EVALUATING DEFAULT MODE NETWORK RESTING-STATE FUNCTIONAL CONNECTIVITYAS A BIOMARKER OF TREATMENT RESPONSE TO MINDFULNESS-BASED COGNITIVE THERAPY FOR ANHEDONIA

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ABSTRACT

Paul Michael Cernasov: Evaluating Default Mode Network Resting-State Functional Connectivity as a Biomarker of Treatment Response to Mindfulness-Based Cognitive Therapy for Anhedonia
(Under the direction of Gabriel Dichter)

Anhedonia is a transdiagnostic symptom referring to impairments in motivation and pleasure. Depression and other anhedonic disorders are associated with aberrant function in the default mode network (DMN), the neural substrates of self-referential processing. Mindfulness practice has shown therapeutic value for mood impairments and alters DMN functioning. The current study examined whether DMN resting-state connectivity is a biomarker for treatment response to Mindfulness-Based Cognitive Therapy (MBCT, n=35), as compared to a novel psychosocial intervention (n=38), in a transdiagnostic sample of adults with clinically-significant anhedonia. Multiple regression and multilevel modeling were used to evaluate relations between connectivity and treatment effects. Anhedonia symptoms and DMN connectivity significantly decreased over time, equally across treatments. Contrary to predictions, baseline and changes in connectivity were unrelated to outcomes. Results showed DMN connectivity was neither a predictor nor mechanism of response to MBCT, but that attenuation of DMN connectivity may be a non-specific psychological treatment effect.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

BATA	Behavioral Activation Treatment for Anhedonia
DMN	Default Mode Network
FDR	False Discovery Rate
GE	Global Efficiency
ICA	Independent Component Analysis
LE	Local Efficiency
LLPC	Left Lateral Parietal Cortex
MBCT	Mindfulness-Based Cognitive Therapy
MBI	Mindfulness Based Intervention
MDD	Major Depressive Disorder
MPFC	Medial Prefrontal Cortex
PCC	Posterior Cingulate Gyrus
RLPC	Right Lateral Parietal Cortex
ROI	Region of Interest

CHAPTER 1: INTRODUCTION

Impairments in pleasure and motivation (i.e., anhedonia) are central to a broad spectrum of psychopathology. Perhaps more than any other condition, Major Depressive Disorder (MDD) is closely associated with anhedonia (Pizzagalli, 2014). Despite a panoply of empirically supported treatments for MDD and its associated symptoms, no treatment is effective for all individuals. Clinical practice for managing MDD symptoms involves trial-and-error selection of various medications, psychotherapy modalities, or neurostimulation techniques. As few as one third of individuals remit within three months of standard treatment (Rush et al., 2006), and the probability of remission decreases as a function of total interventions attempted thereafter (Pigott, 2015). Importantly, anhedonia represents one of the most treatment-resistant symptoms of MDD and other forms of psychopathology (Buckner et al., 2008; Wolf, 2006).

Validated biomarkers are needed to help guide treatment selection for anhedonia. Default Mode Network (DMN) function has received increasing attention as a candidate biomarker of treatment response in psychiatric conditions because DMN abnormalities are associated with various psychiatric symptoms (Sharma et al., 2017; Simon & Engstrom, 2015). Mindfulness-based interventions (MBIs) are empirically-supported treatments that show comparable efficacy to first-line treatments for reducing symptoms of MDD (Strauss et al., 2014). In non-clinical samples, mindfulness practice modulates DMN function; however, the neural mechanisms by which mindfulness treats MDD and related symptoms are unclear (Vignaud et al., 2018). No study to date has identified predictors of treatment response to MBIs for anhedonia, a cardinal symptom of MDD, using functional magnetic resonance imaging (fMRI). The current proposal

seeks to address this gap in the literature by evaluating whether functional connectivity in the DMN is associated with response to an empirically-supported MBI, Mindfulness-based Cognitive Therapy (MBCT), for individuals with clinically significant anhedonia.

The Default Mode Network: Relevance as a Biomarker

The DMN was discovered after a series of positron emission tomography studies revealed consistent deactivation in a constellation of brain regions during attentional, goal-oriented activities (Shulman et al., 1997). Research with fMRI formally established these 'task-negative' regions as an intrinsic neural network by characterizing the temporal coherence of activation patterns during periods of unconstrained mental activity (i.e. resting-states). The medial prefrontal cortex (MPFC), precuneus, posterior cingulate cortex (PCC), and inferior parietal lobules are generally considered the core components of the DMN, although areas such as the thalamus, hippocampus, and lateral temporal cortex are also commonly associated (Raichle, 2015; Whitfield-Gabrieli & Ford, 2012).

The domain-general properties of the DMN (i.e., supporting such wide variety of psychological phenomena as cognition, emotion, perception, and action) have led some researchers to propose this network is part of a unified brain system supporting allostasis, in concert with traditional "salience network" hubs like the insula and anterior cingulate cortex (Kleckner et al., 2017). In terms of cognition, the DMN is most closely associated with internally-oriented focus as in mind-wandering states and self-reflection. DMN deactivation is proportional to task difficulty such that more effortful concentration requires greater DMN suppression (McKiernan et al., 2003), and greater suppression predicts enhanced memory accuracy (Daselaar et al., 2004). Research combining experience sampling with fMRI shows activation in the anterior DMN is positively associated with both performance errors and self-

reported mind-wandering during an attention task (Christoff et al., 2009). In addition to spontaneous cognition, intentional processing has also shown to elicit DMN activation when autobiographical memory or self-reflection is involved (Johnson et al., 2002; Kelley et al., 2002). For instance, evaluating one's character traits (e.g. "I am punctual") elicits robust activation compared to evaluating factual statements (e.g. "There are 60 seconds in one minute"). Although there is overlap between DMN regions active during self-reflection and resting-states, intentional self-reflection preferentially engages the dorsal MPFC (Whitfield-Gabrieli et al., 2011).

Resting State DMN Functional Connectivity in Depression

Individuals with MDD show imbalances in resting-state functional connectivity within the DMN that are occasionally affected by intervention with medication or neurostimulation (see (Mulders et al., 2015) for a review). The two most common approaches for studying resting-state connectivity in MDD are seed-based correlation analyses and independent component analyses (ICA). Studies using a PCC-seed consistently show hyperconnectivity within the whole network in MDD (Alexopoulos et al., 2012; Berman et al., 2011; Zhou et al., 2010), whereas using an MPFC-seed has shown hypoconnectivity between anterior and posterior regions of the DMN (van Tol et al., 2014). ICA studies also typically show hyperconnectivity within DMN in MDD, although findings are inconsistent when component maps distinguish between anterior (i.e., the MPFC) and posterior DMN components. At least one ICA study has shown hypoconnectivity within a posterior subnetwork consisting of the PCC and lateral parietal lobes (Zhu et al., 2012). Disparities across studies may be related to clinical heterogeneity of MDD and underscore the need to evaluate brain functioning with respect to symptoms rather than diagnostic categories alone.

Given the DMN's role in supporting self-referential cognition, alterations in MDD are often interpreted to reflect a bias towards internal-attention. Indeed, hyperconnectivity has been specifically related to measures of rumination and emotion-regulation in adults samples (Johnson et al., 2009; Sheline et al., 2009). Furthermore, connectivity between the PCC and amygdala (a salience network hub) positively correlated with rumination among a sample of adolescents with history of depression Peters et al. (2016).

Neurobiology of Anhedonia

Anhedonia is most typically associated with alterations in cortico-striatal circuitry related to salience and reward processing. Most fMRI research has investigated anhedonia within the context of MDD where individuals show reduced expectations for rewards and reduced willingness to exert effort for future rewards (Pizzagalli, 2014). Review articles suggest hypoactivation of the striatum during reward anticipation and outcomes is trait-like biomarker of MDD (Keren et al., 2018). Although sophisticated preclinical research elucidates a pathway between inflammation, impairments in dopamine synthesis & transport, striatal activity and anhedonia (Felger, 2017), evidence for a "dopamine hypothesis" in humans has not borne out as in rodent models. In a carefully designed study, Schneier et al. (2018) found no differences in striatal dopamine receptor occupancy before or after an amphetamine challenge using positron emission tomography among medication-free individuals with MDD. Moreover, dopamine transmission was also unrelated to symptoms of anhedonia specifically. While further research is necessary to corroborate this finding in other human samples, at minimum this suggests brain areas beyond classic reward processing regions may be relevant to anhedonia.

