

Accepted Manuscript

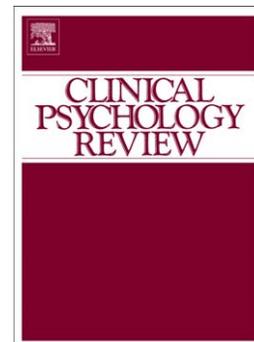
A Systematic Review of Mechanisms of Change in Mindfulness-Based Cognitive Therapy in the Treatment of Recurrent Major Depressive Disorder

Anne Maj van der Velden, Willem Kuyken, Ulla Wattar, Catherine Crane, Karen Johanne Pallesen, Jesper Dahlgaard, Lone Overby Fjorback, Jacob Piet

PII: S0272-7358(15)00020-3
DOI: doi: [10.1016/j.cpr.2015.02.001](https://doi.org/10.1016/j.cpr.2015.02.001)
Reference: CPR 1419

To appear in: *Clinical Psychology Review*

Received date: 11 September 2014
Revised date: 22 December 2014
Accepted date: 3 February 2015



Please cite this article as: van der Velden, A.M., Kuyken, W., Wattar, U., Crane, C., Pallesen, K.J., Dahlgaard, J., Fjorback, L.O. & Piet, J., A Systematic Review of Mechanisms of Change in Mindfulness-Based Cognitive Therapy in the Treatment of Recurrent Major Depressive Disorder, *Clinical Psychology Review* (2015), doi: [10.1016/j.cpr.2015.02.001](https://doi.org/10.1016/j.cpr.2015.02.001)

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Running head: MECHANISMS OF CHANGE IN MBCT

**A Systematic Review of Mechanisms of Change in Mindfulness-Based Cognitive
Therapy in the Treatment of Recurrent Major Depressive Disorder**

Anne Maj van der Velden^{1,2}, Willem Kuyken^{3,4}, Ulla Wattar⁵
Catherine Crane⁴, Karen Johanne Pallesen¹, Jesper Dahlgaard⁶,
Lone Overby Fjorback¹ & Jacob Piet¹

¹Research Clinic for Functional Disorders & Psychosomatics,
Aarhus University Hospital, Aarhus, Denmark

²Department of Psychology, Copenhagen University,
Copenhagen, Denmark.

³Mood Disorders Centre, University of Exeter, Exeter, UK

⁴Department of Psychiatry, University of Oxford, Oxford, UK

⁵Wattar Gruppen, Kognitiv Center, Copenhagen, Denmark

⁶Department of Psychology and Behavioral Sciences,
Aarhus University, Aarhus, Denmark.

Abstract:

Background: The investigation of treatment mechanisms in randomized controlled trials has considerable clinical and theoretical relevance. Despite the empirical support for the effect of Mindfulness-Based Cognitive Therapy (MBCT) in the treatment of recurrent Major Depressive Disorder (MDD), the specific mechanisms by which MBCT leads to therapeutic change remains unclear. **Objective:** By means of a systematic review to evaluate how the field is progressing in its empirical investigation of mechanisms of change in MBCT for recurrent MDD. **Method:** To identify relevant studies, a systematic search was conducted. Studies were coded and ranked for quality. **Results:** The search produced 476 articles, of which 23 were included. In line with the theoretical premise, 12 studies found that alterations in mindfulness, rumination, worry, compassion, or meta-awareness were associated with, predicted or mediated MBCT's effect on treatment outcome. In addition, preliminary studies indicated that alterations in attention, memory specificity, self-discrepancy, activity-pleasantness appraisal, emotional reactivity and momentary positive and negative affect might play a role in how MBCT exerts its clinical effects. **Conclusion:** The results suggest that MBCT could work through some of the MBCT model's theoretically predicted mechanisms. However, there is a need for more rigorous designs that can assess greater levels of causal specificity.

Keywords: Mindfulness, MBCT, Depression, Mediation, Treatment Mechanisms, Review

'Enormous progress has been made in psychotherapy research. This has culminated in recognition of several treatments that have strong evidence in their behalf. Despite this progress, research advances are sorely needed in studying the mediators and mechanisms of therapeutic change. It is remarkable that after decades of psychotherapy research, we can not provide an evidence-based explanation for how or why even our most well studied interventions produce change' (Kazdin, 2007, p. 23)

Introduction

Mindfulness-Based Cognitive Therapy (MBCT) is an evidence-based psychotherapeutic intervention that integrates selected elements of cognitive-behavioral therapy for depression with the clinical application of mindfulness meditation (Segal, Williams & Teasdale, 2013). MBCT is currently recommended in several national clinical guidelines as a prophylactic treatment for recurrent Major Depressive Disorder (e.g. National Institute for Clinical Excellence, 2009), and is considered a cost-effective intervention. MBCT takes the form of 8 weekly group sessions, an all-day silent retreat, and individual daily homework in between sessions. Since the first edition of the MBCT manual was published in 2002, there has been a mounting interest in MBCT and its clinical potential in the prophylactic treatment of depressive disorders (Williams & Kuyken, 2012).

Major Depressive Disorder (MDD) is one of the most prevalent and debilitating affective disorders. MDD severely affects psychological, social and biological functioning, and it is associated with a high degree of subjective distress. The lifetime prevalence rate of MDD is estimated around 16 % (Kessler et al., 2009), and according to the World Health Organization MDD is currently the leading cause of disability worldwide (WHO, 2012). Much of the burden of MDD is a consequence of MDD often taking a recurrent course. After one episode of MDD recurrence risk is about 50%, yet the risk of recurrence increases with

every episode, and after 3 episodes the risk of recurrence may be as high as 90% (Kessing, Hansen, Andersen & Angst, 2004). Thus, optimizing treatments for recurrent MDD is an important priority within the field of mental health.

MBCT is based on a model of cognitive vulnerability to depressive relapse and recurrence (Segal et al, 2013). The model states that patients who have experienced several episodes of major depression have a heightened cognitive vulnerability to depressive relapse and recurrence. This heightened cognitive vulnerability is proposed to be a consequence of increased connectivity between depressed mood and depressogenic cognition having developed during successive episodes of major depression (Kuyken, Crane & Dalgeish, 2012; Segal, Williams & Teasdale, 2013). MBCT was developed to target this cognitive vulnerability, and thereby reduce the likelihood of the configuration of a depressive episode becoming re-established.

Mindfulness has generally been defined as: *‘the awareness that emerges through paying attention on purpose, in the present moment, and non-judgmentally to things as they are’* (Williams, Teasdale, Segal & Kabat-Zinn, 2007, p. 47). MBCT offers participants a systematic training in mindfulness meditation drawing extensively on the mindfulness-based stress reduction (MBSR) program (Kabat-Zinn, 2013). Through the practice of mindfulness exercises, such as the body scan, simple yoga exercises, and prolonged periods of sitting meditation, patients are taught to become aware of, turn towards and relate non-judgmentally to the change and flux of thoughts, emotions and bodily sensations, including intense bodily sensations and emotional discomfort. In addition, MBCT contains elements from Cognitive Behavioral Therapy (CBT) such as psychoeducation about the role of cognition in depression, and exercises to illustrate the interrelatedness of thoughts, emotions, behavior and physiology in inducing and maintaining depressive symptoms. The combination of practices to cultivate mindfulness skills and CBT elements are thought to increasingly enable participants to

recognize the automatic activation of habitual dysfunctional cognitive processes, e.g. depressogenic rumination, and decenter and disengage from these dysfunctional processes.

Two recent high-quality meta-analyses have evaluated the effectiveness of MBCT. Hofmann, Sawyer, Witt and Oh (2010) investigated the effect of MBSR and MBCT on symptoms of anxiety and depression across different clinical groups. In nine studies of MBCT they found a large pooled within-group effect size (Hedges' $g = 0.85$) for reduction of depressive symptoms. Piet & Hougaard (2011) conducted a meta-analysis specifically aimed to evaluate the effect of MBCT for prevention of relapse in patients with recurrent MDD in remission. Based on six large RCTs with a total of 593 participants, they found that MBCT reduced the risk of relapse by 34% compared to treatment-as-usual (TAU) or placebo controls. Furthermore, subgroup analyses revealed a relative risk reduction of 43% for patients with three or more previous episodes, while no risk reduction was found for participants with only two episodes. Finally, results from their meta-analysis indicate that MBCT may be as effective as prophylactic treatment with maintenance antidepressant medication (m-ADM) for patients with recurrent MDD in remission. In addition, a few studies have indicated that MBCT may also reduce residual depressive symptoms and possibly the risk of relapse for patients highly vulnerable to dysphoria-induced depressogenic thinking who have had 2 or less previous episodes of depression, although further research is warranted (Piet & Hougaard, 2011; Geschwind, Peeters, Drukker, Van Os & Wichers, 2012).

Despite an empirically founded theoretical rationale for MBCT and a rapidly increasing body of controlled clinical trials documenting the prophylactic efficacy of MBCT, little is known about precisely how and why MBCT works (Piet & Hougaard, 2011; Fjorback, Arendt, Ornbøl, Fink & Walach, 2011). Understanding how and why MBCT can prevent relapse risk is essential for a number of reasons. If we begin to uncover and understand the mechanisms by which MBCT can prevent relapse, we may be able to optimize treatment

outcomes, and facilitate a better selection of patients that will benefit from the treatment (Holmes, Graskie & Graybil, 2014; Segal et al., 2013). As research initiatives on treatment mechanisms in MBCT has increased exponentially, there is a need for a review that can identify, synthesize and evaluate the studies that have investigated possible treatment mechanisms in MBCT treatment of recurrent MDD. Hence, the aim of this article is to conduct the first systematic review of clinical trials specifically investigating treatment mechanisms in MBCT treatment of recurrent MDD.

Theoretical predictions

As background information for the review an overview of the proposed theoretical mechanisms presented in the MBCT manual (Segal et al, 2013) is first warranted. The combination of mindfulness training and selected elements of CBT is according to the theoretical premise proposed to:

- a) enable participants to increasingly recognize the automatic activation of habitual dysfunctional cognitive processes, e.g. depressogenic rumination.
- b) decenter and disengage from these dysfunctional processes by redirecting attention to the unfolding of thoughts, emotions, and bodily sensations in the present moment.
- c) develop a meta-awareness and become able to observe thoughts and feelings as temporary and automatic events in the mind instead of as facts or true descriptions.
- d) relate to the change and flux of thoughts, feelings, and physical sensations with a non-judgmental and compassionate attitude.

Together these abilities are proposed to be mechanisms facilitating a reduced vulnerability to relapse or recurrence. More specifically, the increase in meta-awareness and the increased ability to recognize and disengage from dysfunctional depressogenic cognition, is thought to prevent the patient from getting caught in a vicious circle of depressogenic thinking and mood, that can escalate into a new depressive episode. In addition, the

compassionate attitude inherent in mindfulness meditation is proposed to be a central ingredient in MBCT having a therapeutic effect (Kuyken et al., 2010), without which disengaging from and not falling back into avoidance-driven dysfunctional cognition may be extremely difficult (Segal et al., 2013).

In addition, to the specific theoretical model behind MBCT, a number of theoretical models have been developed suggesting trans-diagnostic and trans-interventional mechanisms across mindfulness-based interventions (MBI), of which we will provide a short overview. Despite considerable overlap between the various models, it is possible to identify some general hypothesized mechanisms concerning how MBI's may reduce depression risk and build resilience. These include: modification of dysfunctional cognitive biases (e.g. memory, attention and perception); modification of dysfunctional beliefs regarding the self, other and the world; improved top-down and bottom-up ability to regulate emotions and uncomfortable bodily feeling states; increased interoceptive exposure and bodily awareness; decreased habitual reactivity, increased awareness of functional and dysfunctional behavioral patterns and positive events; and improved self-regulation and perception (Carmody, 2009; Garland et al., 2010; Grabovac, Lau & Willet, 2011; Farb, Anderson & Segal, 2012; Hölzel et al., 2011; Shapiro, Carlson, Astin & Freedman, 2006; Vago & Silbersweig, 2012). Biologically, the above proposed mechanisms have been hypothesized to correlate with functional and structural neural plasticity, epigenetic and monoamine alterations collectively resulting in decreased phenotypical vulnerability (e.g., Farb et al., 2012; Hölzel et al., 2011; Vago & Silbersweig, 2012; Young, 2012). However, common in the theoretical models of trans-diagnostic and trans-interventional mechanisms in MBI's is a reliance on a more heterogeneous evidence-base ranging from cross-sectional to randomized controlled trials with both clinical and non-clinical populations. Thus, we do not know whether the proposed mechanisms in these models would be generalizable to the prevention of relapse/recurrence

risk in recurrent MDD.

