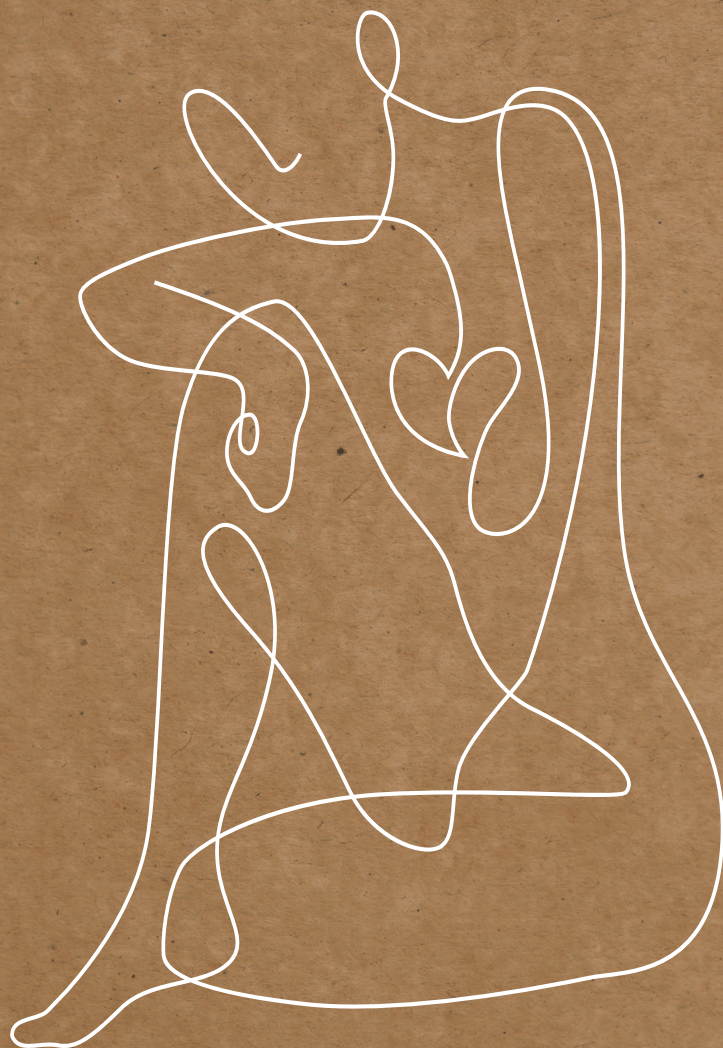


MINDFULNESS-BASED INTERVENTIONS FOR DEPRESSION

*how does it work
and for whom?*



DONDERS
S E R I E S

Marleen Josien ter Avest

Colophon

The research presented in this thesis was carried out within the Radboudumc Center for Mindfulness, Nijmegen, the Netherlands. For reasons of consistency throughout this thesis, some terms have been standardized throughout the text and the same writing style has been applied. As a consequence, the text may differ from the articles that have been published.

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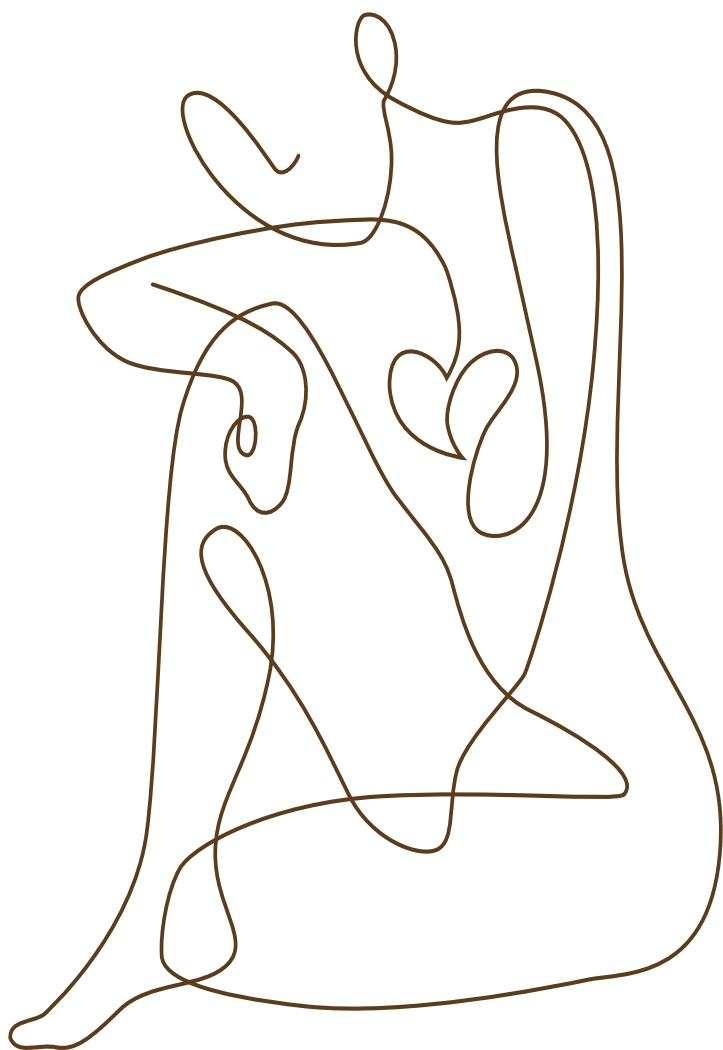
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Het is wat het is
zegt de liefde

