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Depression vulnerability: is it really what you think?

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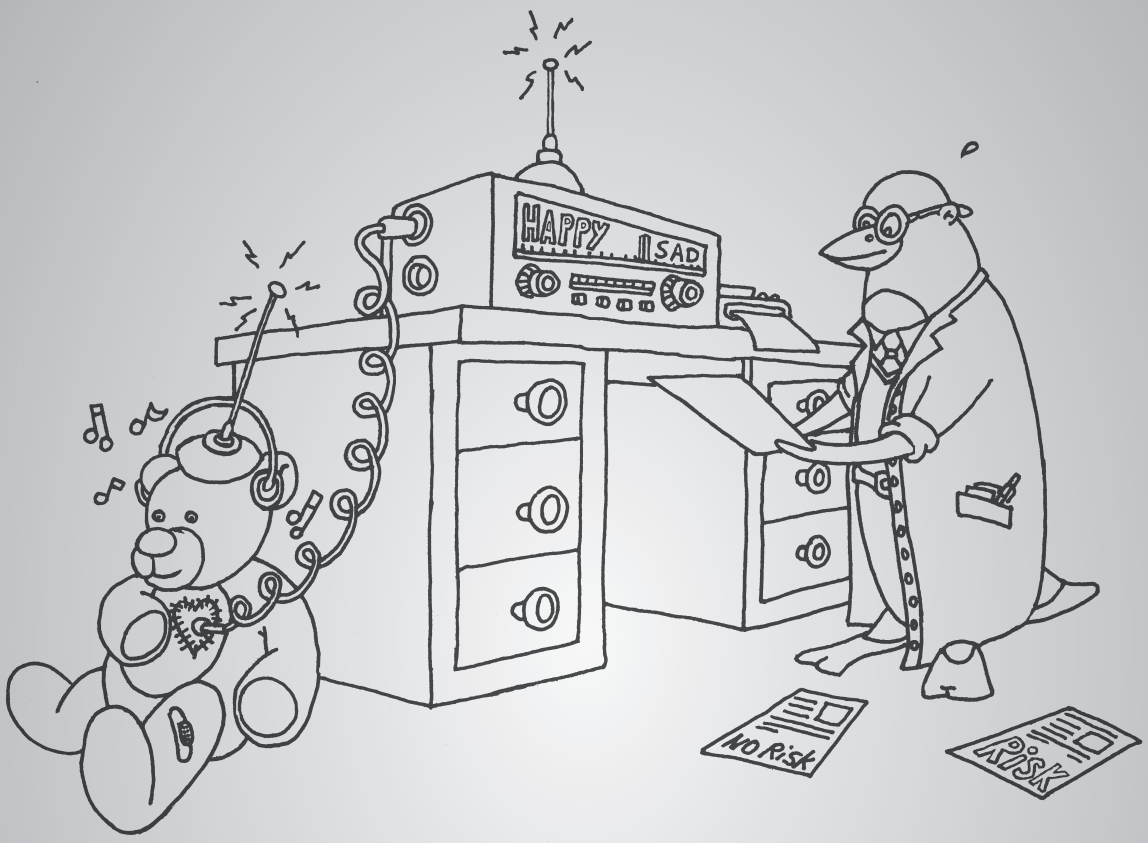
CHAPTER 8

General Discussion



GENERAL DISCUSSION

BACKGROUND

Within the described studies, we examined several important potential predictors of relapse in depression, that either negatively influence the course of depression from early in life onwards, or are potentially modifiable by preventive interventions. We examined the impact of both cognitive and emotional vulnerability as well as daily stress on the course of depression, while also including the possibility of emotional scarring (chapters 2, 4, 5, and 7). Moreover, we examined how personality disorders (PDs) and childhood adversity might exert their long-lasting influence on the course of depression (chapters 3 and 4). We also assessed whether cognitive and emotional vulnerability mediated the preventive effect of PCT on time to relapse (chapter 2). By doing this, we evaluated several cognitive and emotion models, including Beck's Cognitive model of depression (Beck, 1967), Teasdale's extension to the model; the Differential Activation Hypothesis (DAH; Teasdale, 1988), as well as theories on emotional reactivity, Gross' Process model of emotion regulation (Gross, 1998; Gross, 2001), and implications for the DynAffect model (Kuppens et al., 2010). The results help us to better understand potential pathways to relapse in depression. Finally, this thesis was also aimed at evaluating feasible methods for lifelong systematic ways of monitoring patients for depressive relapse (chapters 3 and 6). Potentially, given that it assesses sad mood, a Visual Analogue Mood Scale might be able to predict which patients are vulnerable for depressive relapse and might therefore be useful to monitor patients for relapse in depression.

COGNITION, PERSONALITY, CHILDHOOD ADVERSITY AND DAILY STRESS

Dysfunctional beliefs: content, extremity and reactivity

We examined in chapter 2 whether cognitive reactivity, having an extreme response style, and unprimed dysfunctional beliefs predicted relapse in depression. Analyzing 172 patients with a remitted recurrent depression whom were followed up to 5.5 years, we found that cognitive reactivity was not a predictor of time to relapse, neither when assessed pre- nor post-treatment. These results add to a line of mixed findings on the predictive role of cognitive reactivity for risk of relapse. Whereas some have found higher levels of cognitive reactivity to signal early return of the disorder (Kuyken et al., 2010; Segal et al., 1999; Segal et al., 2006), others have not (Jarrett et al., 2012; Lethbridge & Allen, 2008). Given this highly mixed evidence, and the fact that we found that unprimed dysfunctional beliefs predicted time to relapse in depression directly; one wonders whether cognitive reactivity is a construct of relevance to relapse in depression, and why one would use a complicated and burdening mood induction procedure when an unprimed DAS-A questionnaire is

already predictive of relapse in depression. We do need to take into consideration that our sample, when compared to previous studies on cognitive reactivity, had the highest level of recurrence[1] (*M* = 6.5 previous MDEs in our study, compared to *M*s = 4.8, 1.9 and 6.1 in Segal et al. (1999), Lethbridge and Allen (2008), and Kuyken et al. (2010), respectively). Still, in line with the DAH (Teasdale, 1988) one could also expect cognitive reactivity to become more and more ingrained with increasing numbers of depressive episodes, since patients have gone through more cycles in which negative mood has been associated with negative thinking patterns.