Review aim

Despite the considerable theoretical and empirical support for MBCT, the specific mechanisms by which MBCT leads to therapeutic change remains unclear. Consequently, this systematic review has two primary aims: i) to investigate the extent to which MBCT can be said to work in accordance with the MBCT manual's theoretically predicted mechanisms of change; ii) to determine the field's progress in empirically investigating and understanding the therapeutic mechanisms of MBCT in the treatment of recurrent MDD, and provide suggestions for future research.

Method

The review was conducted in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews (Moher, Liberati, Tetzlaff, & Altman, 2009). The studies were selected based on the following criteria of eligibility:

Eligibility criteria:

Type of studies: Clinical trials on mediation or mechanisms in MBCT treatment of MDD, reported in English.

Type of participants: Participants aged 18 years or above, diagnosed with recurrent MDD according to a formal diagnostic classification system.

Type of interventions: MBCT conducted in accordance with the manual (Segal, Williams & Teasdale, 2002; 2013).

Identification of studies

Electronic databases (PubMed, PsycINFO) were searched to locate studies from the first available year to June 2014 using the following keywords: Mindfulness-based cognitive therapy OR MBCT AND depress*. In addition, reference lists of the identified articles were

inspected for additional relevant studies. The retrieval process was checked by two of the authors (AMV; KJP).

Evaluation of the methodological quality of studies

The quality of studies investigating potential mechanisms can be influenced by lack of proper randomization and selection bias. The methodological quality of study reports was assessed using modified Jadad criteria adopted from Coelho, Canter & Ernst (2007). The Jadad criteria assess appropriate randomization and description, blindness, and number and reasons for drop-outs (Jadad et al., 1996). As double blindness of participants and therapists, as required by the original Jadad criteria, is not possible, the modified Jadad score allocates one point for single blinding of the outcome assessor. This enables a score ranging from 0-4, with 4 being the highest quality measure available.

Evaluation of the causal specificity of studies investigating proposed mechanisms

The evaluation of the causal specificity of the employed designs is based on the framework by Alan Kazdin (2007; 2009; 2011). According to Kazdin (2007), mechanisms provide explanations of how and why an intervention translates into the events that lead to the outcome. In other words they are causal links between treatment and outcome (Kazdin, 2009; Kraemer et al., 2002). The studies examining potential mechanisms vary in terms of the specificity of the articulated mechanism i.e. their ability to point towards potential mechanisms. Correlational designs have little predictive ability, and do not enable causal inferences. Regression analysis enables predictions about potential mechanisms by determining the statistical relationship between treatment, suggested mechanism and outcome. Mediation analysis can determine whether there are important statistical relations between an intervention, the suggested mechanism and outcome, and whether the relationship between intervention and outcome becomes statistically insignificant when the variance from the mediator variable is taken out. However, a mediation analysis is not intended to explain

precisely how the change comes about, and neither mediation analysis nor simpler forms of regression analysis can establish causal specificity (Kazdin, 2009). Thus, in the case of relapse prevention measures, it is important to statistically control for symptom reduction to get an indication of whether the predictive or mediational effect was primarily a result of symptom change. Furthermore, including timeline or temporal precedence measures (i.e. testing whether the hypothesized mediator change before the outcome) helps increase the degree of causal specificity. An optimal measure of temporal precedence includes measuring symptom change and the mediator variable at several simultaneous points throughout treatment to assess whether the mediator variable indeed does change before the outcome variable (Kazdin, 2007). Introducing gradient designs, dismantling designs, experimental manipulations, componential enhancement designs, and individual differences designs can further increase the degree of mechanism specificity (Kazdin, 2011; Kraemer et al., 2002, Kuyken et al., 2010; Murphy, Cooper, Hollon & Fairburn, 2009; Piet, Würtzen & Zachariae, 2012). The specific designs of the included studies are described in Table 1, and evaluated in the Discussion.

Results

Study Selection

The study selection process is illustrated in Figure 1 using the PRISMA flow diagram (Moher et al., 2009) with reasons for exclusion. The search produced 476 articles, of which 23 studies fulfilled the inclusion criteria (see Table 1). The main reasons for exclusion were participants not suffering from recurrent MDD, the intervention not being the MBCT program, or the study not investigating potential mechanisms of change.

=====
Figure 1 about here
=====

Study Characteristics

The characteristics of the 23 included studies are summarized in Table 1. Seventeen out of the 23 studies were independent trials. Sample sizes varied from 22 to 255, with a total of 1880 participants.

=====
Table 1 about here
=====

Theoretical predicted mediators and potential mechanisms of change

Based on the theoretical premise of the MBCT manual increased mindfulness skills, meta-awareness and self-compassion and reduced rumination, worry, and cognitive reactivity have been investigated as mediators and potential mechanisms of MBCT's ability to reduce depressive relapse risk among recurrently depressed individuals.

Mindfulness skills.

We identified seven RCTs and one uncontrolled study that investigated the role of increased mindfulness skills in the reduction in post-treatment depressive symptoms or relapse risk. When post-treatment symptoms of depression were used as the outcome variable, it is because it is generally considered to be a robust marker for relapse risk (Kuyken et al., 2010; Paykel et al., 2008). Mindfulness was measured using either the Mindful Attention Awareness Scale (MAAS: Brown & Ryan, 2003) or the Kentucky Inventory of Mindfulness Skills (KIMS: Baer, Smith & Allen, 2004). Three out of the eight studies found that increased mindfulness was associated with (i.e. correlation analysis) a reduction of post-treatment symptoms of depression, and one found increased mindfulness to predict (i.e. regression analysis) relapse risk. Three studies that conducted a mediation analysis, and two of these found that mindfulness skills significantly mediated post-treatment symptoms of depression,

yet one study did not find an overall mediational effect of mindfulness except on the ‘accept without judgement’ sub measure of the KIMS scale.

A dismantling trial enables testing of the effect of a specific proposed mechanism of change or active therapeutic ingredient such as mindfulness skills. Williams et al. (2014) conducted a large three arm dismantling trial comparing MBCT with both TAU and cognitive psychoeducation (CPE) as the active control. The CPE group was matched on key non-specific and specific factors, so that the main difference between MBCT and CPE was a systematic training in mindfulness meditation. Over the whole group of patients no significant advantage of MBCT was found in comparison to both CPE and TAU, despite a reduction in relapse hazard of 39%. Thus, omitting mindfulness training did not statistically compromise the treatment effect compared with TAU and CPE in the group as a whole. However, the authors found that MBCT provided significant protection against relapse for participants with increased vulnerability to depressive recurrence due to a history of childhood trauma compared with CPE and TAU.

Depressogenic Cognition

Seven randomized controlled studies (RCTs), and one pre-post study with no controls, investigated whether decreased rumination was associated with, predicted or mediated the therapeutic effect of MBCT on depressive symptom reduction or relapse risk. Rumination was measured by the Ruminative Response Scale (RRS: Treynor, Gonzalez, and Nolen-Hoeksema (2003), the Rumination on Sadness Scale (RSS: Conway, Csank, Holm, & Blake, 2000) or a laboratory experiment (Van Vugt, Hitchcock, Shahar & Britton, 2012). Three studies found that decreased rumination was associated with reduced post-treatment symptoms of depression and one study found that decreased rumination significantly predicted relapse risk. The prediction was maintained when controlling for symptom change. In addition, three studies conducted a mediation analysis of which two found a mediation

effect. The mediation effect was maintained when controlling for symptom change. Two studies did not find reduced rumination to be either associated with or mediating post-treatment symptom reduction or relapse risk.

Two RCTs investigated whether worry mediated depressive symptom reduction. In both cases worry were measured by the Penn State Worry Questionnaire (PSWQ: Meyer, Miller, Metzger & Borkovec, 1990). Both trials found that worry significantly mediated the effect on MBCT on post-treatment symptoms of depression (Batink et al., 2013; van Aalderen et al., 2012).

Finally, one RCT found that MBCT treatment was associated with decreased attempts to suppress negative thoughts (Hepburn et al., 2009), and it has been hypothesized that decreased thought suppression might be linked to decreased depressogenic cognition. However, the study was preliminary and it remains to be investigated whether decreased attempts to suppress thoughts would result in decreased depressogenic cognition and subsequent reduced risk of relapse.

Self-compassion and cognitive reactivity.

Cognitive reactivity refers to the ease by which dysphoric mood can reactivate depressogenic thinking patterns. Kuyken et al. (2010) investigated the link between MBCT treatment, cognitive reactivity, self-compassion and relapse risk in a design employing mediation analysis. Cognitive reactivity was operationalized as a change in depressive thinking during a laboratory mood induction. The measure of self-compassion was the Self-Compassion Scale (SCS: Neff, 2003). The MBCT group was tapering out of maintenance antidepressant medication (m-ADM), while the control group remained on m-ADM. The study design of comparing MBCT with m-ADM, which is an active treatment with similar efficacy, enabled testing of effects specific to MBCT. MBCT participants had higher cognitive reactivity post-treatment compared to the m-ADM control group, but cognitive

reactivity predicted poorer outcome only for the m-ADM group, and not for the MBCT group. Furthermore, the authors found a significant interaction between self-compassion and cognitive reactivity, indicating that increased self-compassion moderated and ‘nullified’ the relationship between increased cognitive reactivity and relapse risk in the MBCT group. Finally, increased self-compassion was found to mediate the beneficial effect of MBCT on post-treatment symptoms of depression.

Meta-awareness and decentering.

Meta-awareness, meta-cognitive awareness and decentering are terms employed interchangeably in the MBCT literature. The terms refer to the ability to observe thoughts and feelings as temporary and automatic events in the mind, rather than facts or true descriptions of reality (Teasdale et al., 2002). Three studies investigated whether increased decentering or meta-cognition was associated with or predicted symptom improvement or relapse risk following MBCT treatment. Hargus, Crane, Barnhofer & Williams (2010) found that in symptomatic patients MBCT in addition to TAU was associated with increased meta-awareness of a recent suicidal crisis, which was not the case in the TAU control group. Meta-awareness of the “relapse signature” was measured using an adapted version of the Measure of Awareness and Coping in Autobiographical Memory (MACAM: Moore, Hayhurst, & Teasdale, 1996). Teasdale et al. (2002) found that increased metacognitive awareness of negative thoughts and feelings predicted reduced relapse risk in MBCT plus TAU compared with TAU alone. The findings remained significant after controlling for symptom change. Meta-cognition was measured by MACAM. Finally, Bieling et al. (2012) found that significant increases in decentering was associated with MBCT treatment and not with m-ADM treatment. As in the design by Kuyken et al. (2010), the study design of comparing MBCT with m-ADM, which is an active treatment with similar efficacy, enabled testing of effects specific to MBCT. Decentering as well as wider experiences and curiosity was

measured by subscales of the Toronto Mindfulness Scale (TMS; Lau et al., 2006), and The Experiences Questionnaire (EQ; Fresco et al. 2007). Changes in Wider Experiences and Curiosity predicted lower scores on the Hamilton Rating Scale for Depression at 6-month follow-up, but decentering did not predict lower depression scores at 6-month follow-up.

Additional correlational and mediational studies on potential mechanism of change

Memory specificity.

Overgeneral autobiographical memory (as opposed to specific) is a cognitive style associated with major depression and suicidal behavior (Williams, Teasdale, Segal & Soulsby, 2000). Furthermore, overgeneral memory and depressive rumination appear to be reciprocally reinforcing (Hargus et al., 2009; Watkins & Teasdale, 2001;). Williams et al., (2000) found that MBCT treatment was associated with a decrease in overgeneral autobiographical memory (increased memory specificity) compared with the TAU control group. Memory specificity was measured with the Autobiographical Memory Test (AMT: Williams & Broadbent, 1986). Hargus et al. (2010) found that MBCT in addition to TAU was associated with increased specificity of relapse signatures, i.e. participants were asked to describe the symptoms they experienced prior to the most recent time they felt suicidal or wanted to harm themselves. Relapse signatures were measured by the Relapse Signature of Suicidality Interview (ReSSI), which was developed specifically for this study. Both studies controlled for changes in depressive symptoms. However, the results are preliminary, and it is unknown whether changes in autobiographical memory or relapse signature specificity following MBCT would play a causal role in reducing risk of relapse.