Erich Fried

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6

Summary and general discussion

This chapter contains a short background and an overview of the findings from the current thesis, which will then be elaborated upon in relation to the existing literature. In addition, strengths and limitations are identified and directions for future research and clinical implications are given.

1. Summary

Major depressive disorder (MDD) is a common psychiatric disorder in which emotion regulation plays an important role (Joormann & Stanton, 2016; World Health Organization, 2017). Along with the diminished experience of positive emotions, the frequent experience of negative emotions is a key characteristic of depressive symptomatology (American Psychiatric Association, 2013). Currently, MDD is a leading cause of disease burden worldwide (World Health Organization, 2017). The most commonly used treatment to prevent new episodes of depression is the use of antidepressant medication (Spijker et al., 2013). However, the use of antidepressant medication also has disadvantages (i.a. long-term use and side effects) and many patients prefer psychological interventions (Biesheuvel-Leliefeld et al., 2015). Fortunately, numerous psychological interventions have been developed for MDD which appear a good alternative to antidepressants (Biesheuvel-Leliefeld et al., 2015; Breedvelt et al., 2021), including mindfulness-based cognitive therapy (MBCT; Segal et al., 2002, 2012). MBCT is an eight-week group training, which aims to develop a decentered perspective from currently arising thoughts, emotions, physical sensations and automatic behavioral patterns, and teaches individuals to approach these in an open, curious, accepting and non-judgmental way (Baer et al., 2019; Kabat-Zinn, 1994; Segal et al., 2012). Accumulating evidence suggests that MBCT is effective in both reducing risk of relapse/recurrence as well as reducing depressive symptoms in depressed patients (Thimm & Johnson, 2020). However, many people still experience residual depressive symptoms after MBCT, which are a predictor for relapse into depression (Buckman et al., 2018).

In order to further improve outcomes in individuals with recurrent depression, further knowledge is needed on how to best adapt and apply MBCT to maximize its benefits. Research into how MBCT for depression works and for whom MBCT might be particularly beneficial, is developing. In parallel, mindfulness-based compassionate living (MBCL; van den Brink & Koster, 2015) has been developed as a follow-up training to mindfulness-based interventions (MBIs), with the intention to offer (self-)compassion building on already established mindfulness skills. (Self-)compassion encompasses the capacity to be sensitive to the suffering of self and others, and the commitment to alleviate or prevent this suffering (Gilbert & Choden, 2013). Although there is promising evidence

that MBCL reduces depressive symptoms in individuals with recurrent depression (Schuling, Huijbers, van Ravesteijn, Donders et al., 2020), research into its working mechanisms is still in its infancy. The current thesis aimed to shed more light on how MBCT and MBCL work in individuals with recurrent depression.

Previous evidence supports the notion that increases in mindfulness are associated with increases in positive affect and decreases in negative affect. However, knowledge of the dynamic processes and temporal order of these changes in recurrently depressed individuals during MBCT is still limited. To this end, **Chapter 2** expanded previous literature by investigating the course and mutual associations of mindfulness and both positive and negative affect in patients with recurrent depression in (partial) remission participating in MBCT ($n = 235$). Assessments of mindfulness, positive affect, and negative affect took place prior to each MBCT session. Autoregressive latent trajectory (ALT) modeling showed that mindfulness and positive affect increased over the course of MBCT, while levels of negative affect showed a more irregular course. Individuals with larger increases in mindfulness showed significantly larger increases in positive affect. Moreover, individuals with higher general levels of negative affect showed less increase in their levels of mindfulness during MBCT. Against expectations, no robust evidence was found for reciprocal cross-lagged effects between mindfulness and positive or negative affect between each successive session.