Resting State DMN Functional Connectivity in Anhedonia

While the body of evidence specifically associating the symptom of anhedonia with DMN connectivity is small, overwhelming research suggests DMN connectivity is altered in disorders characterized by anhedonia such as MDD, bipolar disorder, and schizophrenia (Whitfield-Gabrieli & Ford, 2012). A central tenet of the National Institute of Mental Health Research Domain Criteria (RDoc) initiative is that treatment development for such conditions will be hastened by investigating neurobiologically based transdiagnostic constructs related to symptoms rather than traditional diagnostic categories (Cuthbert & Kozak, 2013). To that end, Sharma et al. (2017) examined the relations between reward responsivity and resting state connectivity in a large, heterogenous sample of individuals with affective (i.e, MDD and bipolar disorder) and psychotic disorders (i.e., schizophrenia and high-risk relatives) using a data-driven approach. They found hyperconnectivity within the anterior regions of the DMN was positively related to self-reported anhedonia. Notably, these findings were present in each clinical group, highlighting the significance of using an RDoC framework. In a separate study, symptoms of anhedonia were also specifically associated with hyperconnectivity between anterior and posterior regions of the DMN among a sample of adults with MDD (Rzepa & McCabe, 2018). The triple network model of psychopathology would suggest DMN hyperconnectivity in anhedonic disorders reflects broader impairment in the salience network which shifts dominance between internally-oriented (mediated by DMN) and externally-oriented processing (mediated by frontoparietal network; (Wang et al., 2016)).

Mindfulness-Based Interventions: Relevance to Anhedonia and Neural Correlates

The essence of mindfulness practice is noticing the full array of sensory and cognitive experiences unfolding moment-to-moment with openness, curiosity, and nonjudgment (Gunaratama, 2002). Modern day MBIs are inspired by millenia-old Eastern philosophy. In Buddhist tradition, meditation is a process towards personal transformation through deep awareness of the impermanence of all objects, and the dissatisfaction fueled by attachment to fleeting events (Gunaratama, 2002). In cultivating skillful mindfulness, practitioners train to observe phenomena without self-referential concepts like "*me*" or "*my*" and strive to break the cycles of habitual responding at the root of dissatisfaction. While modern MBIs use jargon from Western psychology the principles remain true to historical foundations.

Meta-analyses confirm that MBIs are effective at managing MDD symptoms and reducing the risk of MDD episode relapse, particularly for individuals with greater residual symptoms (Kuyken et al., 2016; MacKenzie & Kocovski, 2016; Strauss et al., 2014). The largest randomized controlled trial (n=424) comparing 8-weeks of MBCT to antidepressant medication maintenance found no difference between treatments in relapse, residual symptoms, or quality of life at 24 months follow-up, suggesting mindfulness practice is a low-risk, cost-effective alternative to commonly prescribed medications (Kuyken et al., 2016). In clinical trials, improvements in self-reported mindfulness are most-often identified as mediators of treatment response (MacKenzie & Kocovski, 2016). More theoretically speaking, the enhanced present-moment awareness and non-judgmental acceptance are thought to promote cognitive flexibility and decrease maladaptive habitual responses (e.g., rumination, behavioral avoidance, etc.; (Kabat-Zinn, 2005)).

Neural Mechanisms of Mindfulness Practice in Non-clinical Contexts

Given the DMN's association with internally-oriented cognition as in mind-wandering and self-reflection, this network emerges as a natural target for mindfulness practice in non-clinical contexts. Indeed, neural changes induced by meditation largely include deactivation of DMN structures (Simon & Engstrom, 2015). Studies comparing naïve and experienced meditators (frequently defined as > 1,000 hours of practice) across various mindfulness meditations show greater deactivation of the PCC (Brewer et al., 2011; Garrison et al., 2015) and ACC (Garrison et al., 2015) at rest in experienced practitioners. It has been theorized that DMN suppression during mindfulness practice reflects a diminished involvement in habitual modes of self-reference (i.e., a shift toward present-moment awareness and an openness to experience). Few seed-based analyses using the MPFC and PCC show relatively greater connectivity within the DMN of experienced meditators (Brewer et al., 2011; Jang et al., 2011). However, an alternative method of analyzing RSFC, measuring region-of-interest (ROI) to ROI connectivity, showed changes in both directions, with overall more decreases within network observed in pracititioners (Taylor et al., 2013).

Connectivity within the DMN likely changes as a function of total mindfulness practice. In a recent-study Bauer et al. (2019) showed an overall reduction in connectivity within the DMN among experienced meditators relative to controls, but the pattern of connectivity between the DMN and the frontoparietal network differed between those with more or less than three years of daily practice. Relatively less experienced meditators had stronger connectivity (i.e., anti-correlations) between these networks which the authors interpreted as reflection of more frequent suppression of the DMN ongoing during mind-wandering states. In theory, the most

experienced meditators engaged in less frequent mind-wandering at rest resulting in less competition between internally and externally oriented networks.

Potential Neural Mechanisms of Mindfulness Practice for Anhedonia

Interestingly, a longitudinal study showed as few as 40 days of meditation training attenuated RSFC within the anterior DMN for healthy naïve meditators (Yang et al., 2016). This finding is relevant to the treatment of anhedonia for several reasons. First, the anterior DMN overlaps with the neural substrates of self-reflection (Whitfield-Gabrieli et al., 2011). Anhedonia is associated with altered self-referential processing such as reduced endorsement of positive self-referential traits (Johnson et al., 2007). Secondly, hyperconnectivity within this region may be associated with both MDD and anhedonia severity (Rzepa & McCabe, 2018). Thirdly, hyperconnectivity within this network may not normalize with antidepressant medication, highlighting a potential unique mechanism of action for MBIs (Li et al., 2013). Together, these findings raise the possibility that alterations in DMN connectivity relate to the therapeutic benefits of mindfulness practice for anhedonia.

The Present Investigation

The objective of this investigation was to probe DMN resting-state functional connectivity as a candidate biomarker for treatment response to an MBI (i.e., individually adapted MBCT) in a clinically-defined, transdiagnostic anhedonic sample. No study to date has identified fMRI predictors of response to MBI for anhedonia. Baseline and mid-treatment changes in connectivity were evaluated as predictors of symptomatic improvement to test the hypothesis that DMN hyperconnectivity characterizes anhedonia and is remediated by MBI. This investigation occurred in the context of an ongoing clinical trial comparing MBCT against a novel psychosocial intervention called Behavioral Activation Treatment for Anhedonia (BATA).

To determine the specificity of treatment effects on DMN connectivity, MBCT was compared against BATA. Although anhedonia symptoms were the primary clinical outcome of the larger trial, depression symptoms were also studied given the established linkages between depression symptoms and DMN connectivity (Alexopoulos et al., 2012; Berman et al., 2011; van Tol et al., 2014; Zhou et al., 2010).

Aim 1: Evaluate whether baseline connectivity between DMN regions-of-interest (ROIs) predicts anhedonia and depression improvement with MBCT relative to BATA.

Hypothesis: Stronger positive connectivity between ROIs in the DMN will be associated with greater symptom reduction in MBCT than in BATA, highlighting a neural predictor of treatment response for MBI.

Aim 2: Evaluate whether mid-treatment change in connectivity between DMN ROIs predicts anhedonia and depression improvement with MBCT relative to BATA.

Hypothesis: Attenuation of connectivity between ROIs in the DMN from baseline to mid-treatment will be associated with greater anhedonia and depression reductions in MBCT than in BATA, offering preliminary evidence of a mediation effect between MBCT, changes in the DMN, and clinical improvement.

