Therapeutic Neural Mechanisms of Mindfulness-based Therapy in Adults with Autism

A Functional MRI and EEG Characterization

by

Broc Pagni

A Dissertation Presented in Partial Fulfillment
of the Requirements for the Degree
Doctor of Philosophy

Approved September 2022 by the
Graduate Supervisory Committee:

Blair Braden, Co-Chair
Jason Newbern, Co-Chair
Mary Davis
Gene Brewer

ARIZONA STATE UNIVERSITY

December 2022

ABSTRACT

Adults with autism spectrum disorder (ASD) face heightened risk of co-occurring psychiatric conditions, especially depression and anxiety disorders, which contribute to seven-fold higher suicide rates than the general population. Mindfulness-based stress reduction (MBSR) is an 8-week meditation intervention centered around training continuous redirection of attention toward present moment experience, and has been shown to improve mental health in autistic adults. However, the underlying therapeutic neural mechanisms and whether behavioral and brain changes are mindfulness-specific have yet to be elucidated. In this randomized clinical trial, I utilized functional magnetic resonance imaging (fMRI) and electroencephalography (EEG) to characterize fMRI functional activity (Study 1) and connectivity (Study 2) and EEG neurophysiological (Study 3) changes between MBSR and a social support/relaxation education (SE) active control group. Study 1 revealed an MBSR-specific increase in the midcingulate cortex fMRI blood oxygen level dependent signal which was associated with reduced depression. Study 2 identified nonspecific intervention improvements in depression, anxiety, and autistic, and MBSR-specific improvements in the mindfulness trait 'nonjudgment toward experience' and in the executive functioning domain of working memory. MBSR-specific decreases in insula-thalamus and frontal pole-posterior cingulate functional connectivity was associated with improvements in anxiety, mindfulness traits, and working memory abilities. Both MBSR and SE groups showed decreased amygdala-sensorimotor and frontal pole-insula connectivity which correlated with reduced depression. Study 3 consisted of an EEG spectral power analysis at high-frequency brainwaves associated with default mode network (DMN) activity. Results showed MBSR-specific and nonspecific decreases in beta- and gamma-band power, with effects being generally more robust in the MBSR group; additionally, MBSR-specific

decreases in posterior gamma correlated with anxiolytic effects. Collectively, these studies suggest: 1) social support is sufficient for improvements in depression, anxiety, and autistic traits; 2) MBSR provides additional benefits related to mindfulness traits and working memory; and 3) distinct and shared neural mechanisms of mindfulness training in adults with ASD, implicating the salience and default mode networks and high-frequency neurophysiology. Findings bear relevance to the development of personalized medicine approaches for psychiatric co-morbidity in ASD, provide putative targets for neurostimulation research, and warrant replication and extension using advanced multimodal imaging approaches.

DEDICATION

This work is dedicated to the greatest sources of inspiration and teaching in my life. First and foremost are my mother and father, who instilled confidence and virtue, imbued life with a sense of curiosity and adventure, and whose unwavering support and love has kept me afloat throughout my many endeavors. I am humbled by the sacrifices they made and would not be where I am today without them.

To my mentor, Dr. B. Blair Braden, who taught me as much about life as science, and whose journey through science is awe-inspiring. Dr. Braden's gratuitous dedication to my training and personal development is a paragon of what it means to be an extraordinary mentor. Her poised navigation through work and life has inspired me to continuously seek balance and compassion toward others, no matter how turbulent life becomes. I remain forever indebted to her selfless and strategic direction of my academic training, and am filled with immense gratitude to have joined forces with such a magnificent human.

ACKNOWLEDGMENTS

I thank the many who have given me purpose and illuminated my life: Tom and Peggy Yost, for their enduring love and support; Clay Villanueva, my spiritual teacher; Laura Oswald, my beloved counterpart; Brandon Pagni, my brother; and my closest friends – Joey Eberhardt, James Cook, Nicolas Guerithault, Vergil Haynes, Sean Noudali, and Matthew Broussard. You all have played an integral role in my life and I hold you dearly in my heart.

I thank those who have made my educational and scientific journey possible. Dr. Candace Lewis, for being my first scientific role model and encouraging me through my naiveté. Dr. Arthur Glenberg, for pushing me to discover my determination. Dr. Janet Neisewander, for believing in me and giving me an academic home. Dr. Jason Newbern, for taking a leap of faith and serving as my co-chair. My committee members, Drs. Mary Davis and Gene Brewer, for being an absolute joy to work with. Thank you to ASU's School of Life Sciences and the Interdisciplinary Graduate Program of Neuroscience, and the National Center of Complementary and Integrative Health for making this journey possible.

TABLE OF CONTENTS

Page

LIST OF TABLES

Table Page

LIST OF FIGURES

Figure Page

CHAPTER 1

MINDFULNESS-BASED THERAPY FOR ADULTS WITH AUTISM SPECTRUM DISORDER: TREATING CO-MORBID DEPRESSION AND ANXIETY

CO-OCCURRING PSYCHIATRIC CONDITIONS IN ASD

Adults with autism spectrum disorder (ASD) have greater incidence of co-occurring psychiatric conditions, with depression estimated to be fourfold the general population, and anxiety disorders diagnosed in ~40% of autistic individuals (Hudson et al., 2019; van Steensel et al., 2011). Co-occurring psychiatric conditions can have devastating consequences on an already vulnerable population, manifesting as heightened aggression, self-harm, and suicidality, and substantial reductions in quality of life (Hedley et al., 2017; Jokiranta-Olkoniemi et al., 2021; Oakley et al., 2021). Moreover, mental health conditions exacerbate ASD-related impairments in executive functioning and jeopardize the likelihood of acquiring and maintaining independence and employment stability, which remains below other neurodevelopmental conditions (Howlin, 2000; Maddox et al., 2018; Shattuck et al., 2012). While the etiological underpinnings of vulnerability in this population remains unclear, early psychological research points to deficits in emotion regulation, self-awareness, and executive functioning as contributing factors (Lombardo et al., 2007; Mazefsky et al., 2013; Wallace et al., 2016). Additionally, social and societal challenges – such as feelings of 'burdensomeness' – mediate heightened suicidality and predict depression severity, evidencing a complex web of psychological and environmental factors that may serve as therapeutic targets for behavioral interventions.

TREATMENT FOR PSYCHIATRIC CONDITIONS IN ASD

While pharmacological and behavioral interventions have yet to be tailored toward treating psychiatric symptoms in ASD, existing interventions have undergone

investigation for clinical utility. Unfortunately, pharmacotherapies have been largely unsuccessful due to poor medication efficacy and compliance, and negative side effects (Coleman et al., 2019). However, behavioral interventions may mitigate these challenges. Cognitive Behavioral Therapy (CBT), an evidence-based intervention developed to treat depression in patients with Major Depressive Disorder provided early indications of antidepressant and anxiolytic effects in adults with ASD; however, concerns with efficacy and effectiveness have arisen, limiting therapeutic potential. In a head-to-head study, Sizoo and colleagues (2017) compared CBT with mindfulness-based therapy (MBT) in adults with ASD, and suggested MBT may be preferred for a subset of participants with anxiety symptoms and ASD-related cognitive challenges. Further, a systematic review in ASD provided inconclusive evidence for CBT, but strong evidence for MBT's compared to traditional psychosocial and pharmacological treatments (Menezes et al., 2020).

MINDFULNESS-BASED THERAPY FOR ASD

MBT's share the overarching theme of training the continuous redirected of attention toward present moment experience with a nonjudgmental, nonreactive attitude, and have demonstrated efficacy in a myriad of mental health measures in various clinical and nonclinical populations (Goldberg et al., 2018; Kabat-Zinn, 2003; Khoury et al., 2015; Luberto et al., 2018). MBT's were first adapted for adults with ASD in 2013 by Spek and colleagues who reported sustained antidepressant and anxiolytic effects 9-weeks post-intervention relative to a waitlist control group (Kiep et al., 2015; Spek et al., 2013). Since then, mindfulness-based stress reduction (MBSR), an intensive 8-week meditation intervention, has demonstrated high feasibility and become the primary MBT undergoing active study in adults with ASD (Beck et al., 2020). MBSR studies have confirmed mental health improvements and demonstrated additional improvements in quality of life and emotional regulation relative to active controls

(Braden, Pagni et al., 2021; Pagni & Braden, 2021). However, it remains unclear if improvements in depression, anxiety, and autistic traits are mindfulness-specific, as similar improvements have been observed with CBT (Sizoo & Kuiper, 2017).

Overall, sample sizes have been small and prevented conclusive head-to-head comparisons of clinical efficacy (Cachia et al., 2016). Additionally, active control groups controlling for social and educational aspects of MBSR are necessary to identify the "active ingredients" of mindfulness. While outcomes of MBSR have been attributed to enhanced global mindfulness, it remains unclear if changes in mindfulness traits are unique psychological targets of MBT's (Gu et al., 2015). Mindfulness training has also been shown to improve executive functioning in other clinical populations (Basso et al., 2019; Lao et al., 2016), but whether these benefits apply to adults with ASD still needs to be evaluated. Adequately-powered randomized clinical trials are warranted to elucidate MBSR-specific and MBSR-nonspecific therapeutic effects in adults with ASD.

MBSR is theorized to exert therapeutic effects by improving emotion regulation, self-awareness, and executive functioning, all of which are domains of impairment in ASD and contributed to susceptibility to co-occurring psychiatric conditions (Desaunay et al., 2020; Gotink et al., 2016; Hatchard et al., 2017; Lombardo et al., 2015; Wallace et al., 2016; Williams, 2010). Thus, adults with ASD may be a well-suited population to benefit from mindfulness training. Owing to superior effectiveness relative to other behavioral interventions, MBT's may be more easily implemented in community and online settings, without compromising critical therapeutic elements embedded in one-one-one and in-person clinical settings such as psychotherapy and CBT (Gaigg et al., 2020). Importantly, a brain-based characterization of MBSR-specific and nonspecific changes will: 1) inform etiological basis of psychiatric susceptibility in ASD; 2) provide vital insights into psychological and neural correlates of mindfulness; 3) aide the

development of personalized medicine approaches for adults with ASD; and 4) identify neural targets for future neurostimulation research seeking to optimize treatment outcomes.

NEURAL MECHANISMS OF MBT

Therapeutic outcomes of MBSR have been linked to multiple large-scale neural networks – defined as spatially distributed brain regions that display synchronized activity and subserve distinct cognitive and affective functions – including the default mode (DMN), salience (SN), and central executive (CEN) networks (Bremer et al., 2022). The DMN underlies the sense of 'self' and is engaged at rest and when processing self-related information (Northoff & Bermpohl, 2004). Hyperactivity of the DMN during self-referential processing is a consistent feature found in major depressive disorder (MDD) and suspected to underlie negative self-biases and rumination (Nejad et al., 2013). Functional magnetic resonance imaging (fMRI) suggests MBSR modulates DMN activity and connectivity, especially among the medial prefrontal cortex (mPFC) and posterior cingulate cortex (PCC), which correspond with improvements in depression and anxiety (Lin et al., 2018). Additionally, mPFC hypoactivity in adults with ASD during self-reflection is associated with social symptoms, suggesting the DMN distinguishes self- and other-related cognitive processing (Lombardo et al., 2010).

Electroencephalography (EEG) and magnetoencephalography (MEG) research have corroborated fMRI findings and further characterized relations between the DMN and mindfulness meditation, implicating high-frequency brain waves across cortical midline structures. For example, meditation training induces decreases in beta-band power across central anterior and posterior scalp regions (Saggar et al., 2012); gamma power corresponds with meditation expertise (Berkovich-Ohana et al., 2012; 2014); gamma-band decreases accompany the diminution of the "narrative-self"; beta-band

decreases accompany the diminution of the "experiential-self" (Dor-Ziderman et al., 2013); and MBSR-induces spectral power changes to beta- and gamma-band power (Ng et al., 2021). These studies suggest mindfulness meditators exhibit state and trait level changes in high-frequency brain waves across cortical midline sites, theorized to reflect DMN deactivation (Berkovich-ohana et al., 2014). Moreover, effects of mindfulness training on the DMN have been successfully indexed using self-reflection fMRI and resting state EEG (Farb et al., 2007a; Ng et al., 2021). Collectively, research suggests MBSR-mediated DMN modulation may underlie therapeutic improvements in adults with ASD.

Meditation training has been postulated to redirect attention away from the "narrative-self" (ascribed to the DMN) toward the "experiential-self" (ascribed to the SN), thereby attenuating depressive and anxious thought patterns (Farb et al., 2013). The SN is critical for network switching wherein dampened DMN activity and recruitment of the ECN facilitates the transition of internally-oriented attention toward external stimuli (Menon & Uddin, 2010). Such changes to salience detection and attention allocation may bear clinical significance in addressing negative self-biases and rumination in depression and anxiety (Lemogne et al., 2009). Major hubs of the SN – namely, the anterior cingulate cortex (ACC) and insula – are involved in self-referential processing with pronounced abnormalities noted in ASD, ascribed to deficits in self-awareness and social cognition, and in depression (Liu et al., 2017; Lombardo et al., 2010; Paulus & Stein, 2010; Uddin & Menon, 2009a). MBSR-elicited alterations to the ACC and insula have been consistently reported in other populations and typically interpreted in the context of training effects on attention, emotional processing, interoception, exteroception, self-awareness, and empathy (Chiesa & Serretti, 2010; Nakata et al., 2014; Sevinc et al., 2018). Further, meditation-induced increase in ACC

and insula activity have been associated with reductions in pain intensity, providing a behavioral readout of neural changes in these structures (Zeidan et al., 2011). The SN also includes nodes in the amygdala which are amenable to mindfulness training (Seeley, 2019). For example, MBSR-specific increases in PFC-amygdala connectivity is associated with alleviation of anxiety symptoms, and decreases in amygdala activity is associated with reduced emotional reactivity (Gotink et al., 2016). Collectively, these findings suggest the SN, comprised of the ACC, insula, and amygdala, are targets of MBSR and may drive clinical improvement in ASD.