We also found no evidence that the extremity of beliefs on the DAS-A (or their reactivity) made patients vulnerable for relapse. Whereas extremity of responses on the DAS-A was found to be a vulnerability marker for relapse in depression in some studies (Teasdale et al., 2001), while not in other studies (Beevers et al., 2003; Ching & Dobson, 2010; Jacobs et al., 2010; Petersen et al., 2007), reactivity of extremity has not been examined yet until now. Differences in findings with Teasdale's (2001) study might partially be explained by differences in operationalization of extreme thinking. Whereas we used the total number of extreme responses on the DAS-A as a measure of extreme responding, Teasdale et al. (2001) only used the approval subscale of the DAS-A, in combination with three other scales. Moreover, whereas our patients were remitted upon entry, the patients in the sample of Teasdale et al. (2001) had residual depression ($HDRS_{17} \geq 8$) and were on ADM. Recently, it has been suggested that research on extreme responding has to differentiate between positive extreme responses (responding with extreme agreement to positive items and with extreme disagreement on negative items) and negative extreme responses (responding with extreme agreement to negative items and with extreme disagreement on positive items) (Forand & DeRubeis, 2014). Summing scores on (subscales of) the DAS might therefore be biased by including both adaptive and maladaptive responses. During the acute-phase of depression, it was found that extreme positive responding was more prevalent than extreme negative responding (Forand & DeRubeis, 2014). Moreover, having unrealistic optimism relative to a more balanced view was related to relapse in depression (patients with higher risk of relapse even endorsed positive items with an extreme, dysfunctional positive response).

Personality disorders and childhood adversity

In chapter 3 and 4, we aimed to increase our understanding of how personality disorders (PDs) and childhood adversity exert a lasting negative influence on the course of depression (for meta-analyses see: Nanni et al., 2012; Newton-Howes et al., 2006). For PDs we specifically examined their association with potentially modifiable cognitive variables, whereas for childhood adversity we examined whether childhood adversity increased sensitivity to daily stressors later in life (Glaser et al., 2006; Wichers et al., 2009).

We first examined how prevalent PDs were in our sample. In line with previous studies, we found that almost half of the patients had a comorbid PD after remission (Farabaugh

et al., 2007; Pilkonis & Frank, 1988; Sato et al., 1994). Although not previously studied, we found evidence that patients with PDs had higher levels of cognitive reactivity. This supports the idea that the PD itself might generate stress that in turn is an activator of dysfunctional belief levels (Craighead et al., 2011; Ilardi & Craighead, 1999). Similarly, patients with PDs also endorsed more latent dysfunctional beliefs, an association that was even stronger than for cognitive reactivity. Moreover, brooding has not yet been examined in patients with PDs and remitted depression. Our results indicate that both having a PD and personality pathology was related to higher levels of cognitive reactivity and brooding, but not to an extreme response style. Brooding was related to having a cluster C diagnosis within the PD domain and within that cluster an avoidant PD diagnosis specifically. In this light, brooding might serve as a way to avoid both cognitive and active problem solving (Cribb et al., 2006; Moulds et al., 2007). One intriguing finding from chapter 7 was that patients with PDs or higher levels of personality pathology did not score higher on sad mood levels after remission, which would be expected given their stronger endorsement of dysfunctional belief levels. However, chapter 7 reports on a slightly different subpopulation of patients, making a direct comparison difficult. Future studies have to examine more rigorously whether patients with comorbid PDs have different affective experiences than patients without comorbid PDs.

Since dysfunctional beliefs were associated more strongly to PDs than cognitive reactivity, the question arises whether dysfunctional beliefs in this group as assessed with the DAS are already activated due to innate stressors resulting from the PD (Craighead et al., 2011; Ilardi & Craighead, 1999). It still has to be determined whether dysfunctional beliefs accumulate over time and consolidate into a PD, or whether they are a byproduct of the PD itself. Future studies should also examine whether rumination and other modifiable cognitive vulnerability mediate the effects that PDs have on time to relapse. This will help us better understand the pathway(s) to depressive relapse. Subsequently tailoring preventive interventions (i.e., specifically targeting rumination in cluster C PD patients, and possibly, emotion) might improve their efficacy.

Childhood adversity was not related to stress sensitivity, depressive symptomatology, or the number of previous MDEs after multiple episodes of recurrent depression. However, daily stress was related to depressive symptomatology at follow-up. These findings are at odds with previous results that indicate that childhood adversity has a long-lasting influence on the course of depression, potentially through stress sensitization. Methodological differences with previous studies might also explain differences in results. We used a retrospective self-report questionnaire instead of a life-event interview to assess life-events. Moreover, we subsequently selected several life-events, based on the literature, to be included in our analyses (i.e., sexual abuse, physical abuse, and loss of a parent) that were not in all earlier studies related to the number of previous MDEs (e.g., Bernet & Stein, 1999). Unfortunately our life-event measure did not include emotional neglect, which has been related strongly with the prospective occurrence of daily hassles (Liu et al., 2013).

