample. A post-hoc analysis on the dysphoric sample suggested that the participants with relatively mild symptoms of depression might have improved on one of several anxiety measures. For those with higher levels of depression symptoms however, the training had an adverse effect. In

conclusion, the application of dot probe-based ABM treatments of depression has not yielded very encouraging results yet.

In individuals with low self-esteem, however, beneficial effects of an attentional training based on a specific type of visual search task, the "face-in-the-crowd task" (Hansen & Hansen, 1988), have repeatedly been reported (Dandeneau & Baldwin, 2004; Dandeneau & Baldwin, 2009; Dandeneau, Baldwin, Baccus, Sakellaropoulo, & Pruessner, 2007). In this paradigm, image grids of 16 faces are shown. One of the images portrays a smiling face, the others show negative, rejecting expressions. Participants have to locate the image of the smiling face as fast as possible. In the first study, individuals who had engaged in the experimental training experienced less cognitive interference from interpersonal rejecting words (e.g. ignored, disliked) in an emotional Stroop task, compared to a control training group. This effect was confined to individuals with low self-esteem (Dandeneau & Baldwin, 2004). Subsequently, this paradigm was tested in a series of studies assessing a range of outcome measures in diverse populations (Dandeneau, et al., 2007). Following training, less attentional bias towards rejecting faces was found compared to control training. Students who had received the training reported lower levels of exam stress. In a sample of telemarketers, several beneficial effects of the training were found on outcome measures related to stress and work performance. These included higher self-reported self-esteem, lower stress-hormone levels, and higher work performance ratings. In a third paper the finding of less attentional bias towards rejecting faces following training was replicated (Dandeneau & Baldwin, 2009). In addition, participants in the training group reported higher levels of self-esteem, showed more effective emotion regulation behaviour in a stressful anagram task, and reported less feelings of rejection following a simulated social rejection situation.

This visual search ABM task may be a more suitable approach for depression than dot probe-based ABM, since attentional bias for negative information in depression may differ from anxiety-related bias. The availability of elaboration time may be crucial. In depression, attentional bias is more often found in studies that used prolonged stimulus exposure times (750 ms or longer) (Mogg & Bradley, 2005) and there is no difference in effect size between biases detected at 500 and 1000 ms (Peckham, McHugh, & Otto, 2010). In contrast with dot probe-based tasks, the visual search ABM task does not place constraints on the amount of time individuals spend elaborating on the presented stimuli before responding. Moreover, depression may not only be characterized by attentional bias towards negative information but also by a lack of bias towards positive information (Fritzsche et al., 2009; Joormann & Gotlib, 2007; Joormann, Talbot, & Gotlib, 2007). These two biases may be dissociable rather than two ends of a continuum (Shane & Peterson, 2007). The visual search ABM training involves detecting an 'accepting' face in an array of 'rejecting' faces. This training may therefore target bias towards negative information and lack of bias towards positive information simultaneously.

Given the above findings and considering that 'feelings of worthlessness' are a diagnostic criterion of depression (American Psychiatric Association, 2000), we aimed to assess whether visual search ABM training is a suitable approach for depression and dysphoria. The current study tested the hypothesis that a single session of the visual search training

reduces attentional bias towards rejecting and sad facial expressions and increases bias towards happy facial expression in a dysphoric population. By testing this hypothesis, this study specifically aimed to establish whether the proposed mechanism of action, i.e. modification of bias, occurs. The influence of baseline depression symptom levels and mood on the efficacy of training, as well as acute effects of the training on mood was also explored.

Methods

Participants

Participants were dysphoric individuals recruited through advertisement. The Depression subscale of the Hospital Anxiety and Depression Scale (HADS-D) (Zigmond & Snaith, 1983) was used to preselect participants. The sum scores on these seven items range from 0 to 21. A mean HADS-D score of 3.4 was reported for a Dutch general population sample. In psychiatric outpatients, a mean score of 9.3 was found (Spinhoven et al., 1997). A HADS-D score between 4 and 9 was used as the main inclusion criterion. Exclusion criteria were: psychoactive drug use during the past three months and prior participation in ABM studies.

Symptom and mood state questionnaires

The Beck Depression Inventory-II (BDI-II) was used to assess depressive symptoms at baseline. The cut-off scores for mild and moderate depression are 14 and 20, respectively (Beck, Steer, & Brown, 1996). Trait anxiety was assessed with the Y-2 version of the State Trait Anxiety Inventory (STAI-T) (Spielberger, Gorsuch, & Lushene, 1970). Average scores in a student and a psychiatric outpatient sample were 37 and 52, respectively (Van der Ploeg, Defares, & Spielberger, 1980). Worry was assessed with the Penn State Worry Questionnaire (PSWQ). Average scores in a student and a GAD patient sample were 49 and 68, respectively (Meyer, Miller, Metzger, & Borkovec, 1990). The Positive and Negative Affect Schedule (PANAS) (Watson, Clark, & Tellegen, 1988) was administered four times throughout the test procedure. The PANAS consists of 20 items that have to be rated as being descriptive of how the participant feels right now. The answer options range from ‘very slightly or not at all’ to ‘extremely. Two subscales (positive affect, PA and negative affect, NA) each consist of ten items.

Materials

Computerized version of all tests and questionnaires, were created using the E-prime 2.0 software package (Psychology Software Tools, Pittsburgh, PA). Stimulus pictures were selected from the Karolinska Directed Emotional Faces set (Lundqvist, Flykt, & Ohman, 1998) based on expression identification hit rate, intensity, and arousal ratings provided in a validation study (Goeleven, De Raedt, Leyman, & Verschuere, 2008).

Visual search ABM

Participants were instructed to locate a single happy face among 15 disgusted faces in 4*4 arrays. Participants responded by clicking with the mouse on one of the pictures, after which a blank screen was shown for 500 ms, followed by the next stimulus array. In the experimental training task happy and disgusted expressions from sixteen identities (eight male, eight female) were used. Strictly speaking it is not known whether the rejecting

facial expressions used in previous studies testing this training would be classified as disgusted expressions, as these were never rated for this quality. However, at face value those images do resemble disgusting expressions. Moreover, ABM studies targeting Social Anxiety Disorder often feature disgusted facial expressions because these signal social rejection more strongly than sad or angry expressions (Amir, Weber, Beard, Bomyea, & Taylor, 2008; Klumpp & Amir, 2009; Schmidt, Richey, Buckner, & Timpano, 2009). Expression identification hit rate, intensity, and arousal ratings for the happy and disgusted expressions were matched with those for the identities used in the dot probe task. Each of the 16 stimulus identities appeared as the target identity (happy expression) at each of the 16 grid positions once, resulting in a total of 256 trials. Within each trial, the remaining 15 distractor identities (displaying a disgusted expression) were randomly allocated to the 15 remaining positions. The order of target identities and target locations was randomized. The training started with a number of practice trials. These continued until the participant answered six consecutive trials correctly with a minimum of ten practice trials. Every 32 trials a short self-paced break was given. These breaks consist of a display informing the participant that he/she can take a moment of rest and continue the task by clicking a button. Similar to Dandeneau and collegaues (Dandeneau & Baldwin, 2004; Dandeneau & Baldwin, 2009; Dandeneau, et al., 2007), grayscale images of flowers with either five (target) or seven (distractors) petals were created and used as stimuli in the control training. The control training was identical to the experimental training in all other respects. Figure 3.1 shows example stimulus grids from the experimental and the control training.

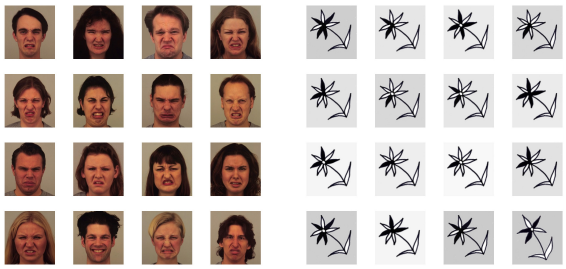

Figure 3.1. examples of stimulus grids used in the visual search training (left) and the flower control training (right).

Attentional Bias Assessment

Attentional bias was measured with a dot probe task. At the start of each trial, a fixation cross was shown in the middle of the display for 500 ms followed by the stimulus display for 750 ms. Upon offset of the stimulus display, the probe was shown on the location previously taken by either one of the stimulus pictures until a response was given after which a 350 ms blank screen preceded the next fixation cross. The probe was a 15*15 pixels black square that was shown either upright (square) or tilted 45° (diamond). Square probes were used because they are entirely identical except for being rotated 45 degrees. Moreover, this probe set does not have an implicit logical ordering, as is the case with the more often used probe sets “E versus F” and “. versus ..”. Using a probe set that has no implicit logical order, reduces possible influence of handedness on motor-response mapping: “E is left, F is right” might be easier to learn for right-handed participants. The happy, sad, disgusted and neutral expressions of 16 identities (eight male, eight female) were used as stimulus pictures. The expression identification hit rate, intensity and arousal ratings for the happy and disgusted expressions were matched with the identities used in the training task. The stimulus display showed two images of facial expressions in

a horizontal arrangement. Each stimulus width was 8° of visual angle. The midlines were 16° apart, leaving 8° of visual angle in between the two stimuli. The probe width was 0.4° of visual angle and the two possible probe locations were 15.6° of visual angle apart. The test started with a number of practice trials. These were neutral-neutral trials showing stimulus pictures not used in the experimental trials or the training task. Practice trials continued until the subject answered six consecutive trials correctly with a minimum of ten practice trials. Participants received no specific instructions regarding where to direct their attention but were instructed to respond to the identity of the probe as fast as possible while answering correctly. Participants responded by pressing one of the two buttons on a mouse that was fixated to the desk, centred in front of the participant. Participants operated the buttons using the index and middle fingers of their preferred mouse hand. Whether the left or the right mouse button corresponded to the square or the diamond shape of the probe, was counterbalanced across participants. Five happy-neutral, five sad-neutral, five disgusted-neutral, and five neutral-neutral trials were administered for each of the 16 stimulus identities, resulting in a total of 320 trials. Thus, one entire administration of the dot probe task consisted of 80 neutral-happy, 80 neutral-disgusted, 80 neutral-sad and 80 neutral-neutral trials. Within trials for each emotional expression, the identities of the stimulus pictures, the position of the emotional stimulus, the position of the probe (location previously taken by the emotional or by the neutral stimulus) and the identity of the probe were counterbalanced and administered in random order. Every 20 trials a short self-paced break was given. These breaks consist of a display informing the participant that he/she can take a moment of rest and continue the task by clicking a button.

Procedure

Upon arrival at the laboratory, participants read an information letter, were given the opportunity to ask questions and signed an informed consent form. Participants were not informed on the purpose of the training; they were lead to believe that the training was just one of several attention measures. The test procedure started with filling out the PANAS followed by the PSWQ, STAI-T and BDI-II. Following the questionnaires participants engaged in the baseline assessment of the dot probe task and a second task with verbal stimuli. We later discovered a flaw in the design of this second task, therefore data for this task are not reported. The order of the two tasks was randomized across participants. A five minutes break was given in between the two task administrations. The baseline assessment was concluded with a second administration of the PANAS. Training took place directly following the baseline assessment and a 5-minute break was given after 128 trials. Following the second part of the training, the PANAS was administered again, after which participants engaged in the post-assessment. In between the two post-assessment tasks participants received a short, 32 trials, retraining session followed by another five minutes break. The post-assessment was concluded by another administration of the PANAS. The duration of the entire procedure was approximately 90 minutes.

Results

Participants

Two hundred and sixty individuals filled out the screening questionnaire. Seventy-three participants, scoring between four and nine on the HADS-D (indicating mild to moderate symptoms of dysphoria), were invited to participate. Forty-eight individuals responded and were scheduled for testing. Three participants were excluded because they had recently participated in another ABM experiment. The data of five participants were discarded due to technical problems. Of the remaining 40 participants, 20 were assigned to the experimental group and 20 to the control group. Participants received either course credits or a small financial compensation for their time.

Baseline group characteristics are given in table 3.1. The mean BDI-II score for the entire group was 15, slightly above the cut-off score for a mildly depressed state (14). For STAI Y-2 and PSWQ, mean scores also fell in between average scores reported for healthy control and patient samples.

Table 3.1. *baseline questionnaire outcomes per condition.*

	Training (*n* = 20)		Control (*n* = 20)			
	M	*SD*	*M*	*SD*	*t*	*p*
BDI-II	16.7	6.8	12.5	7.3	1.896	.066
STAI Y-2	46.5	9.7	41.6	10.4	1.543	.131
PSWQ	52.8	12.2	48.6	15.1	.969	.338
PANAS						
PA (t1)	25.8	5.8	27.3	4.9	-.907	.370
NA (t1)	13.2	2.8	13.8	2.6	-.640	.526

BDI-II = Beck Depression Inventory II; STAI Y-2 = State Trait Anxiety Inventory Y-2; PSWQ = Penn State Worry Questionnaire; PANAS = Positive and Negative Affect Scale; t1 = baseline.

Preliminary analyses

Error rates per participant were explored. Twenty participants performed errorless during the training, 15 made a single error in 256 trials, five made between two and five errors. Error rates did not differ between the experimental and the control training conditions ($t(38) = .145$, $p = .878$). Changes in response times during the training task were evaluated by comparing the median response times for the first and the last 25% of the trials ($n = 2*64$) in a 2*2 repeated measures ANOVA with factors time (first 25% versus last 25% of the training trials) and condition (faces versus flowers task). Outcomes indicated that participants' response times decreased significantly over the course of the training ($F(1,38) = 49.445$, $p < .001$) and that, although response times were higher in the faces version ($F(1,38) = 13.808$, $p = .001$), the reduction in response times over the course of training did not differ between the two conditions ($F(1,38) = .000$, $p = .992$).

Practice trials and error trials (4.1 % of the experimental trials) were removed from the dot

probe task data. Response times below 200 ms or above 2000 ms were also removed (0.1% of the remaining data). The then remaining data were not normally distributed (positive skew and kurtosis) and therefore the median instead of the mean reaction time was used for calculating bias index (MacLeod, et al., 2002)[1]. Bias index was calculated by subtracting the median response time for trials in which the probe appeared on the location of the emotional stimulus (congruent trials) from the median response time for trials in which the probe appeared on the location of the neutral stimulus (incongruent trials). A positive bias index indicates vigilance towards the emotional (happy, sad or disgust) stimulus whereas a negative bias index indicates avoidance of the emotional stimulus. Bias indices were calculated separately for trials of each emotional valence (e.g. happy-neutral, sad-neutral and disgust-neutral trials) for both assessments and each participant[2].

Effects of training on attentional bias

Bias indices did not differ between training and control groups at baseline although there was a trend for the control group to show less bias towards disgust, compared to the ABM group (happy: $t(38) = .505$, $p = .616$; sad: $t(38) = .765$, $p = .449$; disgust: $t(38) = 1.784$, $p = .082$). No correlations were found between the questionnaire outcomes and either of the three baseline bias indices, neither for the entire sample nor within the two condition groups.

The effects of training on the attentional bias indices were evaluated using 2*2 repeated measures ANOVAs with factors time (baseline versus post training) and condition (experimental versus control), for each of the three emotional expressions: happy, sad and disgusted. Since no previous studies reported repeated dot probe measurements with this type of training, it was not possible to perform a priori power analyses. Using the software program G*power we performed sensitivity analyses for the repeated measures ANOVA, calculating the minimum detectable effect sizes requiring a power of .80 (Faul, Erdfelder, Lang, & Buchner, 2007). The minimum detectable effect sizes could range from $f = .32$ to $f = .03$, depending on the correlation between the repeated measurements. Taking the observed correlations into account, the achieved minimum detectable effect sizes for the time by group interaction terms were $f = .21$ (happy), $f = .16$ (sad expressions) and $f = .27$ (disgust expressions).

For happy and sad bias indices, none of the main and interaction effects approached significance (all $p > .15$). For the disgusted bias index, a trend towards an interaction effect of time and treatment was found ($F(1,38) = 3.560$, $p = .067$). Following training, bias for disgusted expressions was non-significantly increased in the control group. Including BDI-II scores as a covariate in these analyses yielded similar outcomes.

1 Analyses using bias indices calculated from mean response times and log transformed mean response times yielded comparable outcomes

2 The reported comparison of bias indices is the most commonly used analysis of dot probe data. The assessment of neutral-neutral trials, however, also allows for separate exploration of effects of vigilance versus difficulty to disengage attention (Koster, Crombez, Verschuere, & De Houwer, 2004). No significant interaction effects were found in 3*2*2 repeated measures ANOVA's comparing the response times on congruent, incongruent and neutral-neutral trials assessed pre- and post training with condition as between subjects factor for each of the three emotional facial expressions.

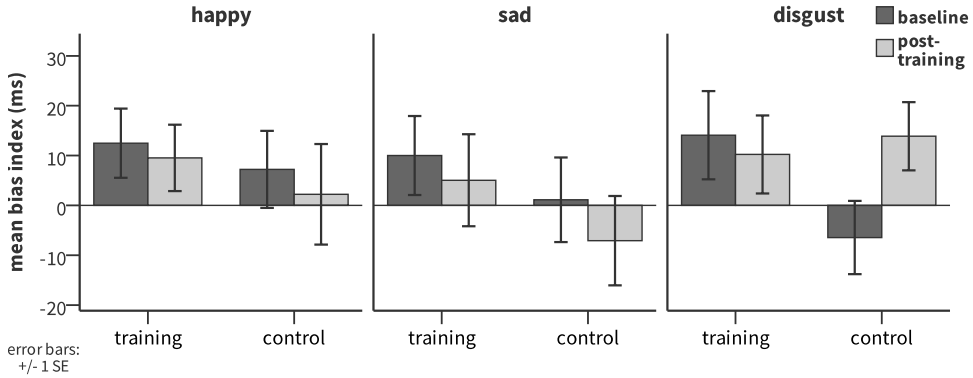

Figure 3.2. bias indices for happy, sad and disgust facial expression, at baseline and post-training for the experimental and the control training groups.

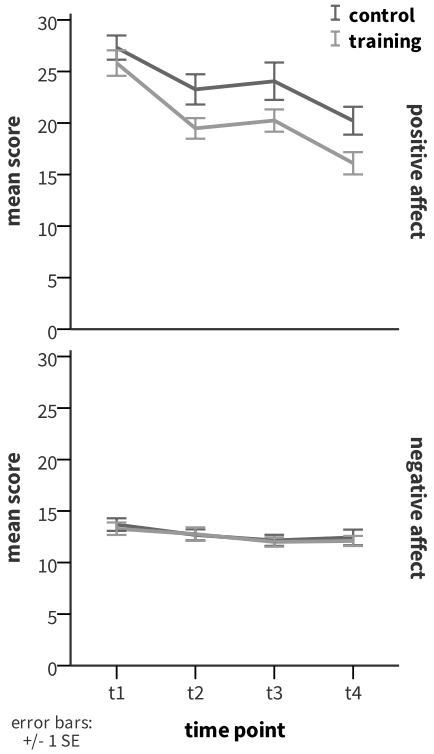

Figure 3.3. positive and negative affect (PANAS) throughout the experimental procedure. t1 = before baseline assessments, t2 = following baseline assessments - pre training, t3 = post training - before post-training assessments, t4 = following post-training assessments.

The analyses were also repeated with the scores on the PA and NA subscales of the PANAS assessed pretraining as covariates. This revealed a main effect of time ($F(1,36) = 9.126$, $p = .005$) and an interaction effect of time and negative affect ($F(1,36) = 10.846$, $p = .002$) on bias for sad facial expressions. Those participants who reported less negative affect pretraining had a larger decrease in bias for sad faces following training, whereas those who reported more negative affect showed an increase in bias for sad faces following the training. A similar trend was observed for bias for disgusted facial expressions (main effect of time: $F(1,36) = 3.233$, $p = .081$, interaction effect time by negative affect: $F(1,36) = 3.038$, $p = .090$). Entering the PANAS scores as covariates did, however, not reveal any effects of training condition. Thus, no effects of the visual search training on attentional bias for happy sad or disgust facial expressions were found (see figure 3.2).

Effects of training on self-reported mood states

Figure 3.3 shows the observed values of PA and NA at all four assessments: at baseline (t1), pretraining, following the pre-assessment tasks (t2), immediately following training (t3), and following the post-assessment tasks (t4). Visual inspection learns that positive affect

decreases considerably throughout the whole procedure, especially during the pre- and post-assessment tasks. In order to statistically explore whether immediate effects of training on mood occurred, two 2*2 repeated measures ANOVAs were conducted with group (experimental vs. control) as between subjects variable, on the PANAS mood ratings assessed immediately pre- and posttraining (t2 and t3). There was a main effect of time on the negative affect scores ($F(1,38) = 5.255$, $p = .028$): following training participants reported less negative affect than before. This effect did not differ between the experimental and the control group as indicated by a non-significant interaction effect ($F(1,38) = .280$, $p = .600$). A significant main effect of condition was found on the positive affect scores ($F(1,38) = 4.752$, $p = .036$): the control group reported higher positive affect than the experimental group. This effect was however not affected by the training as indicated by a non-significant condition by time interaction effect ($F(1,38) = .055$, $p = .816$). Sensitivity analyses showed that, requiring a power of .80, effect sizes on the interaction term as small as $f = .17$ (PA) and $f = .16$ (NA) could have been detected.

Post-hoc exploration of self-esteem related BDI-II items

Since the expected effects were not found, and because Dandeneau and colleagues found some effects specifically in participants reporting low self-esteem, we conducted an explorative post hoc analysis. Three items from the BDI-II were selected which, at face value, tap constructs related to self-esteem: self-dislike (item 7), self-criticalness (item 8) and worthlessness (item 14). Spearman's rank order correlations between the scores on these three items and the change in bias index were calculated. Bias index change scores were calculated by subtracting the baseline bias index from the post-training bias index. The resulting correlation coefficients are shown in table 3.2[3]. Scores on BDI-II item 7, self-dislike, correlated with the decrease in bias index for both disgusted ($r_s(38) = -.67$, $p = .003$) and sad expressions ($r_s(38 = -.56$, $p = .010$) in the experimental but not in the control group. This suggests that the training may change bias for negative facial expressions in participants who endorse BDI-II item 7 (self-dislike).