An improvement in mindfulness skills is hypothesized to be related to mindfulness practice, which is considered a key element in increasing treatment effectiveness of MBCT for depression (Segal et al., 2012). Although there is evidence to support this hypothesis (Parsons et al., 2017), more fine-grained studies are needed into both short- and long-term effects of formal mindfulness practice in MBCT for clinical populations. **Chapter 3** therefore presented the results of investigating prospective associations between the extent of formal mindfulness practice and depression severity, and vice versa, during 15 months of follow-up in individuals with recurrent depression in (partial) remission ($n = 200$). Formal home practice frequency was calculated for each 3-month period. Depressive symptoms were assessed at 3-month intervals: 0 (baseline), 3 (post-treatment), 6, 9, 12, and 15 months. Participants appeared to practice formal mindfulness exercises with a mean of 4 days per week during MBCT, but the frequency of practice declined rapidly thereafter. The level of depressive symptoms did not change over the full study period. Against expectations, no clear evidence was found that the amount of formal mindfulness practice during each 3-month period influences subsequent depressive symptom severity. In contrast, severity of depression did seem to be associated with practicing less frequently during the subsequent 3-month period, suggesting that depressive symptoms might indeed act as a barrier for practice.

Looking at participant characteristics to see who benefits most from MBCT is another way to potentially maximize treatment effect. As described in the general introduction, evidence suggests stronger treatment effects of MBCT for depression in those with increased vulnerability, particularly those with more pronounced residual symptoms at baseline (Kuyken et al., 2016). However, studies to date have methodological limitations, including a limited range of baseline depression levels, a focus on 'negative' outcomes, a restriction to two-way interactions, and no distinction between quantitative and qualitative treatment-subgroup interactions. For optimal treatment assignment in clinical practice, however, knowledge about for which subgroup treatment A outperforms treatment B, and for whom the reverse holds true, qualitative treatment-subgroup interactions are needed. Hence, **Chapter 4** aimed to bring the field further by applying the qualitative interaction trees method (QUINT; Dusseldorp & van Mechelen, 2014), which identifies qualitative treatment-subgroup interactions, allowing for non-linear relationships and considering higher order interaction effects. This method was applied on individual patient data based on three RCTs investigating the effect of MBCT + TAU versus TAU alone ($n = 292$). Individuals were either in (partial) remission, currently depressed or had chronic, treatment-resistant depression. Outcomes were depressive symptoms and quality of life. Results showed that MBCT + TAU outperformed TAU alone in reducing depressive symptoms. For both conditions, the effect of baseline depressive symptoms on post-treatment depressive symptoms was curvilinear. This indicates that in both, MBCT + TAU and TAU alone, individuals who fall into the 'high' and 'low ends' of depression severity were less likely to benefit from either treatment. For individuals with an earlier onset of depression and higher levels of rumination, MBCT + TAU was more beneficial than TAU alone in terms of depressive symptom reduction. For patients with a lower quality of life, MBCT + TAU was more beneficial than TAU alone in terms of improving quality of life.

In parallel to investigating the interplay between mindfulness and affect during MBCT for depression, the possible interplay between self-compassion and affect was investigated during MBCL as follow-up intervention after MBCT. Again, multiple assessments over time were analyzed with the ALT modeling technique. **Chapter 5** expanded previous literature by investigating the interplay between self-compassion and positive and negative affect during MBCL as a follow-up intervention to MBCT in individuals in remission or currently depressed ($n = 104$). Results from the ALT modeling analyses showed that self-compassion increased, while positive affect remained stable and negative affect decreased over time. In addition, no reciprocal effects were found between self-compassion and subsequent positive affect, nor vice versa, between each successive session. Although there were no effects from negative affect at one session to self-

compassion at the next session, we did find evidence for the reverse: higher levels of self-compassion at one session did predict lower levels of negative affect at the next session.

2. General discussion

2.1. “How does MBCT for depression work?”

Theory suggests that mindfulness should increase following MBCT (Segal et al., 2012). This was indeed confirmed in the results from Chapter 2 of this thesis, as for individuals with recurrent depression, levels of mindfulness increased during MBCT. This finding is also consistent with the literature to date (van der Velden et al., 2015). In addition to the increase of mindfulness, the current thesis found increases in levels of positive affect during MBCT for depression. Moreover, greater increases in levels of mindfulness were associated with greater increases in positive affect during MBCT for depression. This is in line with the mindfulness-to-meaning theory (MMT; Garland et al., 2015), which states that mindfulness is a central mechanism for energizing upward spirals of positive psychological processes (e.g., resilience). As Segal et al. (2012) suggested that practicing (self-)compassion without a foundation in mindfulness may trigger vulnerability in clinically depressed individuals, this may be a supportive starting point for exposing oneself to more difficult emotions during MBCT for depression.