These findings have to be interpreted in the light of a highly recurrent sample, and could suggest that, after multiple relapses, the influence of childhood adversity on the course of depression (i.e., levels of depressive symptomatology) is no longer present. Instead, the experience of daily stressors themselves was related to depressive symptomatology levels, and might therefore be an interesting target for preventive interventions. A recent study however suggests that childhood adversity should be taken into account when selecting prophylactic strategies, since MBCT was only more effective in reducing risk of relapse in recurrent depression compared to psycho-education in patients with relatively more childhood adversity (Williams et al., 2013).

SAD MOOD

Mood reactivity

Using a sad mood-induction procedure as described earlier in this thesis (e.g., Segal et al., 1999), we demonstrated that strong mood reactivity (i.e., increases in sad mood) was predictive of relapse in depression over 5.5 years. It has been suggested by previous researchers that this might reflect stress-reactivity, in that remitted patients have stronger emotional responses to stressors (Britton et al., 2012; O'Hara et al., 2014). However, we only found mood reactivity to predict relapse post-treatment, and not before treatment. We were unable to explain this result as a consequence of treatment effects, depressive symptomatology, or time since remission. Speculatively, PCT might not have had a direct effect on mood reactivity, but might have reduced the impact of daily hassles for which circumstantial evidence was found in a previous study (differential effect of TAU + PCT compared to TAU alone; Bockting et al., 2006b). The predictive validity of mood reactivity might therefore reflect patients who were not able to benefit from the effects of PCT on daily stressors.

Putting these findings in perspective of current dominant mood reactivity hypotheses, i.e. emotional context insensitivity (Bylsma et al., 2008; Rottenberg, 2005), mood brightening (Bylsma et al., 2011; Peeters et al., 2003), and increased emotional reactivity (Myin-Germeys et al., 2003; O'Hara et al., 2014), we found some indication that strong emotional reactions signal vulnerability for return of MDD, in line with the emotional reactivity hypothesis. However, since our studies did not include a healthy control group we are unable to state whether our participants were more emotionally reactive than healthy controls or currently depressed patients. These findings are in sharp contrast with the results from Lethbridge and Allen (2008), who reported that patients who did not respond with a drop in positive affect following mood-induction are at risk of relapse. However, they used logistic regression instead of survival analyses and only included 48 participants who were selected from a population sample. Moreover, the Visual Analogue Scales that Lethbridge and Allen (2008) used to assess the effectiveness of the mood-induction deviated from previously used scales, in that they were unipolar. This might

allow for more precise mapping of changes in emotions, but makes it difficult to compare these results to previous studies using the same mood-induction procedure.

Sad mood itself

We subsequently demonstrated in two independent patient samples that sad mood levels after remission are predictive of depressive symptomatology as well as an early return of MDD. Emotion after remission therefore appears to have an important influence on the course of recurrent depression. Even more surprisingly, sad mood levels were assessed with a single-item Visual Analogue Mood Scale (VAMS) which therefore showed predictive validity. We found that every one-point increment on the VAMS increased risk of relapse by a factor 1.15. Since we found that sad mood levels predicted depressive relapse over and above residual symptoms, and moreover, showed comparable levels of explained variance as the HAM-D_{17} interview, these findings indicate that sad mood after remission is not simply a concomitant of the disorder.

In an attempt to better understand the pathway from sad mood to depressive relapse, we examined whether higher sad mood levels were associated with illness-related and potentially modifiable characteristics. Some evidence was found for 'emotional scarring', in that patients with a higher number of previous MDEs reported higher levels of sad mood after remission. The mean difference of 7.8 points between patients with ≤ 4 and >4 episodes appears to be clinically relevant, since every one-point increment on the VAMS increased risk of relapse by a factor 1.15. Although our findings could imply that emotional scarring has occurred, due to our recurrent sample we cannot rule out that higher levels of sadness were already present before the very first episode onset, which increased risk for developing a higher numbers of depressive episodes. Higher levels of sad mood were not related to the experience of a higher frequency of daily hassles, but were associated with the perceived intensity of daily hassles as well as dysfunctional belief levels. However, after correcting for depressive symptomatology, only the number of previous depressive MDEs (and not the potentially modifiable variables) was associated with sad mood. Our findings could imply that after remission, the influence of daily stress and dysfunctional beliefs on sad mood are merely an epiphenomenon of MDD. However, given that we have cross-sectional data and found that levels of sad mood appear to be influenced by the number of previous MDEs, we cannot rule out that sad mood itself might be a consequence of the disorder. This explanation seems unlikely since we were able to replicate that sad mood levels prospectively predicted depressive symptomatology at a trend-level after correction for current levels of depressive symptomatology. Surprisingly, and not in line with recent cognitive models (Teasdale, 1988), cognitive reactivity was not associated with sad mood below the conventional .05 alpha level, and was not included in the multivariate model.

