How does Mindfulness-Based Cognitive Therapy work in the Treatment of Recurrent Major Depressive Disorder?

A Systematic Review of Mediators, Moderators and Mechanisms

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'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)[1]

[1] By using the term evidence-based explanation, Kazdin (2007, p. 23) is referring to *'replicated findings that convey the mechanisms responsible for change for a given treatment and how these mechanisms operate to produce symptom improvement'*.

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Abstract

The investigation of treatment mechanisms and moderators in randomized controlled trials has considerable clinical relevance. Despite an increasing body of empirical support for

Mindfulness-Based Cognitive Therapy (MBCT), it remains unclear to what extent MBCT is working through the theoretical predicted mechanisms in the treatment of recurrent Major Depressive Disorder (MDD). Consequently, the aim of this thesis is by means of a systematic review to a) investigate to what extend MBCT can be said to work in accordance with its theoretical proposed mechanisms, and b) evaluate how the field is progressing in its understanding of mediators, moderators and mechanisms of change in MBCT treatment of recurrent MDD.

The centerpiece of this thesis is the review article 'A Systematic Review of Mediators; Moderators and Mechanisms in Mindfulness-Based Cognitive Therapy in the Treatment of Recurrent Depressive Disorder'. In addition to a systematic review in article form, planned for submission to Clinical Psychology Review Summer 2014, the thesis contains a broad background description including a chapter on a) the definition of recurrent MDD, recovery, remission, and relapse; b) the theoretical, methodological and empirical background of MBCT; and c) relevant constructs in psychotherapy research on mechanisms of change such as mediation, moderation, mechanisms and causality.

The systematic review was conducted in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews. The search strategy produced 465 articles, of which 22 were included. The results of the review indicate that MBCT may work through its proposed mechanisms. More specifically, it was found that alterations in mindfulness, rumination, worry, self-compassion or meta-awareness predicted or mediated MBCT's effect on treatment outcome. Self-compassion was found to moderate the link between cognitive reactivity and relapse risk in one study. In addition, preliminary studies indicated that alterations in attention regulation abilities, memory specificity, self-discrepancy, dysfunctional attitudes, activity pleasantness appraisal, emotional reactivity and momentary positive and negative affect might play a role in MBCT's effect on treatment outcome. However, as mediation analyses cannot establish causal specificity, it is concluded that future studies should employ more rigorous designs that can assess greater specificity, and allow for manipulation of the potential mechanisms.

Introduction

Major Depressive Disorder (MDD) is a very debilitating affective disorder associated with high psychosocial suffering. Furthermore, MDD is associated with a significant suicidal risk, and annually it is estimated 1 million MDD patients commit suicide (Williams, 2013). Lifetime prevalence of MDD has been estimated around 16% (Kessler et al, 2009). Currently, the World Health Organization has estimated MDD to be the leading cause of disability worldwide (WHO, 2012), and MDD is very costly for society at large. In Europe alone MDD is estimated to cost EUR 136 billion per annum due to treatment costs and loss of work capability (Wegener, 2013). Thus, it is clear that optimizing treatments for MDD is an important priority within the mental health field.

Much of the prevalence, burden and cost of depression is a consequence of MDD often taking a recurrent course. After one episode of major depression the risk of experiencing a recurrent episode has been estimated to be around 50%. Yet with every consequent episode the recurrence risk increases, and after 2-3 episodes recurrence risk is estimated to be in the range of 70-90 %. Furthermore, 10-20% of patients with recurrent MDD develop chronic MDD with symptoms persisting for more than two years (Kessing, Hansen, Andersen & Angst, 2004). Consequently, it is of particular importance to develop and optimize prophylactic treatments.

Mindfulness-Based Cognitive Therapy (MBCT) is a cost-efficient and evidence-based psychotherapeutic intervention for recurrent MDD. It is currently recommended in a number of official clinical guidelines (e.g. National Institute of Clinical Excellence, 2009) as a treatment for recurrent MDD. MBCT belongs to a group of cognitive therapies, which asserts that maladaptive thinking patterns play a causal role in inducing and maintaining depressive episodes. More specifically, MBCT is based on a model of cognitive vulnerability to depressive relapse (Segal, Williams & Teasdale, 2013) that proposes that individuals who have previously experienced episodes of major depression develop increased cognitive reactivity to dysphoric mood, meaning that they become more vulnerable to relapse and recurrence. The evidence base for MBCT as a treatment of recurrent MDD is increasing all the time. Specifically, it has been found that MBCT can significantly reduce relapse risk compared to treatment-as-usual (TAU)[2], in particular for participants with three or more previous episodes (Piet & Hougaard, 2011). In addition, a number of trials have indicated that MBCT can be equally as effective a maintenance

[2] Treatment-as-usual (TAU) is a control-entity and which is used to give an indication how a treatment compares to the current clinical standard of treatment.

antidepressant treatment and group Cognitive Behavioral Therapy (CBT) in reducing the risk of relapse (Kuyken et al, 2008; Manicavasgar, Parker & Perich, 2012; Omidi, Mohammadkhani, Mohammadi, & Zargar, 2013; Segal et al, 2010). Finally, preliminary trials have indicated that MBCT can also be effective for treating chronic and treatment-resistant MDD (Eisendrath, Chartier & MeLane et al, 2011).

Although is remains of high importance to continue investigating the efficacy of MBCT for recurrent MDD, it is equally important to investigate how MBCT exert its clinical effects in the treatment of recurrent MDD. The importance of examining change mechanisms has been emphasized throughout the psychotherapy literature (e.g., Kazdin et al, 2011; Murphy, Cooper, Hollon & Fairburn, 2009). Understanding how and why MBCT can prevent relapse risk is essential for a number of reasons. Firstly, if we are able to understand which mechanisms in MBCT are critical to the prevention of relapse risk, then we may be able to optimize MBCT's outcomes and refine treatment manuals. Furthermore, an improved understanding of treatment mechanisms will provide crucial information on which elements must not be diluted to achieve therapeutic change, and what components are critical to include or enhance in the therapy. Finally, knowledge on mechanisms and moderators may help tailor MBCT to specific subgroups of patients with recurrent MDD.

Several studies have tried to identify possible mechanisms of change in MBCT treatment of recurrent MDD. It has been suggested that MBCT may work by reducing rumination (VanVugt et al, 2012), cognitive reactivity (Raes, Dewulf, Van Heeringen, & Williams, 2009), and negative affect (Batink, Peeters, Geschwind, Van Os, & Wichers, 2013). Furthermore, increased mindfulness skills (Van Aalderen et al., 2012), meta-awareness (Teasdale et al, 2002) and self-compassion (Kuyken et al, 2010) have been found to mediate symptom improvement in MBCT. Finally, brain-imaging studies have suggested that MBCT may work through rebalancing lateral brain activation in emotion regulatory regions (e.g. Barnhofer et al, 2007). However, to this date, no article has reviewed and synthesized these findings. The aim of this thesis is therefore to conduct a systematic review of mediators, moderators and mechanisms in MBCT in the treatment of recurrent MDD.

The key question I seek to answer through this review is: **How does Mindfulness-Based Cognitive Therapy work in the treatment of recurrent Major Depressive Disorder?**

Thesis scope

The scope of this thesis is to conduct a systematic review of moderators, mediators and potential mechanisms of change in MBCT in the treatment of recurrent MDD. This implies that I will limit the content of the review and the related discussion of the review findings to the theoretically predicted mechanisms of change, and the findings from the systematic literature search. Other potential moderators and mechanisms of change not identified through this approach will only briefly be touched upon in the discussion of the review findings under recommendations for future research.

Thesis overview

The centerpiece of this thesis is the review article 'A Systematic Review of Mediators; Moderators and Mechanisms in Mindfulness-Based Cognitive Therapy in the Treatment of Recurrent Major Depressive Disorder'. The article is planned for submission to Clinical Psychology Review in July 2014. The method of systematically selecting studies to be included in the review is based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews (Moher, Liberati, Tetzlaff & Altman, 2009), which will be described in more detail in the article method section.

In addition to this article, I will provide a broad background analysis. This background analysis includes:

a) a chapter on the definition of recurrent MDD, recovery, remission, and relapse.
b) a chapter on the theoretical, methodological and empirical background of MBCT.
c) a chapter describing and discussing relevant constructs in psychotherapy research on mechanisms of change such as mediation, moderation, mechanisms and causality.

The thesis ends with an epilogue and concluding comments.

PART I: BACKGROUND

1.0 Major Depressive Disorder

1.1 Defining Major Depressive Disorder

Major Depressive Disorder (MDD) will in this thesis be defined on basis of the symptomatic criteria set out in the Diagnostic and Statistical Manual (DSM-V) (American Psychiatric Association, 2013).[3] According to the DSM-V manual, the diagnosis of a major depressive episode depends on the presence of at least one of two core symptoms, which are present nearly every day for at least 2 consecutive weeks:

- Depressed mood
- Loss of interest or pleasure in nearly all activities

Furthermore, at least four of the following symptoms need to be present for at least 2 consecutive weeks:

- Significant weight changes
- Insomnia/hypersomnia
- Psychomotor agitation or retardation
- Fatigue or loss of energy
- Feelings of worthlessness or excessive guilt
- Diminished concentration ability and/or indecision
- Recurrent thoughts of death and suicide ideation

In addition, the diagnosis of a Major Depressive Episode requires that the symptoms are associated with considerable distress and impairment in social or occupational function, or other important areas of functioning. However, when symptoms are associated with a mixed episode of mania and depression, schizophrenic symptoms, or caused by the direct physiological effects of drugs, a diagnosis of major depressive disorder is ruled out.

[3] Symptom evaluation is based on a diagnostic interview with self-report and observation elements. Although great progress has been made in research describing neuroanatomical, neuro-endocrinological, and neurophysiological correlates of MDD, DSM-V (2013) has concluded that no study has yielded results of sufficient sensitivity and specificity to be used as a diagnostic tool for this disorder.

1.2 Symptom variability and heterogeneity

MDD is recognized as a heterogeneous disorder, due to considerable variation in symptom availability, severity, and subgroups characteristics. The severity of depression can be mild, moderate or severe, and the evaluation hereof is based on the number of symptoms present, the severity of these, and the overall degree of functional disability and distress. At one end of the spectrum are the mild episodes that are characterized by the presence of only five or six clinical symptoms and mild disability. At the other end is severe depression, which is characterized by the presence of most of the criteria symptoms and profound disability in all aspects of social and occupational functioning.

1.3 Defining recurrent Major Depressive Disorder, remission and relapse

MDD is recognized as cyclic disorder. Recovery from an episode of Major Depressive Disorder typically begins between 3-12 months after onset for 80 % of cases. Features associated with lower recovery rates are numbers of previous episodes, psychotic features, prominent anxiety symptoms, and overall symptom severity (DSM V, 2013). After one episode the risk of developing another episode is 50%, yet after 2-3 episodes the risk of developing another episode increases to 70-90 % (NMHDU, 2009).

Recurrent MDD is a form of Major Depression, where there is speaking of recurring depressive episodes with intervals of full recovery in between. The specific diagnostic criteria for recurrent Major Depression are:

A. Presence of two or more separate Major Depressive Episodes. To be considered separate episodes, there must be speaking of full recovery or remission in between, which is defined as an interval of at least 8 consecutive weeks in which the individual do not meet the criteria for a diagnosis of a Major Depressive Episode.

B. The Major Depressive Episodes are not better accounted for by Schizoaffective Disorder, Delusional Disorder, or Psychotic Disorder Not Otherwise Specified.