Specificity of life-goals and goal attainment.

Crane, Winder, Hargus, Amarasinghe & Barnhofer (2012) investigated whether MBCT increased the specificity of life-goals and perceived likelihood of goal attainment. Lack of goal specificity has been identified as a feature of depression and suicidality, and increasing

the specificity of life goals may build resilience and reduce risk of relapse (Crane et al., 2012). Specificity of life-goals was measured by the Measure to Elicit Positive Future Goals and Plans (Vincent, Boddana & MacLeod, 2004). MBCT participants reported significantly more specific life-goals post-treatment and evaluated the likelihood of attainment higher than the waitlist control. Controlling for the impact of changes in symptoms of depression did not alter the findings. Nonetheless, it remains to be investigated whether the increases in life goal specificity and perceived likelihood of goal attainment are associated with a subsequent reduction in relapse or recurrence risk. Furthermore, although an increase in specificity of life-goals is consistent with a broader increase in specificity of self-referent cognition, the way in which MBCT produces these changes remains unclear.

Self-discrepancy.

Crane et al. (2008) explored the effect of MBCT versus TAU on levels of self-discrepancy in patients in remission from depression with a history of severe suicidal ideation. Self-discrepancy refers to perceived distance between current and idealized self-representations, with high levels of ideal self-discrepancy being linked to depressed mood. Self-discrepancy was measured by the Self-Description Questionnaire (SDQ; Carver, Lawrence & Scheier, 1999). The study employed a correlational design and found that individuals receiving TAU showed increases in ideal self-discrepancy across the study period, which may reflect increased vulnerability to relapse. The MBCT group showed no such increase. The findings were not accounted for by changes in residual depressive symptoms. However, it is unclear whether the observed effects of MBCT on self-discrepancy would translate into a reduced risk of subsequent relapse to depression or whether similar findings would be observed in less vulnerable clinical groups of patients with recurrent MDD.

Attention regulation.

MBCT participation may lead to an improved ability to regulate attention and disengage

from depressogenic cognition, which may translate into improved treatment outcomes. Van der Hurk et al. (2012) employed a correlational experimental design and found no changes in attentional processes (alerting, orienting and executive attention) or more general attentional functioning in the MBCT group, nor in the waitlist control group. However, the experimental measure of attention (Attention Network Test) employed was used to investigate how fast and how accurately a target stimulus could be detected amongst alternate cues and stimuli, and as such may not be the most valid measure of attention regulation associated with training in mindfulness meditation.

Employing a correlational design with a task that is arguably more representative for attention regulation during mindfulness meditation, Bostanov, Keune, Kotchoubey & Hautzinger (2012) explored whether MBCT was associated with an improved ability to deploy and maintain attention on a particular focus, employing a mindfulness breathing task with a mood induction stimuli, and a distracting auditory stimulus. They found that the late contingent negative variation (CNV) - an event-related brain potential (ERP) - was increased only after MBCT, and not in the waiting list control group. This finding may indicate an improved ability to deploy and maintain attention on a particular focus during sad mood. The finding remained significant after controlling for changes in mood. However, this study is preliminary and it is unclear whether the attentional effect is of a clinical predictive value.

De Raedt et al. (2012) investigated the effect of MBCT versus no intervention on the facilitation and inhibition of attention for sad and happy faces in a laboratory experiment with a correlational design (Negative Affective Priming Task). After MBCT, participants showed reduced facilitation of attention for negative information and reduced inhibition of attention for positive information, whereas the no-intervention control group showed no change in affective information facilitation. However, due to limitations to the study including a non-randomized design, evidence of key baseline differences between the two groups, and finally

a lack of statistical controlling for symptom change, it is hard to disentangle the findings from self-selection bias and group differences.

Affective changes, and appraisals of pleasant daily-life activities.

Positive affect (PA) and daily reward experience may build resilience, and have been associated with decreased vulnerability to relapse. More specifically, the increased ability to generate PA from pleasant daily life events has been associated with a three-fold reduction in relapse risk in individuals with recurrent MDD (Geswind, Peeters, Drukker, Van Os & Wichers, 2012). The authors found that MBCT treatment was associated with reports of increased experience of momentary positive emotions, as well as greater appreciation of and enhanced responsiveness to pleasant daily-life activities. Both was measured by the Experience Sampling Measure (ESM; Csikszentmihalyi & Larson, 1987.) The wait-list control did not report similar increases. The findings remained significant after controlling for alterations in depressive symptoms, negative emotion, rumination, and worry.

Batink et al. (2013) found that changes in momentary positive and negative affect significantly mediated the efficacy of MBCT, as well as the effect of worry on depressive symptoms, compared with TAU controls. Momentary positive and negative affect was measured by the ESM. In addition, subgroup analyses revealed that changes in cognitive processes (i.e. rumination and worry), and to a lesser extent affective processes (i.e. momentary positive and negative affect) mediated the effect of MBCT for patients with a prior history of two or more episodes of MDD. For patients with three or more previous depressive episodes, changes in positive and negative affect predominantly mediated the effect of MBCT on post-treatment symptoms of depression. It remains to be explored whether changes in momentary positive and negative emotions following MBCT could play a causal role in increasing resilience and thus reducing risk of relapse.

Emotional reactivity to stress may be a marker of depression vulnerability and treatment

response (Britton, Shahar, Szepeswol & Jacobs, 2012). Britton et al. (2012) investigated whether MBCT treatment would alter emotional reactivity to stress. Conducting a laboratory experiment, emotional reactivity to stress was assessed with the Spielberger State Anxiety Inventory (STAI-Y1: Spielberger et al., 1983) before, during, and after the Trier Social Stress Test (TSST: Kirschbaum et al., 1993). The MBCT group showed an overall decrease in emotional reactivity, which was not present in the waitlist control group. The decreased emotional reactivity to stress in the MBCT group was specific to the post-stressor recovery phase. Furthermore, the changes in emotional reactivity partially mediated improvements in symptoms of depression. The study is preliminary with a small sample size, and it remains to be investigated whether the alteration in emotional reactivity to stress can predict a reduction in relapse or recurrence risk.

Neural predictive factors and mechanisms

Neuroimaging research on biomarkers and neural correlates of MBCT treatment of recurrent MDD is still in its infancy. Our search identified only two studies investigating the neural correlates of MBCT treatment of recurrent MDD. Both measured resting-state prefrontal [alpha]-asymmetry. Prefrontal asymmetry has been suggested to be a potential neurobiological indicator of affective style and an endophenotype indicating risk of future episodes of depression (Keune, Bostanov, Hautzinger & Kotchoubey, 2011).

Barnhofer et al. (2007) and Keune et al. (2011) investigated the effect of MBCT in a remitted recurrently depressed population on prefrontal [alpha]-asymmetry with resting electroencephalogram (EEG) employing correlational designs. Barnhofer et al. (2007) found a significant deterioration towards decreased relative left-frontal activation in the TAU control group with no significant change in the MBCT group. Keune et al. (2011) found no difference between the MBCT group and a waitlist control in a bigger sample, with the whole sample showing a pattern indicative of stronger relative right anterior cortical activity. In addition, the

observed shift in alpha asymmetry was not strongly associated with trait rumination or trait mindfulness. Both studies reported having controlled for symptom reduction. However, due to these contradictory findings, it is unclear whether MBCT alters alpha asymmetry more than control treatments. Furthermore, it has been debated whether prefrontal asymmetry is a valid predictor of affective style, and a measure of clinical predictive significance with regard to relapse risk (Fjorback et al., 2011).

Genetic predictive factors and mechanisms

The relevance of investigating the role of genes in psychotherapeutic treatment of depressive disorders has repeatedly been highlighted in the literature. Yet, few studies have investigated the relationship between genes and MBCT treatment of recurrent MDD. Bakker et al. (2014) investigated the relationship between genes involved in reward functioning such as genes coding for dopamine and opioid regulation with changes in positive affect after MBCT treatment. They found that the muscarinic acetylcholine receptor M2 (CHRM2) and the μ 1 opioid receptor (OPRM1) moderated the positive change in PA in the MBCT group (boosting effect). The study further found that increased residual depressive symptoms in the control group were moderated by variation in the brain-derived neurotrophic factor (BDNF) and dopamine receptor D4 (DRD4) genes (deteriorating effect). Together the findings suggest that the hypothesized mechanism of positive affect may be dependent on gene variation, and more broadly that gene variation may moderate the mechanisms by which MBCT works. However, the study examined only a minor proportion of the human genome, and the majority of the single nucleotide polymorphisms (SNP) were either non-coding or non-functional. Consequently, causal associations between gene variation, positive affect and reduced depressive symptoms remain to be investigated further in future trials.

Limitations of the included studies

The reviewed studies have a number of limitations. First, the majority of the examined

studies relied mainly on self-report measures of the mediation or mechanism variables. As participant blinding to the theoretically proposed mechanisms in MBCT is not possible, and education about MBCT's proposed mechanisms is inherent in the MBCT program, it is not possible to discern to what extent participant perception and belief in certain mechanism e.g. mindfulness skills may have impacted the results. Of the 23 examined studies, seven included more objective measures such as laboratory experiments and brain imaging, and of the trials investigating theoretical predicted mechanisms presented in the MBCT manual only two included more 'objective' measures such as laboratory experiments.

In the measurement of mindfulness, two measures were employed i.e. Mindful Attention Awareness Scale (MAAS) or Kentucky Inventory of Mindfulness Skills (KIMS), both considered reliable and validated scales. However, the MAAS measures mindfulness rather narrowly, focusing on mind wandering and negatively focused items. The acceptance factor has been omitted in the recent version, and the MAAS may be restricted in its ability to measure the breath of mindfulness (Bergamo, Tschacher & Kupper, 2013).

Finally, it is difficult to establish to what extent e.g. increases in mindfulness and decreases in rumination were a unique result of the MBCT treatment. In many cases, participants were also on a stable dose of antidepressant medicine while receiving MBCT, and sometimes also received treatment as usual, which may include other psychotherapeutic treatment. Mixed interventions cannot provide a proper indicator of treatment specific mechanisms, but avoiding such designs may due to ethical and clinical concerns not be feasible or advisable. However, in these cases it may be possible to consider sub-group analyses to check for differences amongst participants who received both MBCT and ADM, and participants who only received MBCT.

Discussion

Despite a rapidly increasing body of controlled clinical trials documenting MBCT's

efficacy, little is known about precisely how and why MBCT works in the treatment of recurrent MDD. Understanding how and why MBCT can effectively reduce symptoms of depression and prevent risk of relapse is essential both for theoretical and clinical reasons. The importance of examining change mechanisms has been emphasized throughout the literature (Kazdin, 2011; Murphy et al., 2009). Research on treatment mechanisms can inform the scientific understanding of the processes leading to therapeutic change, help therapists and treatment developers improve MBCT's outcomes and refine treatment manuals, and facilitate a better selection of patients who may benefit from the treatment (Kazdin, 2007; Murphy et al., 2009; Segal et al., 2013).

The purpose of this article was to assess the field's progress in empirically investigating and understanding the mechanisms of change in MBCT for recurrent MDD, and to investigate the extent to which MBCT may be working in accordance with the MBCT manual's theoretically proposed change mechanisms. Towards this aim a systematic literature search was conducted and 23 studies fulfilling the inclusion criteria were selected for the review process. In line with the theoretical predicted mechanisms, twelve studies found that changes in either mindfulness, rumination, worry, self-compassion, decentering or meta-awareness was associated with, predicted or mediated the effect of MBCT on treatment outcome. In terms of mediation analyses, two out of three studies found increased mindfulness to mediate treatment outcome. Two out of three studies found decreased rumination to mediate treatment outcome, and two out of two studies found decreased worry to mediate treatment outcome. No studies employed mediation analysis for meta-awareness, yet one study found increased meta-awareness to predict reduced relapse risk. Finally, one study found increased self-compassion to mediate reduced relapse risk, and to reduce the predictive relationship between cognitive reactivity and relapse risk.