In chapter 6 we assessed whether we might be able to use a VAMS for lifelong relapse monitoring, which is recommended for recurrent depression by leading treatment guidelines (Agency for Healthcare Research and Quality, 2012; American Psychiatric

Association, 2010; National Institute for Health and Clinical Excellence, 2009). Our findings highlight that the VAMS applied in isolation had excellent diagnostic accuracy both in terms of discriminative power (i.e., distinguishing between patients with and without a depression), and in terms of predictive value for a current depression. In this respect, the VAMS did better than other well-known measures of depressive symptomatology including the HAM-D_{17} interview and the IDS-SR. Not missing patients who in fact have a depression (false negatives) is crucial and we found that the VAMS did not miss any patients at a cut-off of 55. However, there was a relatively high number of false positives (53% of diagnoses were true positives). Using Experience Sampling methodology to repeatedly assess sad mood levels might improve the accuracy of the VAMS. Several remaining questions for future research include what the impact of ADM use is on VAMS scores, what the impact of comorbidity (i.e., anxiety disorders, personality disorders) is on the diagnostic accuracy of the VAMS, and whether screening for recurrent depression is cost-effective and improves treatment outcome including reductions in burden of disease.

In sum, these findings suggest that emotion exerts a strong influence on the course of depression, even when cognition is not taken into account. Higher levels of sad mood are associated with a higher perceived intensity of daily stress, dysfunctional beliefs, and the number of previous MDEs (indicative of emotional scarring). Sad mood therefore appears to be a promising monitoring target for depressive relapse. Moreover, sad mood can be assessed using a single-item assessment (VAMS), and higher scores on the VAMS signal early relapse in depression and are predictive of higher levels of depressive symptomatology. Given that the VAMS is easy to administer and simple to interpret, it could be a straightforward and feasible instrument to monitor mood in patients with a recurrent depression. It would be interesting to study whether higher sad mood levels after remission reflect some form of emotion regulation difficulty. A previous study showed that remitted patients, when compared to never depressed controls, showed more ruminative, catastrophizing, and less 'putting things in perspective' emotion regulation strategies (Ehring et al., 2008). Possibly, remitted patients have deficits in effectively regulating their affect.

MECHANISMS OF CHANGE IN PCT

As outlined in the introduction of the current thesis, it is still unknown how preventive interventions exert their effect on time to relapse. Research in this area is very important, because we first have to know how our interventions work before we can improve them. Cognitive reactivity frequently has been suggested as an underlying mechanism of CT, including MBCT (Kuyken et al., 2010; Segal et al., 2006). Curiously, this idea appears to persist despite the presence of disconfirming evidence. For example, Segal et al. (2006) found that patients who were remitted on ADM during the acute-phase of depression had higher cognitive reactivity levels than patients remitted on CBT. Nevertheless, there was no differential risk of relapse between both conditions, which would be expected if CT works through changing cognitive reactivity levels.

In our study we used a combination of emotional and cognitive variables (i.e., dysfunctional beliefs, cognitive reactivity, mood reactivity, and cognitive extremity reactivity) that we examined as potential mediators of the preventive effect of PCT on time to relapse. We were not able to demonstrate that any of these variables mediated the preventive effect of PCT, and therefore it remains unclear how (P)CT works. We have to take several limitations into consideration. Since we only analyzed patients with three or more previous MDEs, our sample was small. Moreover, we cannot exclude the possibility that PCT already produced its effect before our post-treatment measurement of the cognitive and emotional variables, which was three months after our baseline measurement. It is therefore unclear whether our mediators would meet the criteria for statistical mediation, since these criteria imply that changes in the mediator must precede changes in outcome (Kazdin, 2007).

Based on these findings and results of studies during acute-phase CT (e.g., DeRubeis et al., 1990; Simons et al., 1984), it is still not clear how CT works. Previous mechanism studies have been plagued by power problems since Baron and Kenny's (1986) causal steps approach, the most widely used method to examine mediation, requires almost 21000 participants when effect sizes are small (Fritz & Mackinnon, 2007; MacKinnon, Fairchild, & Fritz, 2007). Moreover, although previous studies claimed that cognitive measures were not a mediator of CT because both CT and ADM were effective and changed cognitive variables (e.g., Simons et al., 1984), alternative interpretations including that changes in depression might have changed the mediator in one modality whereas there might have been a direct effect of treatment on the mediator in the other modality are equally likely (Hollon et al., 1987). There is a need for consensus on *how* to study and analyze *how* our interventions work.

Since we only assessed one ingredient of PCT (i.e., challenging dysfunctional beliefs), it could be that the intervention works through the remaining pillars that we did not study: enhancing recollection and encoding of specific positive experiences, and relapse prevention strategies. Other potential mechanisms that might be operating alone or in combination could include: 1) attenuation of the extent to which patients are affected by daily hassles, since a previous study found a differential effect of PCT (added to TAU and compared to TAU alone) on daily hassles (Bockting et al., 2006b); 2) alteration of affective experiences themselves (Batink et al., 2013); and 3) broadening of skills including coping and problem solving, in line with the compensatory model (Barber & DeRubeis, 1989; Strunk, DeRubeis, Chiu, & Alvarez, 2007).

IMPLICATIONS FOR COGNITIVE MODELS OF DEPRESSION

Our findings have several implications for the previously described cognitive models of depression. First of all, we found no evidence for the differential activation hypothesis, which suggests that dysfunctional beliefs have to be activated by mild dysphoric mood to signal vulnerability for depressive relapse (Teasdale, 1988). Instead, we found that

unprimed dysfunctional beliefs predicted time to relapse directly. Specifically the content of beliefs, and not the form of thinking (i.e., extreme responding) was predictive of an early return of depression. These findings are not necessarily in conflict with the original cognitive model (Beck, 1967), as these dysfunctional beliefs might have been activated before (and leading to) depression onset, and have some form of stability thereby still conveying vulnerability after remission (Zuroff et al., 1999). However, we were not able to test the assumption that dysfunctional beliefs become activated by schema-matching life-events directly. Moreover, we were unable to demonstrate that the effect of PCT on time to relapse was mediated through changes in dysfunctional beliefs over treatment as the cognitive model suggest. We are unable to claim that cognitive therapy does not work through changes in dysfunctional beliefs since many studies that used mediation analysis, including ours, are hampered by power issues.