C. There has never been a Manic Episode, a Mixed Episode, or a Hypomanic Episode.

However, individuals experiencing major depressive episodes do not always achieve full recovery. Some only achieve partial remission. Partial remission is a period of at least 2 weeks, where the patient is no longer fully symptomatic. In this period, the patient

may be vulnerable to relapse, which is defined as a return to full symptomology, before having reached full recovery.

1.4 Chapter Summary

In summary, it is clear that depression is a heterogeneous disorder characterized by variability in symptom severity, episode frequency and clinical presentation. Furthermore, MDD tends to be a cyclic disorder, and the risk of developing more episodes of depression increases for every subsequent episode. Recurrent MDD is diagnosed in the case of at least two separate episodes of major depression with full recovery or remission in between. Partial remission is a period of at least 2 weeks, where the patient is no longer fully symptomatic, and relapse is defined as a return to full symptomology, before having reached full recovery.

2.0 Mindfulness-Based Cognitive Therapy

In this chapter I will cover the theoretical, methodological and empirical background of MBCT.

2.1 Mindfulness-Based Cognitive Therapy: The theoretical model

MBCT is a recent psychotherapeutic intervention developed by Segal, Teasdale and Williams (2002) for prevention of recurrence of Major Depressive Episodes. MBCT belongs to the group of cognitive therapies, which asserts that maladaptive thinking patterns play a causal role in inducing and maintaining depressive episodes. More specifically, the MBCT model states that repeated associations between depressed mood and depressive thinking patterns are built during successive episodes of major depression, and consequently the tendency for depressive thinking patterns to become activated by depressed mood increases in patients who have experienced several episodes of major depression.

2.1.1 Cognitive vulnerability to depressive relapse or recurrence

Cognitive reactivity is a term used to describe how easily depressed mood can activate depressive thinking patterns (Beck, 2008). The MBCT model predicts that higher cognitive reactivity makes previously depressed patients vulnerable to relapse. This prediction is based on empirical studies that have indicated that increased cognitive reactivity in remitted patients predicts relapse risk (Ma & Teasdale, 2004). Furthermore, studies have found that depressed mood is more likely to activate patterns of depressive thinking in previously depressed patients, compared with never-depressed controls (Ingram, Miranda, & Segal, 2011). Together, these findings suggest that high cognitive reactivity makes previously depressed patients more vulnerable to relapse.

The main focus in MBCT is to prevent a situation, where a depressive feedback loop is enacted due to high cognitive reactivity. More specifically, due to higher cognitive reactivity previously depressed patients are more vulnerable to a situation, where a reciprocal triggering of depressogenic thinking and depressive symptoms can spiral into a fully symptomatic depressive episode. MBCT aims to 'nip a potential relapse in the bud' by teaching patients skills that can prevent them getting caught in a depressive spiral (Segal et al, 2013).

FIGURE 1: Vulnerability to relapse and recurrence in remitted patients

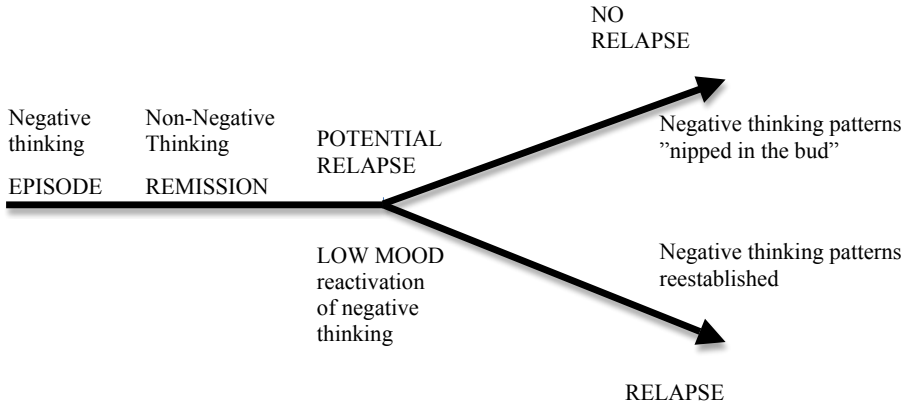


Figure adapted from Segal et al, 2013, p. 37

2.1.2 The doing mode and the being mode

Depressogenic thinking is characterized by the prevalence of negative automatic thoughts, self-devaluation, and by an obsession with discrepancies between the current state of thinking, feeling and behaving, and ideas of how things should be or ought to be e.g. I am a burden on my family, I ought to be happy'. The focus on the discrepancies is feed by the wish to avoid painful experiences (experiential avoidance), and together these aspects are thought to facilitate a negative ruminative cycle (Crane, 2009). Segal et al (2013) terms this form of thinking the 'doing mode', because of the inherent attempt and wish to move away from the current painful situation towards how one thinks things ought to be.

In the MBCT model the antidote to the 'doing mode' is the 'being mode'. According to Segal et al (2013) it is not possible to be engaged in negative rumination and simultaneously have one's full attention and awareness on the experience of being. Thus, it is argued that shifting to a being mode may enable disengagement from depressogenic ruminative thinking by moving one's attention towards the present moment experience of thoughts, feelings and bodily sensations (Ibid, 2013). The following quote captures the potential of the switch from doing to being mode:

'The endless battle of judgmental voices in my head had caused so much pain that I would go out of great lengths to suppress them. I began to learn that, however many thoughts came past-I didn't have to catch any of them. I began to let the buses go by, just

watching them. This was the single most important thing I learnt in this bout of depression. It seems like nothing, but its effects were huge' (Lewis, 2002, as cited in Crane, 2009, p. 59).

In MBCT, participants are taught to shift to and maintain a non-evaluative 'being mode' through mindfulness meditation training. Mindfulness is in MBCT defined as: '*paying attention, on purpose, in the present moment, and non-judgmentally to the unfolding of experience"* (Kabat-Zinn, 2003, p. 145). A central aspect of mindfulness meditation in MBCT is an allowing and non-judging attitude, which is brought to the experienced (also termed approach mode). Without these attitudinal attributes, shifting to a being-mode may be harmful or extremely difficult (Segal et al, 2013; Kuyken et al, 2010). In fact, the compassionate attitude inherent in mindfulness meditation is believed to be a central ingredient in MBCT having a therapeutic effect, without which disengaging from and not falling back into avoidance-driven dysfunctional cognition may be extremely difficult. In other words, where experiential avoidance is believed to feed the ruminative 'doing mode', the 'approach' attitude is thought to be central to the 'being mode' having a therapeutic effect (Ibid, 2013).

In addition to facilitating a way to break the cycles of depressive ruminative thinking, the 'being mode' facilitates an increased awareness of emotional, cognitive and physiological sensations. This awareness is thought to help patients notice when they are experiencing early symptoms of a potential new episode, and enable them to take preventative action. It is further believed that this observational process facilitates a distancing or 'decentering' from the identification with the automatically arising thoughts, feelings, and sensations. Decentering involves cultivating the ability not to be identified or lost within experience (Crane, 2009), and is thought to be a central mechanism in MBCT treatment of recurrent depression.

2.1.3 Chapter Summary

To sum up, the theoretical model of MBCT states that high cognitive reactivity makes remitted patients vulnerable to relapse or recurrence. Hence, it is essential to teach these patients skills that can prevent them getting caught in a new depressive spiral. Patients can increasingly learn to become aware of the automatic and involuntary activation of depressogenic thoughts, feelings, and sensations, and to disengage and decenter from the identification with these experiences. By learning to swift to a non-judgmental and

compassionate being-mode, scarce processing resources that might have been supporting rumination can be weakened. Finally, it is believed that increasing present moment awareness should enable patients to notice, when they could be about to undergo dangerous mood-swings, and enable them to take preventative action.

2.2 Mindfulness-Based Cognitive Therapy: The therapeutic method

MBCT is an 8-week group-therapy program, which integrates teaching in mindfulness meditation from the Mindfulness-Based Stress Reduction programme developed by Kabat-Zinn (1990), with selected elements from Cognitive Behavioral Therapy (CBT).

Mindfulness is taught through various forms of formal or informal exercises (e.g. eating, walking, sitting meditation, 'the bodyscan' and yoga exercises). In essence, these exercises teach participants to observe how their thoughts, feelings and bodily sensations come and go, and to allow the experiences to come and go without trying to change them. The exercises are taught at weekly meetings, and participants are asked to engage in a daily meditation practice at home with guided audio. Substantial time is devoted to the practice sessions and discussion hereof both in class and at home.

In addition to mindfulness exercises several elements from CBT has been included in the MBCT course to make participants aware of maladaptive cognitive processes characterizing depressive episodes, and how affect, cognition, behavior and physiological sensations affect each other in the development of and maintaining of symptoms of depression.

The MBCT program consists of eight weekly sessions of 2.5 hours length, each with its own theme and curriculum, and a long day of silent mindfulness meditation. Before the course there is a private talk with assessment and course orientation. Overall, the first 4 sessions emphasize a) learning to concentrate and pay attention to affective, cognitive and physical experiences without judgment, and b) becoming aware of how the mind wanders and the automaticity of depressogenic thoughts. In session 5-8 the main emphasis is on dealing with changes in mood and difficult thoughts and feelings. In particular, emphasis is on practicing: i) decentering from uncomfortable thoughts and emotions by moving awareness to the change and flux of experiences in the present moment, ii) acceptance and containment (instead of avoidance) of uncomfortable emotions and thoughts. Furthermore, patients are encouraged to identify their 'relapse signature' i.e. affective, behavioral and cognitive patterns indicating increased relapse risk. In the last week, participants are encouraged to develop a home practice that fit their needs so that it can be maintained in the longer term (Segal et al, 2013).

The MBCT therapists are required to have their own private mindfulness practice, so they can have direct experience with the challenges of practicing mindfulness, and

because it is assumed that it facilitates an optimal teaching of mindfulness techniques and a general attitude of empathy, experiential acceptance and compassion with the participants and their experiences (Crane et al, 2009; Segal et al, 2013).

2.3 Mindfulness-Based Cognitive Therapy: Empirical background

The number of randomized controlled trials (RCTs) documenting MBCT's efficacy in treatment of recurrent MDD is increasing all the time. MBCT has been compared with waiting-list controls, placebo controls, treatment-as-usual (TAU), other psychotherapeutic interventions and antidepressant medicine (ADM). Below I will summarize the essence of the findings from these trials:

2.3.1 MBCT in comparison with waiting-list, placebo and treatment-as-usual controls

Several studies have found MBCT to have a superior effect to placebo and waitlist controls in the treatment of recurrent MDD (e.g., Geschwind et al, 2012; Bieling et al, 2012). Evaluating the specific effect of MBCT for prevention of relapse in recurrent MDD, a high-quality meta-analysis by Piet & Hougaard (2011) found that MBCT significantly reduced the risk of relapse or recurrence with a risk ratio of 0.66 compared to treatment-as-usual (TAU), corresponding to a relative risk reduction of 34%. In a pre-planned subgroup analysis the relative risk reduction was 43% for participants with three or more previous episodes, while no additional risk reduction was found for participants with only two episodes (Piet & Hougaard, 2011). However, it has been suggested that it may be premature to rule out the efficacy of MBCT for patients with 2 or less episodes, since MBCT has been found generally to benefit depressed populations (Hofmann et al., 2010), and since patients with three or more episodes formerly have been patients with only two episodes. Furthermore, a recent study found that MBCT was effective in reducing residual depressive symptoms in patients with 2 or less episodes (Geschwind et al, 2012). In several of the reviewed trials in the meta-analysis by Piet & Hougaard (2011) it was found that patients with two episodes reported later first episode onset, and less childhood adversity. Thus, it was been suggested that patients with only two episodes might be derived from a less vulnerable population, and thus less likely to suffer from heightened cognitive reactivity, which may be considered a primary target of MBCT (Ma & Teasdale, 2004; Piet & Hougaard, 2011).

