Depression vulnerability: Studying components of cognitive models

Kruijt, A.W.

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.