Unexpectedly, negative affect did not significantly decrease over the MBCT course (Chapter 2). This is contrary to findings of previous studies, for example Batink et al. (2013), who found that negative affect significantly mediated the efficacy of MBCT for depression. An explanation could be the absence of a clear main effect of MBCT on depression severity found in the clinical trials from which the current data were derived (Huijbers et al., 2015, 2016), which may have been due to the overall lower teacher competency in these studies compared to previous studies (Kuyken et al., 2008; Kuyken et al., 2015; Segal et al., 2010), and the inclusion of individuals in remission at baseline, leaving less room for improvement in terms of depression severity. Another explanation could be that participants became more able to observe negative affect rather than engaging in elaboration or rumination, which can, but does not necessarily, lead to a reduction of negative affect. According to the MMT (Garland et al., 2015), mindfulness helps to decenter from dysphoric schemas which result in attentional biases towards negative life events, and broadens the attentional field to encompass an expanded set of positive and negative life events (i.e., a more balanced view of what is occurring). This touches upon a paradox within mindfulness research. Negative mental health outcomes, such as reduction of depressive symptoms are commonly used, although these may not be the most

suitable outcome for mindfulness research. When developing mindfulness, one learns to approach experiences in a non-judgmental, kind and accepting way rather than striving to change the experiences themselves. Therefore, outcome measures encompassing attitude, resilience, and more positive health outcomes such as well-being or life-satisfaction might be more suitable.

The current thesis revealed that negative affect might act as a barrier to develop mindfulness during MBCT for depression (Chapter 2). While most studies have investigated the association between mindfulness and subsequent levels of negative affect, reverse associations between negative affect and subsequent levels of mindfulness have been studied less and show mixed results (e.g., Gotink et al., 2016; Snippe et al., 2015). An advantage of the analyses used in the current thesis is that the interrelationship between mindfulness and affect was modeled in both directions within a single model (i.e., between mindfulness and negative affect, as well as reversed associations), while controlling for overall trajectories of both variables over time, decreasing the chance to find spurious effects (Voelkle, 2008). However, the possible inhibiting role of negative affect on developing mindfulness needs to be further examined and replicated before clinical implications can be formulated. Preferably with the use of multiple assessments of both constructs over time, also after the intervention period, and the use of advanced statistical techniques (e.g., ALT modeling).

In sum, positive affect plays a prominent role in MBCT for depression in which negative affect might act as a barrier to develop mindfulness. However, results are preliminary and should be replicated first before recommendations for clinical practice can be formulated.

Against expectations, the current thesis found no support for the effect of formal mindfulness practice frequency on depressive symptoms (Chapter 3). This is in contrast to a systematic review and meta-analysis by Parsons et al. (2017), who found a small but significant association between the extent of formal mindfulness home practice and improvements after MBCT and MBSR for a wide range of clinical and non-clinical populations. When taking a closer look at studies that investigated the association between formal mindfulness practice and both short- and long-term outcomes of MBCT in depression, most studies yielded positive effects (i.e., Crane et al., 2014; Hawley et al., 2014, van Aalderen et al., 2012, Geschwind et al., 2012), but some also reported non-significant findings (i.e., Bondolfi et al., 2010; Shallcross et al., 2015).

An explanation for the differences in results found may include differences in the amount of formal mindfulness practice reported, and the rapid decline of engagement in formal mindfulness practice over time. Non-compliance of home practice during and after psychological interventions remains a common problem in clinical practice (Bondolfi et al., 2010; Gaynor et al., 2006). Segal et al. (2019), suggested that improved outcome in individuals with recurrent

depression requires sustained skills utilization beyond the end of MBCT. However, we cannot preclude generalization of adaptive coping skills over time. It might be that individuals tend to engage less in formal but more in informal mindfulness practice over time (e.g., Bondolfi et al., 2010). In addition, non-monotonicity of effects (i.e., an inverted U-curve) of mindfulness practice could provide an overarching explanatory framework for the mix of positive and null findings in mindfulness research (Britton, 2019). For example, it has been suggested that MBCT is less effective for those at the lowest or highest end of the spectrum of depression levels (Kuyken et al., 2016; van Dam et al., 2018). For future research it would be a step forward to examine the effects of adherence prospectively and randomized controlled rather than through secondary analyses (Dimidjian & Segal, 2015). For example, direct comparisons of effectiveness between groups containing different amounts of mindfulness practice, including no mindfulness practice at all, could be considered. Similar research in cognitive behavioral therapy (CBT; Beck et al., 1979), showed that study conditions including homework as a main component produce superior treatment effects to those that do not (Kazantzis et al., 2010). Moreover, next to quantity of practice, quality of practice may also impact outcome (Kazantzis et al., 2016). As discussed before, mindfulness does not only involve self-regulation of attention to the present moment experience (i.e., the ‘what’) but it also involves an open, curious, accepting and non-judgmental attitude towards one’s experience (i.e., the ‘how’; Baer et al., 2019). Recent developments focusing on practice quality show an additive (or even stronger) effect of practice quality on trait mindfulness (Hassed et al., 2020) and outcome (Del Re et al., 2013; Goldberg et al., 2014, 2020) compared to practice quantity. Thus, it is recommended to include both amount of time spent engaged in practice (i.e., quantity) and the acquired skills in meaningful attentional focus and non-judgmental acceptance (i.e., quality) in future research studying the impact of mindfulness practice on outcome.