Two trials did not find evidence for the theoretical predicted variables of either

mindfulness or rumination. It is unclear why the two studies failed to find an effect. The majority of the included trials did not report on treatment fidelity measures (i.e. therapist competence and adherence to the MBCT treatment manual), and it is possible that a lack of adequate treatment fidelity could have led to type III error (i.e. the failure to find a mediation effect due to lack of treatment fidelity). The inclusion of previous meditation experience in the study by van Aalderen et al., (2012) may have contributed to a lack of a differential effect on the mindfulness measure between baseline symptoms and post-treatment symptoms, and have led to the study not finding an overall mediational effect of mindfulness except on the 'accept without judgement' submeasure of the KIMS scale. In the case of rumination, only 2 out of 3 studies found a significant effect. In addition, we are aware of two previous large trials that examined changes in rumination without finding an effect (lack of findings not published). Hence, considering the inconsistent results on rumination measures, and the potential prevalence of a 'file-drawer phenomena' or publication bias in the field, it may be questionable whether rumination is a key mechanism of change. The study by Kuyken et al. (2010) found that cognitive reactivity did not decrease in the MBCT group, yet the predictive link between relapse risk and cognitive reactivity was altered. Likewise, it is possible that rumination scores do not decrease after MBCT participation, but that the predictive link between rumination scores and relapse risk may change, perhaps as a result of reduced identification with the content of negative automatic thoughts. Future studies could benefit from exploring this possibility further. Furthermore, increased awareness of negative ruminative thoughts may also be a consequence of MBCT participation. As a result it is possible that rumination does objectively decrease, but that heightened subjective awareness may cause participants to score relatively higher on rumination self-report questionnaires. Comparing self-report and laboratory measures of rumination may be able to address this question in future research.

Eight studies reported preliminary findings indicating that alterations in attention regulation ability, memory specificity, self-discrepancy, appraisals of positive emotion and activity pleasantness, emotional reactivity and momentary positive and negative affect might play a role in MBCT's effect on treatment outcome. However, it remains to be explored whether these potential mechanisms can predict decreased risk of relapse. In addition, a plausible theoretical account of why MBCT may cause the respective variables to change needs to be articulated.

The reviewed studies varied in terms of specificity in the investigation of potential mechanisms. Our search identified 12 correlation analyses, 4 regression analyses, 6 mediation analyses, and 1 trial with a dismantling design. Two studies employed the recommendations by Kraemer et al. (2002), ensuring that measurement of the mediator variable temporally preceded measurement of the outcome variable (Kuyken et al., 2010; Bieling et al., 2012). However, none of the examined studies included measures of temporal precedence as recommended by Kazdin (2007; 2009; 2011), where both mediator and symptoms are measured at several simultaneous points throughout the treatment period to uncover whether the mediator variable does in fact change prior to change in the outcome variable. One study employed a dismantling design comparing MBCT with an active CPE control group, which was matched on several non-specific and specific factors, with the exception that the MBCT group included a systematic training in mindfulness meditation and associated mindfulness training homework (Williams et al., 2014). The authors found that MBCT provided significant protection against relapse for participants with increased vulnerability due to a history of childhood trauma. However, they did not find a significant difference when comparing MBCT to CPE or TAU over the whole group of patients, despite a reduction in relapse hazard of 39%. It may be that increased statistical power, adjusted to the expectation of a small differential effect, would have been required for a significant difference to be

detectable between MBCT and control groups such as TAU or CPE that are likely to produce a significant effect in and of themselves. The high standards of the TAU control condition in the dismantling design by Williams et al. (2014), where many received ADM and psychoeducation, may have contributed to the lack of significant differential findings between the less vulnerable groups. A similar design with CBT have also found that only the more vulnerable populations benefit more from CBT compared with a psychoeducation active control (Stangier et al., 2013). It is possible that larger samples based on conservative power estimates may generally be required to find significant differences between less vulnerable groups in psychotherapeutic dismantling designs. The results of the dismantling trial may also indicate that other specific and non-specific mechanisms e.g. psychoeducation, group support and expectancy could play a central role in the treatment effect of MBCT in less vulnerable populations. Indeed, the finding that the effects of CPE were intermediate between MBCT and TAU could suggest that psycho-education and group support provided by both MBCT and CPE interventions could be mechanisms that explain some of the effect of MBCT (Williams et al., 2014). Finally, it remains unclear exactly why MBCT was superior for those with a greater history of childhood trauma, and in particular whether this effect reflects some specific benefits of MBCT for those with a history of childhood abuse or neglect, or rather the greater potential to benefit from MBCT for those who are more vulnerable i.e. in this trial childhood trauma was closely associated with overall risk of relapse over 12 months for the population as a whole.

The mean Jadad score was 2.7 based on all the included studies. More specifically, for the three non-randomized trials the mean score was 0, and for the 20 RCTs the mean score was 3.2. This suggests that the included RCTs are generally of a high methodological quality (3.2 out of 4). The non-randomized studies had investigated rumination, mindfulness and attention for negative information and a reduced inhibition of attention. Mindfulness and

rumination were investigated in several relatively high quality trials that found a correlational or mediational effect. Attention for negative information and a reduced inhibition of attention were only studied in one non-randomized trial and as such replication is warranted in a high quality RCT.

The study of specific mechanisms in MBCT treatment of recurrent MDD is still in its early stages. Identifying mediators of change is the first step in establishing how MBCT may work in the treatment of recurrent MDD. Mediation analysis does not establish causality, but only points to potential mechanisms (Kazdin, 2007). Although theoretically plausible, we still do not know whether alterations in the proposed mechanisms such as improved mindfulness skills are causal factors leading to significant reductions in depressive symptoms or relapse risk. Changes in the studied mediators may be a marker for some other effect that is causal (Segal et al., 2013). However, identification of mediators is the first important step in establishing how MBCT works (Kuyken et al., 2010), as it narrows down the search for “facilitative ingredients for treatment to achieve change” (Kazdin, 2007; p. 11). Among all the proposed variables leading to therapeutic change, there is a need for research that can uncover which variables are most critical to the change processes (Segal et al., 2013), and how the various variables interact. Indeed, the investigated mechanisms of change may not be independent factors and there is a need for future research to investigate the shared variance between the various variables. Further investigation hereof may enable candidate factors to be reduced to a more parsimonious number. In addition, to get a better indication of causal relations, there is a need for more rigorous designs moving forward. It has been suggested that a better measure of potential mechanisms could be gained from employing extended temporal precedence measures, gradient designs, componential control designs, and individual difference designs (Kazdin, 2011; Kuyken et al., 2010; Murphy et al., 2009; Kraemer et al., 2002). However, considering the possibility of reciprocal causality between the various

mechanisms and depressive symptoms, some of these designs may also have limitations.

Perhaps the understanding of mechanisms in MBCT could be advanced by connecting psychotherapy research with neuroscience and experimental science research as suggested by Kazdin (2011) and Holmes et al. (2014). The study of exposure-therapy related to fear conditioning, provides an example of how experimental, neuroscientific and clinical approaches to science on fear conditioning collectively can advance the understanding of mechanisms in psychotherapy considerably (Ibid, 2011; 2014).

The number of studies investigating the neural correlates and mechanisms in MBCT treatment of recurrent MDD was limited. The two studies included in this review that investigated neural correlates reported inconsistent findings. A larger body of trials has investigated neural correlates of mindfulness meditation, and may point towards interesting avenues for future research. Of particular interest to MBCT treatment of recurrent MDD may be structural changes to hippocampus reported in participants of the MBSR program (Hölzel et al., 2011), which has been hypothesized to be a central mechanism in successful treatment of depression (Eisch & Petrik, 2012). Furthermore, altered amygdala reactivity has been suggested to play a role in vulnerability to depressive relapse (Beck, 2008). Reduced amygdala reactivity has been reported amongst mindfulness meditators, whereas depressive disorders have been correlated with increased reactivity of the amygdala (Beck, 2008; Way, Creswell, Eisenberger & Lieberman, 2010). Finally, Farb et al. (2010) found indication of a shift from 'medial and left-lateralized cortical regions' to more lateral viscerosomatic representations (e.g. right insula) during a sad mood induction after MBSR that was inversely related to depressive symptoms. Such studies may be worth replicating with MBCT in a clinical sample with recurrent Major Depressive Disorder.

Trials investigating genetic and epigenetic mechanism related to MBCT treatment of recurrent MDD is in its infancy. However, Bakker et al. (2014) found indication that

alterations in SNPs may underlie a differential response to MBCT. In addition, recent studies suggest that interventions with mindfulness meditation is linked with changes in gene expression that may prevent inflammation and oxidative stress implicated in the pathophysiology of MDD (Dahlgaard & Zacharie, 2014). Future research could benefit from further unwrapping the moderating or mediating role of gene variation and gene expression related to MBCT treatment of recurrent MDD. Notwithstanding the explanatory gap between cognitive and physical levels of explanation, a pragmatic clinical approach that employs biological sciences to investigate neural and genetic predictive variables regarding relapse risk may be promising (Shulman, 2013). Furthermore, the investigation of genetic, neural, and psychological mechanisms may open new promising avenues for integrated research.

This review has evaluated clinical studies investigating mechanisms of change specifically in MBCT for recurrent MDD. However, there may be specific and non-specific mechanisms that have not yet been investigated in MBCT treatment of recurrent MDD. Alternative mechanisms have been identified in clinical trials investigating other MBI's or populations, as well as suggested in broader theoretical models and reviews of trans-diagnostic and trans-interventional mechanisms of change in mindfulness-based interventions as a whole (e.g., Chiesa, Serretti & Jakobson, 2013; Garland et al., 2010; Grabovac, Lau & Willet, 2011; Jermann et al., 2013; Farb, Anderson & Segal, 2012; Hölzel et al., 2011; Shapiro et al., 2006; Vago & Silbersweig, 2012). Future research may benefit from exploring a number of these potential mechanisms in MBCT for recurrent MDD. Foreexample, it has been suggested that MBI's may facilitate both bottom-up and top-down emotion regulation (Chiesa, Serretti & Jakobson, 2013; Hölzel et al., 2011). Mindful emotion regulation may require processes distinct from top-down emotion regulation strategies (e.g. cognitive reappraisal), related to present moment sensation, acceptance and suspension of judging experience (Farb et al., 2012; Sipe & Eisendrath, 2012). More specifically, it has been

suggested that mindfulness meditation may facilitate exposure, retrieval and reconsolidation during unpleasant emotional and bodily experiences, leading to an overwriting of previously learned stimulus- response associations (Hölzel et al., 2011). In support of bottom-up processes, neuroimaging trials have indicated reduced prefrontal emotion regulation, and increased functional and structural changes in interoceptive and sensory regions such as the insula, somatosensory cortex and parietal regions associated with decreased reactivity to negative emotions and reduced depressive symptoms following training in mindfulness meditation (Farb et al., 2012; Hölzel et al., 2011). The insula in particular has been associated with body awareness, modulation of subjective unpleasantness and valence of body states, and may play a central role in regulating depressogenic affect and related embodied sensations (Damasio & Calvalho, 2013; Craig, 2002; Farb et al., 2012). Neuroimaging has also indicated that MBI's may lead to cortical and subcortical plasticity, facilitating an increased ability to cognitively reappraise emotional reactions (Hötzel et al., 2011). Hence, it may be that MBI's may facilitate both bottom-up and top-down emotion regulation strategies that together reduce vulnerability for relapse/recurrence.

MBCT may also facilitate changes in how the participant relates to self and others, and MBI's have been hypothesized to lead to more adaptive interpersonal communication, and modification of dysfunctional cognitive biases and beliefs regarding the self, other and the world (Kabat-Zinn, 2013; Siegel et al., 2001; Vago & Silbersweig et al, 2012). Addressing interpersonal relations and dysfunctional cognitive biases and beliefs are central to other psychotherapeutic depression treatments such as cognitive behavioral therapy (CBT) and interpersonal therapy (IPT). Future research needs to determine to what extent MBCT may affect these variables, and their relation to relapse/recurrence vulnerability in a clinical sample with recurrent Major Depressive Disorder.

Many of the practices and proposed mechanisms in MBI's have lineage in Buddhist

psychology, and increasingly the field has started exploring the synergies with cognitive science (Grabovac, Lau & Willet, Teasdale & Chalkalson, 2010). Whilst based in different epistemologies and languages, Buddhist models have several elements that in important respects mirror the psychological mechanisms outlined in MBI's. Within Buddhist models (e.g., the abhidhamma) stimuli (from each of the five senses and the 'mind') are quickly identified as pleasant, unpleasant or neutral. The mind tends to react to pleasant experiences through attachment and unpleasant experiences through aversion, and both can lead to mental proliferation and create suffering. When these patterns are repeated enough times, perceptions, beliefs and behaviors become habitual. The parallels with cognitive accounts are striking and future research may benefit from turning such models into a specific testable set of hypotheses.