A limitation of the cognitive model is that it is unable to explain how cognition and affect are linked. The model does mention affect, but always secondary to cognition. If in fact affect itself might lead to dysfunctional cognition, this might be an interesting starting point for interventions.

One final concern with the cognitive model is that some aspects of this theory are hard to falsify. The cognitive model is not explicit about how and when early critical life-events lead to an accumulation and consolidation of dysfunctional beliefs into MDD, PD or their combination (Beck & Freeman, 1990; Pretzer & Beck, 1996). The same applies to more recent stress models however, since it is unknown how exactly childhood adversity reduces the threshold for being affected by future stressors. Empirical studies that could test how and when specific dysfunctional beliefs are formed and activated would require a longitudinal follow-up of a large population sample of children or adolescents starting long before MDD onset which would have to be followed for years. Although this has been done successfully for a general cognitive-stress diathesis, for example by using a composite measure of cognitive vulnerability in combination with interpersonal stress (Carter & Garber, 2011), and by using the DAS and a composite measure of life-events (Lewinsohn, Joiner, & Rohde, 2001), only few studies have examined specific cognitive vulnerability (i.e., when there is a match between the content of the belief and the stressor or stressful event); and only partially successful (Hammen, Marks, DeMayo, & Mayol, 1985; Hammen & Goodman-Brown, 1990).

IMPLICATIONS FOR EMOTION MODELS

Emotional states or affective experiences have been characterized as a highly dynamic construct (Golder & Macy, 2011; Gross & Muñoz, 1995; Watson & Clark, 1984). Within these dynamics, several authors have recently suggested some stability in the form of core affect (Barrett et al., 2005; Kuppens et al., 2010). According to Feldman-Barrett (2005), core affect is a constant stream of affective information that can be attended to or not. The experience of emotion is the result of paying attention to this stream, and

depends on conceptual knowledge about emotions. Besides core affect, the DynAffect theory describes affect in terms of variability around this core, and a force that regulates negative affect and prevents exacerbation (Kuppens et al., 2010).

We found that sad mood, assessed in the absence of a specific event, was predictive of prospective depressive symptomatology levels and depressive relapse. This could imply that we assessed core affect, as we asked patients to attend to their affective thermostat, in line with both the Circumplex model and the DynAffect model of affect (Kuppens et al., 2010; Russell, 1980). Our results support the notion that stability exists in levels of affect, since we found moderate associations between sad mood levels at baseline and three months later in two independent samples. However, we were unable to examine fluctuations in sad mood levels in the time between assessment points. Furthermore, if we relate our finding of emotional scarring (i.e., higher levels of sad mood in patients with more previous MDEs) to the DynAffect model, the question is raised whether patients might have an increased core affect bandwidth which is attributable to previous MDEs, or whether the attractor strength (i.e., emotion regulator in the DynAffect model) has become weakened and is unable to prevent exacerbation of affect. Alternatively, these problems could have existed prior to first episode onset or could have worsened with depressive episodes.

Several challenges lie ahead for the DynAffect model. First, in the light of depression, it is unclear how patients with a (remitted) depression can be characterized in terms of the DynAffect model. Although it has been suggested that depressed patients have a negatively valenced, low arousal home base in combination with weak attractor strength (Kuppens et al., 2010), this has to be examined empirically. Moreover, it is unclear what the role of attractor strength is, and how this concept relates to, for example, Gross' process model of emotion regulation (Gross, 1998; Gross, 2001).

In terms of Gross' Process model of emotion regulation (Gross, 1998; Gross, 2001), we have mainly focused on response modulation, that is, the use of rumination. Remarkably, brooding was not related to higher levels of negative affect in our study. It has been suggested that rumination is an avoidance strategy (Cribb et al., 2006; Moulds et al., 2007), which in our study appeared to have no detrimental effects cross-sectionally since it was not associated with negative affect. Brooding was also related to having a PD, and specifically in cluster C. It would therefore be interesting to study emotion regulation in patients with cluster C PDs. In borderline PD it has already been demonstrated that these patients appear to over-regulate their emotions, in that they use many different emotion regulation strategies which might deplete resources to regulate their behavior (Chapman, Dixon-Gordon, & Walters, 2013).

Finally, in relation to several models of emotional reactivity, we specifically found that higher levels of mood reactivity were predictive for early relapse in depression, mirroring results from previous Experience Sampling studies (Myin-Germeys et al., 2003; O'Hara et al., 2014). Intuitively it makes more sense for remitted patients to become highly

responsive to stressful events (instead of unresponsive), as this is also what Beck (Beck, 1967) proposed within the cognitive model.