Table 3.2. S*pearman's correlation coefficients for BDI-II items 7, 8 & 14 and bias index change scores.*

	self-dislike		self-criticalness		worthlessness	
	training	control	training	control	training	control
happy bias	-.07	-.10	.07	-.03	.05	.15
sad bias	-.56[a]	.32	-.31	-.07	-.33	-.04
disgust bias	-.64[b]	-.03	.02	.02	-.35	-.03

Change scores = bias index post training – bias index pre training.
[a] p = .010 - 2-tailed
[b] p = .003 - 2-tailed

Comparing the Fisher transformed correlation coefficients showed that the correlation between BDI-II item 7 (self-dislike) and decrease in bias index differed significantly between the experimental and the control group for both disgusted ($Z = -2.1$, $p = .036$) and sad ($Z = -2.79$, $p = .005$) facial expressions.

3 Since this is an explorative analysis, Bonferroni correction was not applied. If applied, the correlation between change in bias for disgust faces and BDI-II item 7 remains significant.

Discussion

We observed no effects of a single session of visual search ABM on attentional bias for either happy, sad or disgust facial expressions. The training also had no differential effects on positive and negative affect states. When self-reported negative and positive affect states were used as covariates in the analyses evaluating the effects of ABM on bias indices, negative affect was associated with bias towards sad facial expressions, but no effects of training were revealed. This lack of effect was unexpected given earlier reports with this type of training.

We used the same control training (the flower task) as in previous studies. Although response times were lower in the control training task than in the experimental task, response times in both conditions decreased to a similar extent over the course of the training, indicating that both groups learned equally well. The main outcome measure in this study, the dot probe task, differs on several parameters from the dot probe task with which previous studies assessed effects of this type of training. Since depression related biases may be more pronounced at longer stimulus durations (Donaldson, Lam, & Mathews, 2007; Mogg & Bradley, 2005; Shane & Peterson, 2007), we used a longer stimulus duration (750 ms versus 500 ms in previous studies). Because we assessed multiple biases, a single session of our dot probe task took as many as 320 trials. This may have affected the outcomes both through fatigue, as well as through the occurrence of learning effects. Over the course of the dot probe task, the images depicting emotional facial expressions may have become less meaningful and less attention capturing. These potential problems were addressed by offering self-paced break opportunities every 20 trials and by using stimulus pictures of 16 different identities so that each emotional expression picture occurred only five times within one assessment. Different stimulus sets were used in the assessment and training tasks to ensure that the dot probe assessed the generalization of training effects rather than effects on a specific set of stimuli.

The current study is the first to evaluate the effects of this training on attentional bias in a pre-post design. In previous studies, attentional bias in treatment and control groups was only assessed post-training (Dandeneau & Baldwin, 2009; Dandeneau, et al., 2007). This might be because the dot probe task has a low reliability in a general population sample (Schmukle, 2005; Staugaard, 2009). There are, however, no tasks or techniques available for assessing preferential spatial orienting of attention that are proven to be more reliable than the dot probe task, and it remains the most often used task for assessing and modifying attentional bias. A within-between design, like we used, is generally considered a more suitable and powerful design for evaluating treatment effects. However, our sample was considerably smaller than in previous studies assessing the effects of this training on attentional bias. Based on the sample size, the minimum detectable effect size on the time by group interaction terms could have ranged from f =.03 to f =.32. Taking the observed correlations between repeated measurements into account, minimum effect sizes of .16, .21 and, .27 could have been detected with 80% power for the effects of training on sad, happy and disgusted attentional bias. Although the exact size of the post training between groups effects on attentional bias reported in previous studies are not known, they could be smaller in size than the minimum effect sizes that we could detect

on the within-between interaction effect. Thus, it is possible that smaller sized effects occurred in the current study but went undetected.

The current study focused on establishing ABM's mechanism of action, modification of attentional bias. We had no strong expectations about immediate effects on mood states or symptoms. One theory is that ABM affects attentional bias which needs time and interaction with the environment to translate into a mood effect (e.g., Wells & Beevers, 2010). However, previous studies with this type of training (Dandeneau & Baldwin, 2004; Dandeneau & Baldwin, 2009; Dandeneau, et al., 2007) did find immediate effects on self-esteem. We observed no differential effects of the training on positive or negative affect, however.

Although cognitive biases in low self-esteem may not be exactly the same as cognitive biases in dysphoria or depression, it has been theorized that all biased cognitive processing in depression occurs as a function of elaborate processing and low self-esteem (Wisco, 2009). In order to explore possible differential influences of self-esteem, we looked at the individual BDI-II items. Correlations were found between the score on item 7, self-dislike, and the attentional bias change scores for both disgust and sad faces in the experimental but not the control group. The Fisher transformed correlation coefficients differed significantly between the experimental and the control group. This suggests that the experimental training may have reduced attentional bias for sad and disgusted facial expressions in those participants endorsing statements at the higher end of a four-point scale running from "I feel the same about myself as ever" to "I dislike myself". This was a post-hoc analysis and the effect was only found for one of three items that are likely self-esteem related. Although the pattern of this effects fits with what would have been expected when a true measure of self-esteem had been assessed, this could be a chance finding.

In conclusion, although small treatment effects may have gone undetected, we found no evidence that engaging in a single session of a visual search ABM modifies attentional biases for happy, sad or disgusted facial expressions.

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chapter 4

The 5-HTTLPR polymorphism, early and recent life stress, and cognitive endophenotypes of depression

Kruijt, A.-W., Putman, P., & Van der Does, A. J. W. (2014)
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Background: Studies associating interactions of 5-HTTLPR and life adversities with depression have yielded equivocal results. Studying endophenotypes may constitute a more powerful approach.
Aim: Assessing whether interactions of 5-HTTLPR with childhood emotional abuse (CEA) and recent negative life events (RNLE) affect possible cognitive endophenotypes of depression, namely attention allocation bias and the ability to recognize others' mind states.
Design: Association study in 215 young adults of North-West European descent.
Results: The ability to classify others' negative mind states was increased with increasing RNLE in carriers of low expressing 5-HTTLPR alleles. Carriers of two low expressing alleles also preferentially oriented attention towards negative information. Gene-environment interactions were not observed for attentional allocation bias. No effects involving CEA were observed.
Conclusion: Low expressing 5-HTTLPR alleles may confer increased risk for depression through enhanced recognition of negative facial expressions following recent negative life events.

The most studied polymorphism in relation to depression is the Serotonin Transporter Linked Polymorphic Region (5-HTTLPR), located in the promoter area of the gene encoding the serotonin transporter protein (SLC6A4; see www.HuGeNavigator.net; Yu, Gwinn, Clyne, Yesupriya, & Khoury). The 5-HTTLPR is a repeat polymorphism, resulting in short (S) and long alleles (L). The S allele is associated with reduced expression of the serotonin transporter protein, which regulates the reuptake of serotonin from the synaptic cleft. Within the L allele, a single nucleotide (guanine/adenosine) polymorphism exists (rs25531), resulting in L_g and L_a alleles. L_g alleles are regarded as functionally similar to the S allele (Hu et al., 2006). Carriers of one or two low expressing alleles (S or L_g) are found to be more sensitive to the effects of environmental adversity than L_A homozygotes. This interaction of 5-HTTLPR and environmental adversity on depression was first observed in a large cohort study (Caspi et al., 2003). Increasing levels of adversity (both childhood maltreatment before age 10 and recent negative life events between age 21-25) were associated with increasing probability of depression and suicidality at age 26 in S carriers, but not in L homozygotes (Caspi, et al., 2003). At that time the L_g/L_a distinction was not yet made. Despite a large number of studies attempting to replicate interaction effects of both early and recent life stress with 5-HTTLPR, the empirical evidence for these gene-environment interactions remains equivocal. Two meta-analyses found no evidence for a direct effect of 5-HTTLPR nor an interaction with recent life events (Risch et al., 2009) or recent and childhood stress (Munafó, Durrant, Lewis, & Flint, 2009) while a third meta-analysis supported interactions of 5-HTTLPR with both recent life events and childhood maltreatment (Karg, Burmeister, Shedden, & Sen, 2011).

These meta-analysis focused on depression as outcome measure. A possible partial explanation for the inconsistent results lies in the heterogeneity of the depression construct, which is likely influenced by a myriad of genetic and environmental factors. An upcoming alternative approach is to study associations with endophenotypes. Endophenotypes are hereditary biological or psychological processes or markers that precede or predispose to the pathology of interest (Gottesman & Gould, 2003; Lenzenweger, 2013). Because endophenotypes are more proximally related to the genotype than the disease itself (phenotype), associations between genotype and endophenotype may be more easily detected. Meta analyses on outcomes such as cortisol reactivity (Miller, Wankerl, Stalder, Kirschbaum, & Alexander, 2012), and developmental problems in children and adolescents (van Ijzendoorn, Belsky, & Bakermans-Kranenburg, 2012) support the existence of 5-HTTLPR by stress interactions.

Potential endophenotypes for depression include cognitive processing biases (Hasler, Drevets, Manji, & Charney, 2004). In the current study two types of processing bias are assessed as candidate endophenotypes: biased attentional allocation for emotional

information, and biases in recognition of emotional facial expression.

Biases in cognitive processing have been implicated in the aetiology of depression since the introduction of cognitive models (Beck, 1967). Among the biases associated with depression is preferential allocation of attention towards negative visual information. This bias is most often assessed with the dot probe task. Attentional bias for negative information has been observed in currently depressed (e.g. Fritzsche et al., 2009; Gotlib et al., 2004; Joormann & Gotlib, 2007), remitted depressed (e.g. Fritzsche, et al., 2009; Joormann & Gotlib, 2007), dysphoric (e.g. Bradley, Mogg, & Lee, 1997; Shane & Peterson, 2007), and at-risk (Joormann, Talbot, & Gotlib, 2007) samples. Several studies reported an additional, and dissociable, bias away from positive information (e.g. Fritzsche, et al., 2009; Joormann & Gotlib, 2007; Shane & Peterson, 2007).

Associations between 5-HTTLPR and attention allocation bias have also been reported. In the largest of these studies, healthy individuals homozygous for the L_a allele showed preferential orienting towards positive pictures and avoidance of negative pictures, which was not observed in carriers of S or L_g alleles (Fox, Ridgewell, & Ashwin, 2009). Other studies reported slightly different patterns of 5-HTTLPR effects, possibly due to the variation in genotype methods (e.g. assessment of L_a/L_g variants), outcome measure (dot probe task, Posner task, task features), and stimulus type (words, facial expressions, pictures). A meta-analysis concluded that individuals carrying two low expressing alleles show preferential orienting towards negative information (Pergamin-Hight, Bakermans-Kranenburg, van IJzendoorn, & Bar-Haim, 2012).

Only one study assessed possible gene-environment interactions involving 5HTTLPR and attention allocation bias in adults. Females carrying one or two S-alleles who reported childhood physical abuse selectively avoided angry facial expressions (Johnson, Gibb, & McGeary, 2010). However, only 13 participants in that study reported some degree of physical abuse, and the subsample of S-carriers must have been even smaller. Two other small studies in children reported evidence for attentional bias occurring as a function of 5HTTLPR and mothers' depression status (Gibb, Benas, Grassia, & McGeary, 2009), or mothers expressed criticism (Gibb et al., 2010).

Biases in the recognition of facial expressions of emotion are also associated with depression. Better recognition of negative expressions has been observed in remitted depressed samples (Anderson et al., 2011; Bhagwagar, Cowen, Goodwin, & Harmer, 2004), whereas currently depressed samples showed impaired recognition of negative facial expressions (Anderson, et al., 2011; Douglas & Porter, 2010). Facial emotion recognition is influenced by administration of selective serotonin reuptake inhibitors, which exert their action at the serotonin transporter (Anderson, et al., 2011; Bhagwagar, et al., 2004). Moreover, tryptophan depletion (a procedure to experimentally lower brain serotonin levels) reduces the ability to recognize fearful expressions in 5HTTLPR S carriers but not in L homozygotes (Marsh et al., 2006). A number of studies reported biased processing of negative facial expressions in children and adolescent samples as a function of 5-HTTLPR (e.g. Lopez-Duran, Kuhlman, George, & Kovacs, 2012; Székely et al., 2011) or an interaction between 5-HTTLPR and mothers' depression history (Jacobs et al., 2011).

One study assessed gene-environment interactions, between 5-HTTLPR and recent negative life events as well as childhood emotional abuse, on facial emotion recognition in adults (Antypa, Cerit, Kruijt, Verhoeven, & Van der Does, 2011). Carriers of a low expressing allele who experienced recent negative life events recognized angry and sad facial expressions better. Furthermore, L_A homozygotes reporting childhood emotional abuse showed impaired recognition of angry facial expressions.

The current study is intended as a conceptual replication of the findings by Antypa and colleagues (2011), and a replication and extension of the findings by Fox and colleagues (2009). We extended the design of the latter study by also assessing gene-environment interactions, while using a very similar measure of attention allocation bias. For the conceptual replication of the findings by Antypa and colleagues (2011), a different measure of emotion recognition was used. The Reading the Mind in the Eyes Test (RMET; Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001) assesses the ability to recognize relatively complex emotional states (e.g., grateful, concerned), rather than basic emotional expressions (e.g., happy, fearful). Similar to studies assessing recognition of basic facial emotional expressions, RMET studies yielded a pattern of increased mind state recognition in dysphoric students and remitted depressed participants (Harkness, Jacobson, Duong, & Sabbagh, 2010; Harkness, Sabbagh, Jacobson, Chowdrey, & Chen, 2005), and reduced recognition in currently depressed patients (Lee, Harkness, Sabbagh, & Jacobson, 2005), although this was not always found (Wolkenstein, Schönenberg, Schirm, & Hautzinger, 2011).

Gene-environment interaction effects were assessed using the same environmental stress measures as in the study by Antypa and colleagues (2011). Self-reported negative life events that occurred during the six months preceding the test were used as an index of recent negative life events. Self-reported childhood emotional abuse was used to index childhood adversity.

We expected carriers of at least one low expressing alleles (S/L_g) to show attentional bias towards negative information and away from positive information, whereas L_a homozygotes were expected to show a relative bias towards positive and away from negative information. We also expected a moderation effect of exposure to early or recent life events, reflecting less stress sensitivity in L_a homozygotes. Considering that our sample was not currently depressed, we expected that carriers of low expressing alleles (S or L_g) would perform better at recognizing others' mind states if they had been exposed to early or recent life stress.

Methods

Participants

Participants were recruited through posters and flyers. Participants were between 17 and 35 years old, were not currently depressed, had normal or corrected to normal vision, and were of middle and northern European descent (all four grandparents born in a region spanning from France to Austria, up to Scandinavia). Data were obtained between February and October 2011.

Measures

Attentional bias

Preferential orienting of attention was assessed with a dot probe task (MacLeod, Mathews, & Tata, 1986). Each trial started with a fixation cross shown in the middle of the display for 500 ms, followed by two stimulus pictures in horizontal arrangement for 500 ms. Upon offset of the stimuli, a small figure (the probe) appeared in the middle of the location previously occupied by either stimulus picture. Participants were instructed to respond to the identity of the probe as fast as possible by pressing either one of two buttons on a mouse that was attached to the desk in front of the participants. The correspondence between mouse buttons (left/right) and probe identities (square or diamond shape) was counterbalanced across participants. Stimulus pictures had a positive, negative or neutral valence and were selected from the International Affective Picture Set based on valence and arousal ratings (IAPS; Lang, Bradley, & Cuthbert, 1999). Negative pictures depicted depression related rather than threatening scenes. See supplementary material for a more detailed description of the dot probe task features, randomizations, and stimulus pictures.

Bias indices were calculated by subtracting response times on trials wherein the probe appeared at the location previously taken by an emotional stimulus (congruent trials) from response times on incongruent trials (MacLeod, et al., 1986). A positive value indicates preferential orienting of attention towards the emotional stimulus.

Reading mind states

The Reading the Mind in the Eyes Test (RMET) was adapted for computerized assessment. Participants received written instructions, followed by a test trial and 36 experimental trials. Within each trial, a stimulus picture was shown at the centre of the display, with four response options at its corners, until participants responded by mouse clicking. The positions of the four answer options were randomized. Our participants were students who were native Dutch and competent at English, therefore both the original English words as well as the Dutch translations were presented side by side. As in the original version, a glossary was provided for reference during the task, listing the English and the Dutch words, their meaning, and an example sentence. No time limit was set for answering, but participants where instructed not to think too long before answering. The 36 trials of the RMET included 8 positive trials, 12 negative trials and 16 neutral or 'other' trials, according to the valence of the correct response (Harkness, et al., 2005, pp. table 1, p 1007.).

Childhood Trauma
The Childhood Trauma Questionnaire – Short Form (CTQ-SF; Bernstein et al., 2003) is a 28 item questionnaire assessing five categories of childhood trauma: emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect. Items are rated on a 5-point Likert scale anchored from (1) never true to (5) very often true. The emotional abuse scale consists of five items assessing whether the respondent felt loved, felt looked out for, was made to feel important, and whether the respondent felt that family was close and a source of strength (Bernstein, et al., 2003).

Recent Negative Life Events
The number of negative life events that occurred during the six months preceding the test was assessed using the List of Threatening Experiences – Questionnaire (LTE-Q; Brugha, Bebbington, Tennant, & Hurry, 1985; Brugha & Cragg, 1990). This questionnaire assesses the occurrence of twelve negative life events such as illness or injuries to the self or close friends and relatives, loss of friends, relatives or partners, loss of job or housing, and being victimized by theft or assault. The LTE-Q is often used in studies assessing possible relationships between recent negative life events, 5-HTTLPR, and depression (Risch, et al., 2009, p. 2464). The derived information is in high agreement with information obtained from interviewing participants or their relatives, and the test-retest reliability is high (Brugha & Cragg, 1990).

Depression
Current and past incidence of major depressive episodes was assessed with the Major Depression Questionnaire (MDQ; Van der Does, Barnhofer, & Williams, 2003). This self-report list assesses the presence of all diagnostic criteria for a major depressive episode. This is done twice, once for a period of two weeks during the past month, and once for any period of two weeks during lifetime. Responses were scored according to DSM-IV criteria for major depressive disorder (American Psychiatric Association, 2000). Participants reporting sufficient symptoms to suggest that a diagnosis of major depressive episode applied to any period of two weeks during the past month were excluded. This should be considered a strict criterion. Comparison of 39 diagnoses derived from the MDQ and the SCID interview (Spitzer, Williams, Gibbon, & First, 1994), suggested that the MDQ has a sensitivity of 100%, yet a specificity of 75% (Williams, Van der Does, Barnhofer, Crane, & Segal, 2008).

Genotyping
Saliva samples were collected in Oragene Self-Collection Kits – DISC format (DNA Genotek Inc, Ottawa, Ontario, Canada). See supplementary material for a description of the PCR and genotyping procedures.

Procedure
Participants were scheduled for 1.5 hours appointments. Upon arrival at the laboratory, participants received written and verbal information on the purpose and procedure of the study and were given the opportunity to ask questions before signing informed consent. The RMET and the dot-probe were the first of four computerized behavioural tasks, followed by computerized administration of questionnaires. At the end of the procedure

participants provided a saliva sample for genotyping. Participants rinsed their mouth during a short break approximately 30 minutes before providing the saliva sample. Finally, participants were debriefed and thanked. Participants received a small compensation for participating. The medical ethics committee of Leiden University Medical Center approved the study protocol.

Analyses

Moderated regression analyses were used to assess interactions of 5-HTTLPR and environmental stress. Analyses started with assessment of bivariate relations, i.e. correlations, between the outcome variables (attentional bias positive, attentional bias negative, RMET total, RMET positive items, and RMET negative items), and the predictors (5,HTTPLR, CEA, RNLE, sex and MDQ status). If sex or MDQ status had been identified as a possible covarying variable, i.e. found to be associated with an outcome variable, it would be included in the subsequent moderated regression analyses. If no possible confounders were identified, the simplest possible model was used to assess significance of the gene-environment interaction term. The simplest model includes three terms: 5-HTTLPR, CEA or RNLE, and the corresponding gene*environment interaction. Significant gene-environment interactions were further explored using simple slopes analyses (Aiken & West, 1991).

The CEA predictor represents the CTQ-CEA score, which has a minimum of 5. Scores of 5, 6, 7, etc. points were recoded as 0, 1, 2, etc. RNLE were coded as 0, 1, 2, etc. for or 0, 1, 2, etc. events. Allelic variants were coded as 0 (SS, SL_g, L_gL_g), 1 (SL_a L_gL_a), or 2 (L_aL_a), representing the number of, high expressing, L_a alleles (Caspi, et al., 2003). Sex was dummy coded (0=male, 1=female), as was self-reported history of major depression (MDQ status, 0=no, 1=yes). For the moderated regression analyses, variables were mean centred (Aiken & West, 1991).

Results

Participants

Data were obtained for 238 participants. Twenty-three participants reporting symptoms indicative of a major depressive episode within the month preceding testing were excluded. Analyses were based on 215 participants. Due to a procedural error, one participant took the dot probe task twice, while the RMET was not administered. Data obtained in the first dot probe assessment were used and this participant was excluded from the RMET analyses.