The current thesis did not find effects of formal mindfulness practice on outcome, but reverse effects were found: higher levels of depressive symptoms at each measurement point (0, 3, 6, 9, 12, and 15 months of follow-up) were followed by less frequent formal mindfulness practice during the subsequent 3-month periods in individuals with recurrent depression following MBCT (Chapter 3). This is a remarkable finding, given that previously found negative associations were based on correlational designs (Parsons et al., 2017) and usually interpreted as improved outcomes due to more mindfulness practice. To date, a reverse effect has not yet been investigated in MBCT for depression, and this might shed a new light on the association between formal home practice and depressive symptoms in MBCT for recurrent depression. The current finding that depressive symptomatology may hinder engaging in mindfulness practices is in line with the previous finding from Chapter 2 that negative affect

might act as a barrier to develop mindfulness during MBCT for depression and with findings by Banerjee et al. (2018) that rumination and worry may increase risk of disengagement which may in turn hinder cultivating mindfulness. Qualitative research into barriers and facilitators associated with engagement in mindfulness practices could provide more insight in the underlying processes. To date, qualitative studies have reported that a lack of group support, physical discomfort, feeling exhausted or disoriented, self-doubt and long practices may hinder engaging in meditation practice, while prior knowledge on mindfulness, positive beliefs, motivation, perceptions of consequences (e.g., improved well-being, change in self-compassion, and increased sense of agency of thoughts) and long-term connection (e.g., refresher sessions, post-course retreats) may facilitate meditation practice (Banerjee et al., 2017; Dobkin et al., 2012; Langdon et al., 2011; Lomas et al., 2015). According to a grounded-theory study on mindfulness practice after MBCT by Langdon et al. (2011), individuals felt they needed to bypass cognitions and feelings that could act as obstacles to practice by “just doing it”. This fits the the well-known advice about practicing “You don’t have to like it, you just have to do it” (Kabat-Zinn, 1990).

To conclude, the interplay between mindfulness practice and outcome might not be as straightforward as assumed. This underlines the importance of replication studies and publishing of negative study results. In addition, preliminary results suggest that depressive symptoms might act as a barrier to carrying out mindfulness practices, which is in accordance with the preliminary evidence found in the current thesis that negative affect might acts as a barrier to develop mindfulness in MBCT for depression.

2.2. “For whom does MBCT for depression work?”

In MBCT, one learns to recognize automatic activation of their habitual dysfunctional cognitive processes that lead to depression (e.g., rumination), and decenter and disengage from these dysfunctional processes. The current thesis suggests that MBCT + TAU is more beneficial than TAU alone for those individuals with an earlier age of onset of MDD and higher baseline levels of rumination, and for those with a lower baseline quality of life (Chapter 4). This is in line with the underlying theoretical model, called the ‘differential activation hypothesis’ (Teasdale, 1988), which assumes that vulnerability to depression increases with each depressive episode, because previous patterns of negative thinking become more easily accessible when feeling low. In addition, current findings are in line with previous studies suggesting that effects of MBCT for depression may be moderated by vulnerability factors such as individuals with three or more previous major depressive episodes, earlier onset of MDD (Ma & Teasdale, 2004; Teasdale et al., 2000), a history of early adversity (Kuyken et al., 2015; Williams et al., 2014) and more fluctuation in depressive symptoms (Segal et al., 2010). Although the current research included patients with a wide range

of baseline depressive symptoms, it should be noted that very severely depressed patients (≥ 37 points on the HRSD-17; Hamilton, 1960), were not included. For this specific patient group, no statements can be made about whether MBCT for depression can be of added value or has a possible countereffect (e.g., less effective or causing harm).

The current thesis did not find support for the hypothesis that baseline depressive symptoms would moderate the intervention effect (Chapter 4). This is seemingly in contrast with the results of the individual patient data (IPD) meta-analysis by Kuyken et al. (2016), which found that severity of baseline depressive symptoms predicted a better response to MBCT in terms of prevention of relapse. It also seems to contrast with the preliminary evidence found in the current thesis that depressive symptoms possibly impede engagement in mindfulness practice (Chapter 3) and that negative affect might act as a barrier to develop mindfulness in recurrently depressed individuals (Chapter 2). However, the IPD meta-analysis was restricted to individuals with recurrent depression in (partial) remission, limiting the range of baseline depression severity, which might be in line with the upward slope of the inverted U-curve (Britton, 2019; ter Avest et al., 2019). In addition, differences in statistical approaches may account for the differences in results found. Most studies into possible moderators of treatment effect assumed linear associations and considered two-way interaction effects (e.g., Kuyken et al., 2016), whereby no distinction could be made between quantitative and qualitative treatment-subgroup interactions. The current thesis used the QUINT method, which focuses on identifying qualitative treatment-subgroup interactions, allows for non-linear relationships and considers higher order interactions effects. Other moderator variables found (e.g., rumination levels, age of onset, quality of life) had a stronger impact on intervention outcome than baseline depressive symptoms, which did not emerge as a clear moderator.