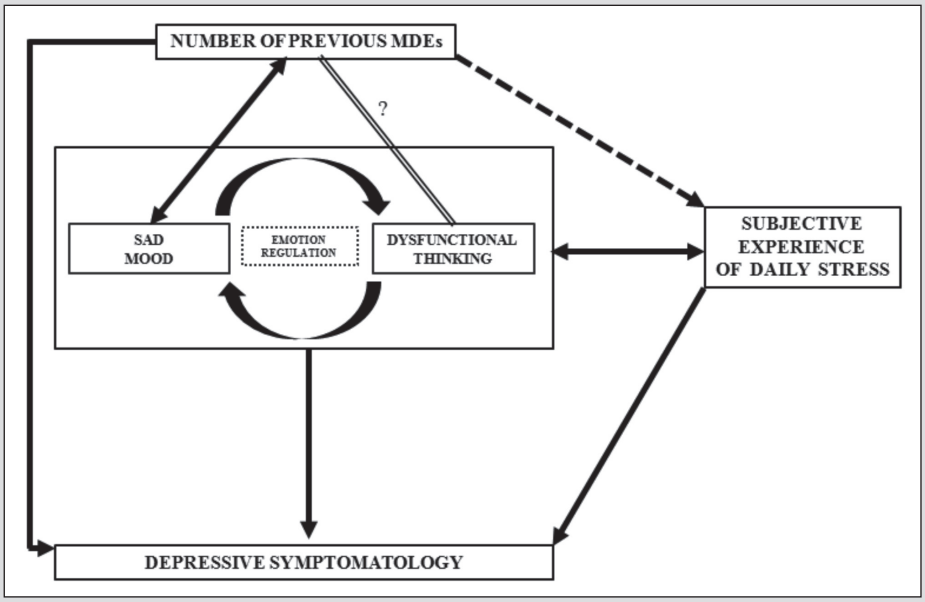
MODEL BASED ON OUR FINDINGS

Figure 8.1 depicts a model that includes several potential pathways to relapse in depression. Most pathways have been examined, although partly cross-sectional, in the current thesis. The pathways depicted are by no means intended to be exhaustive, but merely reflect variables described in the General Introduction of this thesis. They deserve further research which will lead to adjustments and, hopefully, greater specificity. Figure 8.1 is based on our findings that sad mood levels after remission, as well as daily stress (which were associated with each other), predicted depressive symptomatology prospectively, and that we found sad mood level and dysfunctional beliefs to predict relapse in depression directly.

One of the core assets of the model in Figure 8.1 is that it leaves room for individual differences in stress tolerance, emotion regulation, and sad mood after remission. Uninterrupted black arrows reflect potential pathways for which at least some evidence was found, whereas the interrupted black arrow (from number of previous MDEs to subjective experience of daily stress) represents an association that we failed to demonstrate in the current thesis. The line from number of previous MDEs to dysfunctional thinking indicates that it was not examined directly in the current thesis. Within Figure 8.1, the starting point to depressive relapse is open to debate. We embedded an affect-cognition spiral, which reflects the current lack of evidence for a starting point from negative affect to dysfunctional beliefs or vice versa (Segal, 1988).

First of all, it could be that when a stressor occurs, patients vulnerable to relapse react strongly to this stressor with intense sad mood (current thesis, but also O'Hara et al., 2014). It has been demonstrated that remitted patients show increased perceived daily stress intensity compared to never depressed controls (O'Hara et al., 2014). This could result in dysfunctional thinking, leading to a further deterioration of sad mood fueled by poor emotion regulation, found to be present after remission (Ehring et al., 2008). However, it could also be that dysfunctional thinking itself is a (problematic) emotion regulation strategy. This affect-cognition spiral depletes resources and leads to a further reduction in tolerance for subsequent stressors, again fueling the affect-cognition spiral and ultimately leading to depressive relapse. Within this view, the emotional reaction to a stressor is the starting point. It remains unclear whether the intensity of an emotional reaction or the subsequent persistence of this emotion (i.e., emotional inertia; Kuppens et al., 2012) makes patients vulnerable.

Figure 8.1. Pathways to relapse examined in the current thesis



Our study (along with others) has also demonstrated that remitted patients who have relatively higher levels of sad mood in the absence of any clear stressors are at increased risk of depressive relapse (current thesis, but also Rucci et al., 2011). Higher levels of sad mood itself, potentially resulting from emotional scarring by the number of previous MDEs (or premorbid vulnerability), could also be the starting point for the pathway to depressive relapse. Under the influence of higher sad mood levels, stressors that do occur might be tolerated less well, feeding back into the affect-cognition spiral. Similar to the 'chicken and egg' problem with cognition and affect, it also remains unclear whether negative affect results in lower tolerance for daily stressors, whether a lower tolerance for daily stressors results in more negative affect, or both. Note that the presence of childhood adversity and personality disorders are absent in Figure 8.1, as their role needs more research. Furthermore, there is a causal black arrow from the number of previous MDEs to depressive symptomatology, as this has been demonstrated in many previous studies. In chapter 4 however, the number of previous MDEs did not predict levels of depressive symptomatology assessed three months later.

CLINICAL IMPLICATIONS

The current thesis has several important implications for clinical practice. Our findings suggest that negative affect could be a candidate to monitor for relapse in depression. Since a simple VAMS had good diagnostic accuracy, this instrument could provide clinicians with a straightforward and feasible tool to mood monitor patients with a

recurrent depression. Moreover, this monitoring can be done via smartphone application or e-mail, making it as non-invasive as possible. This form of monitoring can have enormous potential for secondary mental health care, where both time and funding are limited. Therapists could use the VAMS as a first step to quickly assess whether a patient is currently having a relapse. Either as the result of emotional scarring or premorbid vulnerability (or both), our results suggest that patients with a relatively higher number of previous episodes should be monitored even more closely for negative affect, as they might be even more at risk for relapse in depression. For now, a score of 55 could be used as a cut-off. If future research is able to demonstrate that a VAMS can also reliably predict future relapses instead of cross-sectionally as we examined in chapter 6, then the rhythm of depression can be interrupted early, reducing distress for patients and societal costs. However, future studies should examine whether this screening is in fact cost-effective, and should make a cost/benefit analysis.