It is important to note, that TAU is a control intervention used to give an indication how a treatment compare to the current clinical standard of treatment. However, because

TAU can encompass everything from no treatment to antidepressant treatment and psychotherapy (Burns et al, 2009), and vary depending on national clinical guidelines, it is not possible to make specific inferences about the active comparison. Below, I will look at studies that have compared MBCT with antidepressant medicine and bonafide treatments[4].

2.3.2 MBCT in comparison with antidepressant medicine

MBCT has been compared to antidepressant medicine (ADM) in a few studies. It has been found that MBCT can reduce residual symptoms of depression and the risk of relapse equal to antidepressant maintenance medication (m-ADM) (Kuyken et al, 2008; Segal et al, 2010). These findings suggest that MBCT can provide an alternative to patients that want to taper out of m-ADM. Furthermore, one study found that MBCT was more effective than m-ADM in improving quality of life perceptions (Kuyken et al., 2008). In addition, a preliminary trial found that MBCT reduced symptoms of depression in subjects with currently symptomatic MDD, who had failed to respond sufficiently to ADM (Chiesa et al, 2013). Given a number of concerns expressed by both patients and clinicians about m-ADM such as non-adherence, non-respondence, kindling and side effects (e.g. Bockting et al, 2011; Willner et al, 2012), the indication that MBCT could provide an alternative to m-ADM treatment is highly promising. Currently, larger trials are comparing MBCT and ADM treatment, and exploring whether MBCT in addition to m-ADM may increase the prophylactic efficacy more than either intervention alone (e.g. Huijbers et al, 2012).

2.3.3 MBCT in comparison with bona fide psychotherapies

Only a few trials have compared MBCT to other evidence-based psychotherapies. To date, I have identified five studies. Three of these compared MBCT with CBT, one compared MBCT with psycho-education, and one employed a dismantling design with a cognitive psychoeducation control.

Manicavasgar et al (2011) and Omidi et al (2013) compared MBCT and CBT for currently symptomatic-MDD for patients with a history of recurrent MDD. Both studies found that MBCT and CBT interventions significantly reduced symptoms of depression, and no difference between CBT and MBCT was found. CBT is known as one of the 'gold-

[4] Bona fide refers to alternative treatments that are delivered by trained therapists, based on sound psychological principles and described in publications (Beck & Alford, 2009).

standards' for treating currently symptomatic MDD, yet these preliminary studies indicate that MBCT might be equally as effective as CBT in the treatment of currently symptomatic recurrent MDD. However, the relative small sample sizes of 30 and 19/26 respectively in each group could also have meant that the studies had insufficient statistical power to detect smaller differences. Another issue that may have effected the results is that CBT is traditionally administrated individually and often over more than 8 times, and hence, it is not clear whether an 8-week group format is an optional way to deliver CBT. Although a recent review suggested that group CBT may be equally effective as individual administrated CBT in the treatment of MDD, the evidence base for group CBT is still very limited (Huntley, Araya & Salisbury, 2012), and 8 week CBT interventions have rarely been studied.

Omidi et al (2013) added behavioral activation components (BA) to MBCT in the treatment of currently symptomatic MDD. The reason for this was that BA components of CBT have been argued to be crucial in the treatment of currently symptomatic MDD, particularly in the early phase of the treatment. However, MBCT without BA components in the study by Manicavasgar et al (2011) also showed equal efficacy to CBT.

Dobson & Mohammadkhani (2007) compared MBCT, group CBT and treatment-as-usual (TAU) as relapse prevention interventions for patients with recurrent MDD in remission. The group CBT intervention used typical elements of CBT (e.g. cognitive restructuring and behavioral activation), but in a preventive manner, given that patients were not acutely depressed. Dobson & Mohammadkhani (2007) did not find any differences in relapse prevention ability between MBCT and CBT, but both interventions were significantly more effective than TAU.

Furthermore, one study found that MBCT was superior to psycho-education in reducing depressive symptoms in subjects with currently-symptomatic MDD, who had not achieved remission following antidepressant treatment (Chiesa, Mandelli & Serretti, 2013).

Williams et al (2014) conducted a large three-arm dismantling trial comparing MBCT with cognitive psychoeducation (CPE) as the active control and TAU. The CPE group was matched on several non-specific and specific factors, which meant that the main difference between MBCT and CPE was the proposed main mechanism, a systematic training in mindfulness meditation. The study found that MBCT provided significant protection against relapse for participants with increased vulnerability due to history of childhood trauma, but showed no significant advantage in comparison to the CPE active control treatment and usual care over the whole group of patients with recurrent MDD. The

findings suggest that MBCT can have an advantaged application in highly vulnerable populations. The findings also fit Ma & Teasdale (2004) suggestive analysis that patients benefiting most from MBCT have a history childhood adversity. However, the findings raise a couple of issues about mindfulness training as a mechanism. Does the effect of mindfulness training depend on the patient population and related etiology? Do these findings mean that mindfulness is not an active mechanism in patients suffering from recurrent MDD without childhood trauma? Or may it be that childhood trauma had a moderating effect on the efficacy of MBCT in treating recurrent MDD, and that in the case of no childhood trauma the mindfulness aspect of MBCT did not have sufficient statistical power to make a smaller difference significant?

2.3.4 Variation in the types of depressive disorders investigated

Although MBCT was originally designed as a relapse prevention intervention for remitted patients only, newer studies have shown that MBCT can substantially reduce depressive symptoms in currently symptomatic MDD (Barnhofer et al, 2009a; Manicavasgar et al., 2011, Omidi et al, 2013; Alderen et al, 2012). Furthermore, MBCT have been shown to reduce symptoms of depression in treatment-resistant depressed patients (Eisendrath et al, 2011), patients with suicidal ideation (Crane et al, 2008), patients with residual symptoms (Kingston et al, 2007), oncology patients (Piet, Würtzen, & Zachariae, 2012), and patients with chronic MDD (Kenny et al, 2007; Barnhofer et al, 2009b).

Together, these findings raise the questions of whether MBCT should mainly be employed as a relapse prevention for recurrent MDD, and further whether there may be mechanisms of change in MBCT treatment of depressive disorders, which are not captured by the theoretical model of MBCT, and which might explain some of the success of applying MBCT to other forms of depressive disorders, besides recurrent MDD.

2.4 Chapter conclusion

In summary, MBCT in the treatment of recurrent depressive disorder has been found to be significantly more effective than placebo and waitlist controls, and significantly reduce the risk of relapse or recurrence compared to TAU for patients with three or more previous episodes (e.g., Piet & Hougaard, 2011; Hofmann et al, 2010). In addition, a couple of trials have found MBCT to be an effective alternative to m-ADM in the prevention of relapse

risk, and currently a number of large trials are being conducted comparing MBCT and ADM treatment (Huijbers et al. 2012). Furthermore, a number of studies have compared MBCT to other bona-fide therapies, and these indicates that MBCT may be equally as effective as group CBT for patients with or without a current episode of depression (Manicavasgar et al, 2011; Omidi et al, 2013; Dobson & Mohammadkhani, 2007), and equal to or superior to psychoeducation (Chiesa et al, 2013; Williams et al, 2014). The reviewed studies also indicate that MBCT is likely to be particular effective for patient populations with heightened cognitive vulnerability due to childhood adversity.

Despite the increasing body of evidence supporting the efficacy of MBCT as treatment for recurrent MDD, little is known about how MBCT works in the treatment of recurrent MDD. Although the theoretical model of MBCT is plausible considering the evidence linking relapse risk and cognitive reactivity, it is unclear whether MBCT decrease relapse risk though the theoretically predicted mechanisms such as increased mindfulness skills, metacognitive awareness and self-compassion and reduced depressogenic rumination and cognitive reactivity. It may be that other potential mechanisms could play a key role (e.g. the role of group support), and that the model's hypothesized mechanisms are in fact not critical to successful treatment. Hence, there has been a call for trials that can examine mediators and potential mechanisms in MBCT treatment of recurrent MDD (Kuyken et al, 2010).

3.0 Mediation, Moderation and Mechanisms in Psychotherapy Research

There are several interrelated and overlapping concepts that are important to distinguish between when examining how and why a therapy may work in the treatment of a particular disorder. The most essential are: mediators, moderators, mechanisms and causality. This chapter will examine each of these, and discuss what the respective constructs can contribute with in the scientific investigation of therapeutic mechanisms of change.

3.1 Causality

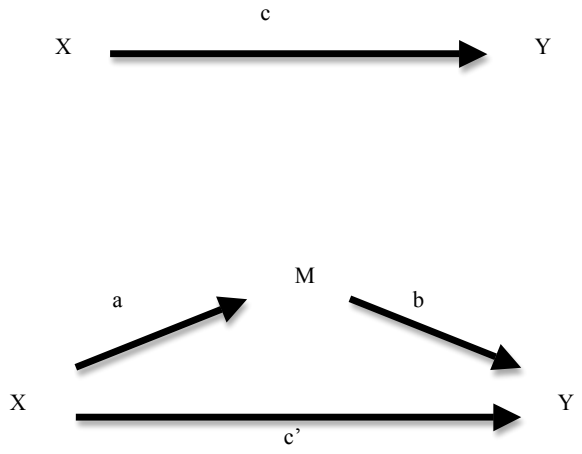
If a randomized controlled trial shows that treatment compared with no treatment leads to therapeutic change, it is possible to infer that the treatment *caused* the change. However, demonstrating a cause does not say *why* the intervention led to the change or how the change came about.

One of the challenges in clinical psychotherapy research is to go from research on efficacy, to looking at what made the treatment work. A great range of factors that range from specific (e.g. mindfulness skills) to non-specific (e.g. group support) may have affected the outcome. Moving towards the identification of causal mechanisms is a complex process, and the first step is often mediation analysis (Kazdin, 2007).

3.2 Mediation Analysis

A mediational analysis can show that there are important statistical relations between the mediating variable, the outcome variable and the psychotherapeutic intervention. Figure 2 below illustrates the key principles in traditional mediation analysis:

Figur 2: Key principles in traditional mediation analysis:



Adapted from Roman & Pardo, 2013, p. 6

1. Treatment intervention (X) must be related to therapeutic change (Y) = c
2. Treatment intervention (X) must be related to the proposed mediator (M) = a
3. The proposed mediator (M) must be related to therapeutic change (Y) = b
4. The relation between the intervention (X) and therapeutic change (Y) must be reduced after statistically controlling for the proposed mediator = c´

A mediational analysis can determine whether there are important statistical relations between an intervention and outcome, and can suggests critical processes that could be related to why change occurs. However, mediation analysis is not intended to explain precisely how the change comes about (Kazdin, 2009). More critically, the mediator cannot establish causal relationships (Murphy et al, 2009; Kazdin, 2011; Kazdin, 2007).

For example, in MBCT treatment of recurrent MDD it might be found that decreased rumination mediates a reduction in symptoms of depression. On this basis, one may hypothesize that a significant decrease in rumination played a causal role in the reduction of symptoms of depression:

MBCT ⇒ rumination decline ⇒ symptom relief

However, on basis of the mediation analysis we do not know whether decreased

rumination caused the reductions in symptoms of depression. It could also be that a reduction in symptoms of depression caused a decrease in rumination.

MBCT ⇒ symptom relief ⇒ rumination decline

In addition, another variable could have caused both rumination and symptoms of depression to decrease, meaning that symptoms of depression and rumination in fact co-vary.

MBCT ⇒ X ⇒ rumination decline and symptom relief

Thus, it must be stressed that mediation analysis involves merely identifying significant associations between putative variables, and it is not possible to establish whether relationship between the variables is causal in nature (Murphy et al, 2009).

3.3 Key challenges to mediation analysis

As illustrated by the previous example, one of the bigger challenges for mediation research is to investigate possible causal relationships. Of particular importance is reducing the risk that the identified mediators are mainly covariates of symptom reduction. A number of ways to address this challenge has been proposed. Firstly, it is important to statistically control for symptom reduction to get an indication of whether the mediation effect was primarily a result of symptom change.

Furthermore, it has been recommended to introduce a timeline or temporal precedence measure. Temporal precedence entails measuring the mediator and outcome variable at two or more points (e.g. 4 weeks into treatment and post-treatment) to access the ordering of the proposed mediator and outcome (Kadzin, 2007). If changes in the mediator precede changes in the outcome variable in time, this would suggest a directional, and potential causal link. For example, if it could be shown that rumination scores decline before symptoms of depression, it could suggest that rumination might play a direct role in reducing symptoms of depression (Kazdin, 2009), and is unlikely to be a byproduct of symptom change.

However, the time-line option is not without challenges. Firstly, a timeline would

not be able to explain possible non-linear relationships. Secondly, individuals vary in their response to treatment, and thus declines in rumination are likely to occur earlier for some than for others. Thirdly, according to the theoretical model of MBCT affective and cognitive symptoms of depression are intimately related, and thus changes to cognition (e.g. depressogenic rumination) may effect symptoms of depression almost instantly, meaning that to establish a timeline, one might need to employ an experimental design, where one would be able to measure the various changes as they occur. Measuring mid-treatment and again post-treatment would in this case most likely not suffice.

Another method to examine whether the identified mediators are mainly covariates of symptom reduction is employing an active treatment control that would decrease symptoms of depression to the same degree as the investigated treatment. This method enables the researcher to make a qualified inference about whether the findings from the mediation analysis were mainly caused by symptom alterations. Forexample, if it could be shown that antidepressant medicne (ADM) and MBCT equally reduce symptoms of depression, but MBCT reduce rumination more than ADM, then one would have reason to suspect that MBCT may work (at least in part) by decreasing rumination.

In addition to the importance of reducing the risk that the identified mediators are mainly covariates of symptom reduction, is of equally high importance in mediation analysis to ensure the plausibility of the tested mediational variables. Because mediation analysis cannot establish causality, it is recommended to have strong theoretical support for the mediation variables. It is in practice possible to find a mediation effect for constructs that are unlikely to be potential mechanisms, but which may for other reasons be connected to both intervention and outcome. Therefore a mediation analysis should ideally be conducted with plausible mediators, which are consistent with theory or scientific knowledge in the area.

Textbox 1: Key constructs and terms (adapted from Kadzin, 2007)

Cause: A variable or intervention that is responsible for the outcome or change

Mediator: An intervention variable that statistically accounts for the relationship between the independent and dependent variable. However, mediator cannot explain the causal processes of how the change came about. A mediator may be a guide that points to possible mechanisms, but is not necessarily a mechanism. It could be a proxy for one or more other variables or be a general construct that is not necessarily intended to explain the mechanisms of change.

Mechanism: Refers to the processes or events that are responsible for the therapeutic change, i.e. the reasons why a change occurred or came about.

Moderator*:* A baseline variable that influences the direction or magnitude of the relationship between the independent and dependent variable. Examples of moderators could be gender, age or etiology factors such as genetic dispositions.

3.4 Moving from the study of mediation to the study of mechanisms

Mediational research is of value when seeking to identify the range of possible mechanisms of change. Identifying mediators of change is the first step in establishing how an intervention may work, but mediation analysis only points to potential mechanisms (Kazdin, 2007). The next step is testing and evaluating the causal status of the identified mediators. As many variables may be involved in the complex process of therapeutic change, it is crucial to seek evidence for the potential causal and critical variables (Segal et al, 2013). For example, we may have identified that decreased rumination mediates depressive symptom relief, but we do not know whether decreased rumination is a critical variable causing a reduction in symptoms of depression, or whether another variable caused a significant change in both rumination and depressive symptoms.

Furthermore, if a mediation analysis only focus on a few possible variables, it becomes hard

to see what role they may play in connection to other variables. Kazdin (2009) raise the issue that many clinical trials conducting mediation analysis only look at a few possible mediators (usually 1-3), yet considering the big costs in terms of financial and human capital in setting a good RCT and conducting mediation analysis, it is comparatively less work to look at additional mediating variables, and it may paint a much more informative picture of possible mechanisms.

3.4.1 Increasing the degree of causal specificity

Mechanisms can explain how an intervention translates into events that lead to the outcome. In other words, mechanisms are causal links between treatment and outcome. The challenge is to establish causal specificity i.e. establish which specific processes or events that are responsible for the therapeutic change (Kazdin, 2009). For example, increased mindfulness skills may mediate treatment outcome, but that does not explain *specifically* how the change come about (i.e., what are the intervening steps between increased mindfulness skills and reduced depressive symptoms). Kazdin (2007), Murphy et al (2009) and Kazdin (2011) have made a number of recommendations for psychotherapeutic research aiming to move from mediation analysis to a further investigation of proposed mechanisms of change. Introducing dismantle designs, gradient methods, componential enhancement designs, and experimental manipulations is argued to help increase the degree of causal specificity (Kazdin, 2011; Kraemer et al, 2002). Each of these will be adressed briefly below:

- **Dismantle designs**

A dismantle design involves using an active treatment control that resembles the investigated treatment in the main non-specific (e.g. time and therapist contact hours) and specific factors (e.g. psychoeducation), expect from the potential mechanism to be investigated (e.g. mindfulness meditation). If a dismantling trial shows the intervention to be more effective than the active control, it would make a strong case for that the hypothesized mechanism plays a causal role in the treatment effect. However, a challenge is ensuing enough statistical power to be able to detect a significant difference between two treatments, which are similar in all aspects expect the proposed main mechanism, and both likely to produce an effect.

- **Gradient measures and componential enhancement designs**

Showing that stronger doses or greater activation of the proposed mediator is associated with greater change in the outcome can help make the case for a potential mechanism. Forexample, conducting a clincial trial where a treatment is enhanced in the specific components thought to be active mechanisms of change (e.g. mindfulness skills), and examine whether the treatment is more effective than the original treatment, would indicate that the investigated variable has a causal influence on treatment response (Kraemer, Wilson, Fairburn & Agras, 2002). In addition to the componential enhancement design, statistical analyses can be conducted to investigate whether variation in the potential mechanism predict treatment outcome. For example, subgroups analyses may reveal whether participants with relatively higher change in the proposed mechanism achieve greater treatment effect.

- **Experimental manipulations**

Experimental manipulations have many advantages as they can enable manipulation of the proposed mechanism in a controlled environment. Furthermore, experimental manipulations allows for a more direct measurement of the potential mechanism, and a temporal investigation on basis of a time span that is shorter than traditional temporal precedence designs.

In addition, to the list with recommended study designs, Kazdin (2009) has argued that the process of studying therapeutic mechanisms of change will require consistency amongst many types of research being carried out e.g. laboratory research, qualitative research, mediation research, and naturalistic studies. As an example, he argues that the progress in understanding the mechanisms behind fear conditioning was a result of many different areas of research collaborating, and together this research have improved the understanding of mechanisms in exposure therapy considerable.

3.5 Moderation

Moderators are baseline variables that influence the direction or magnitude of the relationship between and independent and dependent variable. Examples of moderators can be gender, age or etiology factors such as childhood abuse or genetic dispositions.

Moderators mainly provide information on 'for whom' a treatments work. However, moderators can also give an indication of potential mechanisms of change. Forexample, the finding that MBCT seems to be more effective for patients characterized as having heightened cognitive vulnerablity to relapse, and thus be particularly prone to depressogenic rumination, may indicate that rumination could be a variable to study in mediation analysis.

3.6 Chapter Summary

Mediation analysis is often the first step in trying to identify how a treatment work and what the mechanisms of change may be. However, mediation analysis can only identify associations between putative variables, it cannot establish whether the identified relationship is causal in nature. Consequently, it is important to ensure that the investigated mediators are theoretical plausible, and statistically control for symptom reduction to get an indication of whether the mediation effect was primarily a result of symptom change. Mechanisms provide explanations of how and why an intervention translates into the events that lead to the outcome, and are causal links between treatment and outcome (Kraemer et al., 2002). However, studies examining potential mechanisms vary in terms of their causal specificity. Kazdin (2011), Kazdin (2007) and Murphy et al (2009) have given a number of recommendations on how to increase the degree of causal specificity. In essence, they recommend to a) use designs that can evaluate mediators and potential mechanisms e.g. establish a timeline of the proposed mechanism and outcome, or conduct statistical analyses of gradient relationships; b) to intervene to change or manipulate the mediator and proposed mechanism (e.g. experimental designs, componential enhancement designs or dismantling designs); and to c) examine consistencies across many different types of studies e.g. qualitative studies, laboratory studies, brain imaging and clinical trials. Moderators are baseline variables that influence the magnitude of the relationship between intervention and outcome. Moderators provide valuable information about for whom a given treatment works, but moderators may also provide valuable clues on potential mechanisms.

PART II: ARTICLE

4.0 A Systematic Review of Mediators, Moderators and Mechanisms in Mindfulness-Based Cognitive Therapy in the Treatment of Recurrent Major Depressive Disorder

NB: Link to published, revised and peer-reviewed article in the renowed journal Clinical Psychology Review:

http://www.sciencedirect.com/science/article/pii/S0272735815000203

Part III – Epilogue and concluding comments

5.0 Epilogue and concluding comments

The development and optimization of evidence-based psychotherapies is highly dependent on the theoretical and empirical understanding of treatment mechanisms and moderators. Despite a growing body of evidence supporting MBCT's efficacy, little is known about precisely how MBCT works in the treatment of recurrent MDD. The aim of this thesis was therefore to investigate 'how MBCT works in the treatment of recurrent MDD' by means of a systematic review. More specifically, it was sought to a) investigate to what extend MBCT can be said to work in accordance with its theoretical proposed mechanisms, and b) evaluate how the field is progressing in its understanding of mediators, moderators and mechanisms of change in MBCT treatment of recurrent MDD. In line with theoretical predictions it was found that alterations in mindfulness, rumination, worry, metacognitive awareness, cognitive reactivity and self-compassion are likely to be key ingredients in how MBCT exerts its clinical beneficial effects in the treatment of recurrent MDD. The review also identified a number of other potential mechanisms in MBCT treatment of recurrent MDD, which are worthy of further investigation. Overall, the field has made significant progress in understanding mediators and potential mechanism of change. Nonetheless, more stringent designs that enables increased causal specificity is needed in future trials.

The empirical investigation of therapeutic mechanisms of change is a challenge facing researchers of evidence-based psychotherapies in general (Kazdin, 2009). The field is full of challenges and complexities. Mainly, it remains a considerable challenge to identify critical variables of change, separate byproducts from causal effects, and establish treatment specificity. Yet, given the immense progress made in the field of psychotherapy over the last decades, there is hope that this newer area of investigation will advance and provide the field with valuable knowledge on moderators and mechanisms of change. The value to the field of such knowledge cannot be emphasized enough, as it constitutes a crucial step on the road toward optimized treatment.

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