It is currently unknown whether the studied mediators and proposed mechanisms such as mindfulness, rumination, compassion and decentering are unique to MBCT as a treatment of recurrent MDD. Other therapies such as CBT, IPT, and antidepressant medicine (ADM) may also impact these variables. Both ADM and CBT have been associated with increased metacognitive awareness and reduced rumination (Bieling et al., 2012; Teasdale et al., 2002). As trait mindfulness has been inversely correlated with depressive symptoms (e.g. Sander & Lam, 2010; Way et al., 2010), CBT, IPT and ADM treatment of recurrent MDD may also affect measures of mindfulness. It would be relevant for future research to explore the degree to which other established therapies of recurrent MDD impact mindfulness skills, and whether a greater change in mindfulness skills is associated with MBCT. However, it remains a challenge to determine which effects are byproducts and which effects are causal. Two studies reported findings indicating treatment specificity. Kuyken et al. (2010) found that MBCT patients had higher cognitive reactivity post-treatment in comparison with m-ADM controls, and that cognitive reactivity predicted poorer outcome only for m-ADM patients, but

not for MBCT patients. In addition, only in the MBCT group was a significant interaction between self-compassion and cognitive reactivity found, indicating that self-compassion could have reduced the link between cognitive reactivity and relapse risk in the MBCT group. Bieling et al. (2012) found significant increases in wider experiences and decentering post-MBCT, which was not present in the m-ADM control group. Both studies compared MBCT treatment with m-ADM, and the findings showed an indication of equal efficacy, hence suggesting that different mechanisms of change may be employed in the respective therapies. It would be relevant for future research to explore how MBCT compare with other evidence-based psychotherapeutic treatments of depression (e.g. CBT or IPT) on both non-specific and specific mechanisms. Despite the different theoretical models, there may be an overlap in mechanisms of change and speaking of potential trans-interventional mechanisms (e.g. emotional exposure in a compassionate therapeutic environment). It may also be that the respective therapies primarily work through different focus points (e.g., cognitive biases and beliefs; interpersonal relationships; and compassion and decentering), but all affect an interconnected constellation of cognitive, emotional, bodily and behavioral symptoms.

Most of the reviewed studies have investigated mediators in MBCT treatment for patients with recurrent MDD in remission. Yet, a growing body of evidence suggests that MBCT can also be efficient for MDD patients who are currently symptomatic (e.g. Manicavasgar et al., 2012; Van Aalderen et al., 2012;). Van Aalderen et al. (2012) included currently symptomatic patients and found that the reduction of depressive symptoms was mediated by reduced rumination and worry, independent of whether patients were in remission or currently depressed. However, MBCT treatment of a current episode of depression may entail additional challenges as patients may have highly prevalent depressogenic biases and be behaviorally restricted (Beck & Alford, 2009). Future research may benefit from exploring whether different mechanisms are involved in MBCT treatment

of currently symptomatic recurrent MDD. For example, MBCT may modify depressogenic cognitive biases, - a target of traditional CBT for acute depression.

The majority of the reviewed studies investigated treatment of recurrent depression as one coherent population. However, it has been suggested that MBCT might be particularly effective for particular subgroup populations, e.g. patients with earlier first episode onset and childhood adversity, and less effective for populations where episodes are provoked by stressful life events (Ma & Teasdale, 2004.) Considering that Williams et al. (2014) found that MBCT provided significant protection against relapse for participants with increased vulnerability due to a history of childhood trauma, but showed no significant advantage in comparison to either CPE and TAU over the whole group of patients, future research may benefit from studying potential mechanisms such as mindfulness skills in different base populations among MDD patients. In general, there is a need to investigate developmental, etiological and gender variations in mechanisms and treatment effect for MBCT treatment of recurrent MDD. Considering the heterogeneity of recurrent MDD an improved understanding of moderating patient characteristics could enable improved targeting.

Mechanisms of change may be directionally affected by moderating variables. Therapist competence and adherence may facilitate an increase in potential mechanisms of change such as mindfulness skills. The moderating role of practice motivation and sustained practice during and after treatment would also be relevant to explore. A recent study found that participants who engaged in formal home practice at least 3 days a week during the treatment phase were almost half as likely to relapse as those who reported fewer days of formal practice (Crane et al., 2014). In both cases, future studies may benefit from exploring the moderating impact on both outcome and mechanisms measures.

Ensuring proper treatment fidelity may directly be related to the ability to find a treatment or mediation effect. The importance of trainer competence, adherence and training,

have repeatedly been highlighted in the literature (Crane et al., 2012). Furthermore, the depth of the trainer's personal mindfulness practice as well as the trainer's ability to embody compassion and mindfulness have been highlighted as central to positive outcomes (Kabat-Zinn, 2011). Future studies should aim to report in detail on how treatment fidelity is measured and ensured, and seek to follow established guidelines such as Mindfulness-Based Interventions–Teaching Assessment Criteria Scale, which assesses therapist adherence to the MBCT protocol and competence in its delivery (Williams et al, 2014; Crane et al., 2013; Crane et al; 2012.).

Several studies employed post-treatment depressive symptoms as a marker for relapse risk. Although post-treatment depressive symptoms are generally considered a robust marker for relapse risk (Paykel, 2008) and a non-continuous measure of relapse in mediational analysis can be problematic, future studies should ideally employ measures of both post-treatment depressive symptoms and relapse. Furthermore, it is unclear whether post hoc or a priori hypothesizes were employed in the majority of the reviewed studies. As negative findings may not always be published, it is currently not possible to estimate the potential prevalence of a 'file-drawer phenomena' or publication bias in the field. Consequently, we would recommend that researchers in the field aim to publish study protocols specifying a priori hypothesizes, and in general aim to employ pre-specified hypothesizes, whenever possible.

This review has several strengths. Most importantly, it is to our knowledge the first systematic review specifically on potential mechanisms of change in MBCT treatment of recurrent MDD. As such the review supplements existing reviews of trans-diagnostic mechanisms of change in mindfulness-based interventions as a whole (e.g. Chiesa et al., 2013; Hölzel et al, 2011; Vago & Silbersweig, 2012), by providing important information on potential mechanisms of change specifically in MBCT treatment of recurrent MDD, as well as

a direction for future research. Furthermore, study aims, inclusion and evaluation criteria were generally pre-specified and highly focused. To limit selection bias, the review was conducted in adherence to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) (Moher et al., 2009). The review included an evaluation i.e. modified Jadad criteria (Jadad et al., 1996; Coelho et al, 2007) of the methodological quality of the included studies, providing a measure of the extent the examined studies reduced risk of selection and expectancy bias. Finally, we included an evaluation of the causal specificity of studies investigating proposed mechanisms, providing a measure of the level of mechanism specificity.

Due to the broad range of potential mechanisms investigated, limited statistical power and study heterogeneity, it was not appropriate to conduct a meta-analytical evaluation. However, as the number of mediational studies expands this could be a next appropriate step by focusing on specific proposed mechanisms such as mindfulness, self-compassion, rumination or worry. This review on the other hand provides an overview by including a broad range of studies investigating different potential change mechanisms in MBCT. The review is inherently limited by the results of the systematic search strategy i.e. the clinical studies that have investigated mechanisms of change specifically in MBCT for recurrent MDD. These have predominantly focused on relapse/recurrence or residual depressive symptoms as outcome measures, and we know little about the mechanisms by which MBCT affects other outcome variables such as social and work adjustment, life satisfaction, with attendant reductions in health care utilization and costs, nor specific symptoms such as residual somatic symptoms.

Moving the field of research from mediation research to an investigation of mechanisms is a challenge facing researchers of evidence-based psychotherapies in general (Kazdin, 2009). The scientific study of therapeutic mechanisms of change is complex, perplexing and

'certainly not an easy path on which to embark' (Kazdin 2011, p. 426). MBCT may work for multiple reasons, and two recurrently depressed patients receiving MBCT may respond for different reasons. Specific and non-specific factors as well as linear and non-linear processes may interact and synergistically bring about the preventative treatment effect. However, these complexities are important to investigate further: *'because the best patient care will come from ensuring that the optimal variation of treatment is provided. Understanding mechanisms of treatment is the path toward improved treatment.'* (Kazdin, 2011, p. 426)).

In conclusion, in line with theoretical predictions there is an increasing body of clinical trials suggesting that alterations in mindfulness, worry, meta-awareness, and self-compassion are associated with, predict or mediate reduction in post-treatment depressive symptoms or relapse risk, and thus could be key contributory factors to the beneficial effects of MBCT in the treatment of recurrent MDD. The role of rumination is less clear, and needs to be explored further in future trials. In addition to the theoretical predicted variables, a number of additional psychological, neural and genetic factors have been suggested to be potential mechanisms in MBCT treatment of recurrent MDD, and are worthy of further investigation. Currently, there is a lack of replicated studies that can convey the specific and non-specific mechanisms responsible for change. Future studies need to employ more rigorous designs that can assess a greater level of causal specificity of the potential mechanisms of change.

Acknowledgements

The authors thank Professor Emeritus Mark Williams, University of Oxford, Department of Psychiatry, and Dr. Thorsten Barnhofer, Heisenberg Fellow at Freie Universitat Berlin, for helpful comments to a previous version of the manuscript.

Declaration of interests

This study was not funded by any grants. There are no conflicts of interest.

References

- Baer, R. A., Smith, G. T., & Allen, K. B. (2004). Assessment of mindfulness by self-report: The Kentucky Inventory of Mindfulness Skills. *Assessment*, 11, 191-206.
- Bakker, J. M., Lieveise, R., Menne-Lothmann, C., Viechtbauer, W., Pishva, E., Kenis, G., Geschwind, N., Peeters, F., Van Os, J. & Wichers, M. (2014). Therapygenetics in mindfulness-based cognitive therapy: do genes have an impact on therapy-induced change in real-life positive affective experiences?. *Translational Psychiatry*, 4, e384.
- Baer, R. A., Smith, G. T., & Allen, K. B. (2004). Assessment of mindfulness by self-report: The Kentucky Inventory of Mindfulness Skills. *Assessment*, 11, 191-206.
- Barnhofer, T., Duggan, D., Crane, C., Hepburn, S., Fennell, M. J. V. & Williams, J. M. G. (2007). Effects of meditation on frontal a-symmetry in previously suicidal individuals. *NeuroReport*, 18, 709–712.
- Batink, T., Peeters, F., Geschwind, N., van Os, J. & Wichers, M. (2013), How Does MBCT for Depression Work? Studying Cognitive and Affective Mediation Pathways. *PLoS One*, 23, 8, e72778.
- Beck, A. (2008). The evolution of the cognitive model of depression and its neuobiological correlates. *American Journal of Psychiatry*, 165, 989-977.
- Beck, A., & Alford, B. A. (2009). *Depression: causes and treatment*. (2nd ed.). Pennsylvania: University of Pennsylvania Press.
- Bergamo, C., Tschacher, W. & Kupper, Z. (2013). The Assessment of Mindfulness with Self-Report Measures: Existing Scales and Open Issues, *Mindfulness*, 3, 191-200.
- Bieling, P. J., Hawley, L. L., Bloch, R. T., Corcoran, K. M., Levitan, R. D., Young, L. T., Macqueen, G. M. & Segal, Z. V. (2012). Treatment-specific changes in decentering following mindfulness-based cognitive therapy versus antidepressant medication or placebo for prevention of depressive relapse. *Journal of Consulting and Clinical Psychology*, 80, 365-72.