Although preventive interventions are reasonably effective (Guidi et al., 2011; Piet & Hougaard, 2011; Vittengl et al., 2007), there is room for improvement and we still do not know how these interventions exert their effects. Our studies appear to suggest that PCT does not work through changing dysfunctional beliefs, cognitive reactivity, or mood reactivity, although power issues have to be taken into account with mediation studies. In clinical practice, most important is that these interventions work, and should be offered to patients after remission.

Finally, our results are in line with previous studies on the prevalence of comorbid PDs after remission, and suggest that clinicians should be aware of comorbid PDs as they herald a more chronic and persistent course of MDD.

LIMITATIONS

Besides the limitations already mentioned, several other limitations of our studies have to be taken into account. First, our patient samples were all recruited within the context of several RCTs, and were seeking help in terms of relapse prevention. Moreover, our RCTs included patients between the ages of 18 and 65 (mainly Caucasian) who all achieved remission within the last two years. It is unclear whether our results can be generalized to other populations.

Second, although some of the studies we reported on in chapter 2 and chapter 3 were prospective studies covering an impressive follow-up period of more than five years, most of the other studies were based on either cross-sectional data or had a short follow-up of no more than three months which limits the interpretation of our findings. Our finding that childhood adversity was not related to depressive symptomatology three months later does not exclude the possibility that, as previously found, childhood adversity is associated with a poor prognosis in depression in terms of risk of relapse (e.g., Nanni et al., 2012). Due to our short follow-up period and relatively low levels of depressive symptomatology we might not have been able to detect the effect of childhood adversity. Moreover, it

could also be that childhood adversity does impact depressive symptomatology levels in patients with fewer previous MDEs. In the same line of reasoning we were not able to examine whether brooding moderated or mediated the impact of PDs on risk of relapse. In our study on variables associated with higher sad mood levels after remission we were not able to examine determinants of sad mood, as our study reported on cross-sectional data. Therefore, more prospective studies are needed. Due to staging of the disorder (i.e., multiple episodes of depression), we were also not able to demonstrate the presence of emotional scarring. In fact, premorbid vulnerability might be an explanation for the higher levels of sad mood after remission that we found.

Third, many mediation studies, including ours, are plagued by power issues. In particular, Baron and Kenny's (1986) causal steps approach is severely underpowered when effects are small (Fritz & Mackinnon, 2007; MacKinnon et al., 2007). Within our population of remitted patients this might be especially applicable, since variability was low and small effect sizes were to be expected. We might therefore not have been able to detect changes in both cognitive and emotional characteristics as mediators of the effect of PCT. Moreover, if we had detected characteristics that mediated the effect of PCT, it would have been questionable whether these characteristics would have met criteria for mediation due to our design (Kazdin, 2007).

Fourth, we demonstrated in several chapters of the current thesis that mood has an important impact on the course of depression, and that higher sad mood levels on a VAMS predicted relapse in depression. We have to take into account that although we assessed a paper-and-pencil version of a VAMS in chapter 3, the VAMS in subsequent chapters was assessed by telephone, and had similarities with a numerical rating scale (i.e., patients had to verbally indicate their level of sadness). Despite high correlations between VAMS scales and numerical rating scale equivalents in pain research (r = .93 - .95; Holdgate, Asha, Craig, & Thompson, 2003; Mohan, Ryan, Whelan, & Wakai, 2010), it is unclear whether one might induce more bias than the other. Although we assessed the association of sad mood levels with PDs, we did not include Big Five factors including Neuroticism. Higher levels of sad mood levels might reflect neuroticism since negative affect was related to this personality trait in previous studies (Costa & McCrae, 1980; Watson & Clark, 1992). However, associations were too low for negative affect to be completely explained by neuroticism (r = .39 - .50). Furthermore, if sad mood itself is a risk factor for relapse in depression, one would expect remitted patients to score higher on a VAMS than never depressed controls. Unfortunately, our studies did not include a healthy control group, and previous studies that examined negative affect provided mixed evidence (Gilboa & Gotlib, 1997; Husky, Mazure, Maciejewski, & Swendsen, 2009; O'Hara et al., 2014; Roberts & Kassel, 1996). Future studies should include a measure of Neuroticism to examine its relation with the VAMS, and should compare VAMS scores of a healthy control group with a remitted patient sample.

A final limitation with respect to the VAMS is that, in line with mood induction studies (e.g., Segal et al., 1999; Segal et al., 2006), we interpreted our findings in the light of increases

in sad mood on the VAMS. However, with the anchor points of the VAMS used in our studies (i.e., happy and sad), our findings might also be interpreted as reflecting decreases in positive affect. With ongoing debate on the bipolarity of affect, (i.e., whether positive and negative are two extremes of the same dimension), we cannot exclude this possibility. Positive affect appears to play an important role in the course of depression, since lower levels of positive affect were found to be related to a poorer course of depression (for a review see Morris, Bylsma, & Rottenberg, 2009). Moreover, participants with resilience for depression were able to experience positive affect following stress (Geschwind et al., 2010; Riskind, Kleiman, & Schafer, 2013; Tugade & Fredrickson, 2004). In intervention research, early changes in positive emotions were found to predict response to treatment (Geschwind et al., 2011), and have been suggested as a potential mechanism of preventive interventions (Batink et al., 2013; Geschwind et al., 2011). In patients with three or more previous MDEs, the effect of MBCT on depressive symptomatology was mediated by both positive and negative affect, whereas the mediating effect was largest for positive affect (Batink et al., 2013). Still, it is unknown what this means for risk of relapse in depression.

Finally, some of the questionnaires we used also have their limitations. With respect to our studies aimed at PDs, we assessed PDs with the PDQ-4+. Although this self-report questionnaire directly corresponds to personality disorders in the DSM-IV (American Psychiatric Association, 2000), it is also prone to overdiagnosis (Hyler et al., 1990). After correction of all PD thresholds with one criterion in order to increase agreement with the SCID-II (Van Velzen et al., 1999), we found a similar prevalence rate of PDs compared with studies that assessed PDs with the SCID-II (Farabaugh et al., 2007; Sato et al., 1994). Nevertheless, we cannot exclude the possibility that our prevalence rate reflects an overdiagnosis of PDs. Therefore we recommend future studies to use a diagnostic interview to assess PDs, for example the SCID-II. Similarly, the life-events questionnaire that we used to assess childhood adversity is a retrospective self-report measure. Self-report measures of life-events have been found to result in more interpretation biases by patients, and are problematic because they lack contextual information (Alloy et al., 2010). A limitation of the Everyday Problem Checklist that we used to assess the occurrence of daily hassles is that it does not take the frequency of events into account. In other words, each hassle can only be scored once (present or absent), whereas it is possible that stressors occurred multiple times.

FUTURE DIRECTIONS

Future research should focus on further increasing our understanding of pathways to depressive relapse. First of all, the presence of emotional scarring should be examined in a group at risk for first onset depression. Following this cohort would provide information on whether sad mood is in fact a premorbid risk factor or the result of emotional scarring.

Second, studies should focus on the pathway of negative affect, cognition, and daily stress to depressive relapse. It is difficult to disentangle causality in the relations between

daily stress, negative affect, and cognition (for a review see Boden & Berenbaum, 2010). To test the pathway from negative affect to an increased experienced intensity of daily stress in Figure 8.1, one could randomly assign remitted patients to the Trier Social Stress Task (TSST) with or without a mood induction that precedes this task. This way, we might be able to say whether a stressor especially had detrimental effects under negative affect conditions in terms of stress physiology (i.e., HPA axis (de-) activation) or self-reported intensity of stress. Evidence for an increase in stress reaction (i.e., saliva cortisol levels) in healthy controls was already demonstrated after a negative mood induction, an effect that was not found following a positive mood induction (Mendonça-de-Souza et al., 2007). In remitted individuals, this effect might be even more pronounced.

Alternatively, with the benefit of higher ecological validity, an Experience Sampling study could examine whether the experience of negative affect at time *t-1* is predictive of the experienced intensity of a stressor at time *t*. By having patients fill out the *Everyday Problem Checklist* before the start of Experience Sampling, the experimenter gets an overview of the general average intensity of different daily stressors. We could then follow patients with Experience Sampling for a week with multiple measurements within a day. Patients will be asked to indicate their negative affect, report which stressor occurred as well as the impact of this stressor. After selecting the measurements in which daily stressors occurred that had the same average intensity as indicated on the *Everyday Problem Checklist* (for example: selecting both loosing keys and having an argument, which may both have a stress intensity score of 3 out of 5), one can now assess within individuals whether negative affect at *t-1* increases the intensity of daily stress at *t*. As there might be a vicious circle between negative affect and the impact of daily stress, one could also test the other direction of this pathway: whether this intensity at *t* increases levels of negative affect at a subsequent measurement. Finally, in a different design again using Experience Sampling, future studies could also examine several pathways using multilevel modeling, for example whether individual patterns in 1) the influence of stressors on negative affect can be explained by group differences in the average intensity of daily stress; 2) influence of stressors on dysfunctional beliefs can be explained by group differences in the average intensity of daily stress; 3) influence of stressors on dysfunctional beliefs can be explained by group differences in average negative affect; and finally 4) influence of stressors on negative affect can be explained by group differences in dysfunctional beliefs. The results can provide us with more direction in which characteristics we need to tackle in preventive interventions. Our ongoing study will address those aspects.

Third, studies should focus on *how* preventive interventions exert their effects on time to relapse, in order to be able to tailor these interventions. More studies should be devoted on whether these interventions work similarly in patients with comorbid PDs. Potential mechanisms that could be worthwhile examining include increasing levels of positive affect, decreasing levels of negative affect, and buffering the impact of daily stress (Batink et al., 2013; Bockting et al., 2006b).

Finally, future studies that examine the VAMS could assess the implications of developing two unipolar scales of positive and negative affect (How do you feel: sadness 'not at all' to 'extremely' and happiness 'not at all' to 'extremely') whilst also including a scale that assesses arousal. This would allow us to assess whether specifically positive or negative emotions play a role in the course of depression. Moreover, replication of the diagnostic accuracy of the VAMS as a screener for depressive relapse is required, preferably outside the context of a Randomized Controlled Trial. Future studies should focus on the impact of for example comorbid anxiety disorder on the discriminative validity of the VAMS, and the impact of the use of ADM.

In sum, to increase our understanding of the role of emotion (positive and negative), cognition, and stress in the pathway to depressive relapse more longitudinal studies are needed that include different groups of patients (i.e., patients with and without comorbidity, with and without ADM), and that use repeated assessments in daily life.

Note

[1] Due to the distribution of the number of previous MDEs, it would be preferable to report the median instead of the mean. However, this descriptive index is not mentioned in most of the studies mentioned here. We were unable to compare with Jarrett et al. (2012), since no recurrence levels were reported in their paper.