Gene data

Amongst the 215 participants, 47 were carriers of two low expressing alleles (low expression group: 40 SS, 6 SL_g, 1 L_gL_g), 98 carried one low and one high expressing allele (medium expression group: 89 SL_a, 9 L_gL_a), and 69 participants were homozygous for the L_a allele (high expression group: 69 L_aL_a). The observed distribution of genotypes (S and L_g alleles collated) was in Hardy-Weinberg equilibrium: $\chi^2_{(1,\, n=215)} = 1.36$, $p = .24$. This was also the case for the distribution of the three allelic variants ($S/L_g/L_g$): $\chi^2_{(3,\, n=215)} = 3.00$, $p = .39$). For the remainder of this paper, the terms low, medium and high expression will be used

to indicate 5-HTTLPR groups.

Table 4.1. *demographic information per 5-HTTLPR group.*

5-HTTLPR:	low (*n*= 48)		medium (*n*= 98)		high (*n*= 69)		
	n	%	*n*	%	*n*	%	*p*
female	42	87.5	86	87.8	57	82.6	.606
MDQ status	17	35.4	34	34.7	27	39.1	.833
	M	sd	M	sd	M	sd	
age	20.0	2.2	20.0	2.9	20.1	2.9	.946
CEA	6.8	2.6	7.0	2.3	7.4	3.3	.490
RNLE	1.1	1.0	1.2	1.2	1.2	1.2	.816

For sex and self-reported history of depression (MDQ status), the reported p value is associated with X^2 tests, all other p values are associated with one-way ANOVA F-tests. 5-HTTLPR low = SS, SL_g, L_gL_g, medium = SL_a, L_gL_a, and high = L_aL_a. MDQ status = self reported symptoms indicate past major depressive episode(s), CEA = Childhood Emotional Abuse, RNLE = Recent Negative Life Events. Based on non-centred variables.

Demographics

Table 4.1 lists the demographic and environment measures per 5-HTTLPR group. Chi-square tests and one-way ANOVAs indicated no differences between 5-HTTLPR groups.

Data preparation

Attentional bias

Error trials were removed. On average, participants made 4% errors. Three participants were identified as outliers with respect to error rate (threshold = M+3SD = 14%) and were excluded from further analysis. Trials with response times below 200 or above 2000 ms were discarded (0.2% of remaining trials). The remaining data showed positive skew and kurtosis, therefore median instead of mean values were used to derive bias indices (MacLeod, Rutherford, Campbell, Ebsworthy, & Holker, 2002). Bias indices for positive-neutral and negative-neutral trials were calculated by subtracting the median response times for congruent trials from the median response times for incongruent trials.

Reading mind states

Percentage correct scores were calculated for the total number (36) of RMET trials, and separately for the eight positive and the twelve negative trials (Harkness et al., 2005; table 1, p 1007).

Data inspection

Most variables were approximately normally distributed, only the CEA distribution showed positive skew (2.08) and kurtosis (5.0). Because more extreme data points may disproportionally influence analyses outcomes, scatterplots were inspected to assess possible influences of the distribution on the bivariate analyses. For the moderated regression analyses, Cook's distances and the distribution of the residuals were inspected

to identify influential data points. If such cases were identified, analyses were repeated excluding these cases. Although the RMET positive item score was approximately normally distributed, three possible outliers were identified, each with a 25% correct score. These were initially retained, but analyses on this variable were also repeated excluding these cases.

Table 4.2. *bivariate associations*

		1	2	3	4	5	6	7	8	9
1	DP BI pos.	-								
2	DP BI neg.	.01	-							
3	RMET total	.07	.00	-						
4	RMET pos.	.04	-.02	.40***	-					
5	RMET neg.	-.02	.04	.70***	-.05	-				
6	sex	-.04	-.11	.09	.04	.11	-			
7	MDQ status	.11	-.09	.06	.01	.11	.00	-		
8	CEA	-.01	.01	.06	-.02	.10	-.01	.34***	-	
9	RNLE	-.04	.07	-.02	-.07	.07	.00	.17*	.20**	-
10	5-HTTLPR	-.02	-.14*	.03	.08	-.02	-.06	.03	.08	.02

*Pearson's correlations; * < .05, ** < .01, *** < .001.*
Pos. = positive, neg. = negative, DP BI = dot probe Bias Index, RMET = Reading the Mind in the Eyes Task, CEA = Childhood Emotional Abuse, RNLE = Recent Negative Life Events, MDQ status = self reported symptoms indicate past major depressive episode(s)

Bivariate analyses

Correlations between all variables are shown in table 4.2. As would be expected, RMET total score was highly correlated with the scores for RMET negative items (.70) and positive items (.40). All other correlations were small to moderate in size, and most were non-significant. Attention allocation bias for positive and negative stimuli were not associated, nor were these associated with RMET assessed bias. Self-reported history of depression (MDQ status) and sex were not related to any of the outcome variables (attention allocation or mind state recognition), ruling them out as possible covarying variables. CEA and RNLE were significantly associated (r =.20, p = .004), and both were associated to MDQ status (CEA: r = .40, p < .001; RNLE: r = .18, p = .011). These associations may reflect either a causal role of CEA and or RNLE in the aetiology or depression, or biased reporting of CEA and RNLE by participants with a history of depression. No correlations were observed between 5-HTTLPR groups and the life event variables (RNLE: r = -.001; p = .99, CEA: r = .08; p = .24), ruling out gene-environment correlations.

In line with our first hypothesis, a weak association between 5-HTTLPR and attention allocation bias for negative items was observed (r = -.14, p = .049). T-tests yielded a significant difference in allocation bias index for negative information between the low and high expression homozygous groups ($t_{(113)}$ = 2.03, p=.044), but not between the heterozygous and either of the homozygous groups (both p > .05), also see figure 4.1. None of the observed bias indices differed from zero (all p > .05). Thus, carriers of two low expressing alleles preferentially oriented attention towards negative information, whereas L_a homozygotes showed a relative tendency to avoid negative information. The hypothesized association between 5-HTTLPR and attention allocation bias for positive stimuli was not observed.

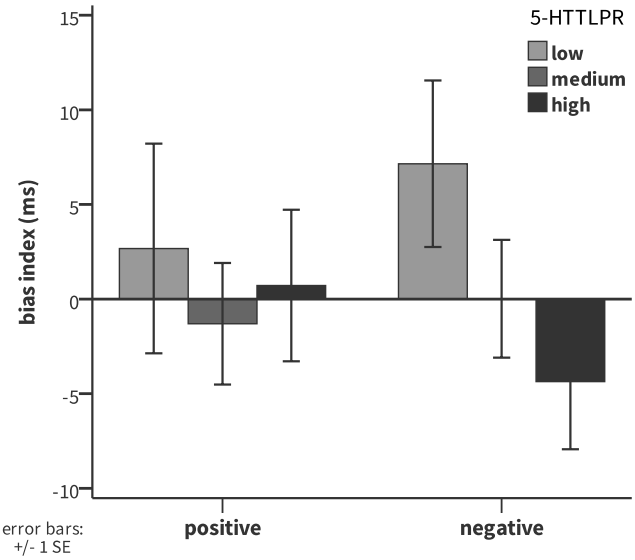

Figure 4.1. attentional bias for positive and negative information by 5-HTTLPR.
low = SS, SL_g, L_gL_g, medium = SL_a, L_gL_a, high = L_aL_a
* t(113) = 2.03, p=.044

All bivariate associations pertaining to the skewed variable CEA were non-significant. Inspection of scatterplots did not suggest that the distribution of CEA influenced associations in any such way that possible significant correlations were obscured. Repeating the bivariate analyses excluding the three, previously identified, possible outliers on RMET positive item score did not meaningfully change outcomes.

Moderated regression analyses:
The moderated regression analyses are presented in full in tables 4.s2a and 4.s2b of the supplemental information.

Attentional bias
Moderated regression analyses yielded no significant interaction effects for 5-HTTLPR by RNLE or for 5-HTTLPR by CEA on attentional bias indices for positive or negative information (see table 4.3).

Reading mind states
A significant interaction of 5-HTTLPR and RNLE was found for RMET negative item scores (b= -2.54, se =1.21, $t_{(210)}$ = 2.10, p =.037; model r^2 = .026). The direction of this interaction was such that carriers of two low expressing alleles (S or L_G) showed increased recognition of negative mind states with increased exposed to negative life events (figure 4.2a). Simple

slope analyses were significant for the low expression group (t(209) = 2.33, *p*= .021), but not for the intermediate (*t*(209) = 1.45, *p* =.148), or high expression groups (*t*(209) = -.97, *p* = .333; figure 4.2b). No other gene-environment interactions were found significant, see table 4.3.

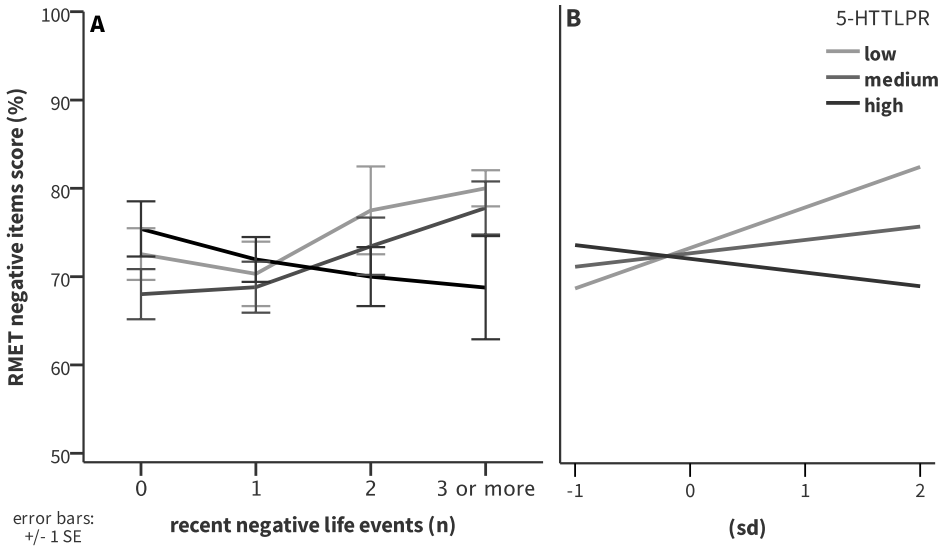

Figure 4.2. 5-HTTLPR by RNLE interaction on RMET negative item score
A) RMET negative item score by RNLE and genotype B) simple slopes plot
5-HTTLPR: low = SS, SL_g, L_gL_g, medium = SL_a, L_gL_a, high = L_aL_a

Influential data points

For all analyses, values of Cook's distance were lower than 1 (maximum values per analysis ranged from .05 to .49). The analyses for RMET positive item scores were repeated without the previously identified possible extreme outliers. All analyses were repeated with standardized residuals < -3 and > 3 removed. Per outcome measure 0 to 4 cases were excluded to achieve that all residuals fell in the -3 to 3 range. Re-analyses did not change the initial outcomes.

Table 4.3. *characteristics of the observed gene-environment interaction effects for each outcome measure and operationalization of adversities (CEA/RNLE).*

	5-HTTLPR * CEA				5-HTTLPR * RNLE			
	B	*SE*	*t*	*p*	*B*	*SE*	*t*	*p*
DP BI pos.	-.90	1.09	-.83	.409	1.70	2.82	.60	.548
DP BI neg.	.64	.98	.65	.518	1.70	2.53	.67	.502
RMET total	.17	.29	.59	.554	-.55	.76	-.72	.472
RMET pos.	-.34	.52	-.65	.519	-.89	1.34	-.66	.508
RMET neg.	-.22	.47	.47	.643	-2.54	1.21	-2.10	.037

*Pos. = positive, neg. = negative, DP BI = dot probe Bias Index, RMET = Reading the Mind in the Eyes Task, CEA = Childhood Emotional Abuse, RNLE = Recent Negative Life Events. Interaction effects assessed in moderated regression models with three predictors: 5-HTTLPR, adversity (CEA/RNLE), and interaction 5-HTTLPR*adversity.*

Additional analyses:

We adopted the statistical method used in he initial paper (Caspi, et al., 2003) and most papers assessing 5-HTTLPR*stress interactions, including one meta-analysis (Risch, et al., 2009). In these regression analyses, 5-HTTLPR is handled as a linear variable, implicating a linearly additive genetic model. A less often used, alternative, approach is to contrast all carriers of a low expressing allele (SS or L_g) with the L_a-homozygotes. A dichotomized representation of 5-HTTLPR complies better with assumptions of regression analysis, but ignores possible variation associated with carrying one versus two low expressing alleles. Analyses were repeated with 5-HTTLPR recoded, such that all S or L_g carriers were coded as 0, and L_a homozygotes as 1 (see tables 4.s3a and 4.sb in the supplemental information). For most analyses outcomes did not chance meaningfully (see supplementary material). The interaction effect of 5-HTTLPR and RNLE was again found significant for RMET negative item score (b = -4.44, se = 1.78, $t_{(210)}$ = -2.49, p = .013, model r^2 = .034). In line with the main analyses, subsequent simple slope analysis was significant for S or L_g-carriers ($t_{(210)}$ = 2.27, p = .024), but not for L_a homozygotes ($t_{(210)}$ = -1.44, p= .151). The bivariate association between allelic variant and attentional bias for negative information was not found when contrasting S/L_G-carriers and L_A homozygotes (r= -.103, p= .134). Moreover, most papers to date assessing main effects (but not gene-environment interaction) of 5-HTTLPR on attentional bias allocation utilized factorial ANOVA analysis, treating 5-HTTLPR as a nominal variable without implicating a genetic model. When no linear model was assumed in ANOVA, the effect of genotype on attentional allocation bias for negative information was not significant: $F_{(2,209)=}$2.010, p=.137. Assessment of the linear contrast in ANOVA yielded a result similar to the bivariate linear analysis: $F_{(1,209)=}$ 3.912, p = .049 (weighted contrast).

Discussion

An interaction effect between 5-HTTLPR and recent negative life events influencing recognition of negative mind states was observed. A weak association was found for RNLE and attentional bias for negative information. No gene*environment interactions were observed for attention allocation bias, nor were any effects involving early life stress (CEA).

The observed interaction effect is a conceptual replication of previously reported improved recognition of angry and sad facial expressions following negative life events in carriers of two low expressing alleles (Antypa, et al., 2011). Effects similar to the previous finding of impaired recognition of angry expressions by L_A homozygotes exposed to CEA (Antypa, et al., 2011) were not observed. This may because the RMET does not assess the recognition of discrete basic emotional expressions (e.g., anger, sadness, disgust), but rather more complex negative affects. Alternatively, the non-replication of any CEA effects may be ascribed to low CEA incidence, as discussed below.

Hypothesized gene-environment interactions affecting attentional allocation bias were not found. The observed main effect of 5-HTTLPR on attentional allocation bias for negative information is a replication of previous findings in smaller samples (meta-analysis: Pergamin-Hight, et al., 2012). However, this effect was only just significant (p = .049) and dependent on the statistical method: it was only found if a linearly additive genetic model was implied in the statistical model, and it was not found when carriers of either one or two low expressing alleles (S or L_G) were collated. A previously reported main effect of 5-HTTLPR on attentional allocation bias for positive information was not found, although a dot probe task with very similar stimuli (IAPS pictures; Lang, et al., 1999) and the same exposure duration (500 ms) was used (Fox, et al., 2009).

With sample sizes in previous studies ranging from n= 27 to n = 106 (Beevers, Gibb, McGeary, & Miller, 2007; Fox, et al., 2009; Johnson, et al., 2010; Kwang, Wells, McGeary, Swann Jr, & Beevers, 2010), the sample in the current study (n=215) was twice as large as the sample is largest study to date assessing 5-HTTLR effects on attention allocation bias in adults. Our sample was slightly smaller than the only other study assessing 5-HTTLPR effects on facial emotion recognition (n = 245; Antypa, et al., 2011).

Given a sample size of 215, effect sizes of f^2 = .036 and larger can be detected with at least 80% power in linear regression models with three predictors. In the context of behavioural science, the effect size measure f^2 was recommended to be interpreted as small at a value of .02, medium at .15, and large at .35 (Cohen, 1992). The observed effect size of the significant 5-HTTLPR RNLE interaction model was f^2 = .026, associated with an estimated achieved power of .65. Therefore, still larger studies are needed to confirm these findings.

Associations between a genotype and an endophenotype, e.g. cognitive bias as assessed in this study, may be relatively easy to detect compared to associations between a genotype and a disease of interest, because a more proximal relation is likely influenced by fewer other factors. However, the endophenotype, i.e. the presence of bias, does not necessarily

result in depression incidence. Thus, the currently reported interaction suggests that carrying S or L_g alleles may confer an increased risk for developing depression in response to negative life events, through increased recognition of negative facial emotion following negative life events. Meta-analyses and longitudinal studies may confirm whether the relationship between 5-HTTLPR, stress, and depression is indeed mediated by biased processing of emotional information.

Additional studies are also needed to extend establish that biased information processing indeed qualifies as an endophenotype. Five criteria have been suggested: that the endophenotype is associated with the phenotype in the population, is heritable, is state-independent, co-segregates with the phenotype within families, and is found in non-affected members of affected families at a higher rate than in the general population (Gottesman & Gould, 2003, p. 639). Several studies on biased information processing provided initial evidence for several of these criteria, yet we are not aware of any studies explicitly assessing these endophenotype criteria for biased attentional allocation or facial emotion recognition. Given the current results, we suggest that such future studies focus on biased facial emotion recognition.

It has been suggested that the assessment of environmental adversity with self-report measures is inferior to interview-based assessment. Stress-moderated 5-HTTLPR effects were more often reported in studies utilizing interview-based measures (Uher & McGuffin, 2007, 2010). In the present study, we observed an interaction effect involving self-reported RNLE. We would like to forward the consideration that interviews are more typically used in smaller sized studies, which could also explain why an association between interview assessment and positive results has emerged. Additionally, the idea that the emotional impact of negative life events is more accurately assessed in an interview also suggests that a confounding may occur between this measure and depression-related outcomes. Nonetheless, the use of retrospective self-report measures for environmental adversity (RNLE and CEA) should be considered a limitation of the present study, as these are vulnerable to recollection bias. The extent to which such bias occurs may also differ between gene variants. In our sample, zero correlation between allele variants and the environmental stress variables was observed. Suggesting both that 5-HTTLPR did not moderate possible self-report bias, as well as absence of gene-environment correlation. Nonetheless, future studies should consider assessing more objective as well as prospective assessment of negative and positive environmental factors.

Another limitation of indexing life stress would remain, namely their low incidence. In the current sample, 6-month incidence of RNLE ranged from 0 to 6 negative events, with a mean of 1.2 events. Sixty-eight per cent of the sample reported at least one negative event, and 30% reported more than one. A longer indexation period would have resulted in higher incidence, yet this could have been at the cost of specificity of RNLE impact.

A limitation of our study is the low CEA incidence, which may explain the absence of the hypothesized CEA effects. Sixty-four per cent of our participants reported some amount of emotional abuse (score 6 or higher). This is similar to the average for both clinical and community samples (Baker & Maiorino, 2010, p.743 table 2). The average level of CEA

reported in the current sample is only slightly, likely not significantly, lower compared to previous studies wherein 5-HTTLPR CEA interactions were observed. However, the authors of the CTQ-SF proposed that a cut-off score of 9 represents at least low emotional abuse (Bernstein & Fink, 1998). A score higher than nine was observed in only 43 of our participants (20%), which is low compared to the average proportion (42%) in community samples (Baker & Maiorino, 2010, p.743 table 2).

Alternatively, one may argue that our finding of no CEA interactions effects fits with cognitive models of depression, considering that our sample was never or not currently depressed. Cognitive models state that negative early experiences (e.g. CEA) may shape a tendency for dysfunctional cognitive processing. However, in adult life dysfunctional cognitive processing is expected to remain latent unless activated following adverse events. Thus, while interaction of 5-HTTLPR and CEA was repeatedly observed in studies assessing effects on depression prevalence, processing biases as a result of 5HTTLPR interacting with CEA could arguably be expected to be 'inactive' in non-depressed individuals when not triggered by RNLE. Following the initial report of 5-HTTLPR interacting with both early and adult life adversities in predicting depression (Caspi, et al., 2003), the forthcoming literature often did not distinguish between these two interactions. A recommendation for future studies assessing 5-HTTLPR by stress interactions on cognitive endophenotypes is to consider theoretical distinctions between childhood and recent life stress.

The current findings suggest that 5-HTTLPR may differentially affect attention allocation bias and reading others' mind states. Speculatively, pending replication, this pattern may be explained by attentional bias reflecting relative automatic processing with less higher-order cognitive involvement than mind state recognition. Future studies could compare implicit and explicit measures of cognitive processing. A pattern of stress moderation on an explicit but not an implicit measure of depression related cognition was observed in a study informed by a dual processing theory of depression (Haeffel et al., 2007). In addition, an interaction of 5-HTTLPR and CEA has been reported for an explicit measure of cognitive reactivity to sad mood (Antypa & Van der Does, 2010).

To summarize, we report tentative evidence of a direct effect of 5-HTTLPR on attention allocation bias, such that individuals carrying two low expressing alleles (S or L_g) showed a relative bias towards negative visual information, compared to those homozygous for the L_a allele. Importantly, this effect was dependent on the implication of a linear model in statistical analysis. No main effect on allocation bias for positive information and no interaction effects of 5-HTTLPR and CEA or RNLE on attention allocation bias were observed. For the ability to recognize other's mind states, an interaction effect of 5-HTTLPR and RNLE was found. This finding suggests that increased risk for depression in carriers of low expressing 5-HTTLPR alleles could be due to enhanced recognition of negative facial expressions following negative life events. Hypothesized interactions between 5-HTTLPR and CEA were not observed. We argue that future studies testing the endophenotype approach may distinct between implicit and explicit measures and, on theoretical grounds, focus on interactions of 5-HTTLPR and RNLE.

Acknowledgements
Analyses of different outcome measures and another polymorphism acquired in the same sample have been reported elsewhere (Drost, Spinhoven, Kruijt, & Van der Does, 2013; Verhoeven et al., 2012). The authors would like to thank Anne Junggeburt, Fabrizio Derubeis, Jessica van Leeuwen, Lili Chu, Ludo Seip, Nadin Mousa, Sebastian Potthoff, Stefan van Liempt, and Stephanie Harmsen for assisting with the data collection for this study. This research was funded by an N.W.O. Vici grant (# 453-06-005) to A.J.W.V.D.D.; P.P. is supported by an N.W.O. VIDI grant (#452-12-003).

Supplemental information

Dot probe task additional details

Stimulus pictures and selection
Stimulus pictures were positive, negative, and neutral pictures selected from the International Affective Picture Set (IAPS; Lang, et al., 1999). Picture selection was based on ratings of valence and arousal, and subsequent selection by AWK. The final selection was discussed and agreed upon by all three authors.

The initial selection of candidate pictures was based on mean valence and arousal ratings provided with the IAPS (based on 9-point Likert scales). Boundary scores used for the initial selection were: valence > 6 & arousal > 5 for positive stimuli; valence < 4 & arousal >5 for negative stimuli; valence 4.5 – 5.5 & arousal < 4.5 for neutral stimuli. A subsequent selection was made ensuring that negative pictures represented depressotypic as much as possible, that pictures where not likely to be perceived much different by our Dutch participants compared to the American raters, and that neutral pictures depicted neutral rather than ambiguous scenes (e.g. picture #4233, for which the ratings fall within our predefined neutral range, depicts a street prostitute, which may not have been recognized by all raters). Stimuli depicting people or human-related scenes (e.g. a cemetery) were preferentially selected. A total of twenty positive, twenty negative and forty neutral pictures were selected.

The selection procedure ensured that valence and arousal ratings differed significantly over the three categories (one way ANOVA's, both p < .001). Paired sample t-tests for each combination of valences showed that positive and negative pictures did not differ in their arousal ratings (t(38)= .03, p =.978), whereas arousal ratings for neutral stimuli differed from both positive and negative stimuli (t(58) = 17.42, p = <.001 and t(58) = 17.40, p = <.001). Valence ratings differed significantly between neutral and positive (t(58) = 23.25, p = <.001), neutral and negative (t(58) = -35.27, p = <.001), and positive and negative stimuli (t(38) = 36.29, p = <.001), also see figure 4.s1.

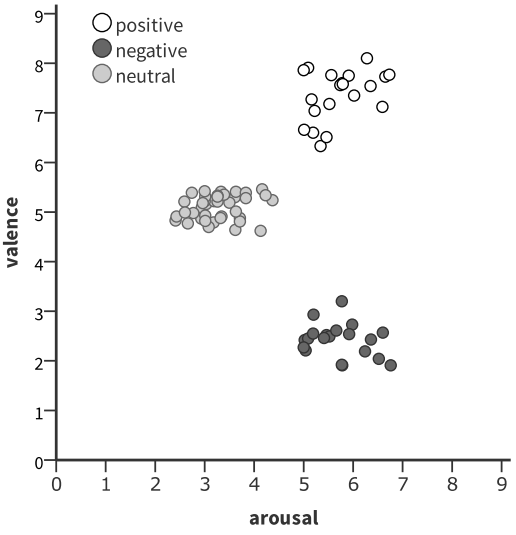

Figure 4.s1. valence and arousal ratings for the selected stimuli
(based on Lang, et al., 1999).

Selected pictures:
positive:
1722, 2058, 2071, 4617, 4626, 4640, 5470, 5622, 5628, 7502, 8033, 8080, 8180, 8190, 8200, 8370, 8380, 8420, 8496, 23521

negative:
2688, 2703, 2710, 2799, 2900, 3030, 3180, 3220, 3550, 6570, 9050, 9120, 9250, 9419, 9421, 9423, 9435, 9520, 9530, 9921

neutral:
1675, 2038, 2102, 2190, 2191, 2200, 2210, 2305, 2357, 2381, 2393, 2396, 2397, 2410, 2441, 2445, 2480, 2495, 2514, 2575, 2595, 2840, 2850, 2870, 2880, 5395, 5471, 5500, 5731, 5740, 7009, 7036, 7037, 7038, 7041, 7242, 7493, 7500, 9070, 27451

Contrary to Fox and colleagues (Fox, et al., 2009; personal communication), we did not create subsets based on arousal ratings (< 4.5 versus > 6) within the valence types. Thus, in our study any observed emotional versus neutral differences (e.g. bias) should be ascribed to a combination of valence and arousal differences. Any observed differences in positive versus negative bias can be ascribed to valence, because these categories do not differ in arousal ratings.

Pictures were converted to gray scale to prevent attention being drawn by either picture within a pair due to color rather than valence differences, and the pictures were resized to 453 by 340 pixels. Presented on the display, the horizontal distance between the pictures was 315 pixels, while participants were seated at approximately 60 cm distance from the display. Therefore, each stimulus subtended approximately 11.3° of visual angle in the horizontal plane and the probe approximately 0.4°. The distance between two stimuli subtended approximately 8°, and the distance between the two possible probe positions about 19.6° of visual angle in the horizontal plane. The probe was a 15*15 pixels black square that was shown either upright (square) or tilted 45° (diamond). These probes are identical in shape and size, and only differ in their orientation.

procedure details:
Within a single administration of the task (320 trials), each of the 80 stimulus pictures was used 8 times. One session consisted of 80 positive-neutral trials, 80 negative-neutral trial, 80 neutral-neutral trials and 80 same valence trials (40 positive, 40 negative). Within trials of each category, the stimulus pictures, the position of the emotional stimulus, the position of the probe (location previously taken by the emotional or by the neutral stimulus) and the identity of the probe were counterbalanced and administered in random order. A short self-paced break was given following every 30th trial: a message appeared on the display, advising the participant to take a moment of rest before continuing the task by means of a button click.

PCR and genotype procedure:
Saliva samples were collected in Oragene Self-Collection Kits – DISC format (DNA Genotek Inc, Ottawa, Ontario, Canada). Approximately 10 ml of saliva was kept in 2ml lysis buffer

(100 mmol/L NaCl, 10 mmol/L EDTA, 10 mmol/L Tris pH 8, 0.1 mg/mL proteinase K, and 0.5% w/v sodium dodecyl sulfate) until further processing.
Triplex polymerase chain reaction amplification (PCR) was used to amplify the region of interest from the SLC6A4 gene, with the following primers: a FAM-labeled primer HTTLPR-FWFAM 5'-TCCTCCGCTTTGGCGCCTCTTCC-3', and a reverse primer HTTLPR-RV 5'-TGGGGGTTGCAGGGGAGATCCTG-3'. Typical PCR reactions contained between 10 and 100 ng genomic DNA template, and 10 pmol of forward and reverse primer. PCR was carried out in the presence of 5% DMSO with 0.5 U of BioThermAB polymerase (GeneCraft, Munster, Germany) in a total volume of 30 µl. The cycling conditions were as follows: an initial denaturation step of 5 min at 95 °C, followed by 40 cycles of 30 seconds at 96 °C, 30 seconds at 61 °C, 60 seconds at 72 °C and a final extension step of 10 minutes at 72 °C. One µl PCR product was mixed with LIZ-500 size standard and formamide and run on an AB 3100 genetic analyzer setup for genotyping with 36 cm capillaries. Results were analysed using GeneMarker software (Softgenetics).

Simple slopes analyses:

Regression model:

$$y = \beta_0 + \beta_{5\text{-HTTLPR}} * x + \beta_{RNLE} * x + \beta_{5\text{-HTTLPR*RNLE}} * xz$$

can be rewritten as:

$$y = (\beta_{RNLE} + \beta_{5\text{-HTTLPR*RNLE}} * x) * z + (\beta_0 + \beta_{5\text{-HTTLPR}} * x)$$

The first part of the above formula is the simple slope. The test of the simple slope is a t-test with t equal to the simple slope divided by its standard error. The t-test has (n - k - 1) degrees of freedom, where n is the sample size and k is the number of predictors, including the interaction term (Aiken & West, 1991).

Simple slope:

$$\beta_{RNLE} + \beta_{5\text{-HTTLPR*RNLE}} * x$$

$SE_{(\text{simple slope})}$:

$$SQRT(\text{covariance}_{(RNLE)} + 2*x* \text{covariance}_{(RNLE,\ 5\text{-HTTLPR*RNLE})} + x\text{^}2* \text{covariance}_{(5\text{-HTTLPR*RNLE})})$$

t-test:

t = simple slope / $SE_{(\text{simple slope})}$
df = 214 – 3- 1 - 210

Table 4.s1. *covariance matrix*

	5-HTTLPR*RNLE	5-HTTLPR	RNLE
5-HTTLPR*RNLE	1.46	.07	-1.69
5-HTTLPR	.07	1.81	-.10
RNLE	-1.69	-.10	2.67

Fill in values of β (table 4.s2b) and covariances (table 4.s1):

$$t(210) = (3.80 + -2.54 * x) / (SQRT (2.67 + 2 *x* -1.69 + x\text{^}2 * 1.46))$$

Fill in x, which represents 5-HTTLPR coded as 0, 1, or 2 (for low, medium, or high expression groups), and determine the asscoiated p-value:

for x = 0: $t(210) = 2.33$, $p = .021$
for x = 1: $t(210) = 1.45$, $p = .148$
for x = 2: $t(210) = -0.97$, $p = .333$

Based on Aiken & West (1991)

Table 4.s2a. gene environment interactions 5HTTLPR*CEA

		5-HTTLPR				CEA				5-httlpr*CEA				
	IC	*B*	*SE*	*t*	*p*	*B*	*SE*	*t*	*p*	*B*	*SE*	*t*	*p*	r^2
DP positive	1.12	-0.69	3.18	-0.22	0.828	1.01	1.62	0.62	0.534	-0.90	1.09	-0.83	0.409	.004
DP negative	6.32	-5.66	2.86	-1.98	0.049	-0.62	1.45	-0.42	0.673	0.64	0.98	0.65	0.518	.021
RMET total	74.46	0.30	0.85	0.35	0.727	-0.02	0.43	-0.04	0.971	0.17	0.29	0.59	0.554	.006
RMET positive	78.25	1.71	1.50	1.14	0.254	0.25	0.77	0.33	0.743	-0.34	0.52	-0.65	0.519	.009
RMET negative	72.51	-0.60	1.36	-0.44	0.658	0.29	0.70	0.41	0.682	0.22	0.47	0.47	0.643	.012

Table 4.s2b. gene environment interactions 5HTTLPR*RNLE

		5-HTTLPR				RNLE				5-httlpr*RNLE				
	IC	*B*	*SE*	*t*	*p*	*B*	*SE*	*t*	*p*	*B*	*SE*	*t*	*p*	r^2
DP positive	0.85	-0.59	3.17	-0.19	0.853	-3.18	3.81	-0.84	0.405	1.70	2.82	0.60	0.548	.004
DP negative	6.32	-5.61	2.84	-1.97	0.05	-0.03	3.42	-0.01	0.993	1.70	2.53	0.67	0.502	.026
RMET total	74.47	0.33	0.85	0.39	0.701	0.49	1.03	0.48	0.634	-0.55	0.76	-0.72	0.472	.004
RMET positive	78.27	1.67	1.49	1.12	0.264	0.02	1.81	0.01	0.992	-0.89	1.34	-0.66	0.508	.014
RMET negative	72.57	-0.59	1.35	-0.44	0.66	3.80	1.63	2.33	0.021	-2.54	1.21	-2.10	0.037	.026

IC = intercept
DP = Dot Probe task
RMET = Reading the Mind in the Eyes Task

Table 4.s3a. gene environment interactions 5-HTTLPR L_a homozygotes versus S/L_g carriers, and CEA

		5-HTTLPR				CEA				5-httlpr*CEA				
	IC	*B*	*SE*	*t*	*p*	*B*	*SE*	*t*	*p*	*B*	*SE*	*t*	*p*	r^2
DP positive	0.04	0.96	4.94	0.19	0.846	0.57	1.17	0.49	0.625	-1.55	1.71	-0.91	0.365	.004
DP negative	2.27	-6.85	4.46	-1.54	0.126	-0.36	1.05	-0.34	0.732	1.10	1.54	0.71	0.478	.013
RMET total	74.48	1.00	1.33	0.76	0.451	0.12	0.31	0.40	0.693	0.15	0.46	0.34	0.737	.007
RMET positive	78.86	3.81	2.34	1.63	0.106	-0.15	0.55	-0.28	0.782	-0.06	0.81	-0.07	0.944	.013
RMET negative	71.72	0.43	2.13	0.20	0.842	0.43	0.50	0.86	0.389	0.23	0.74	0.31	0.755	.011

Table 4.s3b. gene environment interactions 5-HTTLPR L_a homozygotes versus S/L_g carriers, and RNLE

		5-HTTLPR				RNLE				5-httlpr*RNLE				
	IC	*B*	*SE*	*t*	*p*	*B*	*SE*	*t*	*p*	*B*	*SE*	*t*	*p*	r^2
DP positive	-0.01	0.73	4.93	0.15	0.882	-1.93	2.41	-0.80	0.424	2.14	4.17	0.51	0.609	.003
DP negative	2.31	-6.64	4.43	-1.50	0.136	0.82	2.17	0.38	0.706	3.12	3.76	0.83	0.407	.019
RMET total	74.46	1.10	1.32	0.83	0.408	0.30	0.65	0.47	0.643	-1.31	1.12	-1.17	0.246	.010
RMET positive	78.89	3.71	2.33	1.59	0.113	-0.97	1.15	-0.85	0.397	-0.02	1.98	-0.01	0.994	.017
RMET negative	71.64	0.69	2.10	0.33	0.743	2.35	1.03	2.27	0.024	-4.44	1.78	-2.49	0.013	.034

IC = intercept
DP = Dot Probe task
RMET = Reading the Mind in the Eyes Task

chapter **5**

Cognitive reactivity, implicit associations, and the incidence of depression: a two-year prospective study

Kruijt A-W, Antypa N, Booij L, de Jong PJ, Glashouwer K, et al. (2013)
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Background: Cognitive reactivity to sad mood is a vulnerability marker of depression. Implicit self-depressed associations are related to depression status and reduced remission probability. It is unknown whether these cognitive vulnerabilities precede the first onset of depression.
Aim: To test the predictive value of cognitive reactivity and implicit self-depressed associations for the incidence of depressive disorders.
Methods: Prospective cohort study of 834 never-depressed individuals, followed over a two-year period. The predictive value of cognitive reactivity and implicit self-depressed associations for the onset of depressive disorders was assessed using binomial logistic regression. The multivariable model corrected for baseline levels of subclinical depressive symptoms, neuroticism, for the presence of a history of anxiety disorders, for family history of depressive or anxiety disorders, and for the incidence of negative life events.
Results: As single predictors, both cognitive reactivity and implicit self-depressed associations were significantly associated with depression incidence. In the multivariable model, cognitive reactivity was significantly associated with depression incidence, together with baseline depressive symptoms and the number of negative life events, whereas implicit self-depressed associations were not.
Conclusion: Cognitive reactivity to sad mood is associated with the incidence of depressive disorders, also when various other depression-related variables are controlled for. Implicit self-depressed associations predicted depression incidence in a bivariate test, but not when controlling for other predictors.

The central thesis of cognitive theory of depression is that dysfunctional cognitions render an individual vulnerable to developing depressive episodes (Beck, 1979). Dysfunctional cognitions are thought to arise from negative belief systems that develop during childhood. These systems can remain relatively inactive until later in life, for instance when an individual encounters a situation (e.g., a demanding boss) that resembles the circumstances that led to the belief system (e.g., demanding parents) (Beck, 1979). Psychotherapy directed at modifying dysfunctional belief systems, cognitive behavioral therapy (CBT), is more effective at preventing relapse than pharmacotherapy (M. D. Evans et al., 1992; Fava, Rafanelli, Grandi, Canestrari, & Morphy, 1998; Friedman et al., 2004; Paykel, 2007), providing indirect evidence for the causal relation between dysfunctional cognitions and depression risk. However, dysfunctional cognitions, prominent during depressed states, tend to normalize during remission (e.g. Hamilton & Abramson, 1983; Just, Abramson, & Alloy, 2001; Lewinsohn, Steinmetz, Larson, & Franklin, 1981; Silverman, Silverman, & Eardley, 1984; Simons, Garfield, & Murphy, 1984), and research yielded mixed results regarding the question whether negative cognitions are antecedents, consequences or by-products of depression (e.g. Alloy et al., 2006; J. Evans, Heron, Lewis, Araya, & Wolke, 2005; LaGrange et al., 2011; Lewinsohn, et al., 1981).

Findings became more consistent when it was realized that negative cognitions might go undetected unless primed or activated by stress or a dysphoric mood state (Persons & Miranda, 1992; Scher, Ingram, & Segal, 2005; Teasdale, 1988). Cognitive reactivity to sad mood is the extent to which dysfunctional cognitions become activated when an individual experiences mild sadness. Several lines of evidence support the position that cognitive reactivity is a vulnerability marker of depression. Cognitive reactivity is higher in remitted depressed than never-depressed individuals (Merens, Booij, & Van Der Does, 2008; Miranda, Gross, Persons, & Hahn, 1998; Miranda & Persons, 1988; Segal, Gemar, & Williams, 1999; A. J. W. Van der Does, 2005), and it is associated with biological indices of depression vulnerability such as response to tryptophan depletion (Booij & Van der Does, 2007) and the polymorphism in the promotor region of the serotonin transporter gene SLC6A4 (Antypa & Van der Does, 2010). Moreover, cognitive reactivity may have prognostic value: high cognitive reactivity following treatment predicts shorter time to relapse or recurrence (Segal, et al., 1999; Segal et al., 2006). It is unknown however, whether cognitive reactivity is also a risk factor for depression incidence, i.e. whether higher cognitive reactivity precedes first onset of depression.

Another strategy to make dysfunctional cognitions measurable is to rely on laboratory tests instead of self-report. One of these is the Implicit Associations Test (IAT) (Greenwald, 1998; A. G. Greenwald & S.D Farnham, 2000), a reaction time test developed in social

psychology. In this test, the relative speed with which an individual is able to generate the same motor responses to stimuli representing two different concepts, is used as an index of the strength of the individual's association between these concepts (Greenwald, 1998). Implicit associations between the concepts 'self' and 'depressed' are stronger in currently depressed patients and remain elevated when depression is in remission (Glashouwer & de Jong, 2009). Implicit self-depressed associations mediate the relationship between childhood emotional abuse and depression symptom severity (van Harmelen et al., 2010), and are associated with suicidal ideation (Glashouwer et al., 2010). In currently depressed individuals, the strength of implicit self-depressed associations was inversely associated with the chance of achieving remission within a two-year period (Glashouwer, de Jong, & Penninx, 2012). It has not yet been tested whether the strength of implicit self-depressed associations predicts depression incidence.

In the current study, we tested the hypotheses that cognitive reactivity and the strength of implicit self-depressed associations precede and predict the first onset of depressive disorders. A sample of never-depressed individuals was followed over a period of two years. Using multivariable binary logistic regression analysis, the prognostic values of cognitive reactivity and implicit self-depressed associations were assessed and tested against the contributions of a number of background variables and established risk factors of depression.

Methods

Participants

All data were collected within the Netherlands Study of Depression and Anxiety (NESDA). This is a large longitudinal cohort study investigating a range of factors implicated in the onset and course of depression and anxiety disorders (Spinhoven et al., 2010). The cohort of 2,981 participants consists of individuals with a current or lifetime diagnosis of depression or anxiety, and a number of never-depressed and/or never-anxious participants who were included as healthy controls at baseline. Participants were between 18 and 65 years old, and recruited through mental health organizations, primary care practices and in the general population. Detailed information on in-exclusion criteria, participant flow, and sample characteristics is provided by Penninx et al. (Penninx et al., 2008). For the current study, all individuals who had never experienced major depression or dysthymia at baseline were selected.

Measures

Depression incidence, the main outcome measure, was determined using the Composite International Diagnostic Interview (CIDI; World Health Organization [WHO] Version 2.1) at the two years follow-up assessment. Incidence of a major depressive episode or a diagnosis of dysthymia was coded for as 1, versus 0 for no incidence. The CIDI is a standardized interview that assesses the, current and past, presence of psychiatric diagnoses as described in the DSM-IV (Association, 2000). Trained interviewers administered the CIDI (Penninx, et al., 2008).

Cognitive reactivity to sad mood was assessed with the Leiden Index of Depression Sensitivity – revised (LEIDS-r). The LEIDS-r has 34 items that assess the extent to which dysfunctional cognitions are activated when an individual experiences mild dysphoria (A. J. W. Van der Does, 2002; A.J.W. Van der Does & Williams, 2003). Two example items are: 'When in a sad mood, I more often think about how my life could have been different' (rumination subscale) or 'When I feel sad I feel more like breaking things' (aggression subscale). Items are scored on a 5-point Likert scale ranging from 'not at all' (0) to 'very strongly' (4). The LEIDS-r has a total score, and six subscales assessing cognitive reactivity related to Aggression, Hopelessness/Suicidality, Acceptance/Coping, Control/ Perfectionism, Risk Aversion, and Rumination on Sadness. LEIDS-r scores were found to be associated with depression history over and above rumination (Moulds et al., 2008), to be associated with genetic markers of depression (Antypa & Van der Does, 2010; Klok et al., 2011; Verhoeven et al., 2012), and with response to tryptophan depletion, reflecting biological vulnerability to depression (Booij & Van der Does, 2007). Moreover, treatment and other longitudinal studies support the validity of the LEIDS-r as a measure of depression vulnerability (Antypa, Van der Does, & Penninx, 2010; Giesbrecht et al., 2009; Raes, Dewulf, Van Heeringen, & Williams, 2009; Williams, Van der Does, Barnhofer, Crane, & Segal, 2008).