- Bostanov, V., Keune, W. M., Kotchoubey, B. & Hautzinger, M. (2012). Event related brain potentials reflect increased concentration ability after mindfulness-based cognitive therapy for depression: a randomized clinical trial. *Psychiatry research*, 199, 174-180.
- Britton, W. B., Shahar, B., Szepsenwol, O. & Jacobs, W.J. (2012). Mindfulness-based cognitive therapy improves emotional reactivity to social stress: results from a randomized controlled trial, *Behavior Therapy*, 43, 365-80.
- Brown, K. W. & Ryan, R. M. (2003). The benefits of being present: Mindfulness and its role in psychological well-being. *Journal of Personality and Social Psychology*, 84, 822-848.
- Carmody, J. (2009). Evolving Conceptions of Mindfulness in Clinical Settings: Invited Commentary. *Journal of Cognitive Psychotherapy*, 23 (3), 270-280.
- Carver, C. S., Lawrence, J. W., & Scheier, M. F. (1999). Self discrepancy and affect: Incorporating the role of feared selves. *Personality and Social Psychology Bulletin*, 25, 783–792.
- Chiesa, A., Serretti, A. & Jakobson, J. C. (2013). Mindfulness: top-down or bottom-up emotion regulation strategy?, *Clinical Psychological Review*, 33, 82-96.
- Coelho, H. F., Canter, P. H. & Ernst, E. (2007), Mindfulness-based cognitive therapy: evaluating current evidence and informing future research. *Journal of Consulting and Clinical Psychology*, 75, 1000-1005.
- Conway, M., Csank, P. A. R., Holm, S. L. & Blake, C. K. (2000). On assessing individual differences in rumination on sadness. *Journal of Personality Assessment*, 75, 404-425.
- Craig, A. (2002). How do you feel? Interoception: The sense of the physiological condition of the body. *Nature Reviews Neuroscience*, 3, 655–666.
- Crane, C., Barnhofer, T., Duggan, D. S., Hepburn, S., Fennell, M. V. & Williams, J. M. G. (2008). Mindfulness-based cognitive therapy and self-discrepancy in recovered

- depressed patients with a history of depression and suicidality. *Cognitive Therapy and Research*, 32, 775–787.
- Crane, C., Winder, R., Hargus, E., Amarasinghe, M., & Barnhofer, T., (2012). Effects of Mindfulness-Based Cognitive Therapy. *Cognitive Therapy Research*, 36, 182–189.
- Crane, C., Crane, R., Eames, C., Fennell, M., Silverton, S., Williams, M. & Barnhofer, T. (2014). The Effects of Amount of Home Meditation Practice in Mindfulness Based Cognitive Therapy on Hazard of Relapse to Depression in the Staying Well After Depression Trial. *Behavior Research and Therapy*, In Press.
- Crane R. S., Eames C., Kuyken W., Hastings R. P., Williams J. M. G., Bartley T., Evan, A., Silverton, S., Soulsby, J G. & Surawy C. (2013). Development and validation of the Mindfulness-Based Interventions–Teaching Assessment Criteria (MBI:TAC). *Assessment*, 20, 681-8.
- Csikszentmihalyi, M. & Larson, R. (1987). Validity and reliability of the Experience-Sampling Method. *Journal of Nervous and Mental Disease*. 175(9), 526-36.
- Dahlgaard, J. & Zachariae, R. (2014). Gene expression anti-stress effects following a mind-body intervention. *Psychosomatic Medicine*, In Press.
- Damasio, A. & Calhalvo, G.B. (2013). The nature of feelings: evolutionary and neurobiological origins. *Nature*, 14, 142-152.
- De Raedt, R., Baert, S., Demeyer, I., Goeleven, E., Raes, A., Visser, A., Wylmans, M., Jansen, E., Schacht, R., Van Aalderen J. R. & Speckens, A. (2012). Changes in attentional processing of emotional information following Mindfulness-Based Cognitive Therapy in People with a History of depression: Towards an Open Attention for all Emotional Experiences, *Cognitive Therapy Research*, 36, 612-20.
- Eisch, A.J. & Petrik, D. (2012), Depression and hippocampal neurogenesis: a road to remission?. *Science*, 338, 72-5.

- Farb, N.A., Anderson, A.K., Mayberg, H., Bean, J., McKeon, D., & Segal, Z.V. (2010). Minding one's emotions: mindfulness training alters the neural expression of sadness. *Emotion*, 10, 25-33.
- Farb, N.A., Anderson, A.K. & Segal, Z.V. (2012). The mindfulness brain and emotion regulation in mood disorders, *Canadian Journal of Psychiatry*, 57 (2), 70-77.
- Fjorback, L. O., Arendt, M., Ornbøl, E., Fink, P., & Walach, H. (2011) Mindfulness-based stress reduction and mindfulness-based cognitive therapy: a systematic review of randomized controlled trials. *Acta Psychiatrica Scandinavia*, 124, 102-19.
- Fresco, D. M., Moore, M. T., Van Dulmen, M. H. M., Segal, Z. V., Ma, S. H., Teasdale, J. D. & Williams, J. M. G. (2007). Initial psychometric properties of the Experiences Questionnaire: Validation of a self-report measure of decentering. *Behavior Therapy*, 38, 234–246.
- Garland, E.L., Fredrickson, B., Kring, A. M., Johnson, D.P., Meyer, P. S. & Penn, D.L. (2010). Upward spirals of positive emotions counter downward spirals of negativity: Insights from the broaden-and-build theory and affective neuroscience on the treatment of emotion dysfunctions and deficits in psychopathology. *Clinical Psychology Review*, 30, 849-864.
- Grabovac, A.D., Lau, M.A. & Willet, B.R. (2011). Mechanisms of Mindfulness: A Buddhist Psychological Model. *Mindfulness*, 2 (3), 154-166.
- Geswind, N., Peeters, F., Drukker, M., Van Os, J. & Wichers, M. (2012). Mindfulness training increases momentary positive emotions and reward experience in adults vulnerable to depression: A randomized controlled trial. *Journal of Consulting and Clinical Psychology*, 79, 618–628.
- Goyal, M., Singh, S., Sibinga, E., Gould, N. F., Rowland-Seymour, A, Sharma, R., Berger, Z., Sleicher, D., Maron, D.D., Shihab, H. M., Ranasinghe, P.D., Linn, S., Saha, S., Bass,

- E.B., & Haythornthwaite, J. A., (2014). Meditation Programs for Psychological Stress and Well-being: A Systematic Review and Meta-analysis. *JAMA Internal Medicine*, 174, 357-368.
- Hargus, E., Crane, C., Barnhofer, T., & Williams, J. M. (2010). Effects of mindfulness on meta-awareness and specificity of describing prodromal symptoms in suicidal depression. *Emotion*, 10, 34–42.
- Hepburn, S.R., Crane, C., Barnhofer, T., Duggan, D. S., Fennell, M. J. V. & Williams, J. M. G. (2009). Mindfulness-based cognitive therapy may reduce thought suppression in previously suicidal participants: Findings from a preliminary study. *British Journal of Clinical Psychology*, 48, 209–215.
- Hofmann, S. G., Sawyer, A. T., Witt, A. A. & Oh, D. (2010). The effect of mindfulness-based therapy on anxiety and depression: A meta-analytic review. *Journal of Consulting and Clinical Psychology*, 78, 169-83.
- Holmes, E.M., Craske, M.G. & Graybiel, A.M. (2014). A call for mental health science, *Nature*, 511, 287-89.
- Hölzel, B. K., Carmody, J., Vangel, M., Congleton, C., Yerramsetti, S. M., Gard, T., & Lazar, S., (2011). Mindfulness practice leads to increases in regional brain gray matter density. *Psychiatry Research*, 191, 36–43.
- Ingram, R. E., Atchley, R. A., & Segal Z. V. (2011). *Vulnerability to Depression: From Cognitive Neuroscience to Prevention and Treatment*, (1st eds.). New York: The Guilford Press.
- Jadad, R. A. Moore, D. Carroll, C. Jenkinson, D. J. M. Reynolds, D. J. & Gavaghan et al. (1996). Assessing the quality of reports of randomized clinical trials: Is blinding necessary? *Controlled Clinical Trials*, 17, 1–12.

- Jermann, F., Van der Linden, M., Gex-Fabry, M., Guarin, A., Kosel, M.M., Bertschy, G., Aubry, J. & Bondolfi, G. (2013). Cognitive Functioning in Patients Remitted from Recurrent Depression: Comparison with Acutely Depressed Patients and Controls and Follow-up of a Mindfulness-Based Cognitive Therapy Trial. *Cognitive Therapy and Research*, 37 (5), 1004-14.
- Kabat-Zinn, J., Santorelli, S., Blacker, M., Brantley, J., Meleo-Meyer, F., Grossman, P., Kesper-Grossman, U., Riebel, D. & Stahl, P. (2011). *Training teachers to deliver mindfulness-based stress reduction principles and standards*. Retrieved 11 July 2014 from: <http://umassmed.edu/cfm/trainingteachers/index.aspx>.
- Kabat-Zinn, J. (2013). *Full Catastrophe Living: Using the Wisdom of Your Body and Mind to Face Stress, Pain, and Illness*. New York: Bantam Books.
- Kazdin, A. E. (2007). Mediators and Mechanisms of Change in Psychotherapy Research. *Annual Review of Clinical Psychology*, 3, 1-27.
- Kazdin, A. E. (2009). Understanding how and why psychotherapy leads to change. *Psychotherapy Research*, 19, 418-428.
- Kazdin, A. E. (2011). Evidence-based treatment research: advances, limitations, and next steps. *The American Psychologist*, 66, 685-99.
- Kessing, L. V., Hansen, M. G., Kessing, L.V. Hansen, G. M., Andersen, G. & Angst, J. (2004). The predictive effect of episodes on the risk of recurrence in depressive and bipolar disorders,- a life-long perspective. *Acta Psychiatrica Scandinavica*, 109, 339–344.
- Kessler, R. C., Aguilar-Gaxiola, S., Alonso, J., Chatterji, S., Lee, S., Ormel, J., Üstün, B. & Wang, P.S. (2009). The global burden of mental disorders: An update from the WHO World Mental Health (WMH) Surveys. *Epidemiologia e Psichiatria Sociale*, 18, 23–33.

- Keune, P. M., Bostanov, V., Hautzinger, M. & Kotchoubey, B. (2011). Mindfulness-based cognitive therapy (MBCT), cognitive style, and the temporal dynamics of frontal EEG alpha asymmetry in recurrently depressed patients. *Biological Psychology*, 88, 243-52.
- Kirschbaum, C., Pirke, K. M. & Hellhammer, D. H. (1993). The Trier Social Stress Test: A tool for investigating psychobiological stress response in a laboratory setting. *Neuropsychobiology*, 28, 76–81.
- Kraemer, H. C., Wilson, G. T., Fairburn, C. G. & Agras, W. S. (2002). Mediators and moderators of treatment effects in randomized clinical trials. *Archives of General Psychiatry*, 59, 877–884.
- Kuyken, W., Watkins, E., Holden, E., White, K., Taylor, R. S., Evans, A., Byford, S., Radford, S., Teasdale, J. D., & Dalgleish, T. (2010). How does Mindfulness-based Cognitive Therapy work? *Behaviour Research and Therapy*, 48, 1105–1112.
- Kuyken, W., Crane, R. & Dalgleish, T. (2012). Does mindfulness-based cognitive therapy prevent depressive relapse? *British Medical Journal*, 345:e7194. doi: 10.1136/bmj.e7194.
- Lau, M., Bishop, S., Segal, Z. V., Buis, T., Anderson, N. & Carlson, L. Shapiro, S., Carmody, J., Abbey, S. & Devins, J. (2006). The Toronto Mindfulness Scale: Development and validation. *Journal of Clinical Psychology*, 62, 1445-1467.
- Ma, S.H. & Teasdale, J.D. (2004). Mindfulness-based cognitive therapy for depression: Replication and exploration of differential relapse prevention effects. *Journal of Consulting and Clinical Psychology*, 72, 31–40.
- Manicavasagar, V., Parker, G. & Perich, T. (2012). Mindfulness-based cognitive therapy vs cognitive behaviour therapy as a treatment for non-melancholic depression. *Journal of Affective Disorders*. 130 (1-2), 138-44.