In conclusion, the current thesis found the strongest support for vulnerability factors age of MDD onset and rumination to moderate treatment effect of MBCT for depression, in which individuals with an earlier age of onset and higher levels of rumination were more likely to benefit from MBCT.

2.3. “How does MBCL for depression work?”

Theory suggests that self-compassion should increase following MBCL (van den Brink & Koster, 2015; Segal et al., 2012). This was indeed confirmed in a trial of MBCL for individuals with recurrent depression (Schuling, Huijbers, van Ravesteijn, Donders, et al., 2020) and secondary analyses of these data showing week-to-week improvements in self-compassion as reported in this thesis. These findings are also consistent with the literature to date (Ferrari et al., 2019).

As expected, negative affect decreased during MBCL for depression, which was preceded by increases in self-compassion (Chapter 5). This is in line with

previous (experimental) studies (e.g., Diedrich et al., 2014). In MBCT, one develops a non-judgmental stance towards the self and others and becomes more aware of both positive and negative emotions, thoughts, and bodily sensations, and their accompanied automatic reactions. However, according to a recent qualitative study into the added value of MBCL in recurrently depressed individuals (Schuling, Huijbers, van Ravesteijn, Kuyken, & Speckens, 2020), participants stated that, during MBCT, they had been able to remain in a more 'neutral' observing stance towards difficult emotions, thoughts and bodily sensations. As MBCT lacked the active invitation to approach these difficulties, it was possible to continue not engaging with strongly-rooted avoidance patterns. It may be that individuals with recurrent depression need more explicit instructions and practice to develop a compassionate attitude to both self and others, especially during negative experiences, as they are often highly self-critical and suffer from feelings of shame, guilt and inferiority (Gilbert et al., 2012; Gilbert et al., 2008; Gilbert & Procter, 2006). MBCL explicitly focuses on developing (self-)compassion by deliberately exposing oneself to unpleasant feelings, thoughts and bodily sensations, while learning new ways to alleviate and soothe oneself in the midst of this in a non-judgmental and friendly way (van den Brink & Koster, 2015).

Clear differences were found between MBCT and MBCL in the trajectories of positive and negative affect (Chapter 2 and 5), which suggests that different affective processes are taking place in MBCT as compared to MBCL for depression. It might be that positive affect plays a more prominent role in MBCT for depression, which seem to tie in nicely with existing therapies for MDD, such as antidepressants and cognitive therapy, since these therapies are suggested to repair negative affect more effectively than positive affect (Dunn et al., 2020). As previous studies show that repair of positive affect is perceived at least as important as reduction in negative affect in individuals recovering from depression (Demyttenaere et al., 2015; Zimmerman et al., 2006), and existing mainstream treatments fail to normalize levels of positive affect (Dunn et al., 2020), this indicates that there is still room for improvement. Besides MBCT, various drugs (e.g., Jamerson et al., 2003; Lally et al., 2015; Tomarken et al., 2004) and modified psychotherapies targeting positive affect and wellbeing are emerging (e.g., Geschwind et al., 2019; Craske et al., 2019; Ruini & Fava, 2012; Dunn et al., 2019; Chaves et al., 2017). It may be that further normalizing levels of positive affect leads to a more equanimous state of mind.

Whereas positive affect plays a more prominent role in MBCT, cultivating (self-)compassion during MBCL may more explicitly target negative affect. However, results are preliminary and should be replicated first before recommendations for clinical practice can be formulated. In addition, as MBCL was not directly compared to another active control condition as follow-up to MBCT, this leaves little information about the specificity of MBCL. Lastly, as the

sequential treatment design was pragmatic in nature (i.e., participation was offered to all former MBCT participants who met the in- and exclusion criteria), little is known about the characteristics of those who responded versus those who did not. Consequently, possible selection bias cannot be ruled out (e.g., selection of participants for whom MBCT might have been less effective).

2.4. Strengths, limitations and future directions

2.4.1. Statistical approaches

A major strength of the current thesis is the use of advanced statistical methodology. With the inclusion of multiple measurements over time and the use of the ALT modeling technique, a clear distinction could be made between the overall course of each variable over time and the reciprocal effects between the variables on a session-to-session basis. This made it possible to study processes between mindfulness, self-compassion and positive and negative affect over time in much more detail compared to pre-post study designs. As a result, this design increased the opportunity to infer possible causation (Voelkle, 2008).