Implicit self-depressed associations (ISDA) were measured using the Implicit Association Test (IAT) (Greenwald, 1998; A. G. Greenwald & S. D. Farnham, 2000). In this test participants have to respond to words presented on a display by pressing one of two response buttons. Each word belongs to either one of two concept-pairs. In this particular IAT, one set of stimulus words represented either elated (e.g., valuable, optimistic) or depressed (e.g., useless, pessimistic) concepts, whereas another set represented either the self (e.g., me, myself) or others (e.g., you, they)[1]. Within each test block, two concepts share the same button. The combination of concepts sharing a button was varied over blocks, i.e. within one block 'elation' and 'self' shared a button while in another block 'depression' and 'self' shared a button. The difference in reaction times between these two blocks indicates the strength of the implicit association between the concepts 'self' and 'depression'. Raw IAT response times were transformed into the D600-measure recommended by Greenwald et al. (2003) and others (Glashouwer, Smulders, de Jong, Roefs, & Wiers, 2013). The D600-algorithm prescribes that: (i) data from two practice blocks (20 trials each) and two test blocks (60 trials each) are used; (ii) trials with reaction times above 10,000 ms are discarded; (iii) error trials are replaced with the mean reaction times of the correct responses in the block in which the error occurred, plus a penalty of 600 ms; (iv) response times for the self - elated blocks are subtracted from the response times for the self - depressed blocks (separately for practice and test blocks); (v) these difference scores are divided by their pooled standard deviation, and then averaged (Greenwald, et al., 2003). Lower values represent stronger implicit self-depressed associations.

1 Depressed: useless, pessimistic, inadequate, negative, meaningless (Dutch: nutteloos, pessimistisch, ongeschikt, negatief, zinloos). Elated: positive, optimistic, active, valuable, cheerful (Dutch: positief, optimistisch, actief, waardevol, opgewekt). Me: I, myself, self, my, own (Dutch: ik, mezelf, zelf, mijn, eigen). Others: other, you, them, their, themselves (Dutch: ander, jullie, zij, hun, zijzelf)

Demographic information including gender, age, and years of education was obtained in an interview.
The presence of a lifetime anxiety diagnosis was determined with the lifetime version 2.1 of the Composite International Diagnostic Interview (CIDI; World Health Organization [WHO]).

Family history of anxiety and/or depression was assessed using the self report family tree method (Fyer & Weissman, 1999). A positive family history was defined as reporting having at least one sibling or parent diagnosed with a depressive disorder, an anxiety disorder, or both.

Negative Life Events that occurred during baseline and the two years follow-up session were indexed using the Brugha questionnaire (Brugha, Bebbington, Tennant, & Hurry, 1985). This questionnaire assessed the occurrence of twelve negative life events such as illness or injuries to the self or close friends and relatives, loss of friends, relatives or partners, loss of job or housing, and being victimized by theft or assault.

Depressive symptoms were assessed with the 30-item Inventory of Depression Symptomatology – Self Report (IDS-SR; Rush, Gullion, Basco, Jarrett, & Trivedi, 1996). Each item is presented as four statements regarding the severity of a symptom, which are associated with scores ranging from 0 to 3.

Neuroticism was assessed with the NEO-FFI (Costa, McCrae, & Psychological Assessment Resources, 1992). The neuroticism scale consists of twelve items that index the tendency to experience negative emotional states. Items were scores on a 5-point Likert scale ranging from 'strongly disagree' (0) to 'strongly agree' (4).

Procedure
Baseline measures were assessed within a single 3 to 5 hours session. The follow-up measures (CIDI and Brugha) were again assessed within a single session, two years following baseline (Penninx, et al., 2008).

Ethics statement
The protocol for the NESDA study was approved by the Ethical Review Board of the VU University Medical Centre Amsterdam (VUMC), as well as by the review boards of the participating medical centers (Leiden University Medical Center (LUMC) and University Medical Center Groningen (UMCG)). All participants received full verbal and written information about the study, and written informed consent was obtained at the start of baseline assessment. Participants received a 15-euro gift certificate and compensation of travel costs (Penninx, et al., 2008).

Statistical analyses
Binary logistic regression was used to assess predictive values for the incidence of depressive disorders over the course of the two-years. Following bivariate analyses for each of the predictor variables, multivariable binary logistic regression was used to assess the combined prognostic value of the variables. Age, sex, years of education, history

of anxiety disorders, family history of anxiety and/or depression, number of negative life events between baseline and outcome measurement (NLE), baseline depressive symptom level (IDS-SR), and neuroticism (NEO-FFI subscale) were entered in a first block. Implicit self-depressed associations and cognitive reactivity were added in respectively blocks 2a and 2b. The third and final block contained all variables. Regression outcomes are presented as odds ratios and their associated 95% confidence intervals. Odds ratios represent the change in probability of the outcome event to occur, associated with a single unit increase on the predictor's scale.

Predictor probability plots were drawn to provide an additional impression of the possible clinical usefulness for all continuous predictors that were found to be significantly associated with depression incidence in the bivariate analyses. These were based on the regression formula:

$$P_{(incidence)} = e\text{^}(\beta_{(constant)} + \beta_{(predictor)} * x) / (1 + e\text{^}(\beta_{(constant)} + \beta_{(predictor)} * x)) .$$

Using values of $\beta_{(constant)}$ and $\beta_{(predictor)}$ derived from bivariate binary logistic regression analyses, the values x on the instrument's scale associated with .00, .25, .50, .75, and 1.00 predicted probability of depression incidence are represented on the x-axis.

Results

Participant flow

The NESDA cohort (n = 2,981) contained 1,008 individuals who had never experienced a depressive disorder at baseline. Of these 174 persons had missing data on one or more measures and were excluded from the sample: LEIDS-r scores were missing for 85 participants, IAT for 24, and baseline severity or personality measures for 12 participants. Ninety participants dropped out after baseline and had no information on the outcome measure of depression incidence.

Consequently, 834 participants were left for the present analyses: 596 were recruited from primary care, 76 from specialized mental health care, and 162 from the general population

Analyses of excluded participants

In- and excluded participants were compared on all variables used in the analysis, plus recruitment origin (general population, primary, or mental health care). The excluded group differed significantly from the included group on variables years of education ($t_{(1006)}$ = -2.405, p = .016), IDS-SR ($t_{(1000)}$ = 3.132, p = .002), neuroticism ($t_{(1002)}$ = 2.296, p = .022), and the presence of a lifetime anxiety diagnosis ($\chi^2_{(1)}$ = 11.619, p = .001). A previous paper, reporting analyses of attrition over this period in detail, indicated that within the entire NESDA sample lower education and higher baseline symptoms were associated with attrition (Lamers et al., 2012). Importantly, the in- and excluded participants did not differ significantly with respect to the main variables of interest, cognitive reactivity ($t_{(921)=}$ -1.42, p=.155), and implicit self depressed associations ($t_{(981)}$ = -.189, p = .850). A trend towards a difference was found on depression incidence ($\chi^2_{(1)}$ = 3.48, p = .061),

in line with an association between higher baseline symptom levels and attrition. See supplementary table 5.S1 for all comparisons between in- and excluded participants.

Main analyses

Demographic and clinical characteristics at baseline for groups with and without depressive disorder at follow-up are presented in table 5.1.

Table 5.1. *sample characteristics*

	DD incidence (*n* = 84)		no DD incidence (*n* = 750)		total (*n*= 834)		
	n	%	*n*	%	*n*	%	
recruitment site							
primary care	547	72.9	49	58.3	596	71.5	
mental health care	58	7.7	18	21.4	76	9.1	
general population	145	19.3	17	20.2	162	19.4	
female	58	69.0	474	63.2	532	63.8	
lifetime anxiety	52	61.9	223	29.7	275	33.0	
family history	67	79.8	530	70.7	597	71.6	
	M	*sd*	*M*	*sd*	*M*	*sd*	*range*
age	40.1	14.9	41.6	14.4	41.5	14.4	18 – 65
education (yrs)	11.9	3.4	12.8	3.2	12.7	3.3	5 – 18
n NLE	2.1	1.7	1.4	1.2	1.4	1.3	0 – 9
IDS-SR	21.2	10.6	10.4	8.7	11.5	9.4	0 – 48
neuroticism	36.4	7.7	28.9	8.1	29.6	8.4	12 – 56
ISDA	0.25	0.39	0.39	0.38	0.37	0.38	-0.92 – 1.27
CR	35.0	16.5	20.0	14.3	21.5	15.2	0 – 98

DD incidence = incidence of depressive disorders between baseline and two-years follow-up, family history = family history of anxiety and/or depressive disorders, NLE = negative life events, IDS-SR = Inventory of Depressive Symptomatology – Self Report; Neuroticism = neuroticism subscale of the NEO-FFI; ISDA = implicit self-depressed associations (IAT); CR = Cognitive Reactivity (LEIDS-R)

The correlations between depression incidence and all predictor variables were calculated (see supplementary table 5.S2). The largest correlation (r_s= .73) was found between neuroticism (NEO-FFI) and baseline depressive symptom levels (IDS-SR). Most other correlations were significant but small to moderate in size (r_s= .04 - r_s= .57). Therefore multicollinearity was unlikely, which was confirmed by inspection of the variance inflation factor values, which ranged from 1.03 to 2.66.

Bivariate binary regression analyses showed that, as single predictors, most variables, including cognitive reactivity and implicit self-depressed associations, were significantly

associated with first-onset of depressive disorder, see table 5.2.

Table 5.2. *bivariate binary logistic regression for depression incidence*

	Odds ratio	95% confidence interval
gender	1.30	[0.80 - 2.11]
age	0.99	[0.98 - 1.01]
education (yrs)	0.92*	[0.86 - 0.99]
anxiety diagnosis	3.84***	[2.41 - 6.13]
family history anx/dep	1.64	[0.94 - 2.85]
n NLE	1.46***	[1.25 - 1.71]
IDS-SR	1.11***	[1.08 - 1.13]
neuroticism	1.11***	[1.08 - 1.15]
ISDA	0.41**	[0.23 - 0.73]
CR	1.06***	[1.05 - 1.08]

** = p < .05; ** = p < .01 ; *** = p < .001 .*
NLE = Negative Life Events; IDS-SR = Inventory of Depressive Symptomatology – Self Report; Neuroticism = neuroticism subscale of the NEO-FFI;
CR = Cognitive Reactivity (LEIDS-R);
ISDA = Implicit Self-Depressed Associations (IAT).

Predictor probability plots are presented in the supplementary materials (figure 5.s1) for the bivariately associated continuous measures. From these probability plots it can be assessed that baseline symptom levels (IDS-SR), cognitive reactivity (LEIDS-R), and to a lesser extent the number of negative life events, perform relatively well in predicting depression incidence.

The third and final block of the multivariable binary logistic regression analysis is presented in table 5.3 (for the entire multivariable analysis see supplementary information, table 5.S3). Within this model, baseline depressive symptom levels (IDS), cognitive reactivity (CR), and the number of negative life events during the study period (NLE) were significant predictors of depressive disorder incidence over the course of two years. Implicit self-depressed associations were not found to be predictive of first onset of depressive disorders when other predictors were controlled for.

Table 5.3. *multivariable binary logistic regression for depression incidence – final block*

	Odds ratio	95% Confidence Interval
gender	0.99	[0.57 - 1.73]
age	0.98	[0.97 - 1.00]
education (yrs)	0.95	[0.88 - 1.03]
lifetime anxiety	1.55	[0.88 - 2.72]
family history anx/dep	0.87	[0.46 - 1.63]
n NLE	1.34***	[1.16 - 1.65]
IDS-SR	1.08***	[1.04 - 1.12]
neuroticism	0.99	[0.94 - 1.04]
ISDA	1.00	[0.50 - 2.01]
CR	1.03***	[1.01 - 1.05]
model χ^2: 117.90***		

** = p ≤ .05; ** = p ≤ .01 ; *** = p ≤ .001 . NLE = Negative Life Events; IDS-SR = Inventory of Depressive Symptomatology – Self Report; Neuroticism = neuroticism subscale of the NEO-FFI; ISDA = Implicit Self-Depressed Associations (IAT); CR = Cognitive Reactivity (LEIDS-R).*

Additional analyses

Previous papers assessing the predictive validity of self-depressed associations also assessed explicit self-depressed associations (e.g. Glashouwer, et al., 2012). Adding a block 2c, containing the baseline predictors plus explicit self-depressed associations, did not yield a significant outcome for explicit self-depressed associations (OR = 0.90 [0.66 – 1.22] *n.s.,* block 2c χ^2 = .45, *n.s.*), nor did adding this predictor to block 3. Other studies hypothesized and found effects pertaining to specific subscales of the LEIDS-R (e.g. Antypa, et al., 2010). We assessed our model with LEIDS-R total score replaced by each of the six subscales. The control/perfectionism, risk avoidance, and the rumination subscales were significant predictors within the model. The models containing the risk avoidance or rumination subscale may explain slightly more variance than the model containing the LEIDS-R total scale (model χ^2 were 120.99 (risk avoidance), and 120.42 (rumination), versus 117.90 (LEIDS-R total)). These differences are small and it is not possible to formally test whether the fit of two non-nested models differs significantly.

Discussion

The current study assessed the two-year prognostic value for depression incidence of two, prospectively assessed, cognitive risk factors in a large population-based sample. As single predictors, cognitive reactivity and implicit self-depressed associations were significantly associated with depression incidence. When other predictors were taken into account, cognitive reactivity remained associated with depression incidence. Contrary to our hypothesis, implicit self-depressed associations did not. In the multivariable model, baseline depressive symptoms and the number of negative life events between baseline and follow-up were also significantly associated. These measures predicted depression onset over predictors such as neuroticism and the lifetime presence of an anxiety disorder.

The LEIDS-R does not assess the current activation of negative cognitions, but rather an individual's assessment of the extent to which these become more activated during sad mood. This is a crucial difference if one wants to test the assumption that latent negative cognitions predict depression incidence (Scher, et al., 2005). The current findings support cognitive models stating that certain depression-related cognitions precede first onset of depression. Contrary to our hypothesis, implicit self-depressed associations did not contribute to the prediction in the multivariable analysis. Previous NESDA studies reported stronger self-depressed associations in remitted depressed individuals (Glashouwer & de Jong, 2009), and a positive relationship between the number of prior episodes and the strength of individuals' self-depressed associations (Elgersma, Glashouwer, Bockting, Penninx, & De Jong, submitted for publication). Combined with the current result, this suggests that implicit self-depressed associations may not precede first-onset depression, but rather represent a cognitive scar that emerges in response to a depressive episode, rendering remitted patients more vulnerable for new depressive episodes.

Both baseline depressive symptoms and cognitive reactivity significantly add to the multivariable model, despite their moderate correlation of .52. This indicates that these two measures assess distinctive constructs, at least to a certain degree. Neuroticism, an established predictor of depression risk, did not significantly add to the prediction, probably due to shared variance with baseline symptom levels. The correlation between these two measures was .73. Shared variance between implicit self-depressed associations and baseline depressive symptoms may also account for the finding that implicit self-depressed associations do not add to the prediction of depressive incidence in the multivariable model, even though the (highly significant) correlation was only -.28.

To get an impression of the possible prognostic usability of the assessed instruments, graphical displays of the predictions derived from the bivariate regression analysis were provided in the supplementary material (S3). These were based on bivariate analyses, as we were interested to assess predictions derived from single instruments. Visual inspection makes it clear that cognitive reactivity (LEIDS-R) is relatively well suited to discern amongst levels of incidence probability.

A main limitation of these findings is limited generalizability. It should be noted that the NESDA sample is a 'risk enriched' sample, recruited in a large part among depressive

and anxious patients (Penninx, et al., 2008). This the relatively high incidence of 10%, considering that the 12-month incidence of MDD in the Netherlands has been estimated at 2.7% (Bijl, De Graaf, Ravelli, Smit, & Vollebergh, 2002). This also explains why a family history of anxiety and/or depression was reported by as many as 72% of our sample.

The current study tested the hypothesis that two cognitive measures predict depression incidence over a two-year period. From a theoretical perspective it would be interesting to assess the prognostic value of cognitive measures over a longer period. The currently presented two-year prediction may, however, be more interesting from a practical clinical perspective.

In conclusion, cognitive reactivity to sad mood was associated with the incidence of depressive disorders. This association remained when various other risk factors of depression are controlled for. Implicit self-depressed associations were also significant predictors of depression incidence, but only when bivariately tested.

Supplementary information

Table 5.s1. c*omparison of in- and excluded participants on demographic and clinical variables.*

	included (*n* = 834)		excluded (*n*= 174)				
	n	%	*n*	%	*n missing*	χ^2	*p*
recruitment site						0.93	.630
primary care	596	71.5	118	76.8			
mental health care	76	9.1	18	10.3			
general population	162	19.4	38	21.8			
DD incidence					90	0.79	.672
dysthymic disorder	4	0.5	1	0.6			
MDD	80	9.6	13	7.5			
female	532	63.8	101	58.0		2.03	.154
lifetime anxiety	275	33.0	81	46.6		11.62	.001
family history	597	71.6	122	70.5	1	0.08	.778
	M	*sd*	*M*	*sd*		*t*	*p*
age	41.5	14.4	41.3	14.2		-0.12	.906
education (yrs)	12.7	3.3	12.1	3.1		-2.49	.014
n NLE	1.4	1.3	1.7	1.3	90	1.81	.071
IDS-SR	11.5	9.4	14.0	10.4	6	3.13	.002
neuroticism	29.6	8.3	31.3	9.1	5	2.30	.022
ISDA	.37	.38	.37	.38	25	-0.19	.850
CR	21.5	15.2	19.1	16.3	85	-1.42	.155

** several participants had missing data on more than one measure, hence the numbers do not add up to the total of 174 participants excluded.*
DD = depressive disorder, MDD = major depressive disorder, family history = family history of anxiety and/or depressive disorders, NLE = negative life events, IDS-SR = Inventory of Depressive Symptomatology – Self Report; Neuroticism = neuroticism subscale of the NEO-FFI; ISDA = implicit self-depressed associations (IAT); CR = Cognitive Reactivity (LEIDS-R)

Table 5.s2. *correlationmatrix for all variables*

	DD incidence	sexe	age	education (yrs)	lifetime anxiety	family history	*n* NLE	IDS-sr	neuroticism	ISDA	CR
DD incidence	-										
sexe	.037	-									
age	-.033	-.076*	-								
education (yrs)	-.083*	-.052	-.057	-							
lifetime anxiety	.206***	.072*	.031	-.074*	-						
family history	.061	.078*	-.117***	-.071*	.137***	-					
n NLE	.172***	.060	.027	-.056	.075*	.104**	-				
IDS-sr	.344***	.123***	.073*	-.192***	.482***	.151***	.119**	-			
neuroticism	.271***	.129***	-.107**	-.114***	.471***	.196***	.099**	.730***	-		
ISDA	-.105**	-.095**	-.047	.029	-.222***	-.054	-.046	-.277***	-.307***	-	
CR	.296***	.061	-.075*	.057	.334***	.163***	.132***	.519***	.573***	-.231***	-

* = p ≤ .05; ** = p ≤ .01 ; *** = p ≤ .001 .
DD incidence = incidence of depressive disorders, family history = family history of anxiety and/or depression, NLE = Negative Life Events; IDS-SR = Inventory of Depressive Symptomatology – Self Report; Neuroticism = neuroticism subscale of the NEO-FFI; ISDA = Implicit Self-Depressed Associations (IAT); CR = Cognitive Reactivity (LEIDS-R).

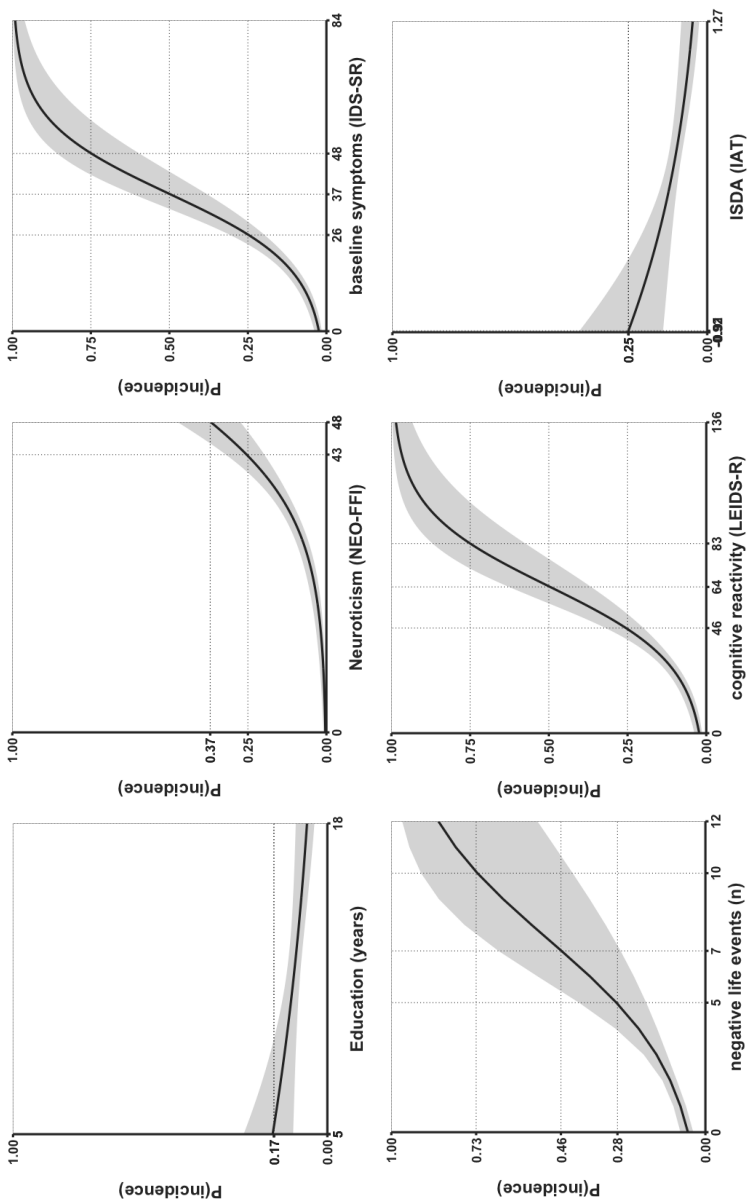


Figure 5.s1. predicted probability plots

Derived from bivariate regression analyses. Grey areas represent 95% confidence intervals. For questionnaires, the x-axis extends the possible range. For the measures education and implicit self-depressed associations, the observed range is represented on the x-axis.

Note that a history of anxiety diagnoses was also found to be significantly associated with depression incidence, yet, being a dichotomous variable, not represented here.

Table 5.s3. *multivariable binary logistic regression for depression incidence*

		Odds ratio	95% confidence interval	χ^2	p
block 1				105.90	<.001
	gender	0.92	[0.54 – 1.58]		.762
	age	0.98	[0.97 – 1.00]		.069
	education (yrs)	0.98	[0.90 – 1.06]		.539
	lifetime anxiety	1.59	[0.91 – 2.76]		.103
	family history anx/dep	0.93	[0.50 – 1.74]		.824
	n NLE	1.41	[1.18 – 1.68]		<.001
	IDS-SR	1.09	[1.05 – 1.13]		<.001
	neuroticism	1.02	[0.97 – 1.06]		.492
block 2a			from 1 to 2a:	.003	.953
	gender	0.92	[0.53 – 1.59]		.758
	age	0.98	[0.97 – 1.00]		.069
	education (yrs)	0.98	[0.90 – 1.06]		.538
	lifetime anxiety	1.58	[0.91 – 2.76]		.105
	family history anx/dep	0.93	[0.50 – 1.74]		.825
	n NLE	1.41	[1.18 – 1.68]		<.001
	IDS-SR	1.09	[1.05 – 1.13]		<.001
	neuroticism	1.02	[0.97 – 1.06]		.503
	ISDA	0.98	[0.49 – 1.95]		.953
block 2b			from 1 to 2b:	11.99	.001
	gender	0.99	[0.57 – 1.72]		.968
	age	0.98	[0.97 – 1.00]		.081
	education (yrs)	0.95	[0.88 – 1.03]		.250
	lifetime anxiety	1.55	[0.88 – 2.71]		.130
	family history anx/dep	0.87	[0.46 – 1.63]		.659
	n NLE	1.38	[1.16 – 1.65]		<.001
	IDS-SR	1.08	[1.04 – 1.12]		<.001
	neuroticism	0.99	[0.94 – 1.04]		.615
	CR	1.03	[1.01 – 1.05]		.001

		Odds ratio	95% confidence interval	χ^2	p
block 3			from 2a to 3:	11.99	.001
			from 2b to 3:	0.00	.997
	gender	0.99	[0.57 – 1.73]		.968
	age	0.98	[0.97 – 1.00]		.083
	education (yrs)	0.95	[0.88 – 1.03]		.250
	lifetime anxiety	1.55	[0.88 – 2.72]		.131
	family history anx/dep	0.87	[0.46 – 1.63]		.659
	n NLE	1.34	[1.16 – 1.65]		<.001
	IDS-SR	1.08	[1.04 – 1.12]		<.001
	neuroticism	0.99	[0.94 – 1.04]		.618
	ISDA	1.00	[0.50 – 2.01]		.997
	CR	1.03	[1.01 – 1.05]		.001
model				117.90	<.001

NLE = Negative Life Events; IDS-SR = Inventory of Depressive Symptomatology – Self Report; Neuroticism = neuroticism subscale of the NEO-FFI; ISDA = Implicit Self-Depressed Associations (IAT); CR = Cognitive Reactivity (LEIDS-R).

chapter 6

General discussion

A publication based on part of this chapter is in preparation.

In two ABM studies presented in this thesis, no evidence was found that ABM modifies bias in a predictable way. These studies were a small scale RCT testing visual search ABM, which was not previously tested for affective disorders, and a *n*=30 case series study assessing six variants of dot probe ABM, which is the most studied method of ABM for affective disorders.

The case series study was intended to inform decisions regarding the design of a future RCT. When we designed the case-series study, the first study on ABM for depression, by Wells and Beevers (2010), had just been published. An unexpected feature of their design were the extremely long stimulus exposure durations: 3000 ms for faces, 4500 ms for scenic stimuli. Such presentation times were unprecedented in the dot probe literature. In the anxiety literature, a 500 ms stimulus duration is considered long, whereas in the depression literature typically either 500, 1000, or 1500 ms were used (Shane & Peterson, 2007). Despite the study's major shortcoming of high attrition, the results of that first study on depression ABM suggested that adapted anxiety ABM procedures could exert beneficial effects on depression (Wells & Beevers, 2010). Another candidate adaptation would be the direction of training. Other than for anxiety, recent depression dot probe studies suggested that an additional bias away from positive information may exist (Shane & Peterson, 2007). We considered that these two parameters allowed for various different adaptations of anxiety ABM for application to depression. We also observed that the then existing anxiety ABM literature focused more on assessing effects on symptoms, than verifying the hypothesized effect on bias itself. Therefore, we decided to not yet perform an RCT, but instead chose a design that could inform decisions for a future RCT design. Case series rank highest in a hierarchy of designs for discovery and exploration, wherein RCT's are the lowest ranking design, which is opposite from a hierarchy of study designs for evaluating therapy effects (Vandenbroucke, 2008). Our case series design also included two not commonly included features that would benefit any ABM study: assessment of bias change using a second, untrained, stimulus set, and assessment of awareness of receiving training.

The results of our case series study (chapter 2) were such that we discontinued studying dot probe ABM for depression. Neither of six dot probe ABM variants had a consistent effect on attentional bias. In two conditions, effects in the desired direction were observed in three out of five participants, but sizable bias changes in the not-intended direction were observed equally often. Changes in bias observed during the training sessions, did not show any consistent relation to changes in bias for a separate set of stimuli, assessed before and after the training sessions. These findings, even though not statistically verified, argue against the efficacy of ABM as a treatment that will benefit a

majority of individuals. Also importantly, we observed a strong association between awareness of receiving training and the change in bias for untrained stimuli. This suggests that participants may show bias change purely as a function of (implicit) awareness of training contingency, rather than training parameters. This finding is difficult to interpret. Certainly, under the currently proposed working mechanism of ABM, change in bias for untrained stimuli would be pivotal for ABM's effect. However, the changes observed in our study were entirely unrelated to bias changes observed during the training. Moreover, results of an anxiety ABM study suggested that informing participants on the rationale of the training, abolishes effects on symptoms (MacLeod, Mackintosh, & Vujic, 2009). Together, these findings outline a possible catch 22: ABM may be modifying bias when participants know that that is the intended effect, yet ABM may not affect symptoms when participants know that that is its intended effect. Whether awareness affects ABM effects needs to be further studied. Treatments with secret active components cannot be considered ethical, or feasible. Therefore awareness effects may even disqualify ABM as a treatment option. Lastly, if awareness could cause the effect on bias, the question arises how ABM would differ from verbally convincing patients that they should direct attention more to positive information. A case series design does not give conclusive or significant evidence, yet our study provided valuable insights for those further pursuing application of ABM to depression.

Changing strategy, our next study featured a relatively straightforward RCT design to assess bias modifying ability of visual search ABM. This methodology was originally developed to target low self-esteem, and beneficial effects on various outcomes, including dot probe assessed attentional bias, had been reported in a series of well-powered studies (Dandeneau & Baldwin, 2004; Dandeneau & Baldwin, 2009; Dandeneau, Baldwin, Baccus, Sakellaropoulo, & Pruessner, 2007). In our study (chapter 3), no effects of visual search ABM on dot probe measured bias for happy, sad, or disgusted facial expressions were observed in a dysphoric student sample. The main limitation of this study was the small sample size. Large and medium, but not small, sized effects could have been detected with 80% or more power.

Although no stern conclusions can be drawn on the basis of a single RCT and a case series design, it appears that it is not entirely easy to modify depression related attentional bias.

These studies add to the literature and can be interpreted in relation to other studies. To my knowledge, nine studies on ABM procedures targeting bias in depression or dysphoria, including the studies in chapters 2 and 3, had been published up to July 2013. Table 6.1 provides a summarizing overview of these studies. Sample and design characteristics, and the reported effects on bias and symptom measures are given. The last column shows the study's conclusion as provided in the abstract.

Reviewing table 6.1, the conclusions presented in the abstracts for most publications imply that ABM shows promise as a new treatment for depression. The two ABM studies in this thesis focused explicitly on assessing whether ABM modifies bias, in order to verify the hypothesized mechanism of action. If ABM does not modify bias, any subsequently observed effects can not likely be ascribed to modified bias. In an RCT, the time by

treatment interaction effect is the test of choice for evaluation treatment effects. For a majority of these studies, six out of eight RCTs, no significant time by treatment interaction effect was reported for the bias targeted by the ABM procedure (Baert, et al., 2010, study1, study 2 ; Blaut, et al., 2013; Browning, et al., 2012; Haeffel, et al., 2012; Kruijt, et al., 2013a).

Moreover, upon closer examination several studies had features or produced results that call their conclusions into question. High attrition (47%) in the study by Wells and Beevers resulted in data for the main finding, a significant interaction effect on depressive symptoms at follow-up, being available for only 7 out of 14 participants in the treatment condition. This was remedied by 'last observation carried forward' so that half the follow-up data were actually acquired immediately post-training (Wells & Beevers, 2010). Baert and colleagues observed adverse effects of ABM on symptoms in the overall analysis of their student sample, and no effects in their patient sample, which was not reflected in the study's conclusion (Baert, et al., 2010). A puzzling finding was reported, but not commented on, by Browning and colleagues (Browning, et al., 2012). While not affecting bias for faces, ABM using face stimuli modified bias for words and subsequently affected symptom and cortisol measures, whereas ABM using word stimuli sorted no effects at al (Browning, et al., 2012). In the study by Haeffel and colleagues, no pre/post effect or post-training comparisons are reported at treatment level (ABM/control). For the analysis, 80 ABM trials were divided into four sets of 20 trials to present development of bias during the training. Given the 95% contingency, each of these indices appears to be based on a single incongruent trial. A significant main effect of condition, which judging by the accompanying graph likely representing baseline differences, was interpreted as indicating ABM effects. A further division of the first 40 trials, likely containing two incongruent trials, was used to calculate four separate bias indices. The authors concluded that only the first ten ABM trials may be effective (Haeffel, et al., 2012). In the study by Tsumura and colleagues post-training bias assessment with a dot probe task was interpreted as a stressor task. Following a post-hoc median split on baseline depressive symptoms, absence of a mood response to the post-training dot probe administration in the high symptoms ABM group was interpreted as ABM induced stress resilience (Tsumura, et al., 2012). The optimistic conclusion in the study by Blaut and colleagues seems unwarranted given that the treatment interaction effect was not reported, and the t-test for the simple effect of ABM on bias in the treatment group was significant only when tested one-sidedly. Hypothesized effects on memory bias were not found. The reported ABM/control difference in the slopes of the association between BDI and post-training negative word recall was again only significant when tested one-sidedly (Blaut, et al., 2013).

I conclude that there are major methodological issues in the ABM for depression literature and that these studies offer only thin evidence of ABM affecting targeted (Browning, et al., 2011; Tsumura, et al., 2012; Wells & Beevers, 2010) or non-targeted (Browning, et al., 2012) cognitive biases, and depressive symptoms in either the intended direction (Browning, et al., 2012; Wells & Beevers, 2010) or the opposing direction (Baert, et al., 2010; Fox, et al., 2011).

Table 6.1. *studies evaluating ABM for depression*

study	sample	design
Wells & Beevers, 2010.	n = 34 dysphoric students BDI ≥ 9	RCT 4 sessions of 196 trials dot probe ABM in 2 weeks stimuli: faces & scenes stimulus duration: 3000 & 4500 ms. follow-up after 2 weeks congruency: 85% away from negative
Baert, De Raedt, Schacht, & Koster, 2010. study 1	n= 55 students BDI-II ≥ 14	RCT 10 sessions of 220 trials cueing ABM in 2 weeks stimuli: words cue duration: 1500 ms congruency: 90% towards positive
Baert, De Raedt, Schacht, & Koster, 2010. study 2	n = 44 depressed in- and outpatients	RCT 10 sessions of 220 trials cueing ABM in 2 weeks cue duration: 1500 ms congruency: 90%
Browning et al., 2011	*n* = 64 healthy participants	RCT 14 sessions of 96 trials dot probe ABM in 1 week stimuli: faces stimulus duration: 500 & 100 ms congruency: 87.5% towards positive four conditions: ABM OR control BY SSRI OR placebo

effect on bias	effect on symptoms	conclusion in abstract
Significant interaction of time (pre/post) and ABM (treatment/control): ABM reduced bias ($F(1, 32)=6.14$, $p=.02$).	ABM reduced depressive symptoms measured at follow-up.	“biased attention may have a causal role in the maintenance of depressive symptoms.”
No significant interaction of time (pre/post) and ABM (treatment/control): ABM did not reduce bias.	Adverse effects of ABM: reduced depression and anxiety symptoms in control but not ABM condition. Post-hoc sample split: Mild depression: beneficial effects. Moderate/severe depression: adverse effects.	”therapeutic effects of attentional bias modification might be dependent on depression severity. ”
No significant interaction of time (pre/post) and ABM (treatment/control): ABM did not reduce bias.	No significant interaction of time (pre/post) and ABM (treatment/control). Overall reduction in BDI-II, regardless of condition	See above.
Significant interaction of time (pre/post), ABM (treatment/control) and probe location, irrespective of SSRI treatment ($F=7.0(1,58)$, $p=0.01$). ABM or SSRI induced positive memory and word categorization biases; ABM+SSRI did not.	No effects of ABM on cognitive reactivity, assessed as resilience to negative mood induction.	”co-administration of an SSRI and a cognitive training intervention can reduce the effectiveness of either treatment alone in terms of anxiety- and depression-relevant emotional processing. ”

continues on page 94

Table 6.1. *studies evaluating ABM for depression - continued*

study	sample	design
Browning, Holmes, Charles, Cowen, & Harmer, 2012.	*n*= 61 recurrent depressed patients in remission	RCT 28 sessions of 96 trials dot probe ABM in 2 weeks four conditions: ABM/control BY face/word stimuli stimulus duration: 500 & 100 ms congruency: 100% towards positive
Tsumura, Shimada, Nomura, Sugaya, & Suzuki, 2012.	*n* = 61 healthy students	RCT 510 trials dot probe ABM stimuli: words stimulus duration: 500 ms congruency: 94.31% away from negative
Haeffel, Rozek, Hames, & Technow, 2012.	*n* = 61 students	RCT 80 trials dot probe ABM stimuli: words stimulus duration:1000 ms plus negative self-referential priming congruency: 95% away from negative

effect on bias	effect on symptoms	conclusion in abstract
No significant interactions of time (pre/post) and ABM (treatment/control): ABM did not reduce the targeted bias. Positive word bias increased in the face ABM condition.	Depression and anxiety symptoms reduced over follow-up period in the face ABM condition Word ABM did not affect symptoms	”ABM may provide a “cognitive vaccine” against depression and offer a useful strategy in the secondary prevention of the illness. ”
Significant interaction of time (pre/post) and ABM (treatment/control): ABM reduced bias ($F(1, 49) = 5.62$, $p = .02$).	Control and low dysphoria ABM groups: depressed mood increased during the post-training dot probe task High dysphoria ABM group: no change in depressed mood during post-training dot probe task: interpreted as ABM induced stress resilience.	”results indicate that attention retraining is efficacious for reducing depressive mood response. ”
three way interaction of condition*time*cognitive vulnerability ($F(1, 52) = 13.79$, $p<.001$) Figure suggests no overall effect of ABM, but an adverse effect in high vulnerable group and a beneficial effect in low vulnerable group (*interpretation by AWK*). Post-hoc division per 10 trials: ABM reduces bias in first 10 trials ($F(3,135) = 2.60$, $p = .056$)	Interactions of time (pre/post) and ABM (treatment/control) not reported Comparisons of median split groups based on bias in last 20 trials within ABM group: individuals with lower end state bias spent more time on a stressor anagram task: interpreted as reduced helplessness. MASQ score difference ‘significant at the level of a trend’ ($p = .07$) (p.498).	”CBM attention training might be most effective in reducing cognitive vulnerability when initially used in small doses. ”

continues on page 96

Table 6.1. *studies evaluating ABM for depression - continued*

study	sample	design
Kruijt, Putman, & Van der Does, 2013a.	*n* = 30 dysphoric students	Single case series 4 sessions of 200 trials dot probe ABM in 1 week stimuli: faces six conditions: duration: 500, 3000 OR random 500-3000 ms BY congruency: 85% away from negative OR towards positiv
Kruijt, Putman, & Van der Does, 2013b.	*n* = 40 dysphoric students	RCT 256 trials visual search ABM stimuli: faces OR flowers
Blaut, Paulewicz, Szastok, Prochwicz, & Koster, 2013.	*n* = 71 students	RCT 320 trials ABM stimuli: words congruency: 90% away from negative

effect on bias	effect on symptoms	conclusion in abstract
visual inspection: neither of six ABM variants consistently modified attention bias during training, nor for untrained stimuli (pre/post measurement). awareness of receiving training was significantly associated with bias change for untrained stimuli (pre/post measurement)	no effects on depression symptoms anxiety symptoms reduced within sad to neutral conditions	”It is unlikely that any of these ABM versions will have a specific effect on symptoms in controlled studies. ”
No significant interactions of time (pre/post) and ABM (treatment/control): ABM did not reduce bias for happy, sad, or disgusted faces. No significant interaction of time (pre/post) and ABM (treatment/control) on visual search training reaction times	no pre/post * condition effect on mood state baseline score BDI-II self-dislike item associated with reduction in bias for negative expressions in ABM but not control group.	”no evidence that engaging in a single session of a visual search ABM modifies attentional biases for happy, sad or disgusted facial expressions. ”
Interaction of time (pre/post) and ABM (treatment/control) not reported. Main effects of condition: reduced bias in ABM group, not in control group (t(33)= 1.9, *p*=0.03, 1-sided) No effect of ABM (treatment/control) on post training memory for negative words. Baseline symptom levels associated with post-training negative word recall in control but not ABM group (t-test inter-group difference: *p*=0.03, 1-sided).	Not assessed.	”results indicate that altering attentional bias can influence elaborative processing of emotional material and that this bias could be one of the causes of mood congruent memory in depression. ”

Table 6.1 presents only studies that focused on ABM for depression. Positive bias modification by Wadlinger & Isaacowitz (2008), and visual search bias modification for low self-esteem by Dandeneau and colleagues (Dandeneau & Baldwin, 2004; Dandeneau & Baldwin, 2009; Dandeneau, et al., 2007) were therefore not included. These studies' positive results did inform studies in this thesis. They were included in a 2011 meta-analysis assessing the combined effects of ABM and a different form of cognitive bias modification (interpretation bias modification, CBM-I) on bias and on symptoms of depression and anxiety (Hallion & Ruscio, 2011). In this meta-analysis, a small sized effect (15 studies; depression, anxiety, self-esteem and positive bias studies combined) on attentional bias was reported. Small sized effects on anxiety symptoms were found directly following training, and following a stressor task (41 and 18 studies, ABM and CBM-I combined). Effects on depressive symptoms were found to be non-significant (23 and 10 studies, ABM and CBM-I combined). Funnel plots suggest publication bias (Hallion & Ruscio, 2011).

One other study that should be mentioned is a study assessing whether ABM effects are influenced by the 5-HTTLPR polymorphism (Fox, Zougkou, Ridgewell, & Garner, 2011). This study was not included in table 6.1, because it was informed by anxiety rather than depression related ABM. Dot probe ABM was used to train attention towards either threatening or positive information. Hypothesized effects on bias were found for training in both directions. These were more pronounced for 5-HTTLPR s-carriers, compared to l-homozygotes. Depression and anxiety ratings increased in both genotype groups following both positive and negative ABM. These increases were also more pronounced in s-, compared to l-homozygotes (Fox, et al., 2011).

Analogous to CBT, which aims to modify dysfunctional cognitions, ABM was quickly identified as a possible new treatment modality: a means to get another handle on the interplay between cognitions and information processing bias. It is not entirely surprising that ABM was soon studied as a new treatment, using study designs for treatment evaluation. A new treatment option, or treatment adjunct, for depression would be a much-welcomed development. It could also become a prime example of translational research in psychology. However, the current state of literature on depression ABM, including the findings in this thesis, appears not to warrant much enthusiasm. For depressed patients to eventually benefit from ABM, or an ABM derivate, the field should not rush into treatment evaluation or even implementation, but carefully experiment to establish task parameters that reliably modify bias and subsequently affect symptoms.

A compelling possibility remains: ABM changes bias, but only so subtly that it cannot be detected with a dot probe task, and the subsequent effects on symptoms can be reliably detected only after a follow-up period wherein an individual 'uses' his modified bias 'in the real world'. Two studies suggested that the dot probe task, on which the most often tested ABM paradigm is based, has a low test-retest reliability (Schmukle, 2005; Staugaard, 2009), possibly hampering its usefulness for evaluating ABM effects in a pre/post design. Additionally, two depression ABM studies reported effects on symptoms first observed two weeks after the training (Browning, et al., 2012; Wells & Beevers, 2010).

Alternatively, ABM may affect symptoms but these effects may not be mediated by bias

change. This option is underscored by one study wherein two anxiety ABM procedures designed to induce bias in opposing directions were compared to control ABM, and were found to have similar beneficial effects on anxiety reactivity to stress (Klumpp & Amir, 2009). In the study by Fox a similar but opposite effect was observed. ABM procedures inducing bias towards negative and towards positive were both associated with increases in depression and anxiety ratings (Fox, et al., 2011). The authors of this latter finding note that it could be attributed to mere exposure to negative stimuli. However, mere exposure cannot explain the finding by Klumpp and Amir (2009). Future studies should focus on establishing effects of ABM on the targeted bias preceding effects on symptoms, and possibly also formulate and test alternative mechanism of action. At the moment there is insufficient evidence to conclude that depression ABM modifies depression related attentional bias, and therefore little reason to assume that it subsequently affects depressive symptoms.

The small number of studies assessing depression ABM contrasts with the rapidly increasing body of literature assessing ABM for anxiety. Although the depression ABM field is informed heavily by the anxiety ABM field, discussing this literature is beyond the scope of this thesis. It is my impression that the anxiety ABM literature suffers some of the same shortcomings as the literature on depression ABM: little evidence directly linking symptom changes to observed changes in bias, and optimistic conclusions being drawn from underpowered studies or flawed analyses. Moreover, commercial interests may have disproportionally influenced the emerging anxiety ABM field. Four out of nine papers included in the first meta-analysis of anxiety ABM (Hakamata et al., 2010) were co-authored by a researcher whom owns a company marketing ABM over internet since 2009, which was not disclosed in scientific literature until June 2012. One third of anxiety ABM papers (10 out of 29) published up till the 2011 were (co-)authored by this researcher. It is with mixed feelings that I observe that recently several larger scale RCT's made it to publication. This is a positive development as, contrary to most initial studies, these tend to adhere to guidelines for reporting clinical trials (e.g. CONSORT: consolidated standard of reporting trials), enabling both researchers and clinicians to better gauge the validity and implications of findings (Altman et al., 2001; Boutron, Moher, Altman, Schulz, & Ravaud, 2008). However, no beneficial effects of ABM were observed in large patient samples (Boettcher, Berger, & Renneberg, 2012; Carlbring et al., 2012; Neubauer et al., 2013; Rapee et al., 2013; Schoorl, Putman, & Van der Does, 2013).

What are the implications of the lack of robust depression ABM effects for cognitive models of depression? It appears to be unexpectedly difficult to modify depression related attentional bias, and not (yet) possible to use bias modification as a tool to experimentally assess whether reducing bias leads to reduced symptomatology. Thus, this link in the cognitive model remains supported only by associational evidence linking bias to depressed and remitted depressed states.

Environmental and genetic influences on processing bias

The study in chapter 4 focused on genetic and environmental influences on biased information processing. An interaction effect of 5-HTTLPR and recent negative life events was found. Corroborating our previous finding of enhanced negative facial emotion recognition as a function of 5-HTTLPR and negative life events, carriers of the low expressing allele showed enhanced recognition of negative mood states as a function of 5-HTTLPR and negative life events in the six months preceding. Our other hypotheses were not confirmed. Gene-environment interactions were not found for attention allocation bias. We speculated that, drawing on dual processing theory, this pattern of effects could indicate that bias in mood state recognition is affected by a diathesis-stress type process, whereas, relatively automatic, attentional allocation bias is not. Gene-environment interactions involving childhood emotional abuse were not found. This may be ascribed to the low incidence of childhood emotional abuse in our sample. Alternatively, and in line with cognitive models, CEA may predispose to latent cognitive vulnerability, but not to continuously active information processing biases. Therefore, the bias endophenotype approach may not be suitable to assess interactions of 5-HTTLPR and CEA, especially not in samples not selected for abuse and for currently active depression. Previously reported main effects of 5-HTTLPR on attention allocation bias were partly confirmed in our study. We observed no effect on attentional allocation towards positive information, but a main effect of 5-HTTLPR on bias towards negative information was found. This main effect was only just significant and conditional on the statistical analysis used.

For the planned analyses, the statistical method used in the seminal paper by Caspi and colleagues (Caspi, et al., 2003) was adopted. In the context of genetic influences, only very small effect sizes are expected. Moreover, underestimation of interaction effects and their sizes is likely to occur when using moderated regression models (Aguinis, Aguinis, & Stone, 1997; Aiken & West, 1991). Some authors proposed that, in order to detect gene-environment effects on dichotomous measures of depression status, samples of several thousand participants may be required (Munafò, Brown, & Hariri, 2008). Considering that the 'common practice' methods may not comply with all statistical requirements and may not achieve sufficient power (also given some typical features of certain measures, such as unequal sample sizes for the genotype groups), combined with small expected effect sizes, the field needs to reconsider their statistical methods and study designs. A promising new development is the polygenic risk profile score approach, assessing the combined risk contribution of several hundred thousand polymorphisms simultaneously (Demirkan et al., 2011; Lee, Goddard, Wray, & Visscher, 2012).

Our study was the first to assess interaction effects of adversities and 5-HTTLPR on attentional bias, and our sample was twice as large as the largest previous sample wherein main effects of 5-HTTLPR on attentional bias were assessed. The study added further support for assessing measures of biased processing, specifically biased facial emotion recognition, as an endophenotype. However, while the endophenotype approach may be an useful and innovative approach to assess genetic influences and their possible interaction with recent life events, it may be less suitable to assess effects of childhood emotional abuse in not currently depressed samples. Moreover, even larger replication

studies, or alternative approaches such as the polygenic risk approach, will have to confirm whether there is a specific genetic component interacting with environmental adversity in contributing to depression vulnerability through biased information processing.

Cognitive reactivity and implicit self depressed associations as precursors to depression

For the last study in this thesis, focus moved from processing bias towards dysfunctional attitudes. The study was aimed to establish a direct association between two measures of cognitive vulnerability and the incidence of depression in a never-depressed sample. The results were relatively straightforward: both cognitive reactivity and implicit self-depressed associations were related to subsequent depression incidence in a community-based sample of never depressed individuals. However, when preclinical symptoms, history of anxiety disorder, and various other measures were controlled for, cognitive reactivity to sad mood still added to the prediction of depression incidence, whereas implicit self-depressed associations did not. Given that implicit self-depressed associations were found to be associated with various measures pertaining the course of depression (Elgersma, Glashouwer, Bockting, Penninx, & De Jong, 2013; Glashouwer & de Jong, 2009; Glashouwer, de Jong, & Penninx, 2012), we concluded that implicit associations may form and deepen as a result of experiencing depressive symptoms, but do not precede depression.

The most important aspect of our findings is that cognitive reactivity remained a significant predictor in the multivariate model, when preclinical depressive symptoms, the occurrence of negative life events, and other factors were statistically controlled for. That cognitive reactivity to sad mood predicts depression incidence, is in line with the mood-state hypothesis. This hypothesis was formulated to explain the lack of evidence that dysfunctional cognitions precedes depression incidence (Persons & Miranda, 1992). It states that at risk individuals will endorse dysfunctional, depression related, cognitions when experiencing sad mood, whereas individuals not at risk will not show increased endorsing as a function of sad mood. The extent to which latent dysfunctional cognitions become activated by a decrease in mood is called cognitive reactivity to sad mood. Since the late 1980s mood induction procedures have been used in not currently depressed individuals, to assess cognitive reactivity and its relationship to depressive symptoms and state (Scher, Ingram, & Segal, 2005; Segal & Ingram, 1994). The LEIDS-r questionnaire was developed to assess cognitive reactivity to sad mood without the need to rely on mood induction or priming procedures (Van der Does, 2002; Van der Does & Williams, 2003). The findings in chapter 5 provide the first evidence that cognitive reactivity to sad mood indeed exists in individuals before they develop a first depressive episode. This is possibly the first study to find that a measure of cognitive vulnerability predicts depression in a large prospective community based sample of never-depressed individuals (Scher, et al., 2005, p. 504). Previous prospective studies reporting evidence of cognitive vulnerability preceding depression did so in smaller and mixed previous- and never-depressed samples (Alloy et al., 2006; Hunt & Forand, 2005; Lewinsohn, Joiner Jr, & Rohde, 2001; Nolen-Hoeksema, 2000). Can we now better predict who will become depressed? Not really. The prediction of depression incidence based on LEIDS-r alone may not be better

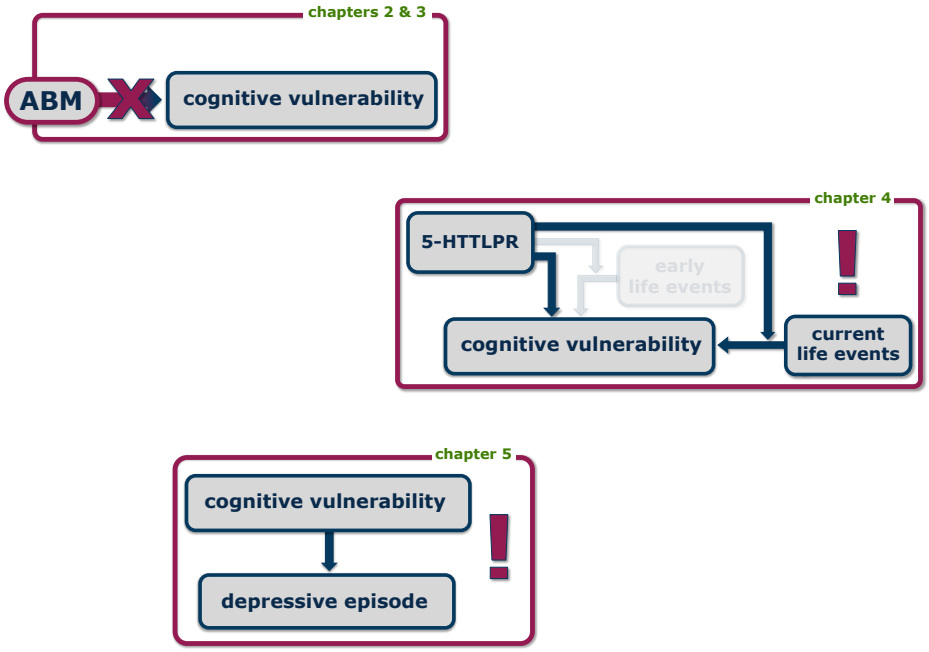
than prediction based on already present, preclinical, depressive symptoms alone. The prediction by LEIDS-r does add predictive power to the combined prediction of already present symptoms and (future) negative life events. The importance of this study is mostly theoretical. It provides evidence for an important assumption of cognitive models: cognitive vulnerability exists before onset of the first depressive episode.

Gaps and future directions

Studies in this thesis did not support the malleability of attention allocation bias through ABM procedures. Moreover, our study assessing relationships between processing biases and 5-HTTLPR allelic variants, differentially associated with depression, yielded stronger evidence for an association with negative facial emotion recognition bias than with attention allocation bias. Future studies may focus on acquiring more, and comparative, evidence for associations between these biases and both current and remitted depression state. If our findings related to 5-HTTLPR variants were to be replicated, a next step would be to expand the findings to assess whether biases that occur as a function of both genotype and environmental adversity also mediate future depressive episodes. Another link that has received little systematic research to date, is the interaction between processing biases and cognitions. Following our finding of cognitive reactivity to precede depression incidence, it will be interesting to assess how cognitive reactivity to sad mood and information processing biases relate to each other. The finding that cognitive reactivity to sad mood predicts depression incidence also requires further study. This finding needs to be replicated, extended over longer periods of time, and its specificity for depression, compared to for instance anxiety disorders, will have to be established.

Summary

The aim of studies in thesis was to further knowledge on the etiology of depression by applying innovative study designs to components of cognitive models for depression. Two studies explored the possibility to experimentally manipulate attentional bias. The evidence relating attentional bias to depression is derived almost exclusively from association designs. No evidence of successful modification of attentional bias by the tested ABM procedures was observed. The ABM studies yielded recommendations for future studies: to assess transfer of ABM effects to untrained stimuli, to heed the possibility of demand effects, to assess an index of training awareness to relate to observed effects, and to focus on establishing ABM's mechanism of action. With respect to assessing possible genetic influences on depression, the study in chapter 4 added further support for assessing measures of cognitive processing as possible endophenotypes. Biased recognition of negative emotional facial expressions was found to be reduced in carriers of the 5-HTTLPR low expressing alleles who reported recent negative life events. Both biased facial emotion recognition and attention allocation should be further studied as putative endophenotypes for depression. A prospective design, like the study in chapter 5, may perhaps not seem very innovative, yet such studies in never-depressed samples are surprisingly rare. Cognitive reactivity to sad mood as measured by LEIDS-r was found to be associated with the first onset of depression over a two-years period, in a large community sample. Following replication and further study, this may turn out to be an important finding in support of cognitive models for depression.



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samenvatting NL

Kwetsbaarheid voor depressie: het bestuderen van componenten van cognitieve modellen.

Introductie

Eén op de vijf Nederlanders wordt tijdens zijn of haar leven depressief. Depressie is een vaak voorkomende aandoening met een hoog risico op herhaalde episodes, en is onder meer geassocieerd met aanzienlijke kosten en een verhoogd sterfte risico. Bovenal heeft depressie een grote impact op het leven van patiënten en hun naasten.

De twee hoofdsymptomen van depressie zijn een aanhoudende gedeprimeerde stemming en een verlies van plezier of interesse in dagelijkse activiteiten. Daarnaast zijn een aantal nevensymptomen gedefinieerd. De diagnose majore depressieve episode wordt gesteld wanneer iemand gedurende minstens twee weken dagelijks lijdt aan minstens vijf symptomen, waarvan in ieder geval één hoofdsymptoom. Bij herhaalde depressieve episoden wordt de diagnose depressieve stoornis gesteld.

In dit proefschrift worden vier studies gebaseerd op cognitieve modellen van depressie gepresenteerd en bediscussieerd. Cognitieve modellen focussen op de cognitieve symptomen: gevoelens van waardeloosheid of schuld, gedachten aan de dood of aan zelfmoord, verlies van plezier of interesse, en hoe deze zich verhouden tot aanhoudend gedeprimeerde stemming of het verlies van plezier of interesse in dagelijkse activiteiten. Gedachten die verband houden met deze symptomen worden aangeduid als disfunctionele cognities.

Cognitieve modellen hebben het onderzoek naar depressie sterk beïnvloed in de afgelopen vijf decennia. Het eerste cognitieve model werd eind jaren zestig opgesteld door de psycholoog Beck. Tijdens zijn onderzoek bemerkte hij dat depressieve patiënten in hun dromen soortgelijke negatieve cognities over zichzelf ervoeren als welke ze uitspraken wanneer ze wakker waren. Dit paste niet goed in de destijds belangrijke psychodynamische theorie van depressie. Het belang van zijn idee dat depressieve patiënten de wereld verstoord waarnemen en interpreteren werd duidelijk toen bleek dat symptomen konden afnemen door het ombuigen van negatieve interpretaties via ‘reappraisal’. Dit werd de kern van cognitieve therapie, later cognitieve gedragstherapie, wat tegenwoordig de belangrijkste therapie vorm is voor depressie en verscheidene andere psychologische aandoeningen.

De term ‘cognitieve kwetsbaarheid’ wordt in dit proefschrift gebruikt om zowel disfunctionele cognities als afwijkende informatie verwerkingsprocessen en hun dynamiek mee aan te duiden. Beck’s cognitieve model veronderstelt dat stressvolle gebeurtenissen latente disfunctionele cognities kunnen activeren, en dat deze op hun beurt informatie

verwerking beïnvloeden. Beck definieerde depressie gerelateerde disfunctionele cognities als negatieve verwachtingen ten aanzien van zichzelf, van de wereld, en van de toekomst. Informatie verwerking kan ingedeeld worden in drie processen: het richten van aandacht, het interpreteren van informatie, en het herinneren van informatie. Tezamen bestrijken deze drie processen praktisch alle informatie die een individu uit zijn of haar omgeving opneemt. Een individu dat disfunctionele cognities ervaart, wordt verondersteld zijn of haar aandacht selectief te richten op negatieve in plaats van positieve informatie, om informatie eerder als negatief dan als positief te interpreteren, en om zich negatieve informatie beter te herinneren dan positieve informatie. Dergelijke 'neigingen' in informatieverwerking zijn automatisch en onbewust. Ze worden aangeduid met de Engelse term 'biases'. Cognitieve modellen veronderstellen dat depressie wordt geïnitieerd en in stand gehouden door de dynamiek tussen disfunctionele gedachten en biases in informatie verwerking.

Over de jaren zijn er vele variaties in cognitieve modellen geformuleerd. De meeste van deze modellen zijn niet onverenigbaar, maar leggen relatief meer nadruk op specifieke (sub)processen of hanteren alternatieve definities van cognitieve kwetsbaarheid.

Empirisch bewijs voor de rol van disfunctionele cognities komt voornamelijk uit behandelingsstudies, terwijl het bewijs voor betrokkenheid van cognitieve biases vooral uit associatieve studies is verkregen. Met de vier studies in deze thesis wordt gepoogd met alternatieve studie designs meer kennis te verwerven over cognitieve kwetsbaarheid voor depressie. Deze studies focussen op drie verschillende componenten/paden in cognitieve modellen:

De vraag of het mogelijk is om aandachtsbias (het selectief richten van aandacht) te modifcieren, om zodoende het veronderstelde causale verband met symptomen aan te kunnen tonen, staat centraal in de eerste twee studies (hoofdstukken 2 en 3). Deze worden samengevat en besproken onder het kopje 'Aandachtsbias modificatie'.

In hoofdstuk 4 wordt de veronderstelde interactieve invloed van genetische factoren en stressvolle gebeurtenissen, zowel tijdens de jeugd als in het volwassen leven, onderzocht met de endofenotype aanpak. In plaats van te kijken naar invloed op depressie zelf, bepaalt deze studie de invloed op twee biases in informatieverwerking. Deze studie wordt samengevat en besproken onder het kopje 'Biases in informatieverwerking als endofenotypes'.

Het veronderstelde causale verband tussen twee maten van disfunctionele cognities en het ontstaan van een eerste depressieve episode wordt onderzocht in de studie in hoofdstuk 5. Dit door middel van een zeldzaam longitudinaal design, welke wordt besproken onder het kopje 'cognities voorafgaand aan depressie'.

In deze Nederlandse samenvatting vat ik onder ieder van drie kopjes steeds informatie uit de introductie (hoofdstuk 1), de empirische studie(s) (hoofdstuk 2 & 3, hoofdstuk 4, of hoofdstuk 5) en de discussie (hoofdstuk 6) samen. Tot slot geef ik een aantal conclusies weer, alsmede suggesties voor toekomstig onderzoek.

Aandachtsbias modificatie

Wetenschappelijk bewijs voor de aanname dat automatische neigingen in informatieverwerking (biases) samenhangen met depressie komt voornamelijk uit zogeheten associatieve studie designs. Dit zijn studies waarin op een enkel moment wordt gemeten of groepen die verschillen op een bepaalde variabele, ook verschillen op een andere variabele. Er wordt slechts waargenomen en niet gemanipuleerd. In dergelijke studies is het niet mogelijk om te bepalen of de ene variabele de andere veroorzaakt, of dat beiden veroorzaakt worden door een (onbekende) derde variabele. Depressieve patiënten en risicogroepen (bijvoorbeeld kinderen van depressieve ouders) vertonen een sterkere negatieve aandachtsbias dan controle groepen. Een (tweede) aandachtsbias naar positieve informatie in controle groepen is juist vaak afwezig in (voorheen) depressieve patiënten. In de afgelopen jaren is er veel onderzoek gedaan naar de mogelijkheid om dergelijke biases te modificeren, en niet slechts te observeren, door middel van zogeheten cognitieve bias modificatie methoden (CBM). Succesvolle CBM maakt experimentele studie designs mogelijk. Bovendien: als biases inderdaad een rol spelen in het ontwikkelen en in stand houden van depressie, dan zou het modificeren van biases kunnen leiden tot een vermindering van symptomen. De hoofdstukken twee en drie presenteren twee studies waarin getest wordt of twee verschillende aandachts bias modificatie (ABM) methoden leiden tot veranderingen in aandachtsrichting bias.

Hoofdstuk 2 presenteert de resultaten van een studie met een ‘single case series design’. In zo’n studie wordt data per individuele deelnemer bekeken, in plaats van op groepsniveau. Dertig dysfore studenten (studenten die niet depressief zijn, maar wel relatief veel depressieve symptomen rapporteren) ondergingen vier sessies ABM met de ‘dot probe methode’. Deze ABM methode is in eerste instantie ontwikkeld met het oog op angststoornissen, en er is nog weinig bekend over het toepassen van deze methode op depressie. Het is aannemelijk dat ABM methoden moeten worden aangepast voor toepassing voor depressie. Daarom werd er in deze studie naar zes varianten van deze methode gekeken. De zes varianten verschilden in de richting waarin aandachtsbias gemodificeerd werd: het modificeren van bias voor treurige gezichten richting neutrale gezichten of het modificeren van bias voor neutrale gezichten richting blije gezichten. Ook varieerde de duur waarmee plaatjes van vrolijke of treurige en neutrale gezichten werden aangeboden tijdens een enkele trial van de taak: kort (een halve seconde), lang (drie seconden), of variabel (tussen een halve en drie seconden). Deze twee parameters zijn gecombineerd tot zes ABM varianten, iedere variant werd door vijf deelnemers gedaan. Bias werd gemeten voorafgaand aan de ABM training, tijdens de vier training sessies, en na afloop. In de voor- en nameting werd een aparte set met foto’s van gezichten gebruikt, om te bepalen of een eventuele verandering in bias ook generaliseert naar plaatjes die niet tijdens de training gebruikt waren. De verandering in aandachtsbiases was de voornaamste uitkomst maat. Verwacht werd dat deze in positieve richting zouden veranderen: van treurig naar neutraal of van neutraal naar blij. Voor geen van de zes varianten werd een consistente verandering in bias gemeten tijdens de vier training sessies. Voor zover deelnemers verandering in bias lieten zien tijdens de training, veranderde de bias voor niet-getrainde plaatjes niet consistent mee, en vaak in tegenovergestelde richting. Wel rapporteerden de deelnemers in de drie ‘treurig naar

neutraal' condities verminderde angst symptomen na de training, terwijl dit niet werd gevonden voor depressie symptomen. Omdat aandachtsbias niet consistent veranderde, is dit mogelijk een vals positieve bevinding, allicht als gevolg van een zogeheten 'demand' effect. In deze studie is ook gekeken of deelnemers zich bewust werden van het doel van de training. Verandering in bias voor niet getrainde plaatjes (in de voor- en nameting) bleek samen te hangen met de mate waarin deelnemers achteraf geloofden dat ze de training, en niet een controle taak, hadden ondergaan. Dit is een belangrijke observatie omdat uit eerder onderzoek is gebleken dat effecten van ABM op symptomen mogelijk enkel optreden wanneer deelnemers zich niet bewust zijn van het feit dat ze een training ondergaan. Dit fenomeen dient verder onderzocht te worden omdat het implementatie van ABM als behandeling in de weg zou staan.

Hoofdstuk 3 presenteert een relatief kleine gerandomiseerde en gecontroleerde trial (RCT) waarin 40 dysfore studenten ABM volgens de 'visuele zoektaak' methode ondergaan. Twintig deelnemers zochten in een blok van zestien plaatjes steeds zo snel mogelijk het blije gezicht tussen vijftien negatieve gezichten. Twintig deelnemers in de controle conditie zochten naar bloemetjes met vijf blaadjes tussen plaatjes van bloemetjes met zeven blaadjes. Met deze vorm van ABM zijn eerder positieve effecten gevonden in deelnemers met een laag zelfvertrouwen. De verwachting was dat deze vorm van ABM ook voor depressie goed zou kunnen werken omdat het tegelijkertijd zowel bias naar negatieve informatie zou wegtrainen, alsook bias naar positieve informatie toe zou stimuleren. Bovendien bepaalt de deelnemer in deze taak steeds zelf hoe lang hij of zij naar de plaatjes kijkt, wat bij ABM voor depressie van belang zou kunnen zijn. Drie aandachtsbiases, voor blijdschap, bedroefdheid, en afschuw uitdrukkende gezichten, werden gemeten met een 'dot probe taak' voorafgaand en na afloop van de training. Er werden geen effecten van de aandachtsbias modificatie op aandachtsbiases gevonden.

In de twee ABM studies in dit proefschrift werd geen bewijs gevonden voor de stelling dat deze methoden aandachtsbias beïnvloeden. Op basis van de twee relatief kleine studies in dit proefschrift is het niet mogelijk om tot een definitieve uitspraak te komen over de effectiviteit van ABM voor depressie. Wel wordt uit deze studies duidelijk dat het niet heel makkelijk is om depressie gerelateerde aandachtsbias te modificeren.

Sinds de start van mijn promotie traject zijn er, naast de studies in dit proefschrift, acht andere studies naar ABM voor depressie gepubliceerd. Deze tien studies zet ik in de discussie (hoofdstuk 6) op een rijtje, en ik kijk naar de designs (veelal kleinschalige RCT's), de uitkomsten, en de conclusies die getrokken worden. In zes van de acht RCT's wordt geen statistisch bewijs gegeven of gevonden dat ABM de beoogde aandachtsbias beïnvloedt. Bovendien blijken kenmerken en bevindingen in een aantal van deze studies de gestelde conclusies in twijfel te kunnen trekken. Ik concludeer dat de huidige literatuur over ABM voor depressie gekenmerkt wordt door methodologische problemen en dat er op zijn best zwak bewijs bestaat voor de stelling dat dot probe ABM effecten heeft op de specifieke bias waarop ze zich richt, of op andere biases, of op symptomen van depressie in de bedoelde danwel de onbedoelde richting.

ABM is al vroeg herkend als een mogelijke nieuwe behandelingsoptie, en het ABM

onderzoek werd al snel gekenmerkt door studie designs bedoeld voor de evaluatie van de effectiviteit van een behandeling (RCT's). Een nieuwe behandeloptie voor depressie zou zeer welkom zijn, en ABM zou een mooi voorbeeld kunnen worden van translationeel onderzoek in de psychologie. Echter, om patiënten uiteindelijk te laten profiteren van ABM (of een ABM afgeleide), is het van belang dat ABM niet enkel in studie-designs voor behandelingsevaluatie wordt onderzocht, en dat ABM niet te snel wordt geïmplementeerd in de klinische praktijk. Het is juist van belang om voorzichtig en nauwkeurig te experimenteren met de verschillende parameters van ABM, om zo een ABM methode te ontwikkelen waarmee bias betrouwbaar gemodificeerd kan worden en waarmee betrouwbare effecten op symptomen worden bereikt.

Ondanks de tegenvallende resultaten, blijft het mogelijk dat ABM wel werkt, maar dat de taak waarmee bias verandering meestal wordt bepaald, de dot probe taak, niet gevoelig of betrouwbaar genoeg is om verandering direct na afloop van de training mee te meten. Een andere mogelijkheid is dat ABM wel een invloed heeft op symptomen, maar niet via verandering in bias. In twee ABM voor angst studies werden vergelijkbare effecten op symptomen gevonden voor ABM training in tegenovergestelde richtingen.

Het kleine aantal studies voor depressie ABM contrasteert met een veel groter aantal studies naar ABM voor angststoornissen. Ook in deze studies is er vaak sprake van effecten van ABM op symptomen, zonder sterk bewijs dat deze via een verandering in bias tot stand komen. Bovendien lijken een aantal van de initiële studies met positieve resultaten beïnvloed door commerciële belangen. Meer recent zijn de resultaten van een aantal grote klinische trials gepubliceerd. De kwaliteit van de rapportage van deze studies is doorgaans hoger, wat onderzoekers en clinici beter in staat stelt om de uitkomsten te beoordelen. Echter, in vijf grote klinische trials zijn geen effecten van ABM gevonden.

Het blijkt onverwacht moeilijk om depressie gerelateerde aandachtsrichting bias te modificeren. Daardoor is het nog niet mogelijk om bias modificatie te gebruiken als een onderzoeksmethode om experimenteel te bepalen of het veranderen van bias leidt tot verandering in symptomen. Deze link in de cognitieve modellen blijft derhalve slechts ondersteund door bewijs uit associatieve studie designs.

Biases in informatieverwerking als endophenotypes

Uit familie en tweelingstudies weten we dat het ontwikkelen van depressie deels genetisch bepaald is, naar schatting voor zo'n 37 procent. Er is echter nog maar weinig bewijs voor de betrokkenheid van specifieke genetische factoren. De belangrijkste kandidaat genetische factor is het serotonine transporter polymorfisme (5-HTTLPR). Dit polymorfisme komt in grofweg twee varianten: lang en kort. Omdat ieder twee allelen heeft, zijn mensen in te delen in dragers van het kort-kort, kort-lang, en lang-lang genotypes. Een belangrijke eerdere studie liet zien dat dragers van het kort-kort genotype vaker depressief raken nadat ze een stressvolle gebeurtenis meemaken of wanneer zij als kind verwaarloosd of misbruikt zijn. Mensen met een lang-lang genotype worden vermoedelijk niet zozeer minder vaak depressief, maar stress speelt bij hen waarschijnlijk minder een rol in het

ontwikkelen van depressie. Echter, drie meta-analyses op basis van studies naar deze gen-omgeving interactie komen tot tegengestelde conclusies. Een mogelijke stap vooruit is om niet te kijken naar het effect van 5-HTTLPR (genotype) op depressie diagnose (fenotype), maar naar het effect op een fenomeen dat een soort tussenstap is op de schaal van gezond naar ziek, zoals cognitieve kwetsbaarheid (endofenotype). Eerdere studie lieten zien dat kort-kort dragers een sterkere aandachtsbias naar negatieve informatie vertonen, terwijl in lang-lang dragers juist een sterkere (beschermende) bias naar positieve informatie wordt gemeten. In de eerdere studies naar informatie verwerkings biases en 5-HTTLPR werd de mogelijke interactie met stressvolle gebeurtenissen niet bepaald.

Hoofdstuk 4 presenteert een studie naar gen-omgeving interactie effecten van 5-HTTLPR en 'emotioneel misbruik tijdens de jeugd' of recente stressvolle levensgebeurtenissen op twee vormen van verstoorde informatieverwerking. 5-HTTLPR genotype, aandachtsbias en bias in herkenning van emotionele gezichtsuitdrukkingen werden bepaald voor 215 deelnemers die nog nooit of niet recent depressief waren geweest,. Een direct effect van 5-HTTLPR op aandachtsbias werd gevonden: kort-kort dragers richten hun aandacht sterker naar negatieve informatie dan lang-lang dragers. Voor deze bias werden geen interacties met stress gevonden. Voor bias in het herkennen van emotionele gezichtsuitdrukkingen werd wel een gen-omgeving interactie tussen 5-HTTLPR en recente stressvolle gebeurtenissen geobserveerd: kort-kort dragers die in de voorgaande zes maanden stressvolle gebeurtenissen hadden meegemaakt, bleken beter in het herkennen van negatieve gezichtsuitdrukkingen.

Een gen-omgevings interactie effect tussen 5-HTTLPR en recente negatieve gebeurtenissen is in lijn met eerder Leids onderzoek waarin ook bleek dat dragers van twee korte allelen beter waren in het herkennen van negatieve gezichtsuitdrukkingen als zij recent een negatieve gebeurtenis hadden meegemaakt. Gehypothetiseerde gen-omgevings interacties met 'emotioneel misbruik tijdens de jeugd' werden niet geobserveerd, en evenmin werden er gen-omgevings interacties voor aandachtsbias gevonden. Evenals in eerder onderzoek toonden kort-kort dragers sterkere bias naar negatieve informatie, en lang-lang dragers keken juist weg van negatieve informatie. Dit effect was net significant en enkel wanneer in de statistische analyse verondersteld wordt dat er een lineair verband bestaat tussen kort-kort, kort-lang, en lang-lang dragers. Een omgekeerd effect voor positieve informatie, zoals in eerder onderzoek gevonden, werd in deze studie niet geobserveerd.

De gebruikte statistische analyse, die in veel gen-omgevings interactie papers gebruikt wordt, kent een aantal nadelen welke ik kort bespreek om tot de aanbeveling te komen dat sterkere studie designs en analyse methoden gevonden moeten worden. Een interessante ontwikkeling op het gebied van genetisch associatie onderzoek zijn de polygenische risicio scores, waarbij de gezamenlijk invloed van enkele tientallen tot honderd duizenden genetische variaties bepaald wordt.

Alhoewel deze studie met 215 deelnemers als een kleine studie moet worden beschouwd, omdat er voor individuele genetische factoren notoir kleine effecten verwacht worden, is deze studie bijna twee keer zo groot als de grootste voorgaande studie naar 5-HTTLPR en

aandachtsbias. Bovendien is dit de eerste studie waarin ook gen-omgevings interacties werden bepaald voor deze uitkomstmaat. Grotere studies en alternatieve methoden, zoals de polygenische risico scores, zullen moeten uitwijzen of er daadwerkelijk een interactie bestaat tussen 5-HTTLPR en stress die via informatie verwerkingsprocessen een invloed heeft op cognitieve kwetsbaarheid voor depressie.

Cognities voorafgaand aan depressie

Het meest overtuigende, alhoewel indirecte, bewijs voor een causale relatie tussen dysfunctionele cognities en depressie is dat reappraisal van negatieve cognities depressieve symptomen doet afnemen en relatief beschermend werkt tegen toekomstige episoden. Er is echter nog vrijwel geen bewijs dat cognitieve kwetsbaarheid voorafgaat aan een eerste episode. Studies waarin grote groepen nooit-eerder-depressieve personen gevolgd worden om te bepalen of bepaalde kenmerken voorspellend zijn voor wie er uiteindelijk depressie ontwikkeld, zijn zeldzaam.

Hoofdstuk vijf presenteert een dergelijke studie. In de jaren tachtig worden varianten van het cognitieve model ontwikkeld rondom het concept cognitieve reactiviteit. Deze benadrukken dat de dysfunctionele cognities die voorafgaan aan een depressie, niet continue actief zijn, maar geactiveerd worden door veranderingen in gemoedsgesteldheid. 'Cognitieve reactiviteit als gevolg van treurige stemming' is de mate waarin depressie gerelateerde gedachten actief worden wanneer iemand een normale treurige stemming ervaart. Bij de één is dat sterker het geval dan bij de ander, en dat verschil zou een verschil in cognitieve kwetsbaarheid voor depressie kunnen inhouden. De Leiden Index of Depression Sensitivity – Revised (LEIDS-R) is een vragenlijst waarmee cognitieve reactiviteit bepaald wordt. Weer andere varianten van het cognitieve model veronderstellen dat impliciete en expliciete cognities een verschillende rol spelen in het ontwikkelen van depressie. Impliciete cognities kunnen worden gemeten met computertaken waarbij de deelnemer niet kan weten wat er precies wordt bepaald. De Impliciete Associatie Test (IAT) bepaald of het voor iemand makkelijker is om dezelfde knop te gebruiken om te reageren op woorden die te maken hebben met 'zelf' (ik, mij, etc.) en positieve of negatieve woorden, danwel of het makkelijker is om positieve of negatieve woorden via dezelfde knop te verbinden aan woorden die verwijzen naar anderen (zij, hen, etc.). De uitkomst is een zelf-depressieve associaties score die de sterkte van iemands impliciete associatie tussen 'zelf' en 'negatief' weergeeft.

De LEIDS-R en de zelf-depressie IAT zijn afgenomen in de Nederlandse Studie naar Depressie en Angst (NESDA). In deze studie worden bijna 3000 Nederlanders langdurig gevolgd. In hoofdstuk vijf wordt bepaald of scores op de zelf-depressie IAT en op de LEIDS-r vragenlijst voorspellen wie er in de twee jaar na de basis meting voor het eerst depressief zijn geworden. De benodigde gegevens waren beschikbaar voor 834 NESDA deelnemers die op baseline nog nooit depressief waren geweest. Wanneer de uitkomstmaten apart worden bekeken blijken beiden toekomstige depressie te voorspellen. Verschillende andere maten (o.a. symptomen die al aanwezig zijn bij de basismeting, neuroticisme, en het hebben van een angststoornis) hangen ook samen met depressie risico. Echter,

wanneer er gekeken wordt naar de gecombineerde voorspelling, zijn enkel nog de reeds aanwezige depressie symptomen, het aantal stressvolle gebeurtenissen gedurende twee jaar, en de LEIDS-R score voorspellend voor het risico op depressie.

In hoofdstuk zes bespreek ik deze studie die bedoeld was om een directe verband vast te stellen tussen twee vormen van disfunctionele cognities en de incidentie van depressie in een nooit-eerder depressieve onderzoeksgroep. Zowel cognitieve reactiviteit als impliciete zelf-depressieve associaties bleken samen te hangen met het optreden van een eerste depressieve episode in de navolgende twee jaren. Echter, in een statistisch model waarin gecontroleerd werd voor de invloed van reeds aanwezige symptomen, negatieve levensgebeurtenissen gedurende de looptijd van de studie, reeds aanwezige angststoornissen, neuroticisme, en een aantal andere variabelen, voegde zelf-depressieve associatie geen voorspellende waarde toe, terwijl cognitieve reactiviteit dat wel deed.

Aangezien eerdere studies op basis van NESDA data hebben aangetoond dat zelf-depressieve associaties samenhangen met het verloop van depressie, ná de eerste episode, lijkt het aannemelijk dat dergelijke associaties zich ontwikkelen en versterken met het doormaken van herhaalde episoden.

De resultaten van deze studie suggereren dat cognitieve reactiviteit reeds verhoogd is voordat een eerste depressieve episode ontstaat. Het concept cognitieve reactiviteit is geassocieerd met de zogeheten ‘mood state hypothesis’, een variant van het cognitieve model dat benadrukt dat disfunctionele cognities enkel actief en meetbaar zijn wanneer een individu in een treurige stemming is. Hieruit volgt dat het afnemen van een vragenlijst naar disfunctionele cognities zonder stemmingsmanipulatie niet voldoet om deze cognitieve kwetsbaarheid te bepalen. De LEIDS-r vragenlijst omzeilt deze horde door te vragen naar de mate waarin iemand bepaalde cognities ervaart wanneer hij of zij zich ietwat treurig voelt. De uitkomsten van deze studie vormen een eerste bewijs dat cognitieve reactiviteit inderdaad voorafgaat aan een eerste depressieve episode. Mogelijk is dit ook de eerste studie waarin wordt aangetoond dat een vorm van cognitieve kwetsbaarheid de eerste depressieve episode kan voorspellen, zelfs wanneer er gecontroleerd wordt voor reeds aanwezige symptomen.

Deze bevinding zal geen directe gevolgen hebben voor de klinische praktijk. Het belang is vooral theoretisch: het levert een eerste bewijs voor een belangrijke aanname van cognitieve modellen: cognitieve kwetsbaarheid gaat vooraf aan de eerste depressieve episode.

conclusies en suggesties voor toekomstig onderzoek

De studies in dit proefschrift zijn bedoeld om meer kennis te verwerven over de etiologie van depressie door het toepassen van innovatieve studie designs op componenten van cognitieve modellen voor depressie.

In twee studies werd onderzocht of het mogelijk is om aandachtsbias te modificeren,

zodat het mogelijk wordt om bewijs voor de causale link tussen aandachtsbias en depressie symptomen te verkrijgen uit experimentele studies. In deze studies lukte het niet om aandachtsbias betrouwbaar te modificeren. Aanbevelingen voor toekomstig onderzoek uit deze studies zijn om steeds te bepalen of eventuele effecten van ABM op aandachtsbias ook generaliseren naar niet-getrainde stimuli, om rekening te houden met de mogelijkheid dat zogeheten 'demand effecten' kunnen optreden op symptoom maten, om in kaart te brengen wat de gevolgen zijn wanneer deelnemers zich bewust zijn van het feit dat ze training ondergaan, en in te focussen op het vaststellen van het werkingsmechanisme van ABM.

De uitkomsten van de genetische associatie studie ondersteunen de gedachte achter onderzoek naar biases in informatie verwerking als endofenotype. In deze studie werd bewijs gevonden voor een interactieve associatie van het 5-HTTLPR polymorfisme en negatieve levensgebeurtenissen met bias in emotionele gezichtsherkenning, alsmede wat zwakker bewijs voor een directe samenhang tussen 5-HTTLPR en aandachtsbias. Toekomstige studies kunnen zich richten op het verzamelen van aanvullend en vergelijkend bewijs voor deze veronderstelde associatie in patiëntgroepen, zowel tijdens als na het doormaken van een depressieve episode. Als de hier gerapporteerde bevindingen met betrekking tot het 5-HTTLPR polymorfisme gerepliceerd worden in grotere studies, kan een volgende stap zijn om longitudinaal te bepalen of een mogelijk (interactief) effect van 5-HTTLPR en stress op depressie incidentie wordt gemedieerd door biases.
De veronderstelde link tussen biases en disfunctionele cognities is vooralsnog weinig systematisch onderzocht. Het kan interessant zijn om in toekomstig onderzoek te bepalen hoe cognitieve reactiviteit en biases in informatie verwerking zich tot elkaar verhouden.

Alhoewel het prospectieve design in hoofdstuk 5 op het eerste gezicht misschien niet heel innovatief overkomt, zijn longitudinale studies met niet-eerder-depressieve deelnemers erg zeldzaam. Cognitieve reactiviteit voor treurige stemming, zoals gemeten met de LEIDS-r, bleek samen te hangen met het ontstaan van een eerste depressieve episode over een periode van twee jaar in een grote groep deelnemers geworven onder de algemene bevolking. Deze bevinding vraagt om verder onderzoek. Replicatie is nodig, ook over langere perioden, en de specificiteit voor depressie, ten opzichte van bijvoorbeeld angststoornissen, moet bepaald worden. Als deze bevinding stand houdt is dit een belangrijk bewijs voor de causale link tussen cognities en symptomen als verondersteld in cognitieve modellen voor depressie.

dankwoord

Het proefschrift in uw handen geldt als de presentatie van de resultaten van het doorlopen van een promotie traject. Echter, een proefschrift geeft maar een mager beeld van de complexe processen, interacties, het vele plezier en de ervaringen (*bloed, zweet, en tranen!*) die een rol spelen in het leerproces dat zijn beslag krijgt in een verdediging. Het werkelijke resultaat is zoveel meer dan een stuk drukwerk.

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CV & publication list

Curriculum Vitae

Anne-Wil Kruijt is geboren in de gemeente Hardenberg op 11 juni 1982. Al vrij snel daarna verhuisde ze naar Vlieland, en negen jaar later naar Elst (Gelderland). Na het afronden van haar VWO aan het Van Lingen College (later: Gelders College) te Arnhem, begon ze haar studie Psychologie aan de Universiteit Utrecht in 2000.

In 2007 studeerde ze af in de 'bio- en neuropsychologie' track. Haar (onderzoeks)stage betrof een studie naar effecten van diazepam toediening op stress reacties in 5-HT1A knock-out muizen. Terugkerend naar mensgericht onderzoek, gaf haar literatuur thesis een overzicht van bevindingen met betrekking tot geslachtsverschillen in het herkennen van emotionele gezichtsuitdrukkingen. Voor haar onderzoeksthesis onderzocht ze effecten van testosteron toediening op twee gedragstaken gerelateerd aan de 'mannelijk brein theorie van autisme' en de 'mannelijke strijder theorie'.

In 2009 begon Anne-Wil aan haar promotietraject aan de Universiteit Leiden. Het resultaat daarvan is te lezen in dit proefschrift.

Sinds maart 2014 is Anne-Wil postdoctoraal onderzoeker aan de University of Oxford. Hier doet zij verder onderzoek naar hoe genetische-, en omgevingsfactoren informatie verwerking beïnvloeden, en naar de invloed van biases in informatieverwerking op kwetsbaarheid, en weerbaarheid, voor psychopathologie.

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