Aim 3: Assess whether graph-theory measures for DMN ROIs predict anhedonia and depression improvement with MBCT relative to BATA. ROIs with significant connections from Aims 1 or 2 will be assessed with respect to their connectivity in the whole-brain network using graph-theory. This approach will help clarify how imbalance within the DMN contributes to anhedonia and depression severity.

Hypothesis: The MPFC will emerge as an important node within the whole-brain network with respect to anhedonia and depression improvement. Decreases in graph measures of

centrality for the MPFC with be associated with greater improvement in MBCT than in BATA, suggesting that MBCT causes a shift away from an evaluative self-referential processing style conducive of negative affect.

Post-hoc Analyses: Findings from the central aims of this investigation were further queried using multilevel modeling on the full sample from the clinical trial to date. This analytic approach is better suited to examine potential moderation or mechanistic effects of DMN connectivity with respect to treatment outcomes.

CHAPTER 2: METHODS

Study Overview

The current investigation took place in the context of a multi-center National Institute of Mental Health clinical trial investigating the biological mechanisms and efficacy of a novel transdiagnostic psychotherapy for anhedonia, BATA, compared to individually-adapted MBCT (ClinicalTrials.gov Identifier NCT02874534). This protocol was approved by the Institutional Review Boards at the University of North Carolina, Chapel Hill (UNC) and Duke University. Participants first completed a screening visit to review eligibility criteria and report baseline symptom severity. Eligible participants were randomized to 15 weeks of individual psychotherapy of either BATA or MBCT. Some early treatment responders (as determined by clinician judgement) elected to complete therapy after 11 sessions. Treatment was administered by PhD-level clinicians trained in behavioral activation and MBCT and supervised licensed clinicians at Duke University and UNC.

Participants presented to the UNC Biomedical Research Imaging Center for a 7 tesla MRI scan at baseline and post-treatment. Participants enrolled during the first two years of the trial also completed mid-treatment scans at weeks 8 and 12. High-resolution structural images and resting state functional images were acquired. Participants were scheduled for their first therapy session as closely to the screening and baseline scan as possible, within one month. Anhedonia symptoms were measured using self-report on approximately on a weekly basis at each treatment and scan session. Depression symptoms were measured using self-report at week 4, 8, 12, and upon treatment completion.

Participants

Eligibility Criteria

Participants were 18–50 years old and free of psychotropic medication use for >30 days. Inclusion criteria were Snaith Hamilton Pleasure Scale (SHAPS) scores > 20 and Clinical Global Impressions-Severity scores > 3 to constitute a clinically-impaired anhedonic sample. Exclusion criteria included contraindications for 7 tesla MRI, concurrent psychotherapy, prior mindfulness practice experience, a history of moderate or severe Substance Use Disorder, or a diagnosis for which pharmacotherapy is a first-line treatment (e.g., Bipolar Disorder, Schizophrenia). Diagnostic and Statistical Manual-5 (DSM-5) diagnoses were assessed by the Structured Clinical Interview for DSM-5, Research Version (First, Williams, Karg, & Spitzer, 2015). Assessors were trained to 100% diagnostic reliability with a standard rater over a minimum of three training interviews.

Sample Size & Attrition

A total of 73 participant were randomized to treatment (35 MBCT, 38 BATA) and attended at least one therapy session, meeting intent-to-treat criteria. Among these participants 51 completed treatment and 22 withdrew their participation or were lost-to-follow-up. While the proportion of participants who dropped out from MBCT (40%) was higher than that in BATA (28.6%), a chi-squared test of independence showed no difference in attrition between groups (χ^2 (1) = 2.27, p = 0.13).

Table 1 Demographics and clinical symptom scores.

Sample Characteristic		*Mean (SD)*	*Range*
Sex	BATA (n=38)	27 Female, 11 Male	
	MBCT (n=35)	24 Female, 11 Male	
Age	BATA	27.9 (8.8)	18 – 47
	MBCT	31.8 (9.2)	19 – 49
SHAPS	BATA	35.7 (3.8)	28 – 44
	MBCT	36.9 (5.3)	27 – 52
BDI	BATA	20.1 (8.2)	1 – 36
	MBCT	24.0 (10.3)	3 – 48

BATA – Behavioral Activation Treatment for Anhedonia; MBCT – Mindfulness-Based Cognitive Therapy; SHAPS – Snaith Hamilton Pleasure Scale; BDI– Beck Depression Inventory II

The nesting structure of the data (i.e., the number of unique observations per person for clinical and connectivity measures) is depicted in Figure 1. The total number of MRI scans acquired at each time point in therapy is as follows; 73 scans at baseline, 37 mid-treatment scans at week-8, 24 mid-treatment scans at week-12, and 59 post-treatment scans. Of note, post-treatment scans did not indicate treatment completion as some participants completed MRI after withdrawing.

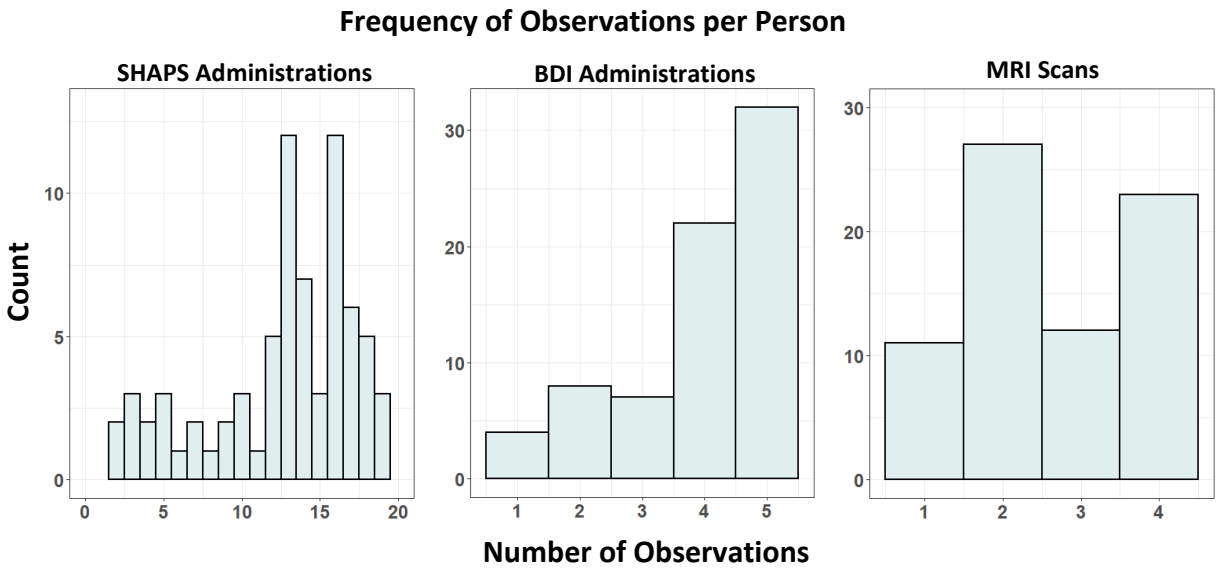

Figure 1. The nesting structure of the data is depicted by the number of unique observations for each respective variable. The large numbers of repeated measurements are best suited for multi-level modeling analyses. *SHAPS – Snaith Hamilton Pleasure Scale; BDI – Beck's Depression Inventory II*

Psychosocial Interventions

Mindfulness-Based Cognitive Therapy

MBCT was administered in an individual format with 15 weekly sessions of 45 minutes. This individual format retains the primary components of the traditional group MBCT including didactic instruction, guided meditations, inquiry of subjective experience, and homework assignments. The current protocol was modeled on the session outlines presented by Wahbeh et al. (2014).