- Meyer, T. J., Miller, M. L., Metzger, R. L. & Borkovec, T. D. (1990). Development and validation of the Penn State Worry Questionnaire. *Behavior Research and Therapy*, 28, 487-495.
- Moher, D., Liberati, A., Tetzlaff, J. & Altman, D. G. (2009). The PRISMA Group: Preferred reporting items for systematic reviews and meta-analyses: The PRISMA Statement, *PLoS Medicine*, 6 (7), p. e1000097.
- Murphy, R., Cooper, Z., Hollon, S. & Fairburn, C. (2009). How do psychological treatments work? Investigating mediators of change. *Behaviour Research and Therapy*, 47, 1–5.
- National Institute for Clinical Excellence. (2009). Depression: the treatment and management of depression in adults: <http://www.nmhd.org.uk/silo/files/depression-in-adults-nice-guideline-update-oct-09.pdf>
- Neff, K. D. (2003). Development and validation of a scale to measure self-compassion. *Self and Identity*, 2, 223-250.
- Paykel, E.S. (2008). Partial remission, residual symptoms, and relapse in depression. *Dialogues in Clinical Neuroscience*, 10(4), 431-37.
- Piet, J., & Hougaard, E. (2011). The effect of mindfulness-based cognitive therapy for prevention of relapse in recurrent major depressive disorder: A systematic review and meta-analysis. *Clinical Psychology Review*, 31(6), 1032-40.
- Piet, J., Würtzen, H. & Zachariae, B. (2012). The effect of mindfulness-based therapy on symptoms on anxiety and depression in adult cancer patients and survivors: A systematic review and meta-analysis. *Journal of Consulting and Clinical Psychology*, 80, 1007–1020.
- Sanders, W. A. & Lam, D. H. (2010). Ruminative and mindful self-focused processing modes and their impact on problem solving in dysphoric individuals. *Behavior Research and Therapy*, 48 (8), 747-53.

- Segal, Z. V., Williams, J. M. G & Teasdale, J. D. (2002). *Mindfulness-Based Cognitive Therapy for Depression: A New Approach to Preventing Relapse*, 1st eds, The Guildford Press, NY.
- Segal, Z. V., Williams, J. M. G & Teasdale, J. D. (2013). *Mindfulness-Based Cognitive Therapy for Depression: A New Approach to Preventing Relapse*, 2nd eds, The Guildford Press, NY.
- Shapiro, S. L., Carlson, L.E., Astin, J. A. & Freedman, B. (2006). Mechanisms of mindfulness, *Journal of Clinical Psychology*, 62(3), 373-86.
- Shulman, R.G. (2013). *Brain imaging: what it can (and can not) tell us about consciousness*, Oxford, Oxford University Press.
- Siegel, D. J. (2001). *The Developing Mind: How Relationships and the Brain Interact to Shape Who We Are*. The Guildford Press, NY.
- Sipe, W. E. B. & Eisendrath, S. J. (2012). Mindfulness-Based Cognitive Therapy: Theory and Practice. *Canadian Journal of Psychiatry*, 57 (2), 63-69.
- Spielberger, C., Gorsuch, R., Lushene, R., Vagg, P., & Jacobs, G. (1983). *Manual for the State-Trait Anxiety Inventory (Form Y)*. Palo Alto, CA: Consulting Psychologists Press.
- Stangier, U., Hilling, C., Heidenreich, T., Risch, A. K., Barocka, A., Schlösser, R. et al. (2013). Maintenance Cognitive-Behavioral Therapy and Manualized Psychoeducation in the Treatment of Recurrent Depression: A Multicenter Prospective Randomized Controlled Trial. *American Journal of Psychiatry*, 170, 624-632.
- Teasdale, J.D., & Chaskalson, M. (2011). How does mindfulness transform suffering? II: the transformation of dukkha. *Contemporary Buddhism*, 12 (1), 103-124.
- Teasdale, J. D., Moore, R. G., Hayhurst, H., Pope, M., Williams, S., & Segal, Z. V. (2002). Metacognitive awareness and prevention of relapse in depression: Empirical evidence. *Journal of Consulting and Clinical Psychology*, 70, 275–287.

- Treynor, W., Gonzalez, R., & Nolen-Hoeksema, S. (2003), Rumination Reconsidered: A Psychometric Analysis. *Cognitive Therapy and Research*, 27, 247-259.
- Vago, D. R., & Silbersweig, D. A. (2012). Self-awareness, self-regulation, and self-transcendence (S-ART): a framework for understanding the neurobiological mechanisms of mindfulness. *Frontiers in Human Neuroscience*, 6, 296.
- Van Aalderen, J. R., Donders, A. R. T., Giommi, F., Spinhoven, P., Barendregt, H. P & Speckens, A. E. M. (2012). The efficacy of mindfulness-based cognitive therapy in recurrent depressed patients with and without a current depressive episode: a randomized controlled trial, *Psychological Medicine*, 42, 989–1001.
- Van den Hurk, P. A. M., van Aalderen, J. R., Giommi, F., Donders, R. A. R. T., Barendregt, H. P., & Speckens, A. E. M. (2012). An Investigation of the Role of Attention in Mindfulness-Based Cognitive Therapy for Recurrently Depressed Patients. *Journal of Experiential Psychopathology*, 3(1), 103-120.
- Van Vugt, M. K., Hitchcock, P., Shahar, B. & Britton, W. (2012). The effects of mindfulness-based cognitive therapy on affective memory recall dynamics in depression: a mechanistic model of rumination. *Frontiers in Human Neuroscience*, 19(6), 257.
- Vincent, P. J., Boddana, P. & MacLeod, A. K. (2004). Positive life goals and plans in parasuicide. *Clinical Psychology & Psychotherapy*, 11, 90–99.
- Watkins, E. & Teasdale, J. D. (2001). Rumination and overgeneral memory in depression: effects of self-focus and analytic thinking. *Journal of Abnormal Psychology*, 110(2), 353-357.
- Way, B. M., Creswell, J. D., Eisenberger, N. I., & Lieberman, M. D. (2010). Dispositional mindfulness and depressive symptomatology: Correlations with limbic and self-referential neural activity during rest. *Emotion*, 10, 12–24.

- Weissman, A. N., & Beck, A. T. (1978). Development and validation of the dysfunction attitude scale: A preliminary investigation. Toronto: Paper presented at the Proceedings of the meeting of the American Education Research Association.
- World Health Organization. (2012). Depression fact sheet, retrieved from <http://www.who.int/mediacentre/factsheets/fs369/en/> March 2014.
- Williams, J. M. G., & Broadbent, K. (1986). Autobiographical memory in suicide attempters. *Journal of Abnormal Psychology*, 95(2), 144-149.
- Williams, J. M., Teasdale, J. D., Segal, Z. V. & Soulsby, J. (2000). Mindfulness-based cognitive therapy reduces overgeneral autobiographical memory in formerly depressed patients. *Journal of Abnormal Psychology*, 109, 150–155.
- Williams, J. M., Teasdale, J. D., Segal, Z. V. & Kabat-Zinn, J. (2007). *The Mindful Way through Depression*. New York: Guilford Press.
- Williams J. M. & Kuyken, W. (2012), Mindfulness-based cognitive therapy: a promising new approach to preventing depressive relapse, *The British Journal of Psychiatry*, 200, 359-360.
- Williams, J. M., Crane, C., Barnhofer, T., Brennan, K., Duggan, D. S., Fennell, M. J., Hackmann, A., Krusche, A., Muse, K., Von Rohr, I.R., Shah, D., Crane, R.S., Eames, C., Jones, M., Radford, S., Silverton, S., Sun, Y., Weatherley-Jones E., Whitaker, C.J., Russell, D. & Russell, I.T. (2014). Mindfulness-Based Cognitive Therapy for Preventing Relapse in Recurrent Depression: A Randomized Dismantling Trial. *Journal of Consulting and Clinical Psychology*, 82(2), 275-86.
- Young, S. N., (2012). Biologic effects of mindfulness meditation: growing insights into neurobiologic aspects of the prevention of depression. *Journal of Psychiatry and Neuroscience*, 36(2), 75–77.

Figure 1

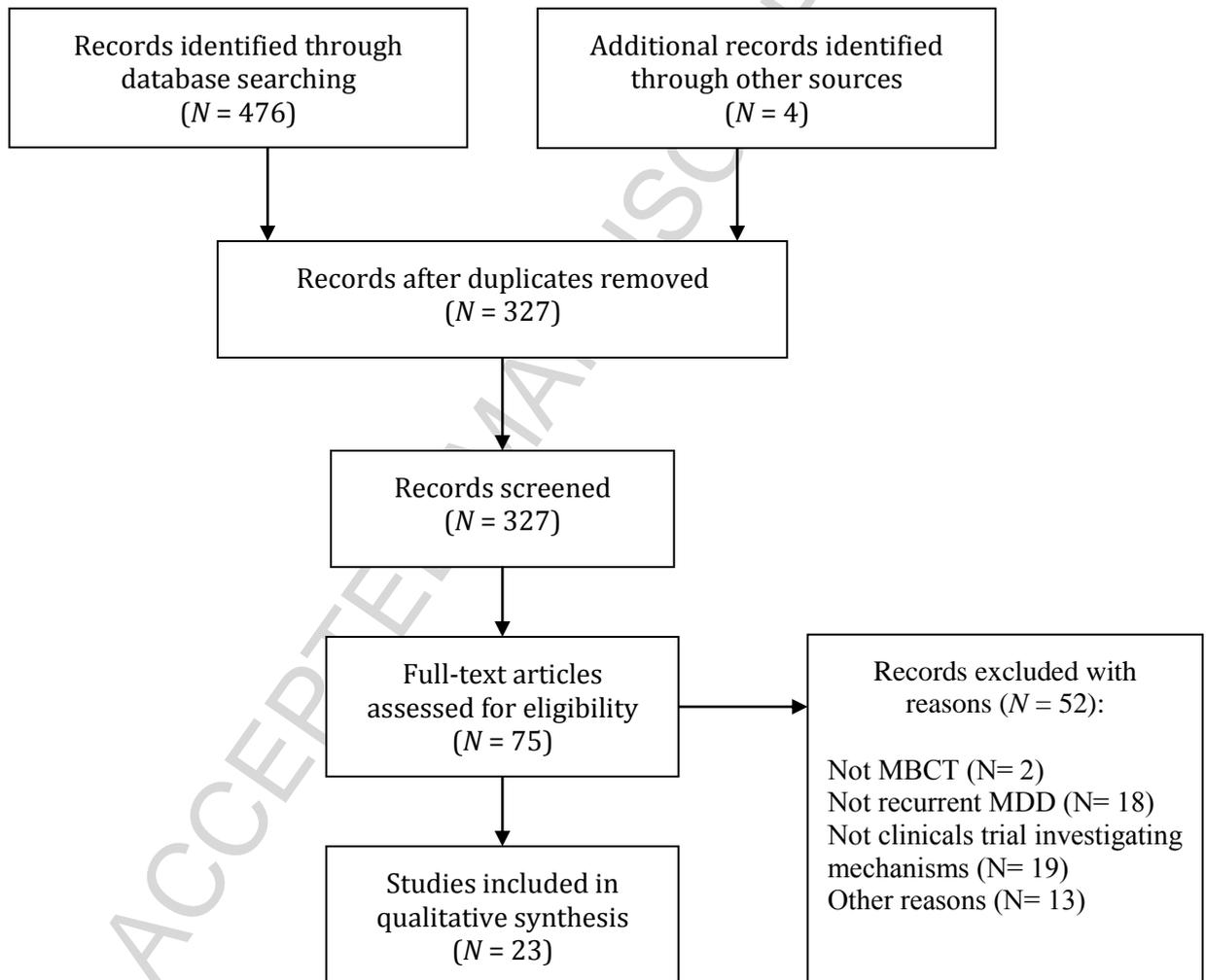


Figure 1. Flow of information from identification to inclusion of studies.

Table 1
Characteristics of studies

Study	Intervention	Participants	Outcome measures	Mechanism measures	Design and Analysis	Findings	Jadad
Bakker et al (2014)	MBCT vs. Waitlist	126 individuals with a recurrent MDD; residual depressive symptoms	Positive affect PA (ESM)	Gene variation: BDNF, CHRM2, COMT, DRD2, DRD4	RCT, Pre-post design. Correlational analysis	CHRM2 and OPRM1 moderated the positive change in PA in the MBCT group (boosting effect). Increased residual depressive symptoms in the control group were moderated by variation in BDNF and DRD4 genes (deteriorating effect)	3
Barnhofer et al (2007)	MBCT vs. TAU	22 individuals with a recurrent MDD; with history of suicidal depression	Depressive symptoms (BDI)	Left-frontal brain activation (EEG). Positive and negative affect (PANAS)	RCT, Pre-post design. Correlational analysis	The TAU group showed a significant deterioration toward decreased relative left-frontal brain activation (EEG), while there was no significant change in the MBCT group	3
Batink et al (2013)	MBCT vs. TAU	130 adults with current residual depressive symptoms (>1 PE.)	Depressive symptoms (HDRS)	Mindfulness (KIMS); Worry (PSWQ); Rumination (RSS); Momentary positive and negative affect (ESM)	RCT, Pre-post design, Mediation analysis.	Momentary positive and negative affect (MPNA), mindfulness skills and worry mediated the efficacy of MBCT. MPNA also mediated the effect of worry on depressive symptoms. Subgroup mediation: ≤ 2 episodes of MDD: cognitive and affective processes mediated the effect of MBCT; ≥ 3 episodes of MDD, affective processes mediated for the effect of MBCT	3
Bieling et al (2012)	MBCT vs. M-ADM	85 individuals with a recurrent MDD in remission (treated with ADM during the acute phase)	Depressive symptoms (HDRS) with 6-month follow-up	Decentering, Curiosity and wider experiences (EQ, TMS)	RCT, Pre-ADM treatment, Pre-MBCT treatment and post-MBCT treatment with 6 month follow-up. Correlation and regression analysis	Post intervention, MBCT showed significant increases in wider experiences and decentering, whereas m-ADM patients did not. Curiosity and wider experiences, but not rumination and decentering, predicted depressive symptoms at follow-up. Rumination did not demonstrate MBCT specific changes	3
Bostanov et al (2012)	MBCT vs. Waitlist	91 individuals with a recurrent MDD in remission	Late CNV (LCNV) response	Attention regulation (LCNV response)	RCT. Pre-post design. Correlation analysis	The late contingent negative variation (CNV), an event-related brain potential (ERP) was increased only after MBCT (mindfulness breathing task with auditory stimulus and mood induction)	3
Britton et al (2012)	MBCT vs. Waitlist	52 individuals with a recurrent MDD in partial remission (>3 PE.)	Depressive symptoms (HDRS)	Anxiety (STAI), measured during and after Trier Social Stress Test (TSST)	RCT. Pre-post design. Mediation analysis	Improvements in anxiety regulation partially mediated the effects of MBCT on depressive symptoms	3

MECHANISMS OF CHANGE IN MBCT

Crane et al (2008)	MBCT vs. Waitlist	68 individuals with a recurrent MDD. In remission. With a history of suicidal ideation	Depressive symptoms (BDI-II)	Ideal and ought self-discrepancy (SDQ)	RCT. Pre-post design Correlation design	MBCT reduced residual depressive symptoms. The MBCT group reported significantly lower levels of discrepancy from their ideal self post-treatment than the waitlist control	3
Crane et al (2012)	MBCT vs. Waitlist	27 recurrently individuals with a recurrent MDD with or without a currently symptomatic episode. With a history of suicidal ideation	Depressive Symptoms (BDI-II)	Memory specificity (AMT); Life-goal specificity (MEPFG)	RCT. Pre-post design. Mediation analysis	Depressive symptoms mediated the effect of intervention on perceived likelihood of goal attainment. Increases in goal specificity were associated with parallel increases in autobiographical memory specificity. Increases in goal likelihood were associated with reductions in depressed mood	4
De Raedt et al (2012)	MBCT vs. Non-intervention.	45 participants individuals with a recurrent MDD	Depressive Symptoms (BDI-II; MINI; HDRS)	Attention (NAP); Mindfulness (MAAS)	Non-randomized, controlled. Pre-post design. Correlation analysis	After MBCT, participants showed a reduced facilitation of attention for negative information and a reduced inhibition of attention for positive information. The control group showed no change in affective information facilitation	0
Geschwind et al (2012)	MBCT vs. Waitlist	130 individuals with a recurrent MDD with current residual depressive symptoms	Depressive Symptoms (HDRS)	Pleasantness of daily life activities, Positive and negative affect; Reward experience; (ESM); Worry (PSWQ); Rumination (RSS)	RCT, Pre-post design. Correlation analysis	Compared to waitlist control, MBCT was associated with significant increases in appraisals of positive emotion, activity pleasantness, and enhanced ability to boost momentary positive emotions by engaging in pleasant activities	3
Hargus et al (2010)	MBCT + (TAU) vs. TAU	27 individuals with a recurrent MDD (>3 PE.) History of suicidal ideation or suicidal behavior	Depressive Symptoms (BDI-II) with 3 month follow-up	Relapse signatures (ReSSI) coded for: meta-awareness and memory specificity	RCT, Pre-post design with 3 month follow up. Correlation analysis	Patients randomized to MBCT+TAU displayed significant posttreatment differences in meta-awareness and specificity compared with TAU patients	4
Hepburn et al. (2009).	MBCT plus TAU vs. TAU	68 individuals with a recurrent MDD and a history of suicidal ideation	Depressive symptoms (BDI-I)	Thought Suppression (WBSI)	RCT, Pre-post design. Correlation analysis	Patients randomized to MBCT+TAU did not display decreased thought suppression, but reported significantly reduced attempts to suppress	3
Keune et al (2011)	MBCT vs. Waitlist.	78 individuals with a recurrent MDD in remission	Depressive Symptoms (BDI-II), Trait rumination (RSQ); Trait mindfulness (FMI)	Resting-state alpha-asymmetry (EGG)	RCT, Pre-post design. Correlation analysis	In comparison with a wait-list control, MBCT reduced depressive symptoms, trait rumination and increased trait mindfulness. Alpha asymmetry remained unaffected by training, and changes in rumination and mindfulness was	3

Kuyken et al (2010)	MBCT vs. maintenance antidepressants (mADM)	123 individuals with a recurrent MDD (>3 PE.), in remission after treatment with ADM	Depressive Symptoms (HRSD); Relapse: (SCID) at 15 month follow up	Mindfulness (KIMS); Self-Compassion (SCS); Cognitive reactivity laboratory paradigm (Segal, 2006)	RCT, Pre-post and 15 month follow up. Mediation analysis	not correlated with alpha symmetry Mindfulness and self-compassion mediated the effect of MBCT on depressive symptoms at 15-month follow-up. Greater cognitive reactivity predicted poorer outcome for mADM patients, but not for MBCT patients	4
Michalak et al (2011)	MBCT (no controlgroup)	24 individuals with a recurrent MDD in remission	Depressive Symptoms (HRSD; BDI), Relapse: SCID (12 month follow-up)	Mindfulness (MAAS)	Not randomized, not controlled. Pre-post and 12 month follow up. Regression analysis	Mindfulness significantly increased during MBCT. Posttreatment levels of mindfulness predicted the risk of relapse/recurrence to major depressive disorder in the 12-month follow-up period	0
Michalak, Hölz & Teismann (2008)	MBCT (no controlgroup)	24 individuals with a recurrent MDD in remission	Depressive symptoms (HRSD; BDI), Relapse: (SCID) at 12 month follow-up	Rumination (RRS)	Not randomized, not controlled. Pre-post and 12 month follow up. Regression analysis	Rumination significantly decreased during MBCT. Posttreatment levels of rumination predicted the risk of relapse/recurrence to major depressive disorder in the 12-month follow-up period	0
Shahar et al (2010)	MBCT vs. Waitlist	45 individuals with a recurrent MDD in partial remission (> 3 PE.).	Depressive symptoms (HRSD; BDI), Relapse: (SCID-I & II) at 15 month follow-up	Mindfulness (MAAS); Rumination (RRS) modified	RCT, Pre-post and 15 month follow up. Mediation analysis	Reductions in brooding (an aspect of rumination) and increases in mindfulness mediated the effects of the intervention on depressive symptoms	3
Teasdale et al (2002)	MBCT vs. TAU	87 individuals with a recurrent MDD in remission	Depressive symptoms (HRSD; BDI), Relapse: DSM-III-R at bimonthly assessment over 1 year	Meta-awareness (MACAM) at 15 weeks post-treatment	RCT, Pre-post design with 1 year follow up with bimonthly assessments. Regression analysis	Compared with TAU, MBCT reduced relapse risk and increased metacognitive awareness of negative thoughts and feelings	3
Van Aalderen et al (2012)	MBCT+TAU vs. TAU	205 individuals with a recurrent MDD (> 3 PE.) with or without a current episode	Depressive symptoms and relapse (HRSD; BDI) at post-treatment and 3, 6, 9 and 12 months follow-up	Mindfulness (KIMS); Rumination (RSS); Quality of Life (WHOQOL); Worry (PSWQ)	RCT. Pre-post design with 3, 6, 9 and 12 months follow-up. Mediation analysis	Patients in the MBCT+TAU group reported less depressive symptoms, worry and rumination and increased levels of mindfulness skills compared with patients receiving TAU alone. MBCT resulted in a comparable reduction of depressive symptoms for patients with and without a current depressive episode. Additional analyses suggest that the reduction of depressive symptoms was mediated by decreased levels of rumination and worry	3
Van den Hurk et al (2012)	MBCT vs. Waitlist control	71 individuals with a recurrent MDD (>3 PE.)	Depressive symptoms (HRSD)	Attention (ANT); Mindfulness (KIMS); Rumination (RSS)	RCT, pre-post design. Correlation analysis	In the MBCT group, depressive symptoms and ruminative thinking decreased and mindfulness skills increased. No changes in the components of attentional processes (alerting, orienting and executive attention) or more general attentional functioning were observed	3

Van Vugt (2012)	MBCT vs. Waitlist	52 individuals with a recurrent MDD in partial or full remission	Depressive symptoms (BDI), anxiety: STAI-Y1	Rumination: Free recall task	RCT. Pre-post design. Correlation analysis	MBCT participants showed a decrease in patterns that may perpetuate rumination on all three types of recall dynamics (Pstart, Pstay, and Pstop), compared to controls	3
Williams et al (2000)	MBCT+TAU vs. TAU	45 individuals with recurrent MDD in remission (>2 PE.)	Depressive symptoms (HRSD)	Memory specificity (AMT)	RCT. Pre-post design. Correlation analysis	Whereas control patients showed no change in specificity of memories recalled in response to cue words, the MBCT group showed a significantly reduced number of overgeneral autobiographical memories (increased specificity)	1
Williams et al (2014)	MBCT +TAU vs CPE +TAU vs TAU	255 individuals with recurrent MDD	Relapse: (SCID) at 3, 6, 9, 12 month post-treatment	Mindfulness meditation	RCT, Pre-post design with 1 year follow up with assessments every 3 months. Dismantling design	MBCT showed no significant advantage in comparison to an active control treatment and usual care over the whole group of patients with recurrent depression. However, MBCT provided significant protection against relapse for participants with increased vulnerability due to history of childhood trauma	3

Note: ADM = antidepressant medication; ANT= Attentional Network Test ; AMT= Autobiographical Memory Test; BDI = Beck Depression Inventory; BDI-II = Beck Depression Inventory-II; BDNF, brain-derived neurotrophic factor; CHRM2, cholinergic receptor muscarinic 2; COMT, catechol-O-methyltransferase; CPE= Cognitive Psycho-Education; DRD2= Dopamine Receptor D2; DRD4= dopamine receptor D4; EQ=Experiences Questionnaire; ESM= Experience Sampling Methodology; FMI= Freiburg Mindfulness Inventory; HDRS= Hamilton Depression Rating Scale; MAAS= Mindful Awareness Attention Scale; m-ADM = maintenance antidepressant medication; MADRS= Montgomery-Asberg Depression Rating Scale; MBCT = mindfulness-based cognitive therapy; MDD = major depressive disorder; MINI= Mini International Neuropsychiatric Interview, NAP= Negative Affective Priming Task; PANAS= The Positive And Negative Affect Schedule; TAU = treatment as usual; KIMS= Kentucky Inventory of Mindfulness Skills; MEPFG=Measure to Elicit Positive Future Goals; PE= Previous Episodes; PSWQ= Penn State Worry Questionnaire; RCT: Randomized Clinical Trial; RSS= Rumination on Sadness Scale, RRS=Ruminative Response Scale; ReSSI =Relapse Signature of Suicidality Interview (ReSSI); SCID= Structured Clinical Interview for DSM; SCS= Self-Compassion Scale; SDQ= Self-Description Questionnaire; RSQ-D = Der Response Styles Questionnaire-D; STAI-Y= The Spielberger State-Trait Anxiety Inventory form Y; TMS:=Toronto Mindfulness Scale; WBSI= White Bear Suppression Inventory (WBSI); WHOQOL= The World Health Organization Quality of Life.

Highlights:

- Mindfulness-Based Cognitive Therapy for Recurrent Major Depression.
- A systematic review of 23 clinical trials investigating mechanisms of change
- MBCT may work according to the theoretically proposed mechanisms
- Better designs that can assess greater causal specificity are needed
- We provide recommendations for future research