Last, early evidence suggests MBT's may improve executive functioning, lending the CEN as a potential substrate of cognitive-related improvements (Lao et al., 2016). The CEN is responsible for guiding decision-making and problem-solving (Menon, 2011) with the dorsolateral PFC (dlPFC) serving as an important hub involved in manipulating information in working memory and directing behavioral responses. Considering transcranial magnetic stimulation of the dlPFC in bipolar patients improved executive functioning abilities and depressive symptoms, it is plausible MBSR training mediates executive functioning by altering dlPFC connectivity patterns (Kazemi et al., 2018). In a recent review of the neural mechanisms of mindfulness in various populations, hubs comprising the DMN (mPFC and PCC), SN (insula, ACC, and amygdala), and ECN (dlPFC) were reported (Gotink et al., 2016). Since research has yet to characterize the therapeutic neural correlates of MBSR in adults with ASD, the culmination of this work served as a springboard for the hypotheses of the studies covered in this dissertation.

RESEARCH OBJECTIVES

The aim of this dissertation was to identify distinct and shared therapeutic neural mechanisms of MBSR in adults with ASD. In the first study, functional magnetic resonance imaging (fMRI) was employed to examine MBSR's effects on the blood oxygen

level dependent (BOLD) signal during self-reflection at brain regions (dorsal anterior cingulate, dACC/MCC; ventromedial prefrontal cortex, vmPFC) reported to be atypically recruited during self-reflection in adults with ASD (Chapter 2). Study 2 examined MBSR-specific and intervention-nonspecific effects on behavior and fMRI self-reflection functional connectivity using a generalized psychophysiological interactions approach (Chapter 3). Study 3 utilized an EEG spectral power analysis to examine MBSR's effects on high-frequency brain waves associated with DMN activity (Chapter 4). In the final chapter, the findings of these studies are interpreted in the context of the broader literature. Implications for the development of personalized medicine and neurostimulation research in ASD, and directions for future research are discussed.

CHAPTER 2

A PILOT FMRI BOLD-CONTRAST INVESTIGATION OF NEURAL CORRELATES OF MBSR

INTRODUCTION

DEPRESSION AND ANXIETY IN AUTISM SPECTRUM DISORDERS

Individuals with autism spectrum disorder (ASD) suffer from greater incidence of depression and anxiety compared to the general population and other developmental conditions (Brereton et al., 2006; Szatmari et al., 2003). Notably, depression has been reported at exceptionally high rates in adults with ASD and is likely related to high rates of suicide among adults with ASD, especially women (Cassidy & Rodgers, 2017; Ghaziddin & Zafar, 2008; Howlin, 2000; Sterling et al., 2008). Further, depression is associated with poor work-related outcomes, including lower productivity and job loss, compounding the challenges of independent living for many adults with ASD (Simon et al., 2000; Lerner & Henke, 2008; Maddox et al., 2018). Pharmacological therapies are largely unsuccessful in treating mood co-morbidities in adults with ASD (Coleman et al., 2019). Collectively, research suggests co-morbid depression and anxiety pose substantial challenges to adults with ASD, and more effective treatments tailored toward this unique population are warranted.

MINDFULNESS INTERVENTIONS FOR DEPRESSION AND ANXIETY

A growing number of studies have examined the application of mindfulness practices for reducing suffering and increasing wellbeing across many populations (Christensen & Marck, 2017; Khoury et al., 2015). One standardized, clinically-based method used widely by the medical and research communities is Mindfulness-Based Stress Reduction (MBSR). The standard MBSR program is an eight-week, evidence-based program that teaches present moment focus by continuously redirecting attention

(Kabat-Zinn, 2003). The efficacy of MBSR in treating depression, anxiety, stress, and pain has been substantiated in a variety of clinical and non-clinical groups with diverse demographics (Abbott et al., 2014; Biegel et al., 2009; Braden et al., 2016; Gold et al., 2010; Joo et al., 2010; Marchand, 2012; Song & Lindquist, 2015). A meta-analysis of the standard MBSR protocol across multiple populations found improved mental health outcomes compared to active control treatments, but the effect size was small compared to studies published with wait-list controls (de Vibe et al., 2017). An MBSR protocol was adapted for adults with ASD in the Netherlands and stipulates the intervention be delivered by a clinician trained in both ASD and MBSR. The initial study compared MBSR to wait-list controls and found reduced depression and anxiety in adults with ASD (Spek et al., 2013). More recently, Sizoo and Kuiper (2017) compared extended treatment durations of the adapted MBSR protocol to Cognitive Behavioral Therapy (CBT) and found both attenuate depression and anxiety. Participants in these studies were intellectually-abled and had average or above average intelligence quotient estimates. However, Sizoo and Kuiper (2017) have asserted MBSR may be preferred over CBT for those with intellectual challenges because CBT instructions may require more cognitive and communication skills. Based on these prior studies, it remains unclear how the adapted MBSR intervention performs compared to an active–control treatment which does not require a credentialed facilitator but controls for social support and stress reduction education. Understanding the benefits of adapted MBSR in comparison to a community member-led support/education group will inform evidence-based approaches that optimize accessibility of care.

SELF-REFLECTION IN ASD

Understanding the mechanism(s) of MBSR-elicited symptom reduction in adults with ASD will help optimize this treatment option. Excessive self-referential cognition is

associated with mood and anxiety disorders (Philippi and Keonigs, 2014). Interestingly, adults with ASD demonstrate diminished self-reflection (Toichi et al., 2002). Philippi and Koenigs (2014) propose an optimal level of self-reflection is crucial to healthy functioning, and aberrant self-reflection on either end of the spectrum may contribute to psychiatric symptoms. In line with this model, the neurocircuitry of self-reflection, underpinned by the ventromedial prefrontal cortex (vmPFC), middle cingulate cortex (MCC), and posterior cingulate cortex (PCC), also shows aberrant function associated with ASD and mood disorders.

Patients with major depression demonstrate elevated activation in the vmPFC, compared to healthy individuals (Lemogne et al., 2012), while adults with ASD demonstrate reduced vmPFC and MCC activation, compared to neurotypicals (Lombardo et al., 2010). Therefore, increasing vmPFC and MCC activity during self-reflection may be of therapeutic value for ASD who display abnormally low levels of self-referential processing. In neurotypical adults, greater dispositional mindfulness is associated with lower resting state activity in self-referential processing regions (mPFC and PCC), whereas greater depressive symptoms are associated with higher resting state vmPFC activity (Way et al., 2010). Although MBSR training induces changes in prefrontal and PCC activity during self-reflection in adults with social anxiety disorder (Farb et al., 2007b; Goldin et al., 2012), it is unknown if MBSR therapeutically shifts self-reflection activation profiles in a more normative direction in adults with ASD. Taken together, MBSR-induced changes to neural systems subserving self-reflection may promote a more optimal profile of self-reflection and thereby be one mechanism to alleviate depression and anxiety symptomatology in adults with ASD. The current study aligns with a growing pursuit to identify therapeutic neural biomarkers in ASD by examining brain-based changes associated with MBSR.

PRESENT STUDY

In this pilot study, 28 adults with ASD were randomly assigned to and completed an eight-week MBSR or social support/education group. Pre- and post-intervention self-report questionnaires and self-reflection functional MRI (fMRI) scans were collected. First, we hypothesized that MBSR intervention would reduce depression and anxiety symptoms, while the support/education group would show no change. Second, we hypothesized those who received MBSR training, but not support/education, would show increased blood-oxygen-level dependent (BOLD) response in regions previously shown to be less activated during self-reflection in adults with ASD versus neurotypical (MCC and vmPFC; Lombardo et al., 2010). Third, we hypothesized that the BOLD signal change in these regions would be correlated with changes in depression and anxiety. Lastly, we ran exploratory analysis on whole-brain functional connectivity changes during self-reflection using MCC and vmPFC as seeds.

METHODS

PARTICIPANTS AND SELF-REPORT MOOD MEASURES

Initial enrollment of 42 adults who self-reported an ASD diagnosis was based on power analysis from Speck et al. (2013). Inclusion criteria were meeting ASD criteria on the Autism Diagnostic Observation Schedule-2 (ADOS-2; Lord et al., 2012), administered by an experienced research-reliable administrator at the Southwest Autism Resource and Diagnostic Center, and an IQ score >70 as measured by the Kaufman Brief Intelligence Test-2 (KBIT-2, Kaufman & Kaufman 1990). Exclusion criteria were history of traumatic brain injury, substance abuse, and active suicidality. Due to our goal of recruiting a representative group of intellectually-able adults with ASD, we did not exclude adults on the basis of sex, age, or general comorbidities (single cases of epilepsy,

Tourette's syndrome, and hearing loss). Further, no handedness restrictions were employed, as non-right-handedness is more common in ASD (Dane & Balci, 2007) and unlikely to influence self-reflection neural activation.

Participants were randomly assigned to an eight-week MBSR group or a stress support/relaxation education (support/education) control group. Self-reported symptoms of depression and anxiety were assessed via the Beck Depression Inventory-2 (BDI-II) and the State-Trait Anxiety Inventory (STAI) at the MRI appointment within one month before and after termination of the intervention (Beck et al, 1996: Spielberger, 1983). Attrition of 14 participants was for the following reasons: Two did not meet ADOS-2 criteria, one did not meet IQ criteria, two dropped after the pre-intervention assessment, two were removed from the study because of disruptive behaviors, two were removed from the analysis because of significant adverse life events during the intervention that were unrelated to the study and confounded symptom presentation, and five were dropped from analyses after attending fewer than half of the classes. The remaining 28 participants attended four or more of the eight classes (MBSR group, n=15; support/education group, n=13); one MBSR participant's neuroimaging data was incomplete due to equipment error. Participant demographics can be found in Table 1. The protocol was approved by the Institutional Review Board and all participants provided written consent.

TABLE 1 Participant demographics and self-report mean, standard deviations, and ranges

	MBSR			Support/education			Baseline group differences
Sample size (M/F)	15(8/7)			13 (11/2)			$\chi^2(26) = 4.37$; $p = 0.037$*; $\varphi = 0.40$
Age, years	32.27 (13.16) range: 18–64			31.15 (13.22) range: 19–62			$t(26) = -0.22$; $p = 0.825$; $d = 0.09$
IQ[a]	106.40 (19.43) range: 70–131			108.38 (17.59) range: 70–139			$t(26) = 0.28$; $p = 0.780$; $d = 0.11$
ADOS-2[b]	11.73 (3.45) range: 8–20			11.31 (3.68) range: 7–17			$t(26) = -0.32$; $p = 0.755$; $d = 0.12$
Classes attended	6.5 (1.2) range: 4–8			7.2 (1.1) range: 4–8			$t(26) = 1.55$; $p = 0.132$; $d = 0.59$
Depressed at baseline (BDI-II[c] ≥ 10)	$n = 10$ (67%)			$n = 7$ (54%)			$\chi^2(26) = 12.18$; $p = 0.431$; $\varphi = 0.66$
Non-depressed at baseline (BDI-II[c] < 10)	$n = 5$ (33%)			$n = 6$ (46%)			$\chi^2(26) = 6.97$; $p = 0.324$; $\varphi = 0.50$
	Pre	Post	Paired *t*-test	Pre	Post	Paired *t*-test	Baseline group differences
BDI-II[c]	13.80 (8.59) range: 2–29	8.73 (6.05) range: 0–17	$t(14) = 3.31$; $p = 0.005$*; $d = 0.68$	14.69 (13.07) range: 0–43	10.15 (7.35) range: 0–22	$t(12) = 1.82$; $p = 0.094$; $d = 0.43$	$t(26) = 0.22$; $p = 0.830$; $d = 0.08$
STAI-2[d]	43.07 (10.68) range: 31–60	39.20 (8.18) range: 27–52	$t(14) = 1.49$; $p = 0.158$; $d = 0.53$	46.50 (16.10) range: 22–72	41.00 (13.07) range: 22–66	$t(11) = 1.73$; $p = 0.112$; $d = 0.44$	$t(25) = 0.67$; $p = 0.512$; $d = 0.15$

[a]Kaufman Brief Intelligence Test-2 Composite.

[b]Autism Diagnostic Observation Schedule.

[c]Beck Depression Inventory-II.

[d]State-Trait Anxiety Inventory-2.

*$p < 0.05$.

INTERVENTION GROUPS

The MBSR training was most similar to and very minimally adapted from the standard protocol designed by Jon Kabat-Zinn at the University Massachusetts Medical School. Class duration was shortened from 2.5 hours to 2 hours, so some practices were reduced in time. We made two other modifications similar to Spek et al. (2013): the protocol did not include an all-day retreat and metaphorical language was removed to ensure comprehensibility. Unique to this study, the intervention was co-instructed by a certified MBSR instructor with over 10 years' experience (author AS) and a Speech-Language Pathologist with over 20 years' experience treating ASD symptoms who also attended a brief, three-day MBSR training (author MD). Participants met for two-hours once/week for eight weeks with about 45 minutes of daily home practice. Practices taught in class focused participant's attention toward an object(s) or thoughts and emotions that appear in awareness with a curious and nonjudgmental attitude. MBSR practices include following the breath; scanning the body; eating, walking, and conversing with mindful awareness; and characterizing personal stressors and observing how they manifest in the body and mind. Daily home practice included meditations (body scan, following the breath, etc.), pleasant and unpleasant events calendar, communication calendar, and a variety of informal activities. Participants had access to a website for recorded mediations and received daily email reminders for home practice. The website also contained class recordings that participants were encouraged to watch if they missed class. The support/education control group met for the same amount of time led by two study team members (authors BB and BP). In alignment with other control group conditions in MBSR studies, participants were given education on relaxation techniques from the National Center for Complementary and Integrative Health (https://nccih.nih.gov/health/stress/relaxation.htm; (Braden et al., 2016;

Hughes et al., 2013; Jain et al., 2007). Participants were encouraged to employ techniques introduced in class at home and discuss their experience with the group, as well as share additional tips and resources for stress reduction. Support/education participants were also sent daily email reminders for home practice (log daily stressors and stress reduction techniques employed) and had access to a website that contained class recordings to be watched if they missed class. In an exit survey, the majority of respondents from both groups reported using techniques learned in class "every other day" on average.

fMRI SELF-REFLECTION TASK

Pre- and post-intervention fMRI scans were collected during a self-reflection task. Participants were required to make yes/no decisions based on trait adjectives across two conditions: (1) Self-condition—participants decided whether the adjective described their character and abilities, and (2) Word-condition—participants decided whether the adjective was positively valenced. The word-condition sought to control for emotional/cognitive processing of the stimuli and valenced adjectives, making evaluative judgments and decisions, and preparing and executing motor responses. Thus, when the self-condition was contrasted to the word-condition, emotional and cognitive neural processing uniquely related to self-evaluation was captured. Participants received training on the task prior to entering the scanner, including instructions for the Self and Word conditions and a short trial run using novel stimuli from the in-scanner task. The task paradigm and adjective set was provided by Schmitz et al. (2004) and contained the following types of adjectives: general (i.e., daring), social (i.e., shy), physical (i.e., weak) and cognitive (i.e., intelligent). The stimuli were presented as "I am…" in the self-condition and as "Is the word positive?" in the word-condition. All participants completed two runs, each four minutes in duration, consisting of 10 blocks (5 blocks per

condition). Each block was 24 s in duration with stimuli being presented every 3 s with a 1 s interstimulus interval (6 stimuli per block; 120 total stimuli across the two runs). A total of 60 trait words were counterbalanced for order and valence for both conditions (30 positively and 30 negatively valenced words). Stimulus presentation was implemented with Presentation software (Presentation, Neurobehavioural Systems, http://www.neurobs.com) and was synchronized with the onset of image acquisition to ensure timing accuracy. Percent response, reaction time, and accuracy for the word condition were recorded and analyzed. Behavioral measures and the fMRI task were completed within one month before the start of the intervention and one month after the termination of the intervention.

fMRI ACQUISITION

All imaging was performed on a 3T Philips Ingenia scanner with a maximum gradient strength of 45mT/m at Barrow Neurological Institute (Phoenix, AZ, USA) in the Keller Center for Imaging Innovation. T_2^* weighted images were acquired with a gradient echo, echo-planar pulse sequence to elicit blood oxygen level-dependent (BOLD) contrast. The scanning parameters were: Slice thickness = 3mm, TE = 30 ms, TR = 2000 ms, flip angle = 90, in-plane resolution= 64 x 64, field of view = 240 mm, and voxel size = 3 x 3 mm. Images from the first 3 TRs were discarded to allow for stabilization. 3D magnetization prepared rapid acquisition gradient echo (MPRAGE) T_1 images were acquired and used for preprocessing: 170 sagittal slices, slice thickness = 1.2 mm, in-plane resolution = 256 x 256, field of view = 240 mm.

fMRI PREPROCESSING AND TASK ACTIVATION ANALYSIS

Preprocessing and statistical analysis of fMRI data were completed in SPM12 (Wellcome Trust Centre for Neuroimaging, http://www.fil.ion.ucl.ac.uk/spm). Preprocessing steps included slice timing correction, realignment to the mean image, co-

registration to the skull-stripped T1, normalization to MNI using the DARTEL method (Ashburner, 2007), and 8 mm full width half maximum Gaussian kernel spatial smoothing. Scrubbing parameters for scans exceeding 2mm relative displacement were generated using the Artifact Detection Tools (ART) toolbox. Both scrubbing and realignment parameters (6 rigid-body transformations) were used as covariates at the 1st level analysis and the signal was high-pass filtered (128 s) to account for low frequency drift. Whole-brain statistical analysis was conducted with a general linear model (GLM). Blocks were convolved with the canonical hemodynamic response function. To evaluate task-specific activation in this sample, a single-sample t-test for the Self>Word contrast was performed collapsing across groups at baseline. Results were threshold at $p<0.05$ with family-wise error (FWE) correction.

INTERVENTION EFFECTS DATA ANALYSIS

Power analyses were based on Spek et al. (2013), using depression as the outcome. This pilot study was initially powered to detect an interaction effect (n=42 required), but due to attrition we only maintained powered to detect within group changes, thus groups were analyzed separately. Normality assumptions were met for the MBSR, but not the support/education group. Therefore, we performed a paired-samples t-test for the MBSR group and a Wilcoxon Signed-Ranks Test for the support/education group to examine pre- to post-intervention changes in depression (BDI-II) and anxiety (STAI-2) in SPSS 16 (http://www.spss.com). To analyze group-level intervention effects for fMRI data, a paired sample t-test was performed specifying Post>Pre or Pre>Post contrasts for Self>Word. Whole brain results were set at a $p<0.001$ threshold and an extent of 25 voxels. ROI analyses were performed for the MCC and vmPFC, using bilateral Anatomical Automatic Labeling (AAL) masks for small volume correction and alpha defined as FWE $p<0.05$. ROIs were selected based on reports of reduced activation

during self-reflection in adults with ASD, compared to neurotypical (Lombardo et al., 2010), with the hypothesis that activation in these regions would increase after MBSR. To examine brain-behavior correlations for intervention-related changes, we conducted correlations between mood symptom changes (depression [BDI-II] and anxiety [STAI-2]) and activation changes in the two neuroanatomical ROIs (MCC and vmPFC). Mean contrast estimates for pre- to post-intervention changes for Self>Word was extracted for the MCC and vmPFC AAL ROIs using the MarsBar SPM toolbox (Brett et al., 2002). Change score outliers were removed based on three standard deviations from the mean criteria (MBSR n=1; support/education n=1). Finally, whole-brain functional connectivity analysis was performed using the CONN toolbox (https://www.nitrc.org/projects/conn) with MCC and vmPFC seeds and a Post>Pre-intervention contrast. The CONN-fMRI toolbox uses anatomical component correction (aCompCor) method to remove noise and movement confounds on a voxel to voxel basis. We regressed out 5 white matter parameters, 5 CSF parameters, and 12 realignment parameters as well as first temporal derivatives for each subject and performed linear detrending. For all behavior analyses, $p<0.05$ two-tailed was used, and for all brain analyses, $p<0.05$ FWE-corrected was used. BDI and STAI t-tests and correlations were not corrected for multiple comparisons in this pilot study due to a priori hypotheses of change and correlations in the MBSR group, but not the support education. Of note, Type I error correction is not necessary with orthogonal planned comparisons (Keppel & Wickens, 2004). A one-tailed $p<0.05$ was used for correlations between behavior changes and brain changes, as we predicted increased neural activation would correlate with decreased symptom presentation.

RESULTS

DEPRESSION AND ANXIETY CHANGES

This study included participants with ASD who endorsed a range of depression symptoms, from severe to normal levels. Participants baseline depression levels are illustrated in the context of clinical cutoffs (Figure 1a). Fifty-seven percent of participants endorsed depression levels above the BDI-II clinical cutoff of 10. No significant group differences in demographic or self-report mood questionnaires were found at pre-intervention (Table 1). Difference scores on the BDI and STAI-2 were normally distributed for the MBSR group, however the support/education group difference scores on the BDI-II violated kurtosis assumptions and scores on the STAI-2 violated kurtosis and normality assumptions. Therefore, a nonparametric test was used for the support/education group. The MBSR group demonstrated significant decreases in BDI-II depression scores with a large-medium effect size, while the support/education control group did not significantly change. The support/education group had one outlier BDI-II difference score and excluding this participant did not influence significance. The MBSR group demonstrated significant decreases in BDI-II depression scores with a large-medium effect size, while the support/education control group did not significantly change. Figure 1a illustrates individual change scores across BDI-II severity categories (Kress, et al. 2003), which demonstrate that many of the individuals in the MBSR group showed clinically significant decreases in symptoms.

Post-hoc analysis examining possible differential floor effects between groups based on level of depression revealed no group differences for baseline BDI-II scores or in the number of participants in the clinically depressed or non-depressed category based on baseline BDI-II scores (Table 1). For the support/education group, depressed participants trended toward a significant reduction ($t(6)=2.409$, $p=0.053$), while non-depressed participants did not ($t(5)=-0.667$, $p=0.534$). For the MBSR group, depressed

participants had significant reductions ($t(9)=3.269$, $p=0.010$), while non-depressed participants did not ($t(4)=1.406$, $p=0.233$). Neither group significantly changed in STAI-2 anxiety scores (Table 1). While clinical severity categories are not available for the STAI, a clinical cutoff of 40 has been proposed (Julian, 2011). Based on this, Figure 1b illustrates a few participants may have experienced a clinically significant decline in anxiety symptoms.

fMRI SELF-REFLECTION TASK BEHAVIOR AND TASK ACTIVATION

Behavioral data during the self-reflection task showed no group differences at baseline and no intervention-related changes in response rate, reaction time, or accuracy (Supp. Table 1). To visualize the general pattern of activation during the self-reflection task, groups were collapsed (MBSR + support/education) and conditions were compared (Self>Word) at the pre-intervention time point. Significant activation in major hubs of the default mode network—mPFC, posterior cingulate cortex, and precuneus—were detected as well as the middle frontal gyrus (Supp. Figure 1; Supp. Table 2). These results are consistent with the neural correlates of self-reflection in other studies (Modinos et al., 2009; Whitfield-Gabrieli et al., 2011). As expected, there were also no group differences in activation patterns at baseline between MBSR and support/education groups.

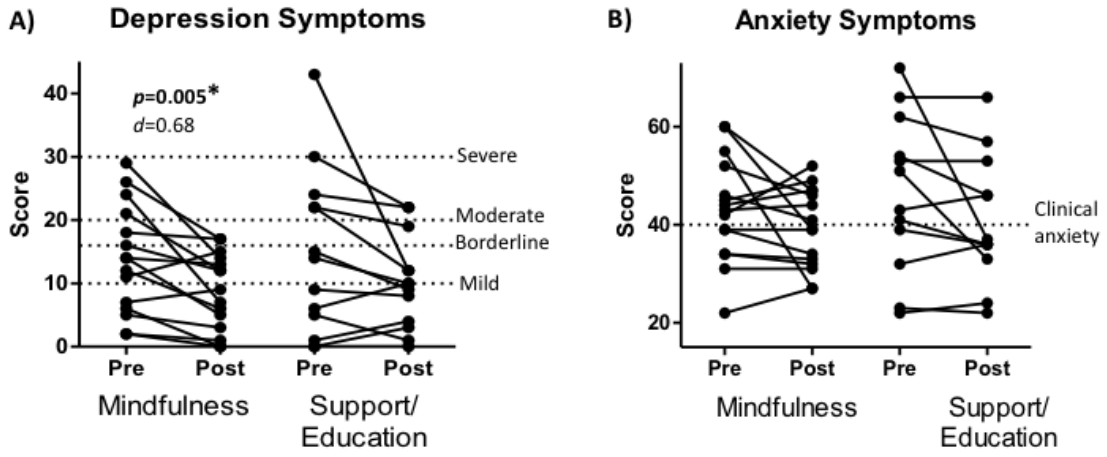


FIGURE 1 Individual pre- and post-intervention scores for the (a) Beck Depression Inventory-II in the MBSR and support/education groups and (b) State-Trait Anxiety Inventory-2 in the MBSR and support/education groups. Statistics are from paired samples *t*-test and Wilcoxon signed-rank test (Table 1). Dotted lines represent clinically cutoffs

ACTIVATION AND FUNCTIONAL CONNECTIVITY CHANGES

Within-group main effects of time (Post>Pre) in the Self>Word contrast demonstrated increased activation in right MCC in the MBSR group (Figure 2a; Table 2a), but no changes in vmPFC activation were observed. The support/education groups did not show activation changes in MCC or vmPFC. Neither group showed any decreases in activation over time (Pre>Post). For functional connectivity analysis with the MBSR group, the right MCC showed increased functional connectivity (Post>Pre) to bilateral pre- and post-central gyrus (Right: p=0.001; Left: p=0.049, FWE; Figure 2c; Table 2). No changes were observed in the support/education group. No changes in vmPFC seed-to-voxel functional connectivity were observed for either the MBSR or support/education groups.

BEHAVIOR-BRAIN RELATIONSHIPS

Decreases in self-reported depression (BDI-II) correlated with increased right MCC activation after MBSR ($r(11)=-0.492$, $p=0.044$; one-tailed; Figure 2b). No significant correlation was observed in the support/education ($r(9)=-0.383$, $p=0.123$; one-tailed) group. No correlations between BDI-II and vmPFC change scores were observed in the MBSR ($r(11)=0.352$, $p=0.119$; one-tailed) or support/education ($r(9)=-0.104$, $p=0.380$; one-tailed) groups. Moreover, changes in anxiety (STAI-II) were not significantly correlated with changes in activation of the MCC or vmPFC for either MBSR (MCC: $r(11)=-0.45$, $p=0.059$; vmPFC: $r(11)=0.355$, $p=0.117$; one-tailed) or the support/education group (MCC: $r(8)=0.406$, $p=0.122$; vmPFC: $r(8)=0.003$, $p=0.497$; one-tailed).

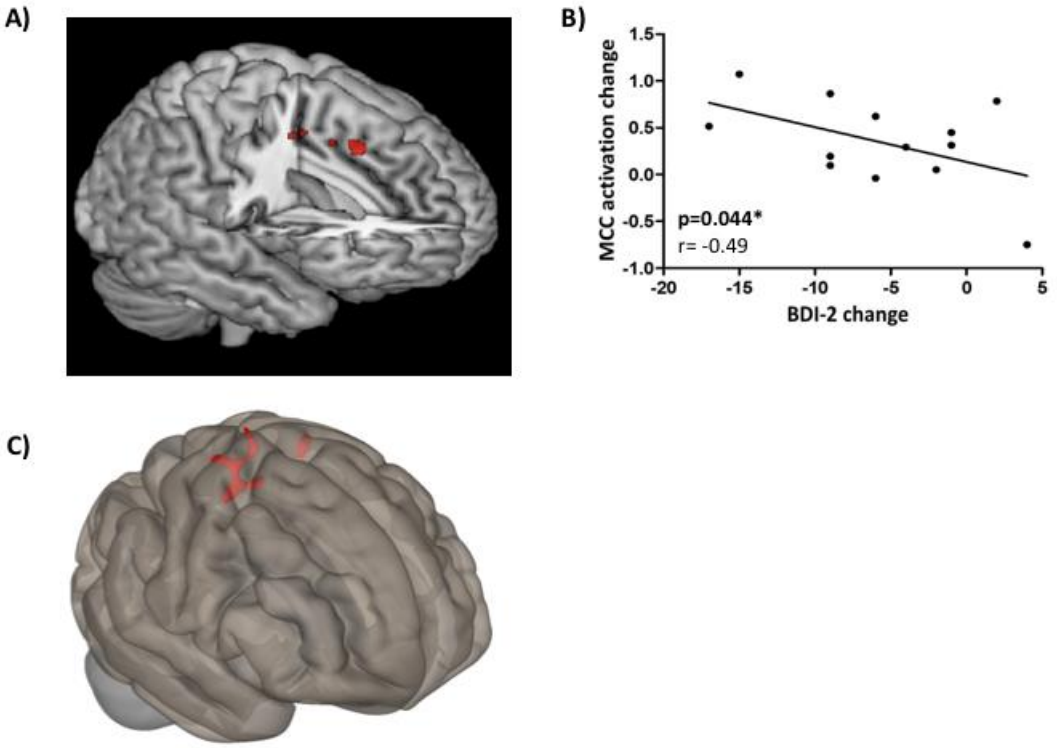


FIGURE 2 (a) Significant increase (Post > Pre) in right middle cingulate cortex (MCC) activation during the Self > Word condition were observed in the MBSR group (small-volume family-wise error (FWE) corrected, $p < 0.05$). There were no differences in the support/education group. (b) Reductions in Beck Depression Inventory-II (BDI-II) scores correlated with increased MCC activation in the MBSR group, but not the support/education group. (c) Right MCC seed-to-voxel functional connectivity analysis identified increased connectivity to bilateral pre/post central gyrus in the MBSR group only.

TABLE 2 (a) MBSR-induced self-reflection activation changes. (b) MBSR-induced self-reflection functional connectivity changes (Right MCC Seed)

A.	Brodmann area	Peak voxel coordinate	Cluster size (K_E)	Peak significance (FWE[a])	Z-score	T-score	Cluster-level (FWE[a])
R middle cingulate cortex (MCC)	32	(6, 22, 40)	69	$p = 0.018$*	3.9	5.54	$p = 0.047$*
B.	**Brodmann area**	**Peak voxel coordinate**	**Cluster size (K_E)**	**Peak significance (FWE[a])**			**Cluster-level (FWE[a])**
R pre/postcentral gyrus	4/1–3	(22, −20, 58)	284	$p = 0.477$			$p = 0.001$*
L pre/postcentral gyrus	4/1–3	(−24, −32, 62)	140	$p = 0.324$			$p = 0.049$*

[a]Family-wise error corrected.

*$p < 0.05$.

DISCUSSION

DEPRESSION AND ANXIETY

In a pilot study, we examined the efficacy of an eight-week MBSR intervention in treating depression and anxiety compared to a stress support group with relaxation education, and identified neural correlates of symptom reduction in adults with ASD. We found significant reductions in depressive symptoms after MBSR training. This effect was nonsignificant in the support/education group. Our findings of decreased depressive symptoms in adults with ASD are in-line with those reported by Spek et al. (2013) and Sizoo and Kuiper (2017). While we did not observe reductions in anxiety as previously reported compared to waitlist control (Spek et al., 2013), effect sizes for anxiety alleviation were moderate for both MBSR and support/education groups. The similar effect sizes for anxiety in both groups may represent non-specific social effects elicited by both MBSR and support/education interventions or two potentially distinct mechanistic pathways. A meta-analysis on various other clinical populations reported robust MBSR-mediated improvements in mood and anxiety, and suggest that MBSR outperforms active control conditions such as health education, relaxation training, and supportive psychotherapy (Hofmann et al., 2010; Hoffmann & Gomez, 2017). Our results extend these general findings to adults with ASD; however, more research in larger samples is required to replicate decreases in depression and characterize effects on anxiety.

NEURAL SELF-REFLECTION

As a neural mediator of mood symptom alleviation, we assessed changes in brain activation during self-reflection. This cognitive process was chosen because of previous work demonstrating the importance of optimal levels of self-reflection for mental health, and that adults with ASD lie on the mal-adaptive, diminished end of the self-reflection continuum (Philippi and Koenigs, 2014). We chose self-reflection MCC and vmPFC ROIs

based on Lombardo and colleagues' (2010) previous self-reflection work in adults with ASD. Our results showed that after MBSR adults with ASD significantly increased MCC activation during self-reflection—an effect that was not observed in the support/education group. Lombardo and colleagues (2010) previously found adults with ASD preferentially recruit the MCC when reflecting on other people as opposed to themselves, a pattern opposite to neurotypical adults. This suggests MBSR may normalize self-reflection neural processes in adults with ASD. Contrary to our hypothesis, MBSR did not lead to an increase in vmPFC activity. This may be due to differential functioning of MCC and vmPFC in adults with ASD. Lombardo and colleagues (2010) found more robust differences between ASD and neurotypicals during self-reflection in the MCC compared to the vmPFC, potentially rendering the MCC more sensitive to intervention-related changes. Secondly, vmPFC activity in adults with ASD correlates with social symptoms (Lombardo et al., 2010). We did not observe improvements in the social domain after MBSR training, thus we speculate vmPFC changes may be more likely observed in an intervention that improves social abilities, and MCC changes may be more related to ASD-specific improvements in depression reduction. Although MBSR has been associated with brain activation changes in other populations (Braden et al., 2016; Farb et al., 2013), this is the first study to demonstrate brain changes in adults with ASD.

Normalization of cognitive processes underlying self-representation may be efficacious for co-morbid mood symptoms in adults with ASD. In alignment with our hypothesis, MBSR-induced depression reduction correlated with increased MCC activity, suggesting that this may be a mediator for MBSR's therapeutic effects. This is in alignment with Philippi and Koenigs' (2014) theory on optimal levels of self-reflection for mental health, and that adults with ASD lie on the low end of this spectrum.

Diminished self-reflection in adults with ASD has been linked to theory of mind (ToM) difficulties (e.g. accurately identifying the thoughts, feelings, and emotions of other people), supporting Frith and Happe's (2003) hypothesis that ToM difficulties in ASD stem from an underdeveloped sense of self to draw inferences about other people. A growing body of literature now supports the connection between diminished self-reflection in ASD and performance on ToM, social cognition, and empathy tasks (Frith, 2003; Williams 2010; Lombardo et al., 2010). Further, others have found the adapted MBSR protocol improves core social communication symptoms in adults with ASD, making MBSR a viable experimental manipulation for uncovering the relationship between self-reflection and core symptoms. (Sizoo and Kuiper, 2017). Although this study did not investigate core symptom changes, future trials with larger sample sizes should assess these changes and whether they are mediated by changes in self-reflection. There are certainly other cognitive and neural processes mediating MBSR benefits in adults with ASD. A major facet of the MBSR intervention is continuous redirection of attentional resources toward incoming bodily signals. MBSR alters interoceptive signal processing in neurotypicals (Haase et al., 2015), and converging neuroimaging evidence suggest that brain regions involved in the representation of internal physiological states contributes to cognition (Critchley & Garfinkel, 2018; Garfinkel & Critchley, 2013). Further, cingulate recruitment has been associated with greater accuracy in identifying interoceptive body signals (Pollatos et al., 2007), and depressed patients exhibit decreased interoceptive sensitivity (Avery et al., 2014). Interoception, among other potential neural mechanisms, will be important considerations in future characterizations of MBSR in adults with ASD.

FUNCTIONAL CONNECTIVITY

Our exploratory analysis on functional connectivity changes between self-reflection hubs and the rest of the brain sheds further light on MBSR mechanisms in adults with ASD. We found increased functional connectivity between right MCC and bilateral pre/postcentral gyrus in the MBSR group only, which may suggest that MBSR facilitates communication between sensorimotor and self-reflection brain regions in adults with ASD. Theories of embodied cognition suggest that sensory and motor systems serve as hierarchical scaffolds for higher-order cognitive and affective processes, such as self-reflection (Shapiro, 2019; Wilson, 2002). This explanation aligns well with MBSR's emphasis on awareness of bodily sensations and movements in practices such as the body scan and mindful walking (Kabat-Zinn, 2003), and previous findings of MBSR-related increases in intrinsic sensorimotor connectivity in neurotypical adults (Kilpatrick et al., 2011). Further, aberrant sensorimotor function in adults with ASD is well-established (Whyatt & Craig, 2013), making intervention-related changes to these neural systems logical and potentially therapeutic. For example, adults with ASD exhibit less functional connectivity between prefrontal areas and somatosensory cortex compared to neurotypicals (Lombardo et al., 2007a), and differences in sensorimotor cortex functioning have been correlated with social cognition in individuals with ASD (Casartelli et al., 2016; Dziuk et al., 2007; Hilton et al., 2007). Heilbronner and Hayden (2016) propose the MCC serves as a monitor and exerts high-level control over decision making and action. Under this view, we propose heightened MCC-sensorimotor connectivity may reflect enhanced bodily awareness which therein provides vital information for top-down regulation of self-referential processing, and subsequently inhibition of depressive symptoms such as rumination. More research is warranted to determine if interventions that facilitate improved hierarchical signal processing and

neural coupling between sensorimotor and cognitive systems may be efficacious in treating comorbid mood symptoms in ASD.

LIMITATIONS

The greatest limitation to this pilot study is the modest sample size, which may be underpowered to detect anxiety reductions. Nevertheless, we showed significant depression reductions, neural activation and connectivity changes, and a neural correlate of symptom alleviation. A future larger sample size is warranted, especially to examine time by treatment group interactions. Although our final sample was underpowered for interaction effects after attrition, our statistical approach allowed us to identify changes that were present in the MBSR group and not the support/education group. The study suffered from considerable attrition for a variety of factors; however, only about 11% withdrew from dissatisfaction with the intervention. Second, our intervention was very close to the standard MBSR protocol but was administered as a dyad consisting of a certified MBSR instructor and experienced ASD clinician with brief MBSR training. This limits comparison to previous ASD studies that used a heavily adapted MBSR protocol and a single, MBSR certified and ASD-experienced instructor (Spek et al., 2013). However, the model used in this study is likely more scalable since requiring instructors be trained in both MBSR and ASD and learn an adapted MBSR protocol may pose challenges for wide-scale implementation. An additional limitation is that participants in the support/education group shared mindfulness resources with one another, such as mobile meditation apps, which may have bolstered some of the improvements in depression and anxiety observed in that group. While no changes in the support/education group were significant, effect sizes approached moderate, suggesting larger sample sizes could reveal benefits of a group of this nature which does not require a credentialed instructor.

To enhance generalizability, we did not exclude on the basis of sex or age and allowed the presence of other health co-morbidities commonly found in adults with ASD (epilepsy, Tourette's syndrome, and hearing loss). We also did not exclude based on left-handedness, which is more common in adults with ASD (Dane and Balci, 2007) and unlikely to influence self-reflection neural activation. Due to random assignment, groups were also unbalanced in sex with only two females in the support/education group. This prevented us from assessing sex differences. Notably, demographic variables such as these are less likely to influence findings in within-subjects designs. However, many fMRI studies in ASD use female, older age, comorbid conditions, and left-handedness as exclusion criteria, which may limit comparison to our study. Additionally, antidepressant effects may have been more robust if only participants with clinical depression were enrolled since those with subclinical depression appear to have introduced floor effects in the MBSR and support/education interventions. However, the sample sizes become exceedingly small when participants are separated by baseline depression levels and should be interpreted with caution. This study was not powered to determine floor effects associated with MBSR or support/education. Finally, our exclusion criteria of IQ scores <70 prevented us from assessing the range of intellectual abilities that may benefit from MBSR. For example, MBSR might not be feasible for those with language impairments, limiting the generalizability to the larger population of adults with ASD. Future studies are warranted to determine the critical factors mediating MBSR or support/education benefits in adults with ASD.

CONCLUSIONS

The current study aligns with a growing pursuit to identify therapeutic neural biomarkers in ASD and is the first to examine brain-based changes associated with MBSR in this population. Our results suggest increases in self-referential information

processing in the MCC may be a mediator for MBSR-induced depression alleviation in adults with ASD, and that MBSR may increase primary sensorimotor communication with higher-order cognitive regions during self-reflection. Associations between self-referential neural activation and depression reported in this study fit with a larger body of literature which has established relationships between atypical self-related information processing and depression; however, findings in ASD may represent opposing poles of self-referential thinking compared to neurotypicals with depression (Philippi & Keonigs, 2014). We hypothesize improvements in mood-comorbidity are mediated by alterations to self-reflection neurocircuitry. This conjecture is supported by reviews which suggests MBSR's therapeutic effects are associated with changes in brain regions involved in self-referential processing (Lin et al., 2018; Hatchard et al., 2018), however more research is needed to elucidate the nature of these changes in the context of improved mood in adults with ASD. Taken together, intervention strategies seeking to normalize self-referential processes, such as MBSR, may hold therapeutic value for adults with ASD.

CHAPTER 3

MBSR-INDUCED FUNCTIONAL CONNECTIVITY CHANGES: A GENERALIZED PSYCHO-PHYSIOLOGICAL INTERACTIONS APPROACH

INTRODUCTION

Autism spectrum disorder (ASD) is one of the most pervasive neurodevelopmental conditions, affecting one in 54 children (Baio, 2012) who are at greater risk for developing co-occurring neuropsychiatric disorders (Brugha, 2010). Estimates put depression risk around quadruple that of the general population (Hudson, et al., 2019), with an anxiety disorder occurrence of ~40% (van Steensel, Bögels, & Perrin, 2011b) in autistic individuals. Consequences can be devastating, including a sevenfold greater likelihood of suicide (Hirvikoski et al., 2016). Moreover, deficits in executive functioning – critical to managing mood and anxiety (Hollocks et al., 2014) – remain impaired across the ASD lifespan (Demetriou et al., 2018). Together, these challenges compound preexisting ASD-related difficulties with maintaining long-term independence and employment (Maddox & Gaus, 2018). While current pharmacotherapies are largely unsuccessful due to poor medication compliance, lack of therapeutic effectiveness, and side effects (Coleman et al., 2019), mindfulness-based therapies (MBT's) show promise at mitigating depression and anxiety symptoms in adults with ASD (Cachia et al., 2016a), and may improve executive functioning as demonstrated in other populations (Sevinc et al., 2021).

Mindfulness-based Stress Reduction (MBSR) is an intensive 8-week in-person meditation intervention aimed at directing attention toward present moment awareness with a nonjudgmental and nonreactive attitude. Spek and colleagues (2013) were the first to adapt the original MBSR protocol for adults with ASD, reporting reductions in depression and anxiety relative to waitlist controls which persisted 9-weeks post-

intervention (Kiep et al., 2015; Spek et al., 2013). Antidepressant and anxiolytic effects of MBSR have since been replicated in randomized clinical trials using cognitive behavioral therapy (CBT) and social support/relaxation education comparison groups (Sizoo & Kuiper, 2017; Pagni et al., 2020). Other improvements in quality of life, emotion regulation, autistic traits, stress, and rumination have also been reported (Braden et al., 2021; Pagni & Braden, 2021; Reed, 2019). Interestingly, social support is embedded in MBT's and the lack thereof has been linked to loneliness and depression in adults with autism (Han et al., 2019). Together, early research with small samples suggests MBT's have broad therapeutic efficacy in adults with ASD, however it remains unclear if these effects are mindfulness-specific. Additionally, the magnitude of therapeutic improvements in ASD has yet to be thoroughly characterized using rigorous clinical designs with active comparison interventions.

To address questions of this nature, identifying underlying neural adaptations supporting therapeutic gains is critical. Little is known regarding the therapeutic neural mechanisms of MBSR in adults with ASD, with the exception of a single pilot study implicating the middle cingulate cortex (or dACC) in MBSR-elicited alleviation of depression symptomatology (Pagni et al., 2020). In major depressive disorder (MDD), MBT's are theorized to exert therapeutic effects by normalizing maladaptive patterns of negative self-beliefs and attentional biases and rumination via cortical midlines structures (Nejad et al., 2013). In adults with ASD, self-focused attention predicts depressive symptoms, supporting this notion (Burns et al., 2019). MBT's enhance decentering, the capacity to take a detached perspective of one's thought and emotions, which is associated with less depression (Mori & Tanno, 2015), and offers a potential mechanism of action in ASD. Accordingly, functional MRI (fMRI) tasks tapping into self-referential cognition activate overlapping brain regions as those modulated by

meditation, including the insula, prefrontal cortex, cingulum, and amygdala (Fox et al., 2014; Johnson et al., 2002; Modinos et al., 2009). A recent systemic review cited these brain regions as key targets of MBSR, irrespective of task and neuroimaging modality (Gotink et al., 2016). Elucidating therapeutic neural mechanisms of MBSR may provide novel insights into the etiology and unique susceptibility of psychiatric comorbidities in ASD, assist in developing personalized-medicine approaches, and inform novel targets for neurostimulation research.

This double-blinded randomized clinical trial compared the clinical efficacy of an 8-week MBSR and a social support/relaxation education (SE) intervention for depression, anxiety, autism symptoms, executive functioning, and mindfulness traits in an adequately-powered sample of adults with ASD. Additionally, this study sought to identify shared and distinct alterations to functional self-reflection neurocircuitry at insula, cingulum, prefrontal cortex, and amygdala ROIs (Gotink et al., 2016; Marchand, 2014). We utilized a generalized psychophysiological interaction (gPPI) approach to identify task-modulated connectivity changes, and associations with therapeutic improvement. We hypothesized: 1) MBSR and SE would elicit reductions in depression, anxiety, and autistic traits based on previous literature on MBSR and social support in ASD (Cachia et al., 2016b; Hedley et al., 2017a; Reed, 2019); 2) MBSR would have additional efficacy for executive functioning and mindfulness traits as found in other populations (Lao et al., 2016; Sevinc et al., 2021); 3) the MBSR group, but not the SE group, would show alterations to insular, anterior cingulate cortex (ACC), and lateral PFC (lPFC) functional connectivity given previous MBSR neuroimaging findings pertaining to interoception, salience detection, and executive functioning (Farb, 2014; Hölzel et al., 2013; Sevinc et al., 2018; Tang et al., 2015); and 4) both groups would show alterations to amygdala, posterior cingulate cortex (PCC), and medial PFC (mPFC)

functional connectivity patterns, based on previous literature showing inverse relationships between social support and depression and anxiety in ASD (Hedley et al., 2017a), and salutary effects of social support on amygdala reactivity and default mode network (DMN) dynamics (Che et al., 2014; Hyde et al., 2011).

METHODS

PARTICIPANTS

Ninety-six adults with ASD met inclusion criteria consisting of: 1) an ASD diagnosis confirmed with the Autism Diagnostic Observation Schedule-2 (ADOS-2; Lord et al., 2012) which was administered by an experienced research-reliable member of the Southwest Autism Resource and Diagnostic Center, and by meeting the Diagnostic Statistical Manual-5 criteria as assessed by an experimental psychologist with 20 years of experience in ASD, and 2) an IQ score >70 on the Kaufman Brief Intelligence Test-2 (KBIT-2). Participants were excluded based on active suicidality, history of traumatic brain injury, and substance abuse, but not on the basis of sex, age, or general comorbidities (single cases of epilepsy, Tourette's syndrome, bipolar disorder, and hearing loss); handedness restrictions were not imposed since non-right-handedness is more common in ASD (Dane & Balci, 2007). An attrition rate of 18.75% led to a final sample of 78 participants with partial or full pre- and post-intervention datasets (see Figure 1 for participant flow chart). Power analyses for repeated measures ANOVA based on MBSR depression findings in ASD by Sizoo and colleagues (2017; medium effect size - $\eta p2=0.35$) suggested a comparable sample of 82 is sufficient to detect medium effects between groups with power set at 0.80 (Sizoo & Kuiper, 2017).

INTERVENTION GROUPS

Participants were randomly assigned to an 8-week MBSR group or a social support/relaxation education (support/education) control group. The standard MBSR

protocol was minimally adapted for adults with ASD as described in Chapter 2. Group demographics are displayed in Table 3.

SELF-REPORTED BEHAVIORAL MEASURES

Pre- and post-intervention questionnaires were collected at the fMRI appointment within 1 month before and after the intervention assessing (i) depression (Beck Depression Inventory-2; BDI-II), (ii) state and trait anxiety symptoms (State-Trait Anxiety Inventory; STAI-1/STAI-2, respectively), (iii) mindfulness traits (Five Facets Mindfulness Questionnaire; FFMQ-Total and five subscales: 'Describe', 'Observe', 'Act', 'Nonreactivity', and 'Nonjudgment'), and (iv) executive functioning abilities (Behavior Rating Inventory of Executive Functioning (BRIEF-Total and eight subscales: 'Working memory', 'Shift', 'Monitor', 'Inhibit', 'Initiate', 'Plan', 'Organize', and 'Emotional Control'). The BRIEF questionnaire was added for the second and third cohorts, and therefore has fewer datapoints (n=51). An intention to treat approach was implemented, allowing participants with complete pre/post datasets to be included in the analysis, regardless of extent of participation in the intervention. Behavioral measures were incomplete – either due to missing pre/post questionnaires or <20% of the questions completed – for the following number of participants: BDI-II, n=2; STAI-1 and STAI-2, n=4; SRS-2, n=2; FFMQ, n=5; BRIEF, n=10 (Figure 3). The protocol was approved by the University Institutional Review Board and all participants provided written consent.

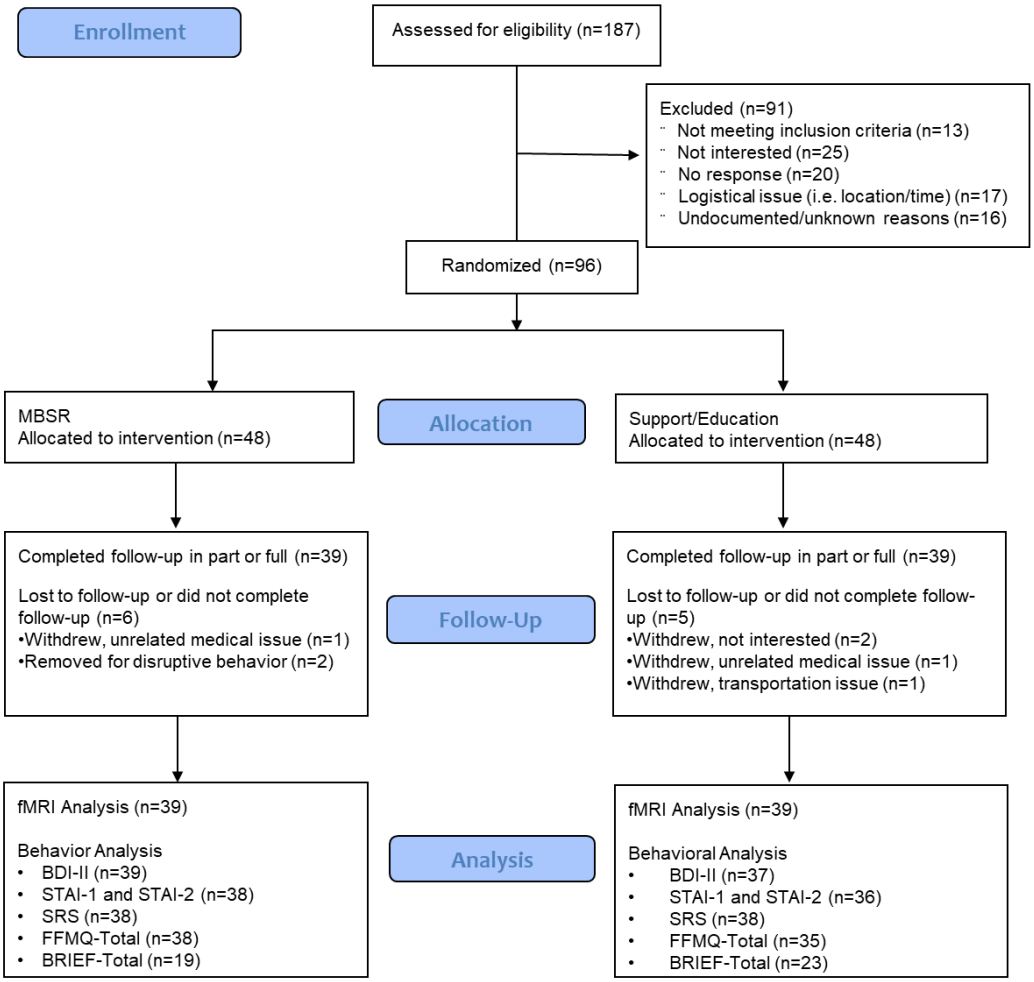


FIGURE 3. Participant flow chart detailing number of individuals assessed for eligibility and randomized to treatment groups, and participant retention and data attrition.

FMRI ACQUISITION

Imaging data were collected on a 3T Philips Ingenia scanner with a maximum gradient strength of 45 mT/m at Barrow Neurological Institute (Phoenix, AZ, USA). T2*-weighted images were acquired with a gradient echo, echo-planar pulse sequence to elicit BOLD contrast. The scanning parameters were: slice thickness = 3 mm, TE = 30 ms, TR = 2,000 ms, flip angle = 90, in-plane resolution = 64 × 64, field of view = 240 mm, and voxel size = 3 × 3 mm. Images from the first three TRs were discarded to allow for stabilization. 3D magnetization-prepared rapid acquisition gradient echo T1 images were acquired and used for preprocessing: 170 sagittal slices, slice thickness = 1.2 mm, in-plane resolution = 256 × 256, field of view = 240 mm.

FMRI SELF-REFLECTION TASK

Pre- and post-intervention fMRI images were collected during a self-reflection task. Participants provided yes/no responses to trait adjectives for two conditions: (a) Self-condition—participants decided whether they possessed the trait adjective and (b) Word-condition—participants decided whether the adjective was positively valenced (see Pagni et al., 2020 for detailed task description).

FMRI PREPROCESSING AND MODELING

Preprocessing of fMRI data were completed in SPM12 (Wellcome Trust Centre for Neuroimaging, http://www. fil.ion.ucl.ac.uk/spm), including slice timing correction, realignment to the mean image, co-registration to the skull-stripped T1, normalization to MNI using the DARTEL method (Ashburner, 2007), and 8 mm full width half maximum Gaussian kernel spatial smoothing. Scrubbing parameters for scans exceeding 5 mm relative displacement were generated using the Artifact Detection Tools toolbox in CONN (https ://www.nitrc.org/ projects/conn). The CONN-fMRI toolbox uses anatomical component correction (aCompCor) method to remove noise and movement

confounds on a voxel to voxel basis. Denoising parameters consisted of white matter (6P), CSF (6P), realignment (6P), and scrubbing (117P); no derivatives or polynomial expansion were applied. Parameters for the effects of pre-word (2P), pre-self (2P), post-word (2P), and post-self (2P) were included with 1st order derivatives. Data were bandpass filtered (0.008-0.09 Hz) and despiked after regression and linear detrended. Generalized psychophysiological interactions (gPPI) were computed using bivariate regression.

FUNCTIONAL CONNECTIVITY ANALYSES

Neuroanatomical ROIs were selected based on a systematic review of MBSR-mediated neural changes implicating the insula, amygdala, cingulum, dlPFC, and mPFC (Gotink et al., 2016). dlPFC was defined as bilateral superior frontal gyrus (SFG); mPFC was defined as the bilateral frontal medial cortex (FMC) and frontal pole (FP). At the 2nd-level, seed-to-voxel analyses were performed using the Harvard-Oxford atlas in CONN at hypothesized ROI's for group by time interactions (MBSR>support/education) and main effects of time (MBSR + support education) for Post-Self > Pre-Self, Post-Word = Pre-Word (contrast: 1 -1 0 0) with number of classes as a covariate. Alpha was set as p-FDR < 0.05 for target clusters. Significant ROI's were Bonferroni-adjusted for left/right hemisphere for the insula, amygdala, SFG, FMC, and FP (p-FDR=0.025); anterior and posterior divisions of the cingulum were corrected similarly [ACC and PCC, respectively; p-FDR=0.025). Due to stringent FDR- and Bonferroni-correction, one- and two-sided tests were accepted. ROI's are displayed in Figure 4.

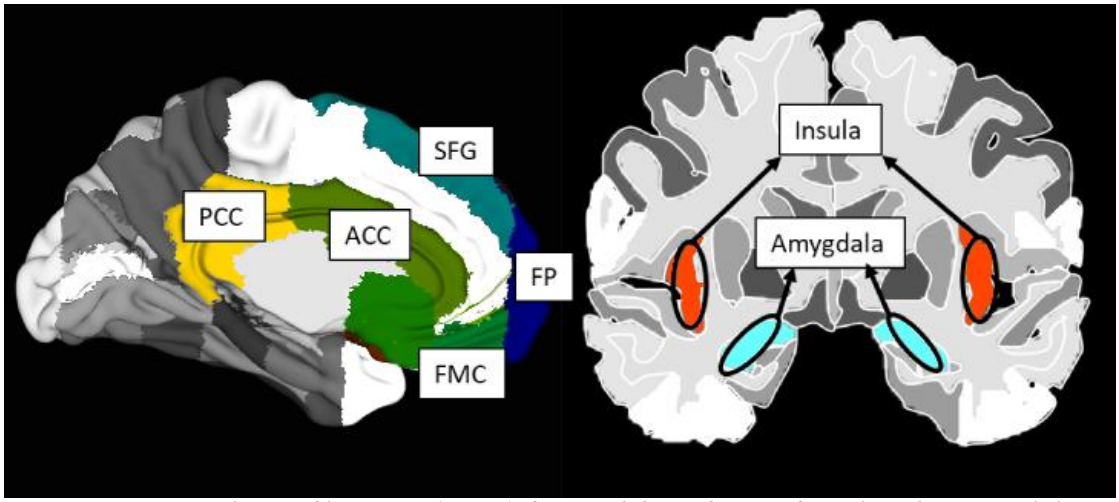


FIGURE 4. Regions of interest (ROIs) for seed-based gPPI functional connectivity analysis. PCC, posterior cingulate cortex; ACC, anterior cingulate cortex; SFG, superior frontal gyrus; FP, frontal pole; FMC, frontal medial cortex; insula; amygdala (Image generated from Neuromorphometrics, Inc. using the Harvard-Oxford human brain atlas)(Desikan RS, Ségonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, Buckner RL, Dale AM, Maguire RP, Hyman BT, Albert MS, 2006; Neuromorphometrics, n.d.)

Behavioral analyses

Repeated measures ANCOVA's were performed in the Statistical Package for Social Sciences – Version 26 (SPSS-26) to examine behavioral group by time interactions and main effects of time, with number of classes attended entered as a covariate. BDI-II, STAI-1, STAI-2, SRS-2, FFMQ-Total, and BRIEF-Total were primary measures of interest; exploratory analyses were performed for FFMQ and BRIEF subscales without multiple comparison correction.

EXPLORATORY BRAIN-BEHAVIOR RELATIONSHIPS

Pre-to-post change scores were calculated for significant behavioral group by time interactions and main effects of time. Next, significant functional connectivity changes that survived FDR- and Bonferroni-correction from the gPPI group by time and main effect of time analyses were extracted and entered into a one-tailed Pearson correlation analysis in SPSS-26 with alpha set at $p < 0.05$, with the connectivity changes hypothesized to be in a therapeutic direction.

RESULTS

PARTICIAIPNT DEMOGRAPHICS AND BEHACIORAL EFFECTS

Groups did not differ with respect to sex distribution, age, IQ, autism severity, or number of classes attended (Table 3).

Table 3. Participant Demographics and Baseline Group Statistics

	MBSR	Support/Education	Baseline group differences
Sample size (M/F)	39(26/13)	39 (23/16)	χ^2 (76)= 0.494; p=0.482; φ =0.080
Age, years	31.15 (13.57; n=39) Range: 18-67	33.89 (13.34; n=38) Range: 18-72	t(75)=-0.862; p=0.392; d=0.204
IQ[a]	104.76 (16.75; n=36) Range: 70-131	108.02 (17.38; n=35) Range: 70-142	t(69)=0.817; p=0.419; d=0.015
ADOS-2[b]	11.50 (3.85; n=38) Range: 6-23	10.95 (3.64; n=37) Range: 7-19	t(73)=-0.641; p=0.524; d=0.147
Classes attended	6.4 (2.3; n=39) Range: 0-8	6.8 (2.0; n=39) Range: 0-8	t(76)=0.785; p=0.435; d=0.186

[a]Kaufman Brief Intelligence Test-2 Composite; [b]Autism Diagnostic Observation Schedule; *p<0.05

Main effects of time (collapsed by group, MBSR+SE) were detected on the BDI-II, STAI-2, and SRS-2, indicating decreases in depression, trait anxiety, and autistic traits across participants; no state anxiety changes (STAI-1) were detected (Table 4; Figure 5a). A group by time interaction for FFMQ-Total score was detected; exploratory analysis revealed an MBSR-specific increase on the FFMQ subscale 'Nonjudgment' (Table 4, Figure 5b). No other FFMQ subscales were significant. There was not a significant group by time interaction for the BRIEF-Total score; however, exploratory analyses revealed a group by time interaction on the BRIEF subscale 'Working Memory', showing an MBSR-specific improvement (Table 4, Figure 5b). No other BRIEF subscales were significant.

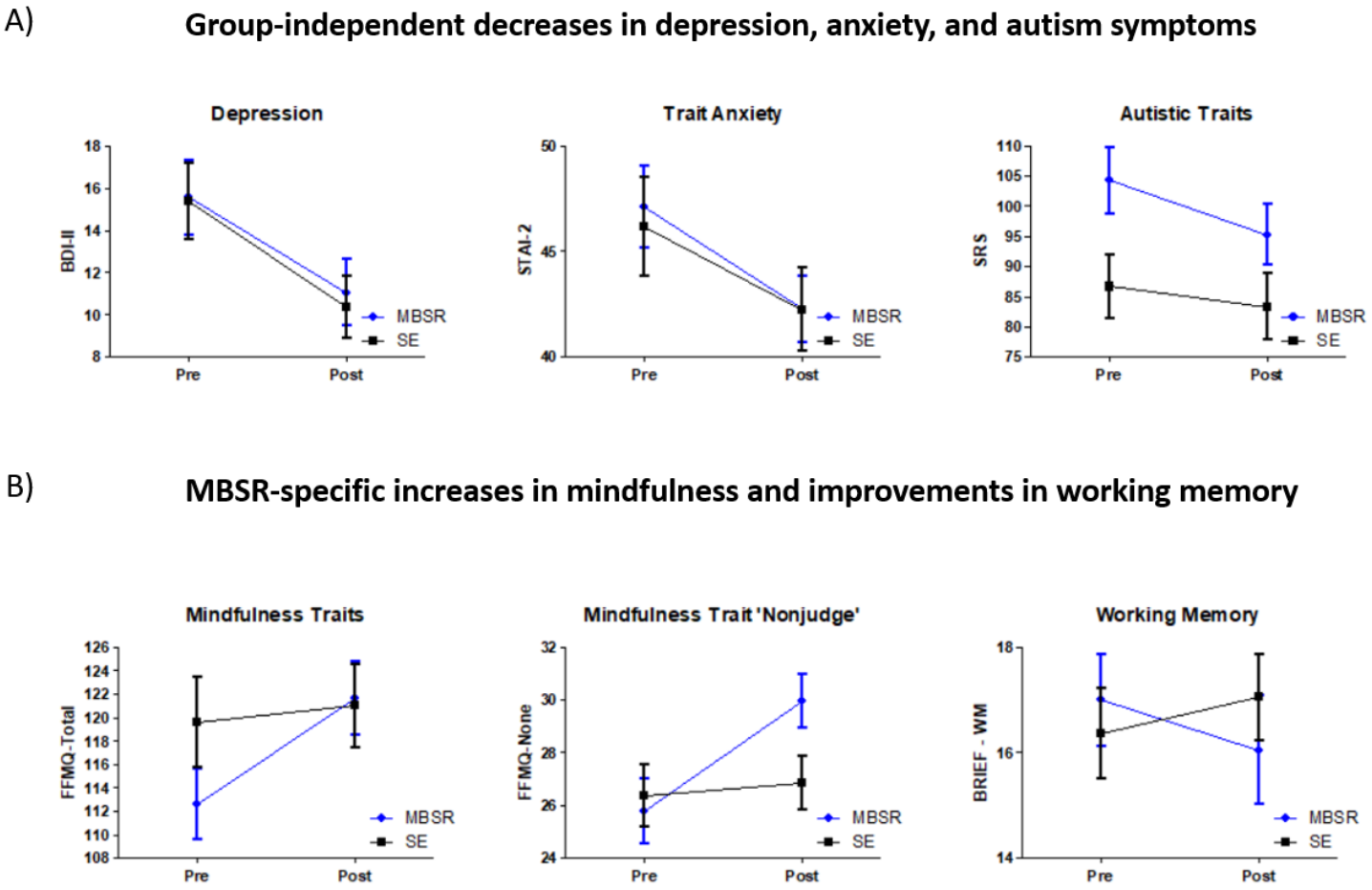


FIGURE 5 Pre- to post-treatment behavioral change for MBSR and SE groups; error bars in SEM. (A) Significant main effect of time ($p<0.05$) on BDI-II, STAI-2, and SRS-2, indicating decreased depression, anxiety, and autistic-traits post-intervention for both intervention groups. (B) Significant group by time interaction ($p<0.05$) on FFMQ-Total, FFMQ subscale 'Nonjudgment', and BRIEF subscale 'Working Memory', indicating MBSR-specific increases in overall mindfulness and mindfulness trait 'Nonjudge", and decreases in executive functioning challenges.

Table 4. Group behavioral means, standard deviations, ranges, baseline differences, and effects

	MBSR		Support/Education				
	Pre Mean (SD) Range	**Post** Mean (SD) Range	**Pre** Mean (SD) Range	**Post** Mean (SD) Range	**Baseline group differences**	**Main effect of Time**	**Group by Time interaction**
BDI-II	15.56 (11.02) 0-48	11.05 (9.86) 0-33	15.37 (11.13) 0-43	10.35 (9.05) 0-35	t(76)=0.11, p=0.91, d=0.02	**F(1,73)=7.22, p<0.01*, ηp2=0.09**	F(1,73)=0.17, p=0.68, ηp2<0.01
STAI-1	42.08 (12.20) 22-79	38.42 (10.37) 21-63	42.19 (13.34) 20-66	38.03 (12.52) 20-68	t(74)=-0.01, p=0.99, d=0.01	F(1,71)=1.40, p=0.24, ηp2=0.02	F(1,71)=0.05, p=0.83, ηp2<0.01
STAI-2	47.13 (12.03) 22-76	42.26 (9.57) 27-67	46.17 (14.01) 22-72	42.25 (11.97) 22-66	t(74)=-0.19, p=0.85, d=0.07	**F(1,71)=4.27, p=0.04*, ηp2=0.06**	F(1,71)=0.15, p=0.70, ηp2<0.01
SRS-2	104.26 (34.01) 24-174	95.32 (30.66) 46-150	86.66 (32.52) 24-148	83.37 (34.62) 21-152	**t(74)=-2.31, p=0.02*, d=0.53**	**F(1,73)=4.32, p=0.04*, ηp2=0.06**	F(1,73)=1.83, p=0.18, ηp=20.02
FFMQ Total	112.63 (18.56) 77-158	121.66 (19.26) 85-162	119.60 (22.90) 63-167	121.00 (21.06) 87-171	t(71)=1.43, p=0.16, d=0.33	F(1,70)=1.50, p=0.23, ηp2=0.02	**F(1,70)=4.81, p=0.03*, ηp2=0.06**
FFMQ 'Nonjudge'	25.79 (7.52) 8-40	29.95 (6.25) 16-40	26.37 (6.99) 9-40	26.83 (6.03) 16-38	t(71)=0.34, p=0.73, d=0.08	F(1,70)=0.57, p=0.43, ηp2=0.01	**F(1,70)=4.51, p=0.04*, ηp2=0.06**
BRIEF Total	142.74 (25.66) 98-185	134.84 (28.56) 90-186	137.23 (30.03) 76-191	133.09 (31.73) 69-196	t(41)=-0.57, p=0.57, d=0.20	F(1,39)=0.32, p=0.57, ηp2<0.01	F(1,39)=0.66, p=0.42, ηp2=0.02
BRIEF 'Working Memory'	17.00 (3.79) 10-23	16.05 (4.48) 9-24	16.36 (4.01) 8-23	17.05 (4.48) 8-23	t(41)=-0.59, p=0.56, d=0.17	F(1,39)=0.82, p=0.37, ηp2=0.02	**F(1,39)=5.20, p=0.03*, ηp2=0.12**

MBSR-SPECIFIC FUNCTIONAL CONNECTIVITY

Left insula showed an MBSR-specific decrease in connectivity with bilateral thalamus (Table 5; Figure 6a). Additionally, left FP showed an MBSR-specific decrease in connectivity with lingual gyrus and posterior cingulate cortex (LG/PCC; Table 5; Figure 6b). No other ROI's showed group-specific effects after FDR- and Bonferroni-correction.

Table 5 Significant Group by Time interactions and main effects of Time at ROI's

	Seed	Target	MNI coordinates	Voxels	Two/One-sided	p-uncorrected	p-FDR cluster
Group by Time interactions	L IC	R/L thalamus	4, -16, 10	249	Two-sided	0.001	**0.019***
	L FP	LG/PCC	-22, 60, 4	229	Negative contrast	0.003	**0.023***
Main effect of Time	**Seed**	**Target**	**MNI coordinates**	**Voxels**	**Two/One-sided**	**p-uncorrected**	**p-FDR cluster**
	R IC	R FP	28, 54, 6	397	Two-sided	<0.001	**0.002***
	L SFG	R FP	16 +68 +00	275	Two-sided	<0.001	**0.009***
	R Amy	L Pre/PostCG & CO	-60, -2, 16	303	Negative contrast	0.001	**0.016***

L=left, R=right; Seeds: IC=insula cortex, FP=frontal pole, SFG=superior frontal gyrus, Amy=amygdala, LG=lingual gyrus, PCC=posterior cingulate cortex, pre/postCG =precentral and postcentral gyrus, CO=central operculum; * = $p<0.025$

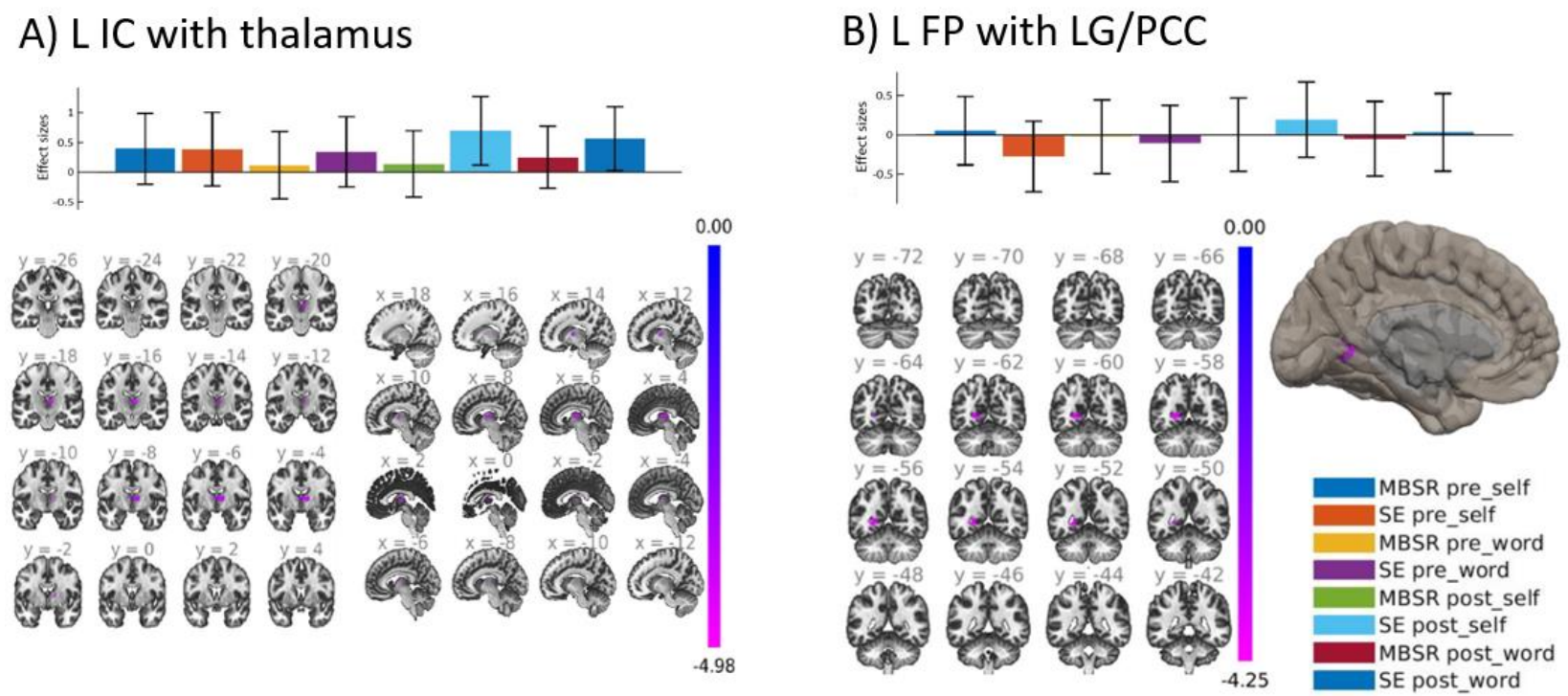


Figure 6 Functional connectivity changes: Group by Time interactions (p-FDR<0.025). Top: bars graphs adjusted for covariate of classes; Bottom left: coronal slice view; Bottom right: sagittal slice view or inflated brain of target cluster. A) Decreased left insula cortex (L IC) connectivity with bilateral thalamus. B) Decreased left frontal pole (L FP) connectivity with lingual gyrus and posterior cingulate cortex (LG/PCC).

NONSPECIFIC FUNCTIONAL CONNECTIVITY

The right insula showed an attenuated anticorrelation with right frontal pole (Table 5; Figure 7a). For the dorsolateral prefrontal cortex, the left SFG transitioned from positive correlation to anticorrelation with the right FP (Table 5; Figure 7b). The left amygdala transitioned from a positive to a negative correlation with left pre- and post-central gyrus and central operculum (Table 5; Figure 7c). No other ROI's were significant after FDR- and Bonferroni-correction.

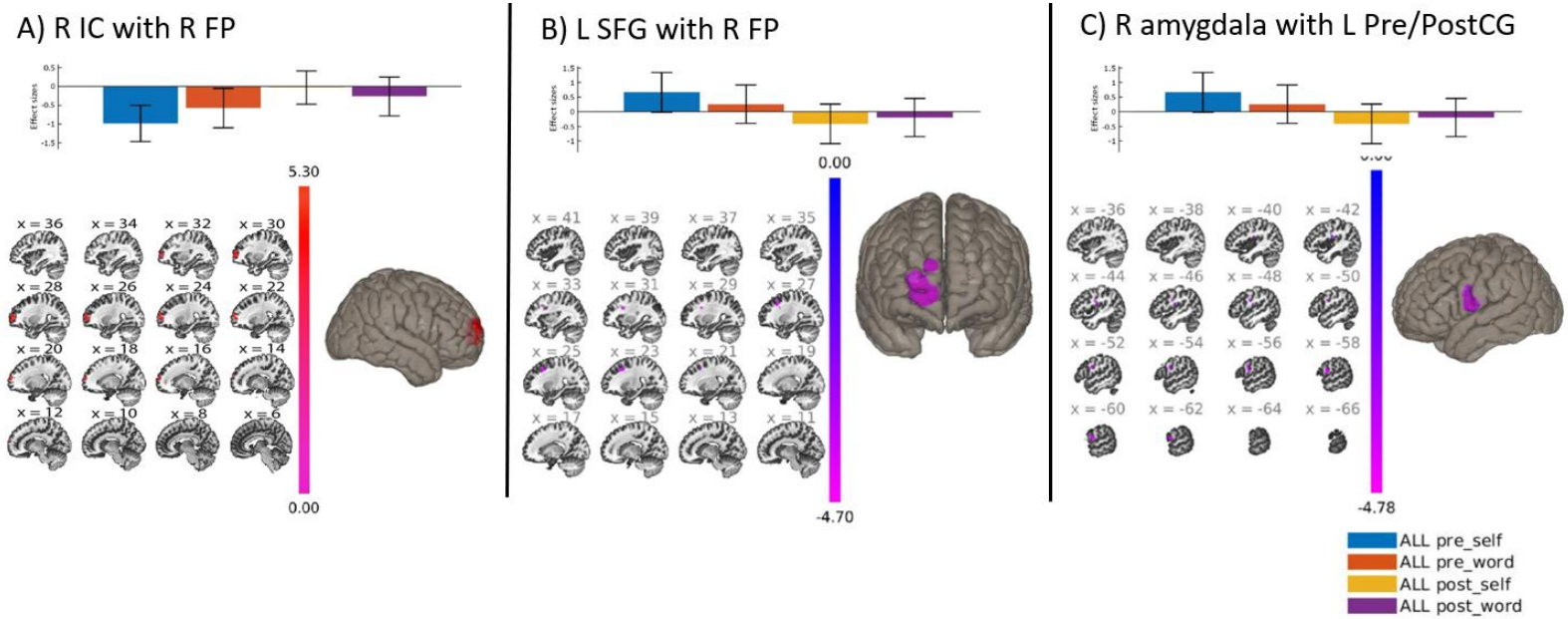


Figure 7 Functional connectivity changes: main effects of Time (across all participants; p-FDR<0.025). Top: bars graphs adjusted for covariate of classes; Bottom left: sagittal slice view; Bottom right: inflated brain of target clusters. A) Increased right insula cortex (R IC) connectivity with right frontal pole (R FP). B) Decreased left superior frontal gyrus (L SFG) connectivity with right frontal pole (R FP). C) Decreased right amygdala connectivity with left pre- and post-central gyrus (Pre/PostCG).

Brain-behavior relationships

For MBSR-specific connectivity changes, decreased insula-thalamus connectivity was associated with decreased trait anxiety across all participants ($r(73)=0.246$, $p=0.018$), increased FFMQ-Total scores across all participants ($r(73)=-0.244$, $p=0.019$), and increased FFMQ 'Nonjudge' across all participants ($r(72)=-0.336$, $p=0.002$) and MBSR-only ($r(37)=-0.327$, $p=0.024$; Figure 8a-c). Additionally, decreased FP-PCC connectivity correlated with working memory improvements (defined as decreases in BRIEF-WM) across all participants ($r(41)=0.296$, $p=0.030$) and MBSR-only ($r(19=0.399$, $p=0.045$; Figure 8d). For group-nonspecific connectivity changes, decreased amygdala-pre/postCG connectivity was associated with reduced depression across all participants ($r(73)=0.267$, $p=0.011$) and SE-only ($r(36)=0.330$, $p=0.025$; Figure 9a). Increased IC-FP connectivity also correlated with decreased depression across all participants ($r(73)=-0.226$, $p=0.028$) and MBSR-only ($r(37)=-0.318$, $p=0.028$; Figure 9b). No other correlations were significant for other behavior or connectivity measures.

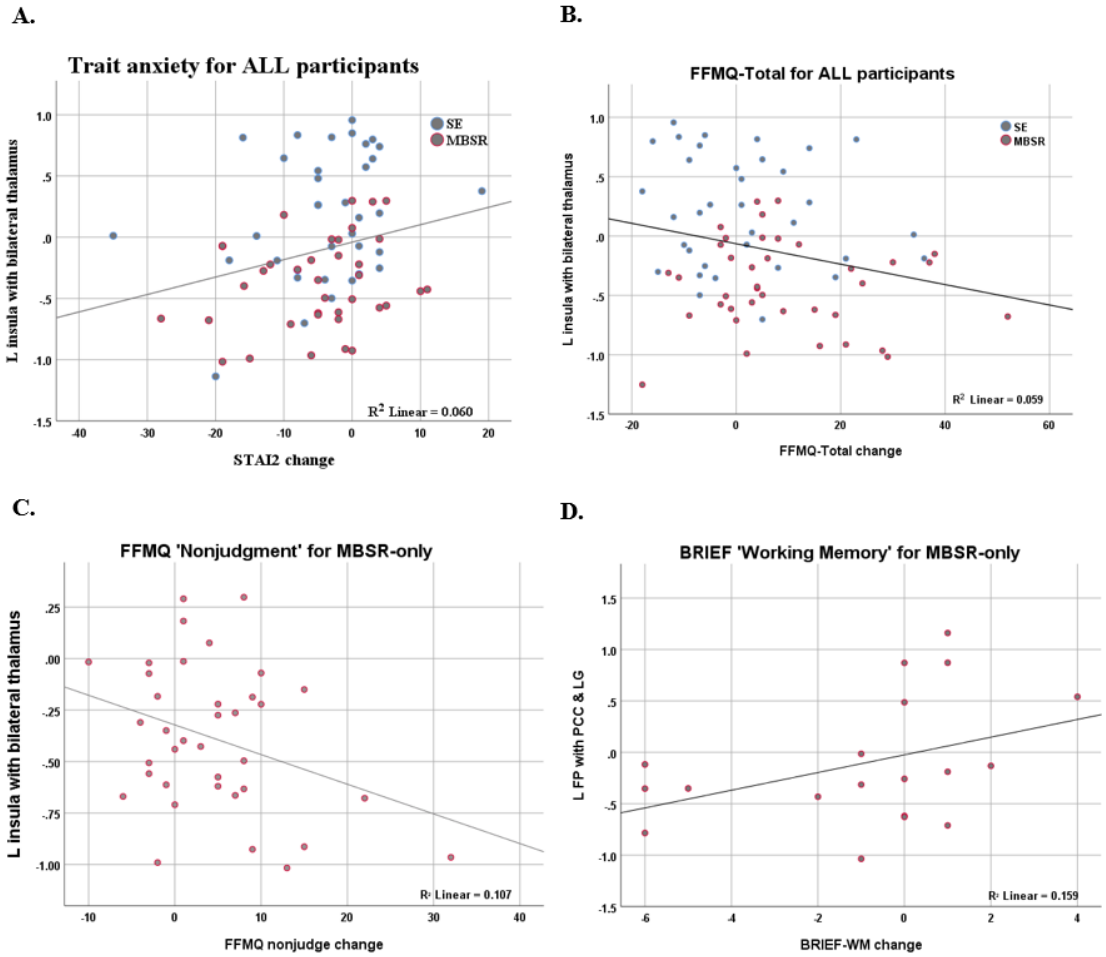


FIGURE 8 Brain-behavior scatterplots for MBSR-specific connectivity changes. (A) Insula- thalamus with STAI-2 across all participants. (B) Insula-thalamus with FFMQ-Total across all participants. (C) Insula-thalamus with FFMQ 'Nonjudge' for MBSR participants. (D) FP-PCC/LG with BRIEF 'Working Memory' for MBSR participants. $p<0.05$.

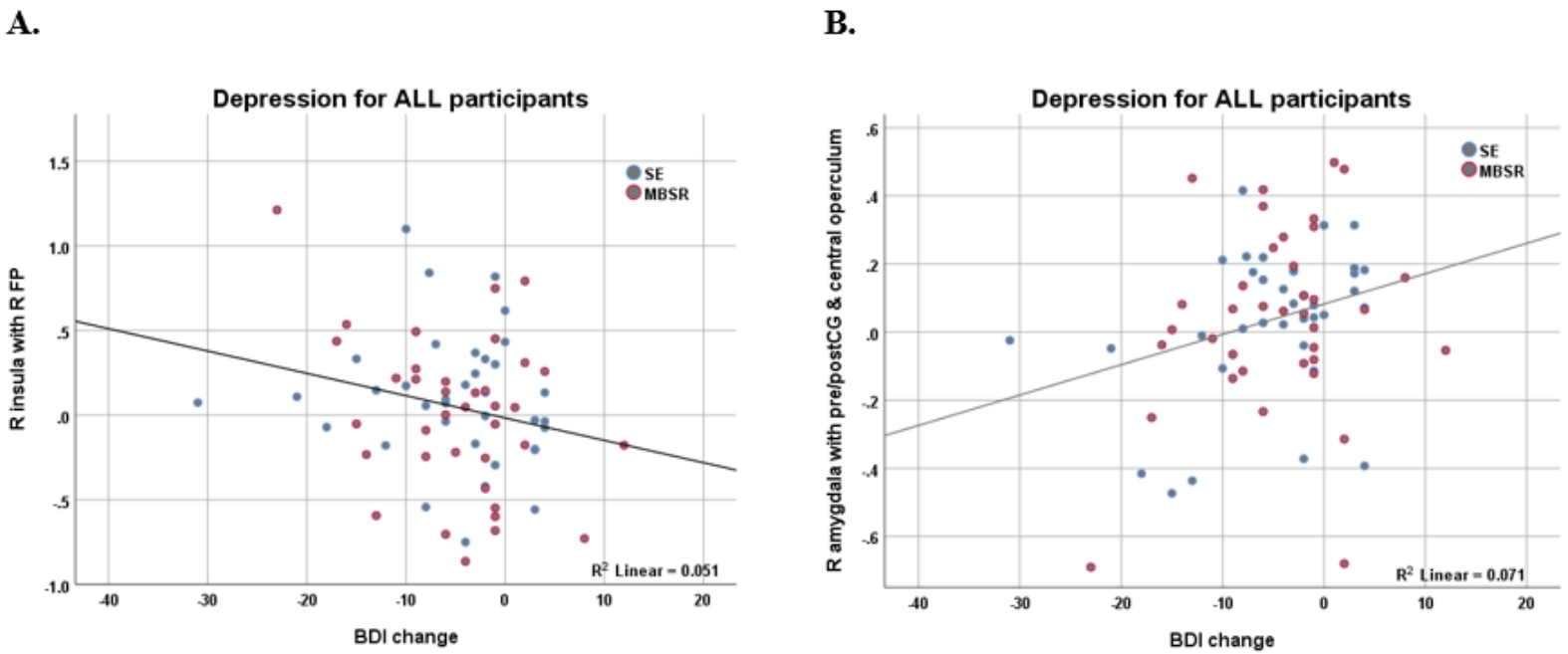


FIGURE 9 Brain-behavior scatterplots for nonspecific intervention connectivity changes. (A) Insula-frontal pole with BDI-II across all participants. (B) Amygdala-pre/postCG with BDI-II across all participants. $p<0.05$

DISCUSSION

BEHAVIOR

As hypothesized, both MBSR and SE groups showed reductions in depression, anxiety, and autistic traits, suggesting social and educational support are adequate in diminishing psychological symptoms and improving mental health. Findings align with Sizoo and colleagues (2017) who found no group differences in antidepressant and anxiolytic effects when compared to cognitive behavioral therapy (CBT; Sizoo & Kuiper, 2017). Such findings urge the utilization of active control groups – rather than waitlist control groups – to discern the "active ingredients" of mindfulness therapy (Cachia et al., 2016a; Spek et al., 2013). Additionally, brain-based investigations are critical to distinguishing whether therapeutic mechanisms are nonoverlapping or overlapping. If nonoverlapping, neural mechanisms can be targeted in an additive manner to maximize efficacy and promote long-term outcomes; if overlapping, social support and relaxation education is sufficient, and potentially preferred since it may be more affordably delivered by community leaders and accessible via online social platforms. However, if mindfulness traits and working memory capacity are outcomes of interest, MBSR may be preferred.

Mindfulness training uniquely enhanced the mindfulness trait 'nonjudgment' and improved working memory abilities, but did not broadly impact mindfulness traits and executive functioning as hypothesized. MBSR-based alleviation of psychological symptoms may be mediated by its emphasis on cultivating a nonjudgmental and nonreactive awareness (Kabat-Zinn, 2003). Lack of changes in mindfulness facets 'acting', 'observing', and 'describing' are in line with a study utilizing a CBT comparison group but not a waitlist control comparison showing increases in all five traits (Carmody & Baer, 2008; Turner et al., 2016). Our results suggest mindfulness training targets

'nonjudgment', but it remains unclear whether this effect is population specific or a product of active control group selection (Turner et al., 2016). Other studies have shown pretreatment levels of trait mindfulness and autism severity predict the magnitude of MBSR outcomes (Reed, 2019; Shapiro, 2007). Additionally, total practice hours mediate mindfulness trait changes which in turn mediate mental health outcomes (Carmody & Baer, 2008), supporting the notion that mindfulness abilities are key, dose-response dependent therapeutic mechanisms. These factors should be considered in future studies aimed at developing personalized medicine approaches for adults with ASD (Goldsmith et al., 2014).

While results on MBSR's influence on broad executive functioning are mixed, improvements in memory have been consistently found in populations ranging from adolescents to adults in the Marine Corporation (Jha et al., 2010; Quach et al., 2016). Corroborating these relationships, the extent of meditation training is associated with working memory and short- and long-term memory performance, suggesting dose-response effects as well (Lykins et al., 2012). Our hypothesis of broad executive functioning improvements was only partially supported, with MBSR-specific improvements being restricted to working memory. Follow-up studies using objective executive functioning measures are required to elaborate these relationships in adults with ASD.

FUNCTIONAL CONNECTIVITY: MBSR-SPECIFIC EFFECTS

MBSR-induced changes in insular activity and functional connectivity are well-established and attributed to alterations in interoception, exteroception, and emotional information processing (N. A. S. Farb, 2014; Gotink et al., 2016; Sevinc et al., 2018). In support of our hypothesis, the present study extends this body of work in adults with ASD by demonstrating MBSR-specific decreases in insular-thalamic connectivity using a

gPPI approach. Mindfulness-dependent changes in insular-thalamic connectivity agree with Farb and colleagues (2013), who suggest mindfulness training facilitates the transition from narrative self-focus, governed by the DMN, to present moment awareness, governed by the insula, thalamus, and sensorimotor cortices. Further, insular-thalamic connectivity differences have been reported in meditators compared to nonmeditators; and after psychopharmacological administration of lysergic diethylamide (LSD) which possesses robust antidepressant and anxiolytic properties (Fuentes et al., 2020; Müller et al., 2017; Preller et al., 2018). These studies in combination with our data suggest IC-thalamus connectivity isn't task- or population-specific and may be a common therapeutic correlate of meditation and psychedelic-assisted psychotherapy.

Brain-behavior correlations showed those with the greatest decreases in insula-thalamus connectivity had greater reductions in anxiety (across all participants) and greater increases in the trait 'nonjudgment toward experience' (driven by MBSR). This relationship mirrors results from Parkinson and colleagues (2019) who found insula connectivity generally correlates with mindfulness traits and Gorman and colleagues (2000) who proposed a "fear network" implicating the insula and thalamus in the context of anxiety disorders. Moreover, individuals with high trait 'worry' also show insula hyperactivation during emotional processing (Weber-Goericke & Muehlhan, 2019); however, no studies have referenced insula-thalamus connectivity in the context of MBSR-induced effects or anxiety. Therefore, this study provides a novel therapeutic neural mechanism specific to mindfulness meditation in adults with ASD.

MBSR-specific FP-PCC connectivity changes align with Kral and colleagues (2019) who found MBSR-specific alterations in this pathway. However, their result was in the opposite direction, likely arising from resting state versus task-based designs or the use of a neurotypical population (Kral et al., 2019). Aberrant FP-PCC connectivity

profiles during self-reflection have been identified in ASD and associated with age, suggesting mindfulness-training may intervene on an ASD-affected circuit (Burrows, Laird, & Uddin, 2016). PCC activity is a common feature of novice, but not expert, meditators, suspected to represent the transition from effortful toward effortless attention toward present moment experience (Brewer & Garrison, 2014; Brewer et al., 2011); therefore, our findings of frontal regulation of the DMN match what is expected in novice practitioners. The PCC cluster identified also encompassed the lingual gyrus – a frequently reported region in the MBSR literature – which contributes to episodic memory and psychiatric neuropathology (Pickut et al., 2013; van der Velden et al., 2022). In line with this, FP-LG/PCC connectivity changes in the present study correlated with working memory improvements. MBSR-specific decreases in connectivity between the FP and PCