Change in decentering and mindfulness mediates the effect of Mindfulness-based cognitive therapy in the treatment of recurrent depression: a randomized controlled design

Anne Maj van der Velden[1,2], Willem Kuyken[2]*, Mia O'Toole[3], Jesus Marin-Montero[2]., Lone O. Fjorback[1], Andreas Roepstorff[1,5]*,

[1] Department of Clinical Medicine, Aarhus University, Aarhus, Denmark
[2] Department of Psychiatry, Oxford University, Oxford, United Kingdom
[3] School of Business and Social Sciences, Aarhus University, Aarhus, Denmark
[4] NIDO, Regional Hospital West Jutland, Herning, Denmark
[5] School of Culture and Society, Aarhus University, Aarhus, Denmark

* shared senior authorship

ABSTRACT

Mindfulness-Based Cognitive Therapy (MBCT) is an effective prophylactic treatment for prevention of relapse risk amongst individuals with a history of recurrent depression. However, only about half experience sustained remission following MBCT. To improve clinical outcomes, we need to identify the key therapeutic mechanisms of change. Eighty participants with a history of three or more episodes of depression were included and randomized to MBCT treatment in addition to treatment as usual TAU (N=50), or to continue with TAU alone (N=30), and completed questionnaires accessing putative change mechanisms of decentering, mindfulness skills, brooding and interoceptive awareness before and after treatment, and depressive symptoms before and after treatment and at three months follow up. Mediators were tested in separate models, using bias-corrected confidence intervals (95% BSCI). In the randomized controlled design, we found statistically significant indirect effects for decentering (BSCI [0.33 to 3.37]) and trait mindfulness (BSCI [0.33 to 2.64]), respectively explaining 50% and 41% of the change in depressive symptoms at three months follow up. Post-hoc analyses within the active treatment phase for the MBCT group showed similar results. Hence, the ability to take a decentered perspective one's experiences and mindfully notice, step back and let go of distressing thoughts and images may be core skills underlying clinical improvement in MBCT for recurrent depression.

INTRODUCTION

Major depressive disorder (MDD) is one of the most prevalent and debilitating affective disorders and a leading cause of disability worldwide (Organization, 2020). Much of the burden of MDD is a consequence of MDD often taking a recurrent course. With every episode of depression, the risk of recurrence increases, and after 3 episodes the risk of relapse or recurrence may be as high as 85%, and many maintain residual or chronic symptoms (Buckman et al., 2018; Kennedy & Paykel, 2004; Muller et al., 1999; Rottenberg et al., 2018). Consequently, improving preventative treatments for recurrence of depression is a high priority within the field of mental health.

Mindfulness-Based Cognitive Therapy (MBCT) is an effective psychotherapeutic intervention for the prevention of recurrent depressive episodes (Kuyken et al., 2016). MBCT is currently recommended as a prophylactic treatment for recurrent major depressive disorder e.g. (National Institute for Health and Care Excellence, October 2009, updated April 2018) and is considered a cost-effective intervention. According to a recent meta-analysis, MBCT is effective in reducing relapse risk, approximately halving relapse risk. This effect is similar to first-line prophylactic treatment involving maintenance antidepressants (Kuyken et al., 2016). However, despite the promising evidence, only about half of individuals receiving MBCT experience sustained remission. To improve clinical outcomes, we need to identify core therapeutic mechanisms, the knowledge of which could enable optimization of treatment elements and applications (Holmes et al., 2018).

MBCT is based on a model of cognitive vulnerability of depressive relapse and recurrence (Segal et al., 2013b). The vulnerability is believed to develop during successive episodes of major depression, such that triggers of low mood over time easily reactivate persistent depressive thinking patterns, thereby increasing the risk of relapse. MBCT targets this cognitive vulnerability, by teaching remitted individuals with a history of recurrent depression skills to recognize, decenter, and disengage from mind states characterized by self-perpetuating patterns of ruminative negative thought, and relate to these negative mind states with a compassionate and non-judging attitude (Grossmann et al., 2016; Segal et al., 2013b).

Several studies have sought to investigate mechanisms of change in MBCT for recurrent depression (Alsubaie et al., 2017; Kearns et al., 2016; Z. V. Segal et al., 2019; van der Velden et al., 2015). Based on the theoretical model, we selected four psychological constructs that speak to change in dispositional mindfulness, decentering, rumination and interoceptive awareness in line with the theoretical predicted change processes. A number of studies have found increased dispositional mindfulness and rumination to mediate treatment response after MBCT treatment of recurrent depression (Alsubaie et al., 2017; Gu et al., 2015; van der Velden et al., 2015), although two studies did not find mindfulness skills to mediate treatment outcome and the findings on rumination have been inconsistent with some indication of publication bias of negative findings (Kearns et al., 2016; van der Velden et al., 2015). A couple of studies have found decentering to predict treatment response to MBCT treatment (Bieling et al., 2012), while one recent study using a factor analytical approach across various questionnaires found that a decentering factor was the best predict reduced relapse risk (Bieling et al., 2012; Z. V. Segal et al., 2019). Finally, there has been a growing recognition of the putative mechanistic role of interoceptive awareness in MBCT treatment, although this has not yet been empirically assessed. MBCT trains adaptive attention regulation and present moment embodied awareness, which is theorized to help individuals with recurrent depression to recognize and decouple from conditioned patterns of ruminative negative thought by shifting the attentional focus to the body (Segal et al., 2013b).

The change processes by which MBCT treatment can reduce depressive symptoms and prevent relapse may be multidimensional (Alsubaie et al., 2017; van der Velden et al., 2015). However, by assessing the relative strength of individual mediation analyses and measures of covariance, we aim to develop a more parsimonious model of key change processes. Identifying the core psychological skills by which MBCT can prevent depressive relapse is important for optimizing treatment effects (Holmes et al., 2018; van der Velden et al., 2015).

Here we investigated putative mechanisms of change for MBCT in the treatment of recurrent depression. First we investigated whether the proposed mediators (i.e. decentering, mindfulness skills, brooding, and interoceptive awareness) changed in the MBCT group compared with a treatment as usual (TAU) control group. Second we investigated whether change in the proposed mechanism predicted proximal (i.e. post treatment) and distal (3 months follow up) clinical response.

Subsequently, we conducted individual mediation analyses and assessed the percentage of variance predicted by each proposed mechanism using the controlled design.

METHODS

Study design and participants

To speak to putative mechanisms of change for MBCT in the treatment of recurrent depression, we set up a randomized controlled design, comparing MBCT in addition to treatment as usual (MBCT+TAU) to TAU alone. We measured proposed mediators (i.e. decentering, mindfulness skills, brooding, and interoceptive awareness) before randomization and after treatment, and clinical outcome before randomization, post treatment as well as 3 months follow up. This enabled us to create a temporal distance between invention allocation (baseline), mechanisms change (treatment phase), and subsequent clinical outcome (3 months follow up).

The trial and study design are described in full elsewhere (van der Velden et al., in prep). In brief, we included 80 participants with a history of recurrent depression, who were symptomatic with mild to moderate symptoms or in remission. Inclusion criteria were: a diagnosis of recurrent major depressive disorder with or without a current episode; three or more previous major depressive episodes; age 18 years or older and, if on antidepressants, a stable dose of SSRI or SNRI medication for a minimum of 8 weeks, were recruited from general practices and local psychiatric units in the region of Midtjylland in Denmark. Exclusion criteria were: a) anti-psychotic medication and benzodiazepines; b) formal concurrent psychotherapy; c)) a history of schizophrenia, schizoaffective disorder, bipolar disorder, current severe substance abuse, organic mental disorder, current/past psychosis, pervasive developmental delay, persistent antisocial behavior, persistent self-injury requiring clinical management or a current severe major depressive episode; d) having previously completed either MBCT training; Mindfulness-based stress reduction training or having extensive meditation experience (i.e. regular meditation practice or having attended a meditation retreat). All participants gave written informed consent. Full details on the recruitment procedure can be found in (van der Velden et al., in prep.) The study design was preregistered at ClinicalTrials.gov (Identifier: NCT03353493), and the protocol was approved by the Regional Ethics Council.

Randomisation

Eighty participants were included in the study, after which an independent researcher randomly allocated them to receive either MBCT+TAU treatment (n=50) or adhere to TAU treatment (N=30). The ratio of 5:3 was chosen as the trial was designed as both a controlled design and as a prospective study with the MBCT group having a longer follow up period of 12 months. Hence the MBCT group was larger allowing for more attrition during prospective analyses (see van der Velden et al., in prep). This choice was also made out of concerns of participant preference for early intervention. The randomization was generated by a random number sequence and stratified by antidepressant use and symptomatic status on basis of the BDI-II Beck Depression Inventory-II (A. T. Beck et al., 1996)with less than 13 being asymptomatic, and greater than or equal to 14 being symptomatic. Questionnaires were administered online. At baseline, participants were masked to treatment allocation, but given the nature of psychological treatment, participants and MBCT trainers were made aware of treatment allocation after baseline assessment.

Intervention and procedures

MBCT

MBCT is an eight week group-based program developed to teach participants skills to prevent relapse or recurrence of depression(Segal et al., 2013b). MBCT combines a systematic training in mindfulness meditation techniques from mindfulness-based stress reduction (MBSR) with psychoeducational elements from cognitive behavioral therapy for depression. MBCT was taught by two highly experienced therapists in accordance with the treatment manual and consisted of a pre-class interview, weekly classes of 2.25 h during an eight weeks period with homework.

TAU

Treatment as usual (TAU) for recurrent depression may consist of antidepressant medication and psychological therapy. In this study, we restricted TAU to no psychotherapeutic intervention and either a stable dose antidepressant medication or no medication at the time of treatment to enable to us draw conclusions of the effect on MBCT.

Measurements

Clinical outcome

Depressive symptoms. We measured depressive symptoms using the Quick Inventory of Depressive Symptomology (QIDS_SR16 (Rush et al., 2003). Participants were assessed at baseline (before randomization) and within 1 month after the end of the 8-week MBCT program, and at 3 months follow up (Trivedi et al., 2004). Cronbach's alpha in the present study was α =0.85 (pre-treatment).

Mechanism outcomes

Decentering: We measured decentering at baseline and within a month after treatment using the Experiences Questionnaire (EQ) – decentering factor (Fresco, Moore, et al., 2007), which measures metacognitive awareness, and the ability to take a decentered or an observer's stance on one's experiences and thoughts, combined with attitudinal aspects of acceptance and self-care. Cronbach's alpha was α=0.86 pre-treatment.

Interoceptive Awareness: We measured Interoceptive Awareness at baseline and within a month after treatment using the Multidimensional Assessment of Interoceptive Awareness (MAIA) (Mehling et al., 2012) which measures multiple aspects of interoceptive awareness. We included the preselected the subscales of noticing (α=0.74), emotional awareness (α=0.68), body listening (α=0.82), attention regulation (α=.087), trusting (α=0.90), and not-distracting (α=0.47).Given the low alpha value for not-distracting at in the present study, we removed this subscale.

Mindfulness skills: We included the 15-item version of the Five Factor Mindfulness Questionnaire (FFMQ) (Gu et al., 2016) to speak to multidimensional aspect of mindfulness skills including five subscale assessing observing, describing and acting with awareness, and attitudinal components of non-reactivity and non-judgement to inner experience. We measured dispositional mindfulness (FFMQ) at baseline and within a month after treatment. Cronbach's alpha was α=0.83 pre-treatment.

Rumination: We included the Ruminative Response Scale (RRS) to assess dispositional rumination. We measured rumination using the RRS brooding subscale (Kasch et al., 2001) at baseline and within a month after treatment. Cronbach's alpha was α=0.72 pre-treatment.

Clinical efficacy analyses

Depressive symptoms over time were analyzed in SPSS with a multilevel model (MLMs) where time (level 1) was nested within individuals (level 2), based on the intent-to-treat sample with two-sided p-values. The intercepts were set as random in all models, to allow for the estimation of a separate intercept for each individual, and the slope was specified as random if it significantly improved the model fit. Missing data at the item level were handled by mean substitution, but only considered for participants with less than 50 % missing data (See Van der Velden et al., in prep for further description).

Mediation analyses

We performed mediation analyses on the per protocol sample (i.e. participants attending at least half the sessions of the MBCT treatment) as a proper dose of MBCT is required to investigate putative mechanisms. We only included putative mechanisms, where we identified change specific to the MBCT group, when compared to treatment as usual. Mediators were tested in separate models, using bias-corrected confidence intervals (95% BSCI). Bootstrapping is a nonparametric resampling procedure that does not impose the assumption of normality of the sampling distribution (A. F. Hayes & Scharkow, 2013). By repeating this process, an empirical approximation of the sampling distribution of *ab* (the product term between *path a (*between the group variable and the mediator) and *path b* (between the mediator and the dependent variable controlling for the independent variable)) is built and used to construct confidence intervals for the indirect effect. A significant mediating effect is considered when the referenced 95% BSCI does not include zero (Lockhart, MacKinnon, & Ohlrich, 2011). Effect sizes for these models were expressed as the proportion of the total effect accounted for by the proposed mediator, i.e., mediated effect / total effect based on absolute values (A. F. Hayes & Rockwood, 2017).

We examined mediation effect using the randomized controlled design creating a temporal distance between invention allocation (baseline), mechanisms change (treatment phase), and subsequent clinical outcome (3 months follow up) in separate mediation models. We estimated mediation using Hayes Process Macro version 2 model 4 in SPSS based on the principles of ordinary least squares regression with bias-corrected bootstrapping (A. F. Hayes & Rockwood, 2017). 95% confidence intervals and point estimates were estimated for the indirect effects using 5.000 iterations. Significant mediation effects were interpreted when zero was not contained within the confidence interval.

As the change in the putative mechanism and clinical outcomes happens specifically in the treatment phase in the MBCT group (van der Velden et al., in prep), we also ran post-hoc analyses of mediation on the acute treatment period (pre to post treatment) using the same strategy.

RESULTS

Baseline characteristics were balanced between the two groups on sociodemographic and clinical variables, as well as on outcome scores (See Table 1). Study flow is summarized in Figure 1.

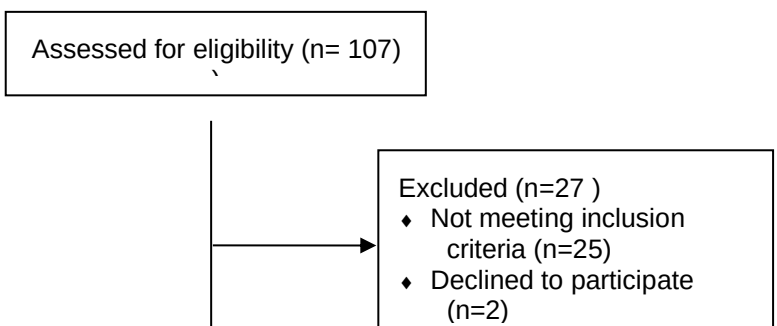
Clinical results have been reported in full elsewhere (van der Velden et al., in prep, paper I in this dissertation). In brief, MBCT treatment significantly reduced depressive symptoms (B=4.11, CI: -6.47 to -1.78, g=0.82, p= 0.001) compared with the TAU group at post treatment, and at 3 months follow up (B=-1.78, CI: -2.92 to -.63, g=0.51 p=0.002). Mean attendance to MBCT was 6.75 out of 8 sessions with (N=45, 93.88 %) of the MBCT group attending at least 4 sessions.

TABLE 1: Baseline characteristics

	MBCT+TAU (N=50)	TAU (N=30)
Sociodemographic characteristics	N=48	N=28
Age	43.17 (14.22)	45.25 (12.01)
Gender (Female/Male)	35/15 (70%)	23/5 (82%)
Educational level		
Low (<2 years further education)	15 (30%)	3 (11%)
Medium (2-4 years further education)	24 (48%)	21 (75%)
High (>5 years further education)	9 (18%)	4 (14%)
Marital status		
Married/cohabiting	43 (90%)	21 (75%)
Single/not cohabiting	5 (10%)	7 (25%)
Occupational status		
Employed	24 (50%)	14 (50%)
Unemployed/benefits	10 (10%)	4 (14%)
Student	3 (6%)	1 (4%)
Retired	7 (15%)	4 (14%)
Other	9 (19%)	5 (18%)
Clinical Characteristics	N=50	N=28
Symptomatic (QIDS>5)	43 (83%)	25 (76%)
Antidepressant usage	43/7 (86%)	21/7 (75%)
Childhood Trauma	58.79 (6.22) N=42	58.96 (6.33) N=26
Previous episodes of depression	3.90 (1.44) N=41	3.80 (1.36) N=23
Outcomes	N=48	N=27
QIDS	9.23 (4.58)	9.68 (5.10)
EQ	31.43 (7.12)	31.26 (7.06)
MAIA_AR	17.22 (5.03)	17.78 (4.99)
MAIA_BL	6.25 (2.07)	7.40 (3.25)
MAIA_TR	8.89 (3.31)	8.40 (3.77)
MAIA_NO	12.79 (2.61)	13.96 (3.38)
MAIA_ND	9.17 (2.64)	9.01 (2.45)
MAIA_EA	15.32 (3.51)	16.57 (4.23)
FFMQ	44.21 (8.88)	45.33 (80.2)
RRS	53.38 (9.80)	57.51 (8.24)

Table 1. Baseline characteristics and questionnaire scores for each group reported as means with standard deviations in brackets or percentage ratio for each group. MBCT+TAU: Mindfulness-based cognitive therapy plus treatment as usual; TAU: treatment as usual. QIDS: Quick Inventory of Depressive Symptomology (Rush et al., 2003); PSS: Perceived stress scale (Cohen et al., 1983) EQ: Experience Questionnaire (Fresco, Moore, et al., 2007); FFMQ: Five Factor Mindfulness Questionnaire (R. A. Baer et al., 2008); RRS: Rumination Response Scale (Roelofs et al., 2006); MAIA (Multidimensional Assessment of Interoceptive Awareness(Mehling et al., 2012) and the subscales of AR: Attention Regulation; BL: Body listening; NO: Noticing; TR: Trusting; ND: Non distracting; EA: Emotional awareness

FIGURE 1: Participant flow



Prediction of clinical outcomes

We first examined which putative mechanism changed as a result of treatment. MBCT treatment compared with treatment as usual increased decentering (p<0.001, g=0.98, 95% CI [3.76, 11.01]), mindfulness (p<0.001, g= 0.68, 95% CI [1.49, 9.57]), the ability to notice bodily sensations (MAIA_noticing subscale, p<0.001, g= 0.95, CI [1.60-4.76]), the awareness of the manifestation of emotions in the (MAIA_emotional awareness subscale p<0.001, g= 1.10, CI [2.82, 7.12]); active listening to the body for insight (MAIA_body listening subscale p<0.001, g= 1.19, CI [1.63-3.85]) and the ability to sustain and control attention to body sensations (MAIA_attention regulation subscale p<0.001, g= 1.00, CI [2.56-7.44]). See supplements for all group x time effects.

Secondly, we examined which putative mechanisms predicted reduced depressive symptoms. Increases in decentering, mindfulness, active listening to the body for insight and the ability to sustain and control attention to body sensations all predicted both depressive symptoms at post treatment and at 3 months follow up (see table 2).

Mediation results

In the randomized controlled design, we found statistically significant indirect effects for decentering (BSCI [0.33 to 3.37]) and mindfulness (BSCI [0.33 to 2.64]), respectively explaining 50% and 41% of the change in depressive symptoms at 3 months follow up. Only 3 participants did not fulfill PP requirements. With both mediators the direct effect (total effect accounting for the role of the mediators) was not significant, suggesting full mediation. Given that the treatment effect on decentering, mindfulness and depressive symptoms was driven by change during the active treatment phase (pre to post treatment) we also ran post-hoc mediation analyses during the treatment phase. Here we also found statistically significant indirect effects for decentering (BSCI [0.63 to 3.43]), explaining 54% of the change in depressive symptoms post treatment, and for mindfulness (BSCI [0.47 to 2.77]), explaining 39% of the effect (see figure 2).

Further explorative analyses (see supplements) showed that the strength of the inverse association between decentering and depressive symptoms were stronger post treatment (r=-0.62, p=0.000) than at baseline (r=-0.37, p=0.002), and stronger for the MBCT group (r=-0.61, p=0.000) than the TAU group post treatment (r=-0.46, p=0.002). Likewise, the strength of the inverse association between mindfulness and depressive symptoms were stronger post treatment (r=-0.51, p=0.001) than at baseline (r=-0.34, p=0.025), and stronger for the MBCT group (r=-0.51, p=0.001) than the TAU group post treatment (r=-0.19, p=0.372). Moreover, the correlation between change in decentering and mindfulness was high r=0.74, P>0.001. We did not find an effect for active listening to the body for insight (MAIA_body listening subscale) (BSCI [-0.13 to 2.51]) and the ability to sustain and control attention to body sensations (MAIA_attention regulation subscale) (BSCI [-0.34 to 2.33]), although these predicted clinical outcomes post treatment and at 3 months follow up, and explained respectively 35% and 28% of the clinical effect.

Table 2: Prediction of clinical outcomes

Change in mechanisms predicting clinical outcomes at three months follow up

	Unstandardized	Coefficients	Standardized Coefficients			95% Confidence Interval for B	
Model	B	Std. Error	Beta	t	Sig.	Lower Bound	Upper Bound
EQ	-.261	.065	-.456	-4.002	.000	-.391	-.130
FFMQ	-.265	.061	-.484	-4.324	.000	-.387	-.142
MAIA_AR	-.267	.102	-.319	-2.625	.011	-.471	-.064
MAIA_BL	-.634	.216	-.352	-2.938	.005	-1.066	-.203
MAIA_EA	-.228	.123	-.231	-1.856	.068	-.473	.018
MAIA_NO	-.104	.166	-.080	-.624	.535	-.436	.229

Caption: Change scores of psychological processes predicting depressive symptoms at three months follow up (QIDS 3 months follow up minus QIDS pre-treatment). EQ: Experience Questionnaire(Fresco, Moore, et al., 2007); FFMQ: Five Factor Mindfulness Questionnaire(R. A. Baer et al., 2008); RRS: Rumination Response Scale(Roelofs et al., 2006); MAIA (Multidimensional Assessment of Interoceptive Awareness(Mehling et al., 2012) and the subscales of AR: Attention Regulation; BL: Body listening; NO: Noticing; TR: Trusting; ND: Non distracting; EA: Emotional awareness. Only significant group x time effects were tested.

DISCUSSION

MBCT is an effective treatment for recurrent depression (Kuyken et al., 2016). However, only about half experience sustained remission following MBCT. To improve clinical outcomes, we need to identify the key therapeutic mechanisms of change (Gu et al., 2016). In this study we investigated whether change in decentering, mindfulness, interoceptive awareness or brooding would mediate proximal and distal clinical outcomes in separate models. In the randomized controlled design, dispositional decentering and mindfulness mediated depressive symptoms at 3 months follow up respectively explaining 50% and 41% of the change. As the change in the putative mechanisms and clinical outcomes occurred specifically in the treatment phase in the MBCT group, we also ran post-hoc analyses of mediation on the acute treatment period within the MBCT group, showing similar results with decentering and the mindfulness mediated depressive symptoms post treatment, explaining 54% and 39% of the change respectively. Hence, decentering and mindfulness may be core skills that underlies clinical improvement in MBCT for recurrent depression.

MBCT was developed on basis on a theoretical model stating that the ability to take a decentered or an observer's stance on one's experiences could help individuals with recurrent depression recognize and disengage from ruminative thought patterns and hence be an important ingredient in reducing depressive symptoms and depressive relapse prophylaxis (Segal et al., 2013). Consistent with this premise, change in decentering explained the largest percentage of the clinical change, both in the randomized controlled design and in post-hoc analyses within the MBCT group. These findings are also consistent with a recent factor analysis across several questionnaire finding the decentering factor to best predict relapse or recurrence risk following MBCT treatment (Z. V. Segal et al., 2019), along with other trials showing that MBCT increase decentering (Bieling et al., 2012; N. Farb et al., 2018; Z. V. Segal et al., 2019).

In addition to decentering, mindfulness also explained a large proportion of the clinical change. This is consistent with several trials (Alsubaie et al., 2017; Kearns et al., 2016; van der Velden et al., 2015) showing increased mindfulness mediating improved clinical outcomes following MBCT treatment. Furthermore, the correlation between change in decentering and mindfulness was high, and hence it is possible that the mediating role of both decentering and mindfulness may refer to a similar mechanism or highly related change processes. Indeed, the FFMQ subscale on non-reactivity to inner experience examines the ability to 'notice', 'step back' and 'let go' of 'distressing thoughts and images' which is conceptually closely related to the ability to take a decentered perspective on one's experiences. Of the subscales in the FFMQ, the strongest correlation was between decentering (EQ) and the 'non-reactivity to inner experience' subscale of the FFMQ, but correlations between decentering and the other FFMQ subscales (i.e., Observing, Describing, Acting with Awareness, Non-Judging of inner experience) was also high. Although these may appear to be conceptually somewhat different mechanisms, MBCT treatment may concurrently train awareness of sensations, a non-judging attitude and a decentered perspective to what is experienced, and these mechanisms may interact as part of a bigger mechanisms system of change. For example, increased awareness of body sensations may make it easier to see the temporal nature of thoughts, and subsequently take a decentered perspective on what is experienced (N. Farb et al., 2015). Future research could benefit from dismantling these concurrent processes experimentally, by modifying the mindful training and psychoeducation components in MBCT to target a particular putative mechanisms (e.g. awareness training, decentering training, attitude training of non-judgement to inner experiences) to further understand which of these putative mechanisms play the biggest role in improving clinical outcomes and to what extend they interact and are part of a bigger mechanistic system.

The study has a number of strengths and limitations. While numerous studies have looked at putative mechanisms of MBCT, little is known about the relative explanatory power of these. A strength of the study is therefore that by comparing multiple putative mediators, and their explanatory effect, we were able to access the strongest and most robust mediators. Our choice of TAU as control group is on one hand a strength, in terms of generalizability, external validity and real-life application of MBCT, yet it is also a limitation. While both groups received treatment as usual, in the absence of a psychotherapeutic control group, we cannot infer whether the change in decentering and mindfulness are specific to MBCT treatment or whether other effective psychotherapeutic treatments may yield similar effects. However, previous research on MBCT for recurrent depression has found that change in decentering and mindfulness is specific to MBCT when compared with antidepressant treatment (Bieling et al., 2012; Kuyken et al., 2010), whereas Cognitive Behavioral Therapy (CBT) also increase decentering (N. Farb et al., 2018), consistent with the contention that, both MBCT and CBT help participants develop metacognitive skills despite the different teaching strategies (J. D. Teasdale et al., 2002).

Another limitation is that we did not conduct a priori mediation power analysis, meaning the study might be underpowered to detect small-medium mediation effects. For example, active listening to the body for insight (MAIA_body listening subscale) and the ability to sustain and control attention to body sensations (MAIA_attention regulation subscale) both predicted clinical outcomes post treatment and at 3 months follow up, and explained respectively 35% and 28% of the clinical effect, but were not significant mediators. This means that we cannot preclude as to the mechanistic relevance of these variables. However, as we were interested in identifying the strongest and most robust mediators, the results on decentering and mindfulness coming out highly significant and explaining 50 % and 41 % respectively of the effect, can be considered robust findings in terms of both effect and statistical uncertainty. Furthermore, several of the questionnaires employed assessed related aspects of putative mechanisms e.g. mindfulness including the ability to notice, step back and let go of distressing thoughts and images, interoceptive awareness, and decentering, and conceptually and statistically the questionnaires have overlapping variance. Hence, our findings do not suggest

these are competing mechanisms per se nor that only decentering and mindfulness offers a potential mechanistic explanation, but rather that decentering (as measured by the EQ) and mindfulness (as measured by the FFMQ) may be particular promising in explaining clinical outcomes, considering both statistical robustness and mediational effect.

Although we included a temporal gap in measurement of our mediator and clinical outcome, our results cannot establish causality between mediator and treatment outcome, as the clinical change and the mechanistic change both happened during treatment. However, a couple of things suggest that it is unlikely that change in decentering and mindfulness is only related to symptom change. For one, previous research has found that decentering seems only to increase in active treatments targeting decentering like MBCT and Cognitive Behavioral Therapy (Segal et al; 2019), but not in treatments not targeting decentering like antidepressant medication (Bieling, et al 2012). The same pattern seems to be the case for mindfulness (e.g. Kuyken et al., 2010). Furthermore, the strength of the inverse association between decentering and depressive symptoms were stronger post treatment than at baseline, and stronger for the MBCT group than the TAU group post treatment, making it less likely that change in decentering and mindfulness would be mainly a byproduct of symptom change. To establish temporal precedence, future studies could investigate the concurrent changes during the treatment, e.g., by including session-by-session measures, allowing for a more fine-grained temporal analysis. However, it is possible that changes in decentering, mindfulness and depressive symptoms is a result of an interactive and reciprocal process, and in this case, it may not be possible to establish temporal precedence. Instead future research could employ an experimental, component enhancing or dismantling design where decentering and mindfulness are manipulated to improve causal inferences, although the latter may require a large sample to detect smaller differential effects (Williams et al., 2014; van der Velden et al., 2015).

Future research may also want to assess the robustness of decentering and mindfulness as key mediators by using a meta-analytical approach. Furthermore, triangulation across methods (e.g. neuro imaging) could help improve the mechanistic understanding of the role decentering and mindfulness play in treatment for depression. Finally, decentering as measured by the experience questionnaire and mindfulness as measured by the FFMQ may also have biomarker potential i.e. participants experiencing increased decentering and mindfulness following MBCT may show long term benefits, and those that do not change may need further treatment, which could be investigated in a prospective trial.

CONCLUSION

While multiple mindfulness skills may play a role in MBCT's effect in reducing depressive symptoms, this study shows that particularly the ability to take a decentered perspective on one's experiences, and mindfully notice, step back and let go of distressing thoughts and images may be a core skill underlying clinical improvement in MBCT for recurrent depression.

Contributors
AMV, AR and WK were responsible for the original proposal and AMV secured funding for the trial. AMV developed the design and protocol, and AR, WK advised on the design. AMV was responsible for the general management of the study and LOF oversaw the clinical management of the study. AMV, and LOF collected the data. AMV, JMM, MSO, AR and WK created the analysis strategy. MSO and AMV analyzed the data. AMV, MSO, JMM, AR and WK interpreted the data. AMV wrote the initial draft. All authors contributed to, and approved, the final manuscript.

Acknowledgments
This research was funded by a Mind & Life Varela Award and Aase & Ejnar Danielsen Fonden to AMV. WK was supported by the Wellcome Trust (107496/Z/15/Z). The views expressed in this publication are those of the authors and do not necessarily reflect those of the funders. We thank all the GP practitioners and psychiatric units who helped with recruitment and Jacob Piet and Antonia Sumbundu for running the MBCT therapy. We thank Jonathan Kingslake and colleagues at P1vital for facilitating a platform for online data collection and provision of administrative support. We also thank the colleagues at the Danish Mindfulness Center, Interacting Minds Centre, Center for Functionally Integrative Neuroscience, Aarhus University and the Oxford Mindfulness Center, Oxford University, who have contributed to the study, through help with advice, recruitment, outcome assessment or provision of administrative support. Finally, we are grateful to the participants for their time in taking part in this trial.

Data sharing statement and trial registration
Deidentified individual participant data that underlie the results reported in this article, is available upon request to researchers with a methodological sound proposal. Proposals should be directed to the corresponding author. Group data, study protocol and analytical code will be made available for download on Github. The study was registered at ClinicalTrials.gov (NCT03353493).

Conflicts of interest
The author(s) declares the following potential conflicts of interest. WK is the director of the Oxford Mindfulness Centre. He receives payments for training workshops and presentations related to MBCT and donates all such payments to the Oxford Mindfulness Foundation, a charitable trust that supports the work of the Oxford Mindfulness Centre. WK was until 2015 an unpaid Director of the Mindfulness Network Community Interest Company and gave evidence to the UK Mindfulness All Party Parliamentary Group. He received royalties for several books on mindfulness published by Guilford Press. LOF is director of the Danish Centre for Mindfulness. She receives payments for presentations, workshops and teacher training related to MBSR and MBCT and donates payments to the Danish Centre for Mindfulness.

REFERENCES

1. Organization, W.H. *Depression fact sheet*. 2020; Available from: https://www.who.int/news-room/fact-sheets/detail/depression.
2. Buckman, J.E.J., et al., *Risk factors for relapse and recurrence of depression in adults and how they operate: A four-phase systematic review and meta-synthesis.* Clin Psychol Rev, 2018. **64**: p. 13-38.
3. Rottenberg, J., et al., *The Curious Neglect of High Functioning After Psychopathology: The Case of Depression.* Perspect Psychol Sci, 2018. **13**(5): p. 549-566.
4. Kennedy, N. and E.S. Paykel, *Residual symptoms at remission from depression: impact on long-term outcome.* J Affect Disord, 2004. **80**(2-3): p. 135-44.
5. Muller, M.J., et al., *Three dimensions of depression in patients with acute psychotic disorders: a replication study.* Compr Psychiatry, 1999. **40**(6): p. 449-57.
6. Kuyken, W., et al., *Efficacy of Mindfulness-Based Cognitive Therapy in Prevention of Depressive Relapse: An Individual Patient Data Meta-analysis From Randomized Trials.* JAMA Psychiatry, 2016. **73**(6): p. 565-74.
7. National Institute for Health and Care Excellence. *Depression in adults: recognition and management*. October 2009, updated April 2018.
8. Holmes, E.A., et al., *The Lancet Psychiatry Commission on psychological treatments research in tomorrow's science.* Lancet Psychiatry, 2018. **5**(3): p. 237-286.
9. Segal, M. Williams, and J.D. Teasdale, *Mindfulness-Based Cognitive Therapy for Depression*. 2nd ed. 2013, New York: The Guilford Press.
10. Grossmann, I., B.K. Sahdra, and J. Ciarrochi, *A Heart and A Mind: Self-distancing Facilitates the Association Between Heart Rate Variability, and Wise Reasoning.* Frontiers in behavioral neuroscience, 2016. **10**: p. 68-68.
11. van der Velden, A.M., et al., *A systematic review of mechanisms of change in mindfulness-based cognitive therapy in the treatment of recurrent major depressive disorder.* Clin Psychol Rev, 2015. **37**: p. 26-39.
12. Alsubaie, M., et al., *Mechanisms of action in mindfulness-based cognitive therapy (MBCT) and mindfulness-based stress reduction (MBSR) in people with physical and/or psychological conditions: A systematic review.* Clin Psychol Rev, 2017. **55**: p. 74-91.
13. Segal, Z.V., et al., *Practice of therapy acquired regulatory skills and depressive relapse/recurrence prophylaxis following cognitive therapy or mindfulness based cognitive therapy.* J Consult Clin Psychol, 2019. **87**(2): p. 161-170.
14. Kearns, N.P., et al., *Does rumination mediate the relationship between mindfulness and depressive relapse?* Psychol Psychother, 2016. **89**(1): p. 33-49.
15. Gu, J., et al., *How do mindfulness-based cognitive therapy and mindfulness-based stress reduction improve mental health and wellbeing? A systematic review and meta-analysis of mediation studies.* Clin Psychol Rev, 2015. **37**: p. 1-12.
16. Bieling, P.J., et al., *Treatment-specific changes in decentering following mindfulness-based cognitive therapy versus antidepressant medication or placebo for prevention of depressive relapse.* J Consult Clin Psychol, 2012. **80**(3): p. 365-72.
17. Beck, A.T., et al., *Comparison of Beck Depression Inventories -IA and -II in psychiatric outpatients.* J Pers Assess, 1996. **67**(3): p. 588-97.
18. Rush, A.J., et al., *The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression.* Biol Psychiatry, 2003. **54**(5): p. 573-83.
19. Trivedi, M.H., et al., *The Inventory of Depressive Symptomatology, Clinician Rating (IDS-C) and Self-Report (IDS-SR), and the Quick Inventory of Depressive Symptomatology, Clinician Rating (QIDS-C) and Self-Report (QIDS-SR) in public sector patients with mood disorders: a psychometric evaluation.* Psychol Med, 2004. **34**(1): p. 73-82.

20. Fresco, D.M., et al., *Initial psychometric properties of the experiences questionnaire: validation of a self-report measure of decentering.* Behav Ther, 2007. **38**(3): p. 234-46.
21. Mehling, W.E., et al., *The Multidimensional Assessment of Interoceptive Awareness (MAIA).* PLoS One, 2012. **7**(11): p. e48230.
22. Gu, J., et al., *Examining the factor structure of the 39-item and 15-item versions of the Five Facet Mindfulness Questionnaire before and after mindfulness-based cognitive therapy for people with recurrent depression.* Psychol Assess, 2016. **28**(7): p. 791-802.
23. Kasch, K.L., D.N. Klein, and M.E. Lara, *A construct validation study of the Response Styles Questionnaire Rumination Scale in participants with a recent-onset major depressive episode.* Psychol Assess, 2001. **13**(3): p. 375-83.
24. Hayes, A.F. and M. Scharkow, *The relative trustworthiness of inferential tests of the indirect effect in statistical mediation analysis: does method really matter?* Psychol Sci, 2013. **24**(10): p. 1918-27.
25. Lockhart, G., D.P. MacKinnon, and V. Ohlrich, *Mediation analysis in psychosomatic medicine research.* Psychosom Med, 2011. **73**(1): p. 29-43.
26. Hayes, A.F. and N.J. Rockwood, *Regression-based statistical mediation and moderation analysis in clinical research: Observations, recommendations, and implementation.* Behav Res Ther, 2017. **98**: p. 39-57.
27. Cohen, S., T. Kamarck, and R. Mermelstein, *A global measure of perceived stress.* J Health Soc Behav, 1983. **24**(4): p. 385-96.
28. Baer, R.A., et al., *Construct validity of the five facet mindfulness questionnaire in meditating and nonmeditating samples.* Assessment, 2008. **15**(3): p. 329-42.
29. Roelofs, J., et al., *On the measurement of rumination: a psychometric evaluation of the ruminative response scale and the rumination on sadness scale in undergraduates.* J Behav Ther Exp Psychiatry, 2006. **37**(4): p. 299-313.
30. Farb, N., et al., *Prevention of relapse/recurrence in major depressive disorder with either mindfulness-based cognitive therapy or cognitive therapy.* J Consult Clin Psychol, 2018. **86**(2): p. 200-204.
31. Farb, N., et al., *Interoception, contemplative practice, and health.* Front Psychol, 2015. **6**: p. 763.
32. Kuyken, W., et al., *How does mindfulness-based cognitive therapy work?* Behav Res Ther, 2010. **48**(11): p. 1105-12.
33. Teasdale, J.D., et al., *Metacognitive awareness and prevention of relapse in depression: empirical evidence.* J Consult Clin Psychol, 2002. **70**(2): p. 275-87.

Supplement S1: Correlations across treatment group and time

Correlations

Interven			EQ_pre	EQ_post	QIDS_pre	QIDS_post	FFMQ_pre	FFMQ_post
MBCT	EQ_pre	Pearson Correlation	1	.218	-.307*	-.043	.681**	.119
		Sig. (2-tailed)		.166	.043	.784	.000	.452
		N	48	42	44	44	48	42
	EQ_post	Pearson Correlation	.218	1	-.311*	-.614**	.169	.768**
		Sig. (2-tailed)	.166		.042	.000	.286	.000
		N	42	43	43	43	42	43
	QIDS_pre	Pearson Correlation	-.307*	-.311*	1	.387**	-.338*	-.211
		Sig. (2-tailed)	.043	.042		.008	.025	.174
		N	44	43	46	46	44	43
	QIDS_post	Pearson Correlation	-.043	-.614**	.387**	1	-.074	-.506**
		Sig. (2-tailed)	.784	.000	.008		.634	.001
		N	44	43	46	46	44	43
	FFMQ_pre	Pearson Correlation	.681**	.169	-.338*	-.074	1	.313*
		Sig. (2-tailed)	.000	.286	.025	.634		.044
		N	48	42	44	44	48	42
	FFMQ_post	Pearson Correlation	.119	.768**	-.211	-.506**	.313*	1
		Sig. (2-tailed)	.452	.000	.174	.001	.044	
		N	42	43	43	43	42	43
TAU	EQ_pre	Pearson Correlation	1	.702**	-.463*	-.369	.694**	.489*
		Sig. (2-tailed)		.000	.020	.070	.000	.015
		N	27	24	25	25	27	24
	EQ_post	Pearson Correlation	.702**	1	-.373	-.472*	.607**	.741**
		Sig. (2-tailed)	.000		.080	.023	.002	.000
		N	24	24	23	23	24	24
	QIDS_pre	Pearson Correlation	-.463*	-.373	1	.590**	-.277	-.195
		Sig. (2-tailed)	.020	.080		.002	.180	.372
		N	25	23	25	25	25	23
	QIDS_post	Pearson Correlation	-.369	-.472*	.590**	1	-.062	-.245
		Sig. (2-tailed)	.070	.023	.002		.770	.261
		N	25	23	25	25	25	23
	FFMQ_pre	Pearson Correlation	.694**	.607**	-.277	-.062	1	.751**
		Sig. (2-tailed)	.000	.002	.180	.770		.000
		N	27	24	25	25	27	24
	FFMQ_post	Pearson Correlation	.489*	.741**	-.195	-.245	.751**	1
		Sig. (2-tailed)	.015	.000	.372	.261	.000	
		N	24	24	23	23	24	24

*. Correlation is significant at the 0.05 level (2-tailed).

**. Correlation is significant at the 0.01 level (2-tailed).

Abbreviations: QIDS: Quick Inventory of Depressive Symptomology (Rush et al., 2003); EQ: Experience Questionnaire(Fresco, Moore, et al., 2007); FFMQ: Five Factor Mindfulness Questionnaire(R. A. Baer et al., 2008); pre: pre treatment; Post: post treatment; MBCT: Mindfulness-based cognitive therapy; TAU: treatment as usual.

Supplement S2: Correlations between change scores in the mediators

Correlations[a]

		FFMQ_AA_change	FFMQ_NJ_change	FFMQ_NR_change	FFMQ_DE_change	FFMQ_OB_change	EQ_change	FFMQ_change
FFMQ_AA_change	Pearson Correlation	1	.198	.220	.026	.448**	-.343*	-.537**
	Sig. (2-tailed)		.209	.161	.870	.003	.026	.000
	N	42	42	42	42	42	42	42
FFMQ_NJ_change	Pearson Correlation	.198	1	.519**	.436**	.402**	-.447**	-.774**
	Sig. (2-tailed)	.209		.000	.004	.008	.003	.000
	N	42	42	42	42	42	42	42
FFMQ_NR_change	Pearson Correlation	.220	.519**	1	.430**	.615**	-.637**	-.815**
	Sig. (2-tailed)	.161	.000		.004	.000	.000	.000
	N	42	42	42	42	42	42	42
FFMQ_DE_change	Pearson Correlation	.026	.436**	.430**	1	.162	-.457**	-.549**
	Sig. (2-tailed)	.870	.004	.004		.305	.002	.000
	N	42	42	42	42	42	42	42
FFMQ_OB_change	Pearson Correlation	.448**	.402**	.615**	.162	1	-.661**	-.765**
	Sig. (2-tailed)	.003	.008	.000	.305		.000	.000
	N	42	42	42	42	42	42	42
EQ_change	Pearson Correlation	-.343*	-.447**	-.637**	-.457**	-.661**	1	.728**
	Sig. (2-tailed)	.026	.003	.000	.002	.000		.000
	N	42	42	42	42	42	42	42
FFMQ_change	Pearson Correlation	-.537**	-.774**	-.815**	-.549**	-.765**	.728**	1
	Sig. (2-tailed)	.000	.000	.000	.000	.000	.000	
	N	42	42	42	42	42	42	42

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

a. Interven = 1

Correlations between change scores in the mediators in the MBCT group. Abbreviations: QIDS: Quick Inventory of Depressive Symptomology (Rush et al., 2003); EQ: Experience Questionnaire(Fresco, Moore, et al., 2007); FFMQ: Five Factor Mindfulness Questionnaire(R. A. Baer et al., 2008); and the subscales NR: Non-reactivity to inner experiences; NJ: Non-judging of inner experiences; DE: Describing; AA: Acting with awareness; OB: Observing.

Supplement:S3 Group x time effects

ANOVA based on treatment allocation

		Sum of Squares	df	Mean Square	F	Sig.
FFMQ_change*	Between Groups	526.080	1	526.080	8.362	.005
	Within Groups	4026.238	64	62.910		
	Total	4552.318	65			
EQ_change*	Between Groups	881.048	1	881.048	16.768	.000
	Within Groups	3362.839	64	52.544		
	Total	4243.887	65			
RRS_change	Between Groups	150.717	1	150.717	1.290	.260
	Within Groups	7475.420	64	116.803		
	Total	7626.137	65			
MAIA_NO_change*	Between Groups	150.286	1	150.286	14.679	.000
	Within Groups	655.244	64	10.238		
	Total	805.530	65			
MAIA_ND_change	Between Groups	12.175	1	12.175	1.433	.236
	Within Groups	543.643	64	8.494		
	Total	555.818	65			
MAIA_EA_change*	Between Groups	388.285	1	388.285	20.746	.000
	Within Groups	1197.847	64	18.716		
	Total	1586.132	65			
MAIA_AR_change*	Between Groups	415.247	1	415.247	17.869	.000
	Within Groups	1487.238	64	23.238		
	Total	1902.485	65			
MAIA_BL_change*	Between Groups	115.500	1	115.500	23.617	.000
	Within Groups	313.000	64	4.891		
	Total	428.500	65			
QIDS_change*	Between Groups	273.547	1	273.547	11.610	.001
	Within Groups	1625.777	69	23.562		
	Total	1899.324	70			

Abbreviations: QIDS: Quick Inventory of Depressive Symptomology (Rush et al., 2003); EQ: Experience Questionnaire(Fresco, Moore, et al., 2007); FFMQ: Five Factor Mindfulness Questionnaire(R. A. Baer et al., 2008); RRS: Rumination Response Scale(Roelofs et al., 2006); MAIA (Multidimensional Assessment of Interoceptive Awareness(Mehling et al., 2012), and the subscales of AR: Attention Regulation; BL: Body listening; NO: Noticing; TR: Trusting; ND: Non distracting; EA: Emotional awareness.