Differential effects of mindfulness-based cognitive therapy (MBCT) versus matched psycho-education on depression symptom networks in the Staying Well after Depression trial: A network intervention analysis

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Introduction

The dodo-bird verdict is approaching its 100th year anniversary since Rosenzweig claim that all psychotherapies, regardless of their specific components, produce equivalent outcomes (Rosenweig, 1936). Despite significant evolution in psychotherapies, trials and meta-analyses still reach similar overall conclusions in support of Rosenweig's claim (Cuijpers et al., 2019). The interpretation of this finding has led to a divergence in views. For some researchers this suggests that the largely equivalent performance is due to the common factors that all therapies share. For other researchers, there exist specific elements unique to a therapy's modality but is being disguised by the largely similar outcomes. Recent theoretical and statistical advances may provide an avenue through which to demarcate this divergence.

Psychotherapies have been shown to be largely effective at treating a wide range of psychopathologies (Depression (Cuijpers et al., 2014), Anxiety related disorders (Pompoli et al., 2018) and PTSD (Cusack et al., 2014)). However, the specific mechanisms of change through which these therapies achieve outcomes, whilst largely unknown, is theorised to be different. For example, elements of cognitive behaviour therapy (CBT) and mindfulness-based interventions (Acceptance and Commitment Therapy (Hayes et al., 2009) & Mindfulness Based Stress Reduction (Kabat-Zinn, 1996) have opposing notions in relation to dealing with experience. CBT attempts to change a person's perception of events through a change in belief structures (Beck & Beck, 1995) whilst mindfulness-based interventions, instead attempt to alter the relationship and function to the experience. Despite such contrasting approaches, these therapies have achieved largely similar outcomes (Manicavasgar et al., 2011; Kladnitski et al., 2020; Tovote et al., 2014). Compounding this problem, Cuijpers et al., (2019) identified that most studies have focused on showing that a treatment works rather than investigating how it works. As such it is unclear whether therapies work through common factors or specific factors which have been postulated. Indeed, as Dalgleish et al., (2020) explored, the additional efficacy of a specific therapy over and above the common factors which therapies share are likely to be small and therefore most studies may be underpowered to detect such effects.

Traditional randomised controlled studies comparing active treatments, carry with it a number of limitations. For example, Forman et al (2007) compared CBT to ACT in the treatment of anxiety and depression to explore potential mechanisms of action. Both treatments contained strong behavioural components, which means the hypothetical mechanism of action is confounded. Similarly, most trials tend to compare a treatments effectiveness through the comparison of sum-

scores and diagnosis. Research has suggested this may be inappropriate, as symptoms have been shown to differ respect to predicting work related performance (Johnston et al., 2019) and functional outcomes (Fried & Neese., 2014). As this is incommensurate with the notion of symptom equivalence and diagnostic approaches, new approaches have argued for a symptom focused approach.

In recent years there has been a challenge to the current conceptualisation of mental disorders. Network theory argues that psychopathology is the result of dynamic interactions between symptoms rather than the symptoms being the product of a latent construct (Borsboom et al., 2017). Research has now begun to explore whether treatments effect specific symptoms within and structure of the network. Blanken et al., (2019) used network analysis to investigate weekly treatment (CBT for insomnia) effects on symptom networks. Encouragingly, Blanken et al., (2019) found that CBT for insomnia was directly targeting symptoms related to the maintenance of the disorder and was consistent with the therapy's content and progress. Interestingly, Blanken et al.,(2019) found evidence to suggest the structure of the network also changed over the course of treatment. Recently developed techniques may help to elucidate these structural effects.

In an attempt to better understand networks of symptoms, moderated network models have recently been proposed as a way to investigate more complex interactions (Haslbeck et al 2019). Currently within the state-of-the-art network models (GGM or Ising), interactions between pairs of variables represent conditionally independent relationships. This means that symptoms are investigated as dyads and assumes that the relationship between two variables is not dependent on a third variable. This may be problematic when we consider that there exist many such moderation effects in psychological treatments (e.g. Newman et al., 2019, Kolko et al., 2000)). Such relationships may not be captured accurately using traditional network models and may result in a network that is averaged across such moderator effects (Haslbeck et al., 2019). Given treatments are hypothesised to work across symptom and network levels (Borsboom et al., 2017) differential treatment effects may be observed at this level of analysis.