Mindfulness is presented as a means of empowering individuals by granting more flexibility over habitual response patterns (Segal, 2002). In early phases of treatment, the emphasis is largely on developing core meditation skills of concentration, refocusing, and nonjudgmental acceptance. Foundational exercises taught in the program are focused awareness of breathing and mindful body scanning. Breathing exercises encourage participants to pay attention to the physical sensation of the breath wherever it is most salient, and to follow it

naturally without effortful control. Body scan exercises have participants slowly guide their awareness through one region of the body at a time, developing interoceptive sensitivity. Mind-wandering is an inevitable part of practice. Participants are discouraged from engaging in self-criticism by framing these moments as opportunities to make choices and resume skillful mindfulness. Later sessions of MBCT emphasize generalizing the meditation skills to cope with stressors and mood shifts in daily life. Psychoeducation is geared toward appreciating the interrelations between negative thoughts, emotions, and sensations, and developing plans to manage stressors.

Most sessions begin with a guided meditation varying in length from 3 – 10 minutes followed by a discussion about subjective experience (i.e. inquiry). Next, participants will reflect on home assignments and discuss barriers to mindfulness practice encountered throughout the week before new topics and exercises are reviewed. At the end of every session participants receive handouts summarizing the content, and at least 30 minutes of daily practice are assigned. Guided meditation CDs are provided to aid in home practice and adherence is monitored through participant report logs (Wahbeh et al., 2014).

Behavioral Activation Therapy for Anhedonia

BATA, the experimental active comparison treatment, was administered for up to 15 weekly individual sessions of 45 minutes. BATA was developed as a modification to Behavioral Activation Treatment for Depression to treat anhedonia transdiagnostically. BATA frames patient's experiences with anhedonia in a neuroscientific perspective, using language pertinent to reward and learning processes.

Session 1 of BATA focuses on psychoeducation and introduces the concept of activity monitoring. Sessions 2-3 include structured values clarification of 10 major life areas to enhance

motivation for sustainable behavior change. Following value clarification and broad goals, activity hierarchies are developed, establishing behavioral targets across valued life areas, prioritized by ease of implementation. Session 4 focuses discussion on the reduction of behavioral avoidance. Session 5 and above assess completion of previously established goals, discuss perceived barriers to implementing goals, and assign goals for the following weeks. Specific differences from traditional behavioral activation include focus on initiating new behaviors which may or may not be pursued in the future (i.e., dabbling in activities), and present moment-savoring exercises as a means to enhance consummatory reward processing experiences.

Under the framework of BATA, patients are encouraged to engage in activities that increase contact with personally relevant, values-congruent reinforcers. While achievable goal-setting is often impaired in the context of anhedonia, therapists use motivational techniques to elicit goal-directed behaviors such as tying goals to stated-values, open-ended questioning, reflective listening, and functional analysis to problem solve barriers. Increased positive affect and decreased negative affect are theorized to result from reduced behavioral avoidance and consequent increased contact with potential reinforcers.

Design Considerations

My original Master's proposal indicated only participants in the MBCT group would be evaluated. However special considerations motivated the decision to include BATA as a comparison group. Including a comparator treatment increases the rigor of the design by parsing general treatment effects from the "specific ingredients" in MBCT. The parent study uses participant-level randomization so that every therapist delivers both types of treatment. This therapist crossed design helps isolate treatment-related effects. An ideal comparison group is

identical to the experimental treatment in all respects but the purportedly unique mechanisms. As previously noted, BATA and MBCT overlap on certain therapeutic principles, namely BATA includes instruction on present-moment savoring during pleasant activities. This may arguably impact DMN function as present-moment awareness engages the frontoparietal network and deactivates the DMN (Raichle, 2015). While this similarity is of mild concern, it is noteworthy that MBCT encourages momentary awareness decontextualized from positive affective experiences. Moreover, MBCT is believed to facilitate clinical improvement largely through formal meditation practice. It stands to reason that repeated disengagement and suppression of the DMN during extended periods of concentration would facilitate greater resting-state functional connectivity change in MBCT than in BATA.

Clinical Symptom Measures

Snaith Hamilton Pleasure Scale

Anhedonia was measured by the SHAPS, a 14-item self-report questionnaire that assesses the degree to which a person has the capacity to experience pleasure, or the anticipation of a pleasurable experience "in the last few days" (e.g. "I would find pleasure in my hobbies and pastimes" (Snaith et al., 1995)) . Each item has four possible responses – strongly disagree, disagree, agree, or strongly agree – for a total score ranging between 14 – 56 using the ordinal scoring of Franken et al. (2007), with higher values reflecting greater hedonic impairment. Items belong to four general domains of hobbies, social interaction, sensory experience, and food. This scale has shown adequate overall psychometric properties in clinical and non-clinical samples.

Beck Depression Inventory – II

Depressive symptoms were evaluated by the Beck Depression Inventory-II (BDI), a 21-item self-report questionnaire inquiring about cognitive (e.g. pessimism, self-criticism) and somatic (e.g. changes in appetite or sleep pattern) symptoms over the past week. Items are rated using a Likert scale with total scores ranging from 0 to 63 and higher numbers indicative of greater severity. The BDI has excellent internal reliability and test-retest stability (Beck & Steer, 1984).

Treatment Differences in Clinical Outcomes

A series of longitudinal multilevel models (i.e., growth curves) were estimated using the nlme package in R (Pinherio et al., 2016) to examine treatment differences in baseline clinical symptoms and change over time. Model building procedures are detailed in the "Post-hoc Analyses" section.

7T Magnetic Resonance Imaging

Acquisition Parameters

Anatomic and functional resting state imaging data were acquired at the UNC Biomedical Research Imaging Center using a 7T Magnetom MR system equipped with a 32-channel head coil. T1-weighted anatomical images are collected with the following parameters: echo time (TE) = 2.78 ms, repetition time (TR) = 2200 ms, inversion time (TI) = 1050 ms, flip angle = 7°, and voxel size of 1 x 1 x 1 mm^3. Resting state data were acquired during a 8-minute gradient-echo echoplanar imaging sequence (ep2d_bold) using the following parameters: TE = 22.2 ms, TR = 1000 ms, flip angle = 45°, and voxel size of 1.6 x 1.6 x 1.6 mm^3. During the resting state scan participants were instructed to keep their gaze fixed on a cross hair and not to fall asleep.

Image Preprocessing

T1-weighted anatomical images were bias-corrected using FSL (v5.0.9) to enhance removal of non-brain tissue with FreeSurfer (v6.0). FreeSurfer derived brain-masks, gray matter, white matter (WM) and cerebrospinal fluid (CSF) segmentations were imported into CONN toolbox (v18b; (Whitfield-Gabrieli & Nieto-Castanon, 2012)) along with raw functional data for remaining preprocessing procedures. Spatial preprocessing of functional volumes included realignment and estimation of motion parameters (three translational and three rotational directions), slice-timing correction, and normalization. FreeSurfer masks were eroded to minimize partial volume effects and normalized to MNI space. Functional outlier volumes were identified using the Artifact Detection Tool with a conservative threshold of > 0.5 mm. Realignment parameters plus their first-order derivates, the top five principal components estimated from WM and CSF masks (aCompCor method; (Behzadi et al., 2007)), and outlier timepoints were included as covariates in a multilinear regression to remove BOLD signal variance explained by these confounds. Lastly, the residual timeseries were subject to a high-pass filter (0.01 Hz < f). Participant runs were discarded if the number of volumes scrubbed exceeded 20% of the total volumes.

Planned Analyses – Aims 1 & 2

Estimating Default Mode Network Functional Connectivity

DMN connectivity was calculated using the CONN toolbox Networks atlas. This atlas is comprised of 32 ROIs defined by CONN's independent component analysis of 497 participants from the Human Connectome Project. Within this atlas, the DMN consists of four ROIs (see Table 2 for ROI details). Pearson correlations between the mean BOLD time series of each ROI pair within the network were computed and Fisher r-to-Z transformed, resulting in six DMN

edges. In addition to bivariate correlations, partial correlations were computed as an alternative measure of RSFC. Whereas bivariate correlations measure the associations between paired ROI timeseries in isolation, partial correlations consider multiple sources simultaneously and estimate the unique contributions from each source.

Table 2 List of seed regions-of-interest from the CONN Toolbox *Networks* atlas

Network	*ROI Name*	*MNI Coordinates (x,y,z)*	*Voxel Size*
Default Mode Network	Medial Prefrontal Cortex (MPFC)	(1, 55, -3)	1,346
	Left Lateral Parietal Cortex (LLPC)	(-39, -77, 33)	1,041
	Right Lateral Parietal Cortex (RLPC)	(47, -67, 29)	1,326
	Posterior Cingulate Cortex (PCC)	(1, -61, 38)	4,833

Evaluating ROI-to-ROI Predictors of Treatment Response

Multiple regression was used to predict symptomatic improvement from baseline and mid-treatment change in DMN connectivity. Clinical symptom change scores were calculated by subtracting post-treatment from baseline values, with larger values indicative of greater improvement. An intent-to-treat approach was used, such that the last observations were used as post-treatment scores for participants who dropped out of the study. Connectivity change was calculated by subtracting baseline from mid-treatment values. All models included demeaned age and sex as covariates given their influence on DMN connectivity (Ramirez-Barrantes et al.,

2019), as well as baseline symptom severity to account for potential treatment differences. Critically, an interaction term between treatment condition and connectivity was used to identify unique predictors of treatment response to MBCT.

12 unique connectivity values were calculated for each participant in Aim 1 (i.e., six bivariate correlation and six partial correlation edges), and 12 connectivity values for Aim 2 (mid-treatment minus baseline values of edges). Given two clinical symptoms measures (i.e., the SHAPS and BDI), a total of 48 multiple regressions were evaluated. Correction for multiple comparisons was implemented using false discovery rate (FDR) adjusted p-values (Benjamini & Hochberg, 1995).

Finally, diagnostics were performed on significant regressions to assess whether assumptions of the general linear model were met. Cook's distance was used to identify outliers with excessive leverage on predicted values. Observations with greater than 4 times the mean Cook's distance were subsequently removed.

Planned Analyses – Aim 3

Calculating Graph-Theory Metrics of Connectivity

To calculate graph-based network metrics, each participant timepoint's ROI-to-ROI correlation matrix was converted to a binary graph (i.e. an adjacency matrix) using a set threshold. There is no consensus on the most appropriate method for thresholding graphs, however, proportional thresholding (i.e. including a certain percentage of the strongest connections) may obfuscate group comparisons or changes over time, thus an approach using absolute correlation coefficient values was preferred (Hallquist & Hillary, 2019). Negative edges were discarded in these analyses as is standard practice (De Vico Fallani et al., 2014).

Neural and other "small-world" networks demonstrate greater global efficiency (GE) than lattices and greater local efficiency (LE) than random graphs of similar sizes (Achard & Bullmore, 2007). Thus, the adjacency matrix correlation coefficient threshold was selected on the basis of optimizing the small-worldness of the data using the following formula across a range of values within CONN toolbox:

Small-Worldness = (GE Dataset) – (GE Lattice Graph) + (LE Dataset) – (LE Random Graph)

Evaluating Graph-Theory Metrics as Predictors of Treatment Response

ROIs identified from significant connections in Aims 1 or 2 were examined as predictors of treatment response using graph-based metrics. Specifically, degree, clustering coefficient, nodal efficiency, and betweenness centrality examined the function of DMN nodes within the whole-brain network (Wang et al., 2010). Degree is a basic measure of centrality that represents the number of edges a node has in a binarized graph. Clustering coefficient refers to the probability, ranging from 0 – 1, that a node's neighbors (other nodes connected by an edge) are also connected with each another. Nodal efficiency is defined as the inverse of the average shortest-path length (fewest number of edges) from a given node to all other nodes in the graph. Finally, betweenness centrality refers to the proportion of the shortest paths within the network that pass through a given node. As in Aims 1 & 2, clinical symptom change scores were regressed on graph-based metrics, including covariates for demeaned age, sex, baseline symptom severity and an interaction term between connectivity and treatment condition.

Post-hoc Analyses: Probing Moderation and Mechanistic Effects of DMN Connectivity with Multilevel Modeling

Rationale

The planned analyses above employ a subset of the total data currently available. Only half of participants randomized to date completed a mid-treatment scan at week 8 pertinent to calculating changes in connectivity for Aims 2 and 3. Multilevel modeling is a statistical technique that accounts for naturally arising dependencies within nested data (e.g., repeated measures within participant; (Curran & Bauer, 2011)). A principle advantage of this approach is that it permits flexible modeling of time such that data collected at uneven intervals and from participants with varying numbers of time points (i.e., missing data) can be included in the same analysis, increasing the sample size and ability to detect effects.

Any connectivity variables that emerged as significant predictors of treatment response from Aims 1–3 were investigated using multilevel modeling to characterize connectivity change over time and symptom-relations with superior accuracy to the multiple regression models. First, connectivity was used an outcome variable to examine cross level interactions between treatment condition and time. These conditional growth curves indicated whether MBCT was associated with differential changes in connectivity as compared to BATA. Next, baseline connectivity was examined as a participant level predictor of clinical outcomes in a three-way interaction with treatment and time. This model suggests whether DMN connectivity is a moderator of treatment response to MBCT. Lastly, connectivity was examined as a time-varying covariate of clinical outcomes. This strategy probes whether DMN connectivity is a plausible mechanism of treatment response to MBCT. While this model does not test for a mediation directly, it provides the early evidence that change in symptoms track connectivity within person.

Model Building Procedures

The following model building procedures were applied for all outcome variables (clinical or connectivity). First, the intraclass correlation coefficient (ICC) was calculated using random effects analysis of variance to decompose variance within and between participants in the outcome. Secondly, linear and quadratic effects of time were modeled across the entire sample, allowing random variation in intercepts from participant to participant. Time was coded in weeks relative to the first therapy session. Third, random slopes were examined, allowing the relation between time and the outcome to vary participant to participant. Fourth, alternative error structures were examined by fitting a model with serially correlated residuals (i.e., autoregressive 1; (Schwartz & Stone, 1998)). At each step in the model building procedure, fit was assessed by comparing change in log likelihood values with a chi-square difference test and change in Akaike Information Criterion (AIC), with lower values indicative of superior fit.

Once the optimal unconditional growth curve was identified from the steps above, participant level factors, such as age & sex, were included to explain variation in intercepts (i.e., outcome at baseline). Variation in slope was predicted by adding time-varying covariates and any cross-level interactions with time. To distinguish within-person & between-person effects of time-varying covariates, both mean-centered within-person and grand-mean-centered person means were entered in the model (Curran & Bauer, 2011).

CHAPTER 3: RESULTS

MBCT vs BATA Effects on Clinical Outcomes

The ICC for SHAPS indicated 56% of the variability in anhedonia severity was attributed to between-person differences across the entire sample. Stated otherwise, there was a correlation of 0.56 between SHAPS scores within-person, highlighting strong dependency in the data. Growth curve modeling procedures showed a significant linear effect of time indicating SHAPS decreased about .57 points every week of therapy across the sample ($p<.001$). A small positive quadratic term was trending towards significance ($p=.08$) suggesting faster decreases in SHAPS earlier in therapy, but this effect did not significantly improve model fit (χ^2 (1) = 3.06, $p=.08$) and was not retained. Model comparison favored incorporating random slopes (χ^2 (2) = 243.7, $p<.001$) indicating the presence of variability in participant change in SHAPS over time. An autoregressive error structure also improved model fit (χ^2 (1) = 41.7, $p<.001$) demonstrating that observations closer in time were more similar. There was a weak negative correlation between the effects of random intercepts and random slopes ($r=-.09$) such that participants with higher baseline SHAPS tended to improve slightly more quickly over time. Incorporating participant level predictors in the model showed no effect of age, sex, treatment, or a cross-level interaction between treatment and time. In other words, there were no differences between MBCT and BATA in baseline anhedonia severity or in symptom change over time, with both groups significantly improving.