In addition to the ALT modeling technique, the QUINT method was applied. This method identifies subgroups of individuals in which one treatment is more beneficial than another, which makes it especially suited for situations in which many potential moderating variables might be interacting with the treatment variable without clear *a priori* hypotheses. The result of an analysis with QUINT is a binary tree from which (new) hypotheses on treatment assignment criteria can be derived, relevant for clinical practice. The current thesis found support that MBCT in addition to TAU is more beneficial than TAU alone for those with higher rumination levels and an earlier age of MDD onset, and for those with a lower quality of life. However, before definite treatment assignment criteria can be formulated and implemented in clinical practice, the current findings should be replicated, treatment outcome of the cut-off scores should be estimated in an independent test dataset and, preferably, also long-term outcomes should be included in future research. Currently, the field of personalized psychological treatment is expanding rapidly and new approaches, such as network estimation techniques (Boschloo et al., 2019), machine learning (Lutz et al., 2019), and the use of large observational data from routine practice (Kessler et al., 2019) are promising developments, which is setting in a shift from a nomothetic to a more idiographic approach (Hofmann & Hayes, 2019). While new statistical approaches may add to the knowledge for whom existing therapies could be most beneficial, they could also lead to further knowledge about the underlying mechanisms of change, which may lead to combining elements from different interventions in order to target the underlying process more effectively (Hofmann & Hayes, 2019; Rosen and Davison, 2003).

2.4.2. Design and population

The findings of this thesis advance previous and mostly cross-sectional correlation research, by using prospective study designs including multiple measurements over both short- and long-term periods. In addition, most studies were based on multicenter RCTs which were embedded in standard clinical practice with few exclusion criteria. This real-life setting increases the generalizability of the current findings to (recurrently) depressed individuals in both secondary and tertiary care. There were also some limitations.

First of all, when investigating processes of change, the current studies did not include process data of the control groups. Therefore, it cannot be ruled out that the associations found in the current studies are not specific to MBCT and MBCL. Future research should collect process data from both an intervention and a -preferably active- control condition to determine specificity of change. In addition, it is encouraged to use state-of-the art experience sampling methods (ESM; Larson & Csikszentmihalyi, 1983) that use a high sampling frequency and app-based measurements to investigate the processes of change during MBCT and MBCL on a smaller time scale and with enhanced accuracy. Moreover, it would be valuable to include outcome measures (e.g., depressive symptoms, quality of life) to further determine changes in process measures (e.g., mindfulness, self-compassion, affect) as possible mechanisms of change in MBCT and/or MBCL for depression (Kazdin, 2007).

Secondly, the current thesis only investigated the influence of mindfulness practice in terms of its quantity, lacking data on its quality. To shed further light on the relationship between mindfulness practice and outcome, future research should routinely assess quality as addition to quantity. Ideally, this would be consistently operationalized and in the same way across studies to facilitate comparison. For example, practice quality could be assessed with the 7-item Practice Quality-Mindfulness (PQM; Del Re et al., 2013) or with the single-item PQM (Goldberg et al., 2020) to reduce participant burden and increase response rates. More recently, the Mindfulness Adherence Questionnaire (MAQ; Hased et al., 2020) has been developed, which makes a clear distinction between formal and informal mindfulness practice in addition to practice quality and quantity.

Thirdly, research into the working mechanisms of MBCT and MBCL in acute and chronically, treatment-resistant depressed individuals should further be explored. Lastly, MBCL was provided as a follow-up to MBCT in the current thesis. It is suggested that individuals who suffer from relatively severe depressive symptoms might especially benefit from a sequential approach (Cuijpers et al., 2020). However, future studies must be performed to confirm this. For example, by directly comparing the effectiveness and possible working mechanisms of MBCT and MBCL in depression. To further make a distinction if the sequence of interventions matter, both interventions could be presented in a counter-balanced order. Though Segal et al. (2012) suggested that practicing

self-compassion without a foundation in mindfulness may trigger vulnerability in depressed individuals, offering MBCL at an earlier stage or as a stand-alone treatment might significantly reduce the treatment trajectory for individuals with high levels of self-criticism or avoidance tendencies (Schuling, Huijbers, van Ravesteijn, Donders, et al., 2020). In addition, this may lead to further reductions in healthcare costs, as Schuling, Huijbers, van Ravesteijn, Donders, et al. (2020) found that MBCL participants made less use of health care services than those in the control group, except for attending the general practitioner.