In efforts to better elucidate a treatment's mechanism of action, so called dismantling trials have been conducted. These trials involve the active comparison between two active intervention which differ with respect to a component. For example, Williams et al., (2014) conducted a randomised controlled dismantling trial of mindfulness based cognitive therapy for preventing relapse in people with recurrent depression that was in remission. The trial compared a mindfulness training program (MBCT), a cognitive psychological education program (CPE) and treatment as usual, an active control condition in which participants were instructed to seek help should they require. The trial had two

active treatments (MBCT and CPE) which only differed with respect to the addition of the meditation component in session and through homework practice. Analysis revealed that there was no main effect for treatment group in relation to risk of relapse. However, the analysis only evaluated the effects of the intervention in relation to sum scores and binary outcome measures pre and post intervention. Given both active treatments only differed with respect to the meditation component and had comparable effects, this trial represents an opportunity to explore whether network based analytic methods could be used to explore unique treatment effects. It is hypothesised that despite the largely similar outcomes there will be differences observed between each treatment in relation to the symptoms they are affecting.

Method

Sample

Data come from the Staying Well After Depression (SWAD) trial (Williams et al., 2014). In this trial, 255 remitted depressed patients were randomly allocated between three groups (MBCT n = 108, CPE n = 110 and TAU n = 55) in a 2:2:1 ratio. The participants had a mean age of 43 years (SD = 12; range = 18-68) at entry to the study; 198 (72%) were female). (see Williams et al., 2014).

Measures

The nine-item Patient Health Questionnaire (PHQ-9) is a reliable and valid measure of depression severity across the previous week (Kroenke et al., 2001). Items are scored as 0 (not at all), 1 (several days), 2 (more than half the days), or 3 (nearly every day). For the analysis each item is analysed on an individual basis. Details of each item is provided in Table 1.

The seven item Generalized Anxiety Disorder scale (Spitzer et al., 2006) has excellent reliability and validity as measure of anxiety symptoms across the previous week (Löwe et al., 2008) Items are scored as 0 (not at all), 1 (several days), 2 (more than half the days), or 3 (nearly every day). For the analysis each item is analysed on an individual basis. Details of each item is provided in Table 1.

Table 1. Individual items of the PHQ-9 and GAD-7

	PHQ-9	GAD-7
Item 1	Little interest or pleasure in doing things	Feeling nervous, anxious, or on edge
Item 2	Feeling down, depressed, or hopeless	Not being able to stop or control worrying

Item 3	Trouble falling or staying asleep or sleeping too much	Worrying too much about different things
Item 4	Feeling tired or having little energy	Trouble relaxing
Item 5	Poor appetite or overeating	Being so restless that it is hard to sit still
Item 6	Feeling bad about yourself – or that you are a failure or have let yourself or your family down	Becoming easily annoyed or irritable
Item 7	Trouble concentrating on things such as reading the newspaper or watching television	Being afraid as if something awful might happen
Item 8	Moving or speaking so slowly that other people could have noticed? Or the opposite – being so fidgety or restless that you have been moving around a lot more than usual	
Item 9	Thoughts that you would be better off dead or of hurting yourself in some way	

Procedure

Trial participants underwent a detailed baseline assessment involving a semi-structured clinical interview and self-completed questionnaires, including the PHQ-9 and the GAD-7. Following this, patients were then randomised into three different groups, two of which were the active treatments, and the focus of the current study. The two treatments, MBCT and CPE (see below), both consisted of weekly classes each of two hours duration, for a total of 8 weeks. Prior to the beginning of each session, each participant completed the PHQ-9 and GAD-7 in relation to their experience of these symptoms in the previous week since the previous treatment session. Following the completion of the eight-week program, participants then completed a post treatment assessment, including the PHQ-9 and GAD-7. In summary, therefore, there was a total of 10 assessment time points, with 8 time points specifically occurring during the active treatment phase, that were used in the current analysis.

Active Interventions

Mindfulness-Based Cognitive Therapy

MBCT is a manualized eight-week group skills training program (Segal et al., 2002) that integrates the psycho-education aspects of CBT for depression with meditation components drawn from mindfulness-based stress reduction (MBSR; Kabat-Zinn, 1990). The MBCT delivered in the SWAD trial followed the manual of Segal et al. (2002) but with a greater focus on suicide prevention. The training in meditation skills included practicing sustained attentional focus and adopting a decentred view of thoughts, both during the group sessions and individually as homework.

Cognitive Psycho-Education (CPE)

CPE was developed specifically for the trial and comprised all elements of the MBCT program except the experiential cultivation of mindfulness through meditation practice. The program was focused on learning about psychological processes and participants were provided with tools and techniques for recognising warnings signs of depression and disengaging from unhelpful cognitive processes such as rumination and experiential avoidance. CPE followed the same format as MBCT. The CPE group completed the same homework as the MBCT group, but without the meditation practice.

An overview of the key weekly elements including the rationale, structure and homework, for the respective interventions is provided in the Supplementary Materials; Table S1.

Missingness

The current analytic methods cannot handle missing data therefore list-wise deletion was used. As the networks were estimated individually each week, we did not need to omit a participant altogether, only for the week they were not in attendance. The average missingness for the MBCT group was 16 people per week, whilst the average for the CPE group was 14 people per week. A summary of weekly data missingness is provided in the Supplementary Materials; Table S2

Analysis Plan

Analysis was conducted in R version 4.0.0 (R Core Team, 2013). As the networks included a dichotomous variable (treatment condition [MBCT or CPE]) and continuous variables (PHQ-9 and GAD-7 symptoms), the R-package *mgm* (Version 1.2; Haslbeck & Waldorp, 2020) was used to estimate pairwise mixed graphical models to explore both pairwise interactions and moderation effects. This package uses the glmnet package (Friedman et al., 2009) to fit penalized generalized linear models to perform neighbourhood selection (Meinshausen & Uhlmann., 2006). The analysis aimed to explore the moderation effects of the two active treatment interventions on depression and anxiety symptoms, by using the estimation procedure outlined below.

Estimation Procedure

Network Intervention Analysis (NIA) was conducted following procedures outlined by Blanken et al., (2019). This type of analysis allows us to evaluate the differential impact of the two treatments on individual symptoms. Specifically, unregularized Gaussian graphical models were constructed from items from the PHQ-9 and GAD-7 in conjunction to a treatment allocation variable (MBCT or CPE). Unregularized Gaussian graphical models were used as Epskamp et al. (2017) identified this to be an appropriate procedure when the researcher's aim is towards discovery. Cross-validation was used to select the optimal tuning parameter using 10 folds. In the estimated networks, edges represent unique linear relationships between pairs of variables while adjusting for all other variables (i.e., conditional dependence relationships). Since the variable "treatment" can influence the symptom variables, but not vice versa, an edge between the treatment node and a symptom identifies the symptoms that are directly affected by treatment. To evaluate the robustness of the networks, we evaluated the accuracy of the edge-weights using bootstrapped 95% Cis. Cis were calculated using the range of 100 bootstrapped samples for each edge-weight.

We used Moderated Network Models (MNMs) to evaluate the differential impact of the two treatments on the *relationships* between symptoms. In MNM each pairwise interaction can be a function of a specified set of moderator variables. That is, this model includes moderation, or 3-way interactions. Similar to the unregularized Gaussian graphical models, the treatment node was set as the moderator, with MBCT encoded as 1 and CPE encoded as 0. Similar to the above, since the treatment allocation was randomized, it cannot have been influenced by any of the other variables (i.e., symptoms) in the model. Cross-validation was used to select the optimal tuning parameter which was set to 10 folds. In addition to this, an additional thresholding was applied to control the rate of false-positive edges (Haslbeck et al., 2019). In NMNs, edges indicate which variables are associated, with the thickness of the edge indicating the strength of the effect and the number a quantification of this strength. To investigate the nature of the effect of any observed moderation effects, the treatment variable is conditioned on each of its values (0,1). The pairwise MGMs are then computed using qgraph, to observe the conditional dependent relationships between the variables. Finally, to assess the stability of the moderated network models, we will inspect the bootstrapped distribution of all parameters

We also computed the proportion of variance of each node explained by all of its neighbours, in both networks (Haslbeck & Waldorp, 2018). Termed predictability, this is represented by the ring around each symptom node in the graph.

Results

The means and standard deviations across the two treatments and the eight sessions for the PHQ-9 and the GAD-7 are presented in the supplementary (Table S3). At baseline there were no significant differences between the MBCT and CPE groups.

Network Intervention Analysis

The analysis focused on exploring the symptom-specific treatment effects across the active treatment sessions. The questionnaire asks participant to self-report on symptoms from the previous week. This means that the effects of that session will be localised to the following session when the participant completes the questionnaire.

The NIA results comparing MBCT and CPE are presented in Figure S4-S11, which shows the sequential session-by-session development of symptom-specific treatment effects throughout the active treatment sessions. In these graphs, positive green edges between the "treatment" variable and symptoms indicate that participants in the MBCT group (encoded as 1) had, on average, higher scores on that symptom than participants in the CPE group (encoded as 0). Likewise, negative red edges between the "treatment" variable and symptoms indicate that participants in the CPE group (encoded as 0) had, on average, higher scores than participants in the MBCT group (encoded as 1). The size of the treatment effect on each symptom is represented by the thickness of the edge, with thicker lines indicating a larger effect.

The edges between the treatment and symptom variables revealed differential treatment effects evident immediately following Session 1, on understanding the nature of the mind and cycle of symptoms. The MBCT group scored lower on the PHQ-item-6 (Self-Criticism; Edge Weight (EW) = .12) and the PHQ-item-1 (Anhedonia; EW = .11) and higher on the GAD-item-6 (Irritability; EW = .14. Following Session 4, on understanding our reactions to events through present based awareness, the MBCT group interestingly scored higher on the PHQ-item-4 (Tiredness; EW = .11). Following Session 5 on Cultivating Acceptance, the MBCT scored lower on the GAD-item-4 (Trouble Relaxing; EW = .8) and this continued following Session 6 on 'thoughts are not facts' (EW = .17) and Session 7 on How Can I Best Take Care of Myself (EW = .09). Following Session 5 the MBCT group also scored lower on the PHQ-item-9 (Suicide; EW = .13). Finally, after the last Session (Using What You Have Learned), the MBCT group scored lower on the PHQ-item-7 (Concentration Difficulties; EW = .1) and higher on the PHQ-item-5 (Appetite Changes; EW = .13). A summary of these findings is presented in Table 1.

Table 1. Summary of the treatment effects across treatment sessions for the MGMs

Session	Symptom	Edge Weight (EW)	CPE (mean(SD))	MBCT (mean(SD))
1	PHQ-1 Anhedonia	.12	0.68 (.84)	0.47 (.60)
1	PHQ-6 Self-criticism	.11	0.76 (.91)	0.54 (.65)
1	GAD-6 Irritability	.14	0.69 (.75)	0.82 (.70)
4	PHQ-4 Tiredness	.11	0.84 (.85)	1.13 (.89)
5	GAD-4 Trouble Relaxing	.80	1.15 (.95)	0.90 (.88)
5	PHQ-9 Suicide	.13	0.16 (.52)	0.06 (.23)
6	GAD-4 Trouble Relaxing	.17	1.03 (.84)	0.89 (.82)
7	GAD-4 Trouble Relaxing	.09	0.82 (.87)	0.89 (.84)
8	PHQ-7 Concentration Difficulties	.10	0.57 (.82)	0.41 (.73)
8	PHQ-5 Appetite Changes	.13	0.43 (.74)	0.66 (.97)

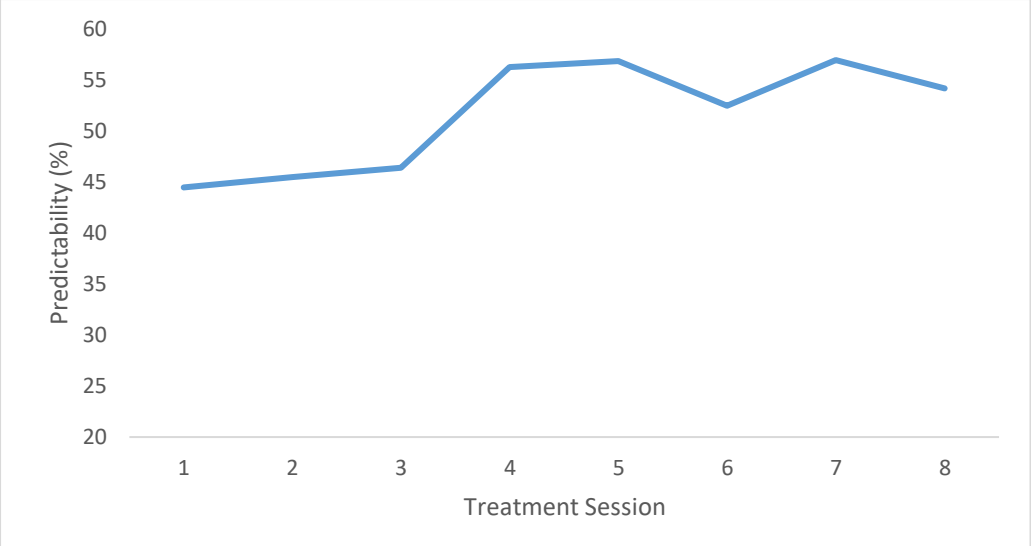
For the moderated network models, there were both differential treatment effects on the symptoms as in the previous analysis, but also differential treatment effects on the relationships between symptoms (see Figures S12-S19). Following Session 5 (Acceptance, Holding, Allowing and Letting Be), a three-way interaction revealed that treatment moderated the association between GAD-item-1 (Feeling Nervous/Anxious) and GAD—item-6 (Irritability) such that MBCT was associated with a stronger association between these symptoms relative to the CPE group (see Figure S16). Following Session 6 (Thoughts Are Not Facts, a three-way interaction was observed between treatment, GAD-item-4 (Trouble Relaxing) and GAD-item-7 (Feeling Afraid) with the MBCT group showing a stronger relationship between these symptoms relative to the CPE group (see Figure S17). (see Table 2).

Table 2. Summary of the Moderated treatment effects in the MNMs

Session	Symptom	Relationship	Direction of Effect	Edge Weight
5	Treatment-GAD 1-GAD 6	3-way	Positive	0.16
6	Treatment-GAD 4-GAD7	3-Way	Positive	0.25

The Predictability of the nodes systematically increased over time from on average 44.5% at Session 1 to 54.2% following Session 8, with the maximum predictability occurring following Session 7 (57%) (see Figure 3.). There was no systematic increase or decrease in symptom variance over the course of treatment that drove the increase in predictability, highlighting that the network was becoming more self-determined and less influenced by variables not included in the analysis, suggesting that treatment alters the structure of the network.

Figure 3. Predictability of Nodes across Treatment Sessions



Stability

Stability analysis in which we bootstrapped the sampling distribution of all the parameters. For both the NIA and the MNM, we see that the variances are larger relative to their means. This indicates that the effects observed are potentially unstable and the results must therefore be interpreted with caution.

Discussion

Evaluating treatment effects has traditionally focused on analysing differences in sum-scores in a pre-post experimental design and comparing the unique components of different therapies. The current research investigated whether differential treatment effects could be investigated using two novel network analysis techniques. The current research found differential treatment effects for two active interventions MBCT and CPE on specific symptoms. The current analysis also found evidence that treatment moderated the relationship between symptoms. Given the subtraction design of the study, this suggests the unique effects of meditation. Taken together, the analysis found that whilst MBCT and CPE achieved similar outcomes in terms of relapse prevention, the mechanism through which it achieved this outcome appeared to be different.

According to the network perspective, psychopathology behaves as a complex dynamic system (Borsboom., 2017; Borsboom & Cramer 2013). The development of a disorder or a relapse from this perspective is synonymous with the spread of a contagion (Fried et al., 2017; Schmittman et al., 2013). That is, the tendency of activation in one symptom causes a cascade of activation, which in turn causes the network to evolve into a self-sustaining state of high activation. The results of this study suggest two processes through which treatment in this context may prevent relapse. Firstly, treatment appears to reduce or prevent the activation of a particular symptom. Secondly,

treatment appears to influence the relationship between symptoms either; modifying the relationship to encourage more deactivation in other symptoms or reducing the strength of the relationship between symptoms. Thus, where the development of a disorder is characterised by a cascade of activation, treatment may be conceptualised as being a deconstructive and decoupling process.

Overall, the analysis revealed that the meditation treatment effects were more localised to anxiety and physiologically based symptoms as opposed to depression symptoms. This may not be surprising given patients current diagnostic status with regards to depression was 'remitted.' Nevertheless, the most consistent and strong direct effect was observed for the MBCT group scoring lower on the 'Difficulty relaxing' symptom. In meditation exercises, relaxation is framed as a by-product of the exercise rather than the focus, but this effect accords with self-reported experience (Sears et al., 2011). Indeed, the physiological effects of meditation and relaxation have been shown to be comparable (Jain et al., 2007; Lehrer 1983) particularly in beginner meditators (Fell et al ., 2010). Interestingly, where the meditation appeared to have direct symptom effects the cognitive intervention appeared to work through a different mechanism.

The moderation effects were localised to the latter weeks of treatment. These moderation effects were observed to occur between physiological symptoms and cognitive symptoms. The direction of the effect suggests that the cognitive intervention moderated the activation of these symptoms more so than in the MBCT group. This mechanism of change accords with the hypothesised mechanism of action in a cognitive intervention such that change in perception modifies a person's reaction to the stimulus (Beck & Beck., 1995). Such moderation effects also correlate with the content of the week whose major theme was 'thoughts are not facts.' That this moderation occurred during the latter stages of treatment highlights that cognitive processes may reflect a slow change process whereas changes to physiological symptoms represent a fast change process. Given the exploratory nature of this research, further investigation will be required.

Considerations

Two experimental techniques were used in the analysis of this data. Given the sample size and the exploratory nature of this research, cross validation was used to select the tuning parameter, which can increase the chances of a type 1 error. Indeed, one direct symptom effect occurred in the first week before treatment had even begun. Results of the bootstrapping indicated that there existed reliable edges, which highlight the potential for these techniques to be used to further utilised to enhance our understanding of a treatments effect. However, in the models there is an assumption that 'treatment' was the only moderating variable. This means that we did not

consider whether a specific symptom could moderate the relationship between two other symptoms, however such methods are not currently available.

Another important consideration relates to the simultaneous comparison between MGM and MNM graphs. When we directly compare across the two different approaches, some of the two-way interactions found in approach one were not recovered in approach two. This is most likely a 'power problem' because more edges are being estimated in the MNMs. Further research is required to validate this study's current findings especially considering the potential new insights that such an approach may offer.

Conclusion

The current investigation explored differential treatment effects on symptoms of anxiety and depression. This exploratory research appeared to show treatment dependent direct and indirect symptom effects. Whilst results of this analysis requires replication in larger samples, this approach may provide an avenue through which to uncover the mechanisms of psychological treatments. Such insights will be essential for understanding how to best optimise and provide the most potent intervention and assist Clinician's decision making.

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