Approximately 52% of the variability in BDI was attributed to between-person differences. A significant linear effect of time indicated BDI decreased .79 units every week of

therapy ($p<.001$). There was no significant quadratic effect of time. There was significant variability in the change of BDI over time evinced by superior model fit with random slopes ($\chi^2(2) = 20.1$, $p<.001$). Incorporating serial correlations in the error structure did not improve the unconditional growth curve. A weak negative correlation between random effects for intercepts and slopes ($r=-.09$) indicated slightly greater rates of decrease for participants with higher baseline depressive severity. Age, sex, treatment and the cross-level interaction between treatment and time were not significant. Once more, MBCT and BATA did not differ in baseline depression severity or change over time, with both groups significantly improving. The fixed effects from the conditional growth curves for SHAPS and BDI are denoted in Table 3.

Table 3. Fixed effects estimates for full conditional growth curve models of clinical outcomes

	SHAPS			**BDI**		
Predictors	*Estimates*	*CI*	*p*	*Estimates*	*CI*	*p*
(Intercept)	35.41	33.82 – 37.00	**<0.001**	18.73	15.61 – 21.85	**<0.001**
Time	-0.51	-0.64 – -0.37	**<0.001**	-0.76	-0.98 – -0.54	**<0.001**
Treatment (MBCT)	0.95	-1.18 – 3.08	0.378	2.57	-1.59 – 6.73	0.227
Age	-0.03	-0.15 – 0.08	0.559	-0.07	-0.30 – 0.16	0.528
Sex (M)	-0.66	-2.94 – 1.62	0.568	-1.61	-6.05 – 2.82	0.475
Time * MBCT	-0.15	-0.35 – 0.04	0.128	-0.15	-0.48 – 0.17	0.358
Participants	73			73		
Observations	902			285		

SHAPS – Snaith Hamilton Pleasure Scale; BDI – Beck Depression Inventory II; CI – Confidence Interval; MBCT – Mindfulness-Based Cognitive Therapy

Motion During fMRI

A total of 7 participant scans (across all time points) were excluded from analyses for excessive motion (> 20% of volumes censored), including 3 baseline scans, 2 scans at week 8, and 2 scans at week 12. Overall motion of the remaining sample was low, with a mean framewise displacement of 0.15 (SD = 0.05) across participant timepoints. The mean number of discarded volumes per scan was 20.3 (SD = 17.3) out of 480, or about 4%.

Planned Analyses Aim 1

Estimating DMN Connectivity

The DMN showed strong positive connectivity at baseline across the sample with a mean connectivity across all six edges of .55 (SD=.16) z-scores. Strongest connectivity was evinced between the left and right lateral parietal cortices, z=.76 (SD=.21), while weakest connectivity was between the medial prefrontal cortex and left lateral parietal cortex, z=.36 (SD=.28). Average connectivity from partial correlation analyses was expectedly much weaker with a mean of .12 (SD=.01) z-scores.

Evaluating Baseline ROI-to-ROI Connectivity as Predictors of Treatment Response

There were no significant baseline connectivity predictors of either SHAPS or BDI change scores using bivariate or partial correlations. This was true of both the main effect of connectivity and the treatment-by-connectivity interactions (all *p*'s>.05).

Planned Analyses Aim 2

Evaluating Mid-treatment Changes in ROI-to-ROI Connectivity as Predictors of Treatment Response

There were no significant treatment-by-connectivity interactions predicting either SHAPS or BDI improvement (all *p*'s >.05). There were no significant main effects of connectivity using partial correlations (all *p*'s >.05).

Using bivariate correlations, a main effect of connectivity change on SHAPS improvement was detected with all three edges in the DMN emanating from the PCC (MPFC *p*=.02; LLPC *p*=.01; RLPC *p*<.001). Results from all edges showed a positive relation between change in connectivity and symptomatic improvement. In other words, mid-treatment increases (and/or lesser decreases) in connectivity between the PCC and the DMN predicted greater reductions in anhedonia severity. See Figure 2 for a graphical depiction of these associations.

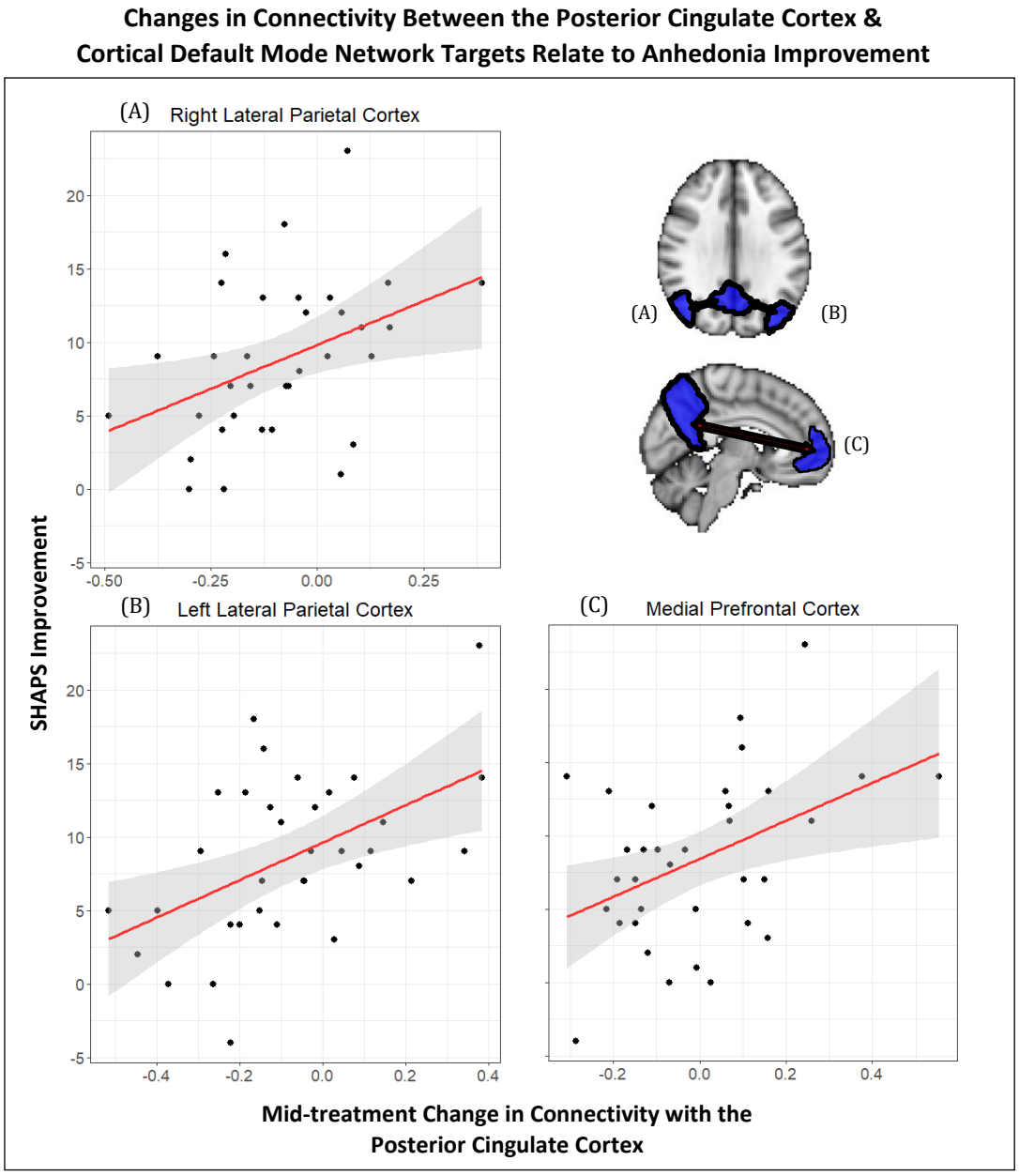

Figure 2. Significant regression models demonstrating positive relations between mid-treatment changes in posterior cingulate cortex connectivity with the default mode network and improvement in anhedonia across all subjects. Shading denotes 95% confidence intervals from predictions of the general linear model. Only connectivity with the right lateral parietal cortex was significant after false discovery rate adjustment for multiple comparisons. This connection was further examined in post-hoc analyses; *SHAPS - Snaith Hamilton Pleasure Scale*

Notably, only the effect of PCC-RLPC connectivity remained significant after FDR adjustment for 48 tests (p_{FDR}<.001). One outlier was removed from the model due excessive leverage (i.e., Cook's distance > 4 times the mean). The final model was significant and explained 50% of the variance in SHAPS improvement (adjusted R^2=.50, F(6,27)=6.504, *p*=.018). For a given increase in PCC-RLPC connectivity by one tenth of a z-score, SHAPS scores were predicted to improve by a total of 2.1 points. Baseline SHAPS (β=.48, *p*=.01) and the main effect of treatment (β=3.81, *p*=.01) were also significant indicating that in this subset of participants, greater baseline anhedonia was associated with greater improvement and that MBCT improved anhedonia more than BATA did.

Planned Analyses Aim 3

Calculating Graph-Theory Metrics of Connectivity

A Fisher r-to-z transformed correlation coefficient of .35 was identified as maximizing the Small-Worldness properties of the whole brain network for the full baseline sample and was selected to compute adjacency matrices across all timepoints.

Evaluating Graph-Theory Predictors of Treatment Response

Given the findings from Aim 2, graph-theory metrics of the PCC and RLPC within the whole-brain network were examined as predictors of SHAPS improvement. There were neither significant main effects nor interaction effects predicting SHAPS improvement (all *p*>.05).

Post-hoc Analyses: Probing Moderation and Mechanistic Effects of DMN Connectivity with Multilevel Modeling

Time and Treatment Effects on PCC-RLPC Connectivity

Approximately 48% of the variability of PCC-RLPC connectivity was attributed to between-person differences. A significant linear effect of time indicated connectivity decreased .005 z-scores every week of therapy (p=.007). Next, a small positive quadratic effect of time emerged as significant (p=.006) and improved model fit (χ^2 (1) = 7.43, p<.001), indicating connectivity decreased faster at the start of therapy. Neither incorporating a random effect of time on slope, nor serial correlations in the error structure improved the growth curve model, suggesting limited variance between persons in the rate of change in DMN connectivity over time. There were no significant effects of age, sex, treatment, or the cross-level interactions between treatment and linear or quadratic effects of time. These results show connectivity did not differ between MBCT and BATA at baseline or over the course therapy but that both treatments attenuated DMN connectivity. The model-implied unconditional growth curves are depicted in Figure 3.

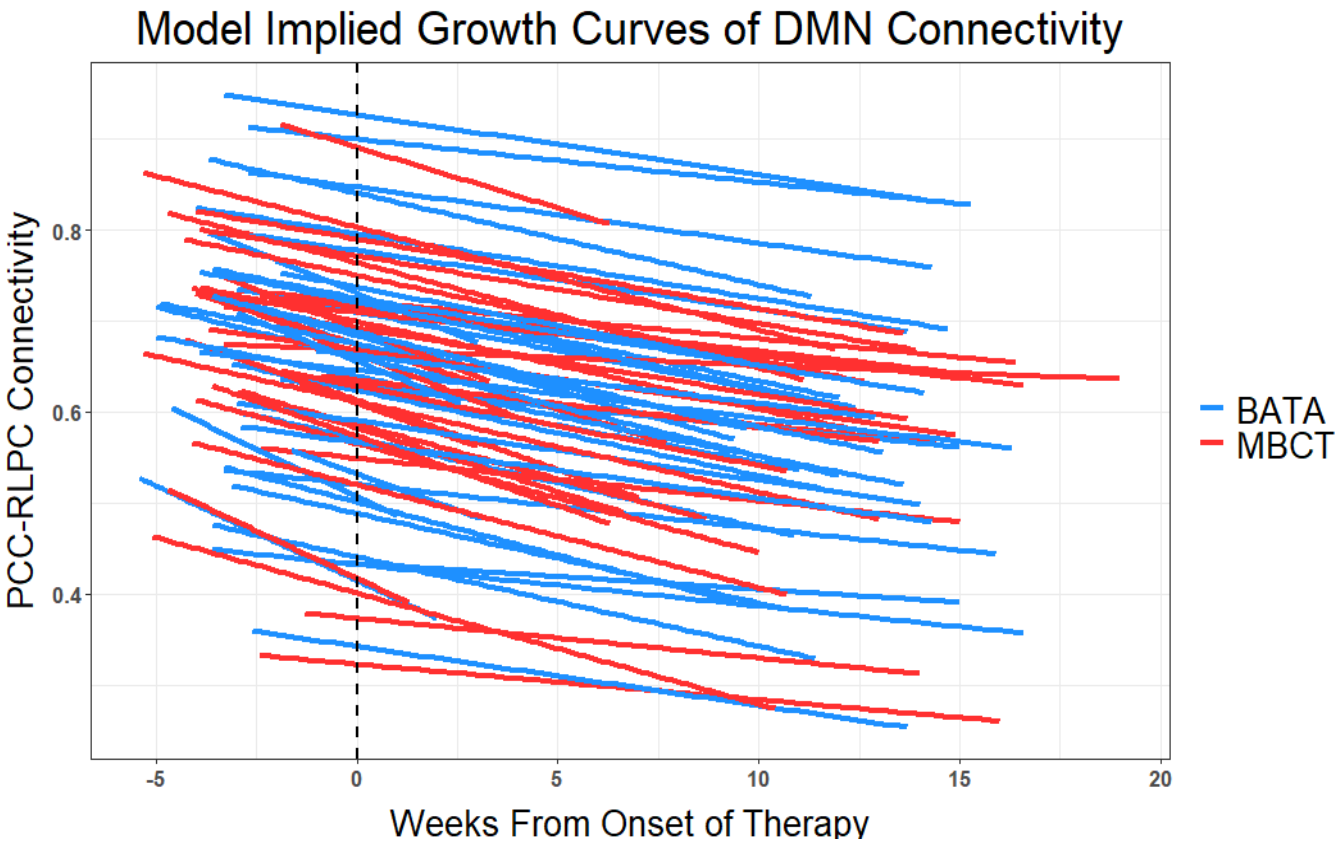

Figure 3. Growth curve modeling procedures indicated that PCC-RLPC connectivity significantly decreased over time across the sample. A small positive quadratic effect of time was significant, indicating connectivity decreased more rapidly early in treatment. There was limited variation in the slope of connectivity change over time as evidenced by non-significant random effect for slope. Change in connectivity did not differ between groups over time. *DMN – Default Mode Network; PCC – Posterior Cingulate Cortex; RLPC- Right Lateral Parietal cortex; BATA – Behavioral Activation Therapy for Anhedonia; MBCT – Mindfulness-Based Cognitive Therapy*

Baseline PCC-RLPC Connectivity as a Moderator of Treatment Response

Optimal parameters from the unconditional growth curves for SHAPS scores were retained (i.e., random slopes plus random intercepts for time, autoregressive error structure) while testing a three-way interaction between treatment x baseline connectivity x time. This interaction term was not significant, indicating baseline PCC-RLPC connectivity did not moderate treatment response.

Time-Varying PCC-RLPC Connectivity as a Mechanism of SHAPS Improvement

Optimal parameters from the unconditional growth curves for SHAPS scores were retained while testing time-varying PCC-RLPC connectivity as a predictor. Neither the within-person nor the between-person effects of connectivity were significant predictors of SHAPS. These results show changes in PCC-RLPC connectivity did not track symptomatic improvement over the course of therapy.

CHAPTER 4: DISCUSSION

The goal of this study was to evaluate DMN resting state functional connectivity as both a predictor and a mechanism of treatment response to an MBI in a clinically-defined transdiagnostic anhedonic sample. MBCT was compared against BATA, a novel psychosocial intervention for anhedonia, on self-reported symptoms of anhedonia and depression using the SHAPS and BDI. Multiple regression was used to predict change scores in symptoms from baseline and mid-treatment changes in DMN connectivity and multilevel modeling queried candidate biomarkers further.

DMN Connectivity as a Predictor of Treatment Response

Overall, this investigation found no evidence to suggest DMN connectivity serves as a predictor of treatment response to MBI in the context of anhedonia. Baseline connectivity values between key ROIs in the DMN were unrelated to symptomatic improvement in response to MBCT or across both treatment groups. Multilevel model analyses also failed to show a moderation effect of baseline connectivity on treatment effects over time. These findings stand contrary to hypotheses that individuals with stronger DMN connectivity would show greater benefit from MBCT due to the psychological mechanisms entailed in mindfulness practice (i.e., present-moment awareness & non-judgmental acceptance) targeting those connections. There have been no other studies to identify unique fMRI predictors to MBI for anhedonia.

While increased DMN hyperconnectivity has been more widely documented in the context of anhedonic disorders, Korgaonkar et al. (2019) recently showed hypoconnectivity of the DMN was a moderator of MDD remission with sertraline, escitalopram, and venlafaxine

treatment. Treatment non-responders showed lower baseline connectivity compared to controls which remained unperturbed over the course of treatment. Other recent studies have also reported hypoconnectivity in the DMN among first episode drug-naïve patients (Shi et al., 2020) and patients with recurrent MDD (Yan et al., 2019). These findings challenge the notion that DMN hyperconnectivity operates as a trait-like characteristic in MDD. Future research should employ multiple analytic techniques (i.e., data drive and atlas-based connectivity) within the same sample to better characterize these patterns.

DMN Connectivity as a Mechanism of Treatment Response

There was limited evidence supporting the hypothesis that attenuated DMN connectivity is a mechanism by which treatments improve anhedonia symptoms. Changes in connectivity between the PCC and other DMN regions (the RLPC, LLPC, and MPFC) from baseline to week 8 were related with improvement in anhedonia across both treatment groups. These findings were in the opposite direction of hypotheses, with increases in connectivity associated with greater reductions in SHAPS scores across all PCC connections. One study found increased connectivity between the PCC and salience network regions (the anterior cingulate and insula) following 8 weeks of MBCT was correlated with improvement in anxiety among individuals with generalized anxiety disorder (Zhao et al., 2019). More broadly speaking, graph-based research suggests the PCC operates as an inflow hub not only in the DMN, but also across the whole-brain network, with strong input from salience and frontoparietal networks (Li et al., 2018) highlighting it's transdiagnostic relevance to psychopathology. Increased connectivity with the PCC may reflect an adaptive shift towards more efficient integration across the whole-brain, although this hypothesis was not borne out by the nodal analyses of the PCC in Aim 3.

While the relations between increases in PCC – RLPC connectivity and greater SHAPS improvement remained significant after FDR correction for multiple comparison, there are several reasons to caution against over-interpreting these results. The magnitude of the effect was relatively small, with a tenth of a z-score increase in connectivity associated with a total 2.1-point improvement in SHAPS. More importantly, this finding was detected in a subset of the data including 35 subjects. When multilevel models were used to investigate PCC – RLPC connectivity across all participant timepoints a mechanistic effect of connectivity on SHAPS scores was not observed. Neither changes within-person, nor between-person in PCC – RLPC connectivity were associated with changes in SHAPS, indicating connectivity didn't track symptom improvement. It is possible a model including lagged effects would be more appropriate to probe treatment mechanisms such that previous timepoint connectivity predicts subsequent SHAPS, and this remains to be explored.

Treatment Effects on DMN Connectivity

PCC – RLPC connectivity was also investigated with respect to change over time independent of symptoms. Growth curve models indicated that connectivity between these DMN regions significantly decreased over the course of therapy, with more rapid decreases early in treatment. Incorporating a cross-level interaction term of treatment by time showed that MBCT was trending towards greater attenuation in connectivity than BATA, but this effect was not significant and did not improve model fit. It is noteworthy that BATA and MBCT performed equally on both symptom measures and brain outcomes. MBIs are purported to impact DMN connectivity by shifting cognition away from internally-oriented and self-referential processing (e.g., self-criticism, rumination, etc.). If self-report measures of rumination and self-perception were available, we would be able to examine whether the general treatment effects on

connectivity are due to overlapping psychological mechanisms between BATA and MBCT. As previously mentioned, eastern philosophies promote meditation as a means towards personal transformation and value-clarification. It would be interesting to examine whether participants who most benefitted from MBCT also engaged in more value-congruent behavior as is encouraged in BATA.

The attenuation of DMN connectivity observed is consistent with previous research in MDD samples using non-psychosocial interventions. Serotonin norepinephrine reuptake inhibitors (Posner et al., 2013) and transcranial magnetic stimulation (Liston et al., 2014) have both been shown to reduce hyperconnectivity within the DMN. Although MDD and anhedonia are closely related, it is notable that biomarkers occasionally differ between samples defined on the basis of DSM diagnosis and dimensional symptom severity. As an example, depressed patients show a tendency to increase discounting of large future rewards (i.e., preference for immediate rewards (Pulcu et al., 2014), while a sample defined by elevated SHAPS showed a reduced delay discounting effect (Lempert & Pizzagalli, 2010). In schizophrenia studies, increased connectivity between the PCC and MPFC (Zong et al., 2019), and the PCC and left lingual gyrus (Duan et al., 2020) has been observed following risperidone treatment, but these increases were associated with improvement in positive symptoms of psychosis and not negative symptoms such as anhedonia.

Limitations

There are several limitations to consider in the present study. First, a lack of a non-anhedonic comparison group precluded full exploration of the hypothesis that anhedonia is related to hyperconnectivity within the DMN. As Korgaonkar et al. (2019) showed, opposite patterns of connectivity relative to controls were apparent between depressed individuals who

improved with antidepressants and those who did not. A similar effect may be obscured within our sample. Secondly, the DMN was defined with respect to an atlas using only cortical nodes while anhedonia is known to have significant subcortical contributions. This decision was motivated in part by the relatively few numbers of connections to query with an ROI-to-ROI approach (decreasing the number of statistical comparisons and thus the probability of a Type I error) and evidence suggesting cortical connections are more reliable than subcortical ones (Noble et al., 2017). Additionally, if anhedonia reconfigures the DMN dramatically enough, it may be possible that essential nodes were omitted from this analysis (i.e., perhaps the anterior cingulate is strongly connected to the DMN in our sample). Using a data-driven approach such as ICA to define the DMN may be more appropriate for future investigations.

Finally, and most importantly, the total amount of resting-state date available is likely inadequate to explore individual differences in psychological constructs and treatment effects. Research shows the test-retest reliability of one 8-minute session of resting-state data is exceptionally poor (Noble et al., 2017). Fair reliability may be achieved with a minimum of 24 minutes, but over the course of four separate sessions. While the overall design of the trial has many strengths, null findings for these hypotheses must be considered in light of these constraints.

Future Directions

Future research should examine anhedonia from a triple network model perspective to test hypotheses that salience network regions contribute to imbalance within and between the DMN and frontoparietal networks. Lag models may be better suited to investigate relations between change in networks and symptomatic improvement following treatments, especially therapies that encourage long-term changes in behavior. Multiple methods of analysis should be

used to define resting state connectivity (i.e., data-driven and atlas-based approaches) within the same sample and task-based connectivity may be especially useful to probing anhedonia with respect to the triple network model during reward processing tasks.

Poor reliability of resting state connectivity measures remain a challenge for clinical trials in psychiatry. While recent efforts have pushed for increasingly larger sample sizes, an alternative approach might be increasing the amount of data collection from a smaller sample of participants to achieve more reliable estimates of biomarkers. Although it is fascinating to consider mid-treatment changes in connectivity, limited resources may be better utilized by collecting multiple pre- and post-treatment scans within participants for more confident interpretation of treatment effects.

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