2.4.3. Measures

The current thesis used self-report questionnaires which are at risk for recall and response bias. Although moderate support has been found for the differential sensitivity to change of mindfulness questionnaires in mindfulness-based programs (Goldberg et al., 2018), establishing a consensus about a more precise definition of mindfulness has been difficult (Baer et al., 2019) and the validity of mindfulness questionnaires are still disputed (Bergomi et al., 2013; Grossman & van Dam, 2011; van Dam et al., 2018). For example, some researchers suggest that the meaning of items comprising self-report mindfulness questionnaires tend to be interpreted differently based on one's level of mindfulness (Grossman & van Dam, 2011; van Dam et al., 2009). In addition, the Self-Compassion Scale (SCS) is under debate. Some state that the negative domain of the SCS, containing the subscales *self-judgment*, *isolation*, and *over-identification*, "contaminates" the total self-compassion score, given that this negative domain has been found to correlate moderately to strongly to psychopathological constructs such as negative affect, depressive symptoms and rumination (e.g., López et al., 2015; Muris et al., 2018). However, others support the notion that both the negative and positive domains represent the relative balance of compassionate and un-compassionate responses to suffering, and that both are important contributors to the overall concept of self-compassion (e.g., Krieger et al., 2016; Neff, 2016). For future research, it is recommended to concomitantly collect self-report measures as well as more objective behavioral measures (Hadash & Bernstein, 2019) and physical, biological and neuroscientific data (van Dam et al., 2018) in order to further establish their validity. Lastly, with regard to affect measures, it seems important to include more subtle emotions too in future research (e.g., calm, relaxed), considering that particularly these emotions are assumed to increase during meditation (Jones et al., 2018).

Given that the roots of MBIs can be found in Buddhist psychology, it may be interesting to further build upon these ancient pieces of wisdom. For example, modern interventions might benefit from integrating practices that, next to compassion and kindness, more explicitly cultivate sympathetic joy and equanimity, which may have additive value in individuals with recurrent depression. Furthermore, in the context of studying adherence to practice, it

could be interesting to consider the five hindrances that can be found in Buddhist teachings, which are mental factors that hinder progress in meditation practice. Outcome measures such as sensory desire, aversion, restlessness and worry, fatigue or lack of energy, and doubt or a lack of trust can be targets of future investigation to understand better why people adhere to the practice or not. For example, it could be that the tendency to seek for pleasurable experiences might make it more challenging to allow difficult or uncomfortable feelings or sensations when they arise during practice.

2.5. Clinical implications

There are several clinical implications that could be derived from the current thesis. First, a clear role for positive affect in MBCT for depression was found, which suggests that a further refinement of MBCT for depression might be possible by placing more emphasis on exercises that cultivate positive affect, or even adjusting the program by expanding the section on pleasurable experiences. For example, by adding exercises from positive psychology. Secondly, current findings emphasize that depressive symptomatology may have a potentially hindering effect on engaging in mindfulness practice and developing mindfulness. It might be of added value to discuss this issue in clinical practice at an early stage, and regularly address it to provide proper guidance. Perhaps, for those who experience high levels of depressive symptomatology, more intense monitoring may be of benefit (e.g., with the use of apps). Thirdly, although replication is still warranted, individuals with high levels of rumination and early onset of MDD might especially benefit from MBCT as addition to TAU (e.g., antidepressants). Lastly, MBCL may particularly target negative affect via (further) increases in self-compassion. Residual depressive symptoms (e.g., negative affect) are an important predictor of depressive relapse and recurrence, therefore this finding supports the potential clinical relevance of MBCL, and its possible influence on relapse rates. Future research hopefully will reveal whom might especially benefit from MBCL, and whether MBCL is preferably offered as an additional treatment to MBCT for depression (or vice versa), or that MBCL can be offered as a stand-alone intervention. Moreover, it would be interesting to investigate whether integrating self-compassion in a more explicit way in MBCT may improve its effectiveness.

2.6. Conclusion

This thesis included studies investigating the dynamic interplay between mindfulness and affect in MBCT and between self-compassion and affect in MBCL for depression, the effect of formal mindfulness practice in MBCT for depression and the differential treatment effect of MBCT in individuals with depression. Preliminary evidence suggests that increases in positive affect play a more prominent role in MBCT for depression, while this is the case for

decreases in negative affect in MBCL for depression. In addition, the effect of formal mindfulness practice might not be as straightforward as expected, and reverse effects might also play a role. Lastly, MBCT in addition to TAU may be more beneficial for those who ruminate more and had their first depressive episode at an earlier age. These findings may lead to further refinement of MBCT for depression and targeting of MBCT in this population.

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Wat het is

Het is onzin
zegt het verstand

Het is wat het is
zegt de liefde

Het is ongeluk
zegt de berekening
Het is alleen maar verdriet
zegt de angst
Het is uitzichtloos
zegt het inzicht

Het is wat het is
zegt de liefde

Het is belachelijk
zegt de trots
Het is lichtzinnigheid
zegt de voorzichtigheid
Het is onmogelijk
zegt de ervaring

Het is wat het is
zegt de liefde

Erich Fried - 1983

Vertaling: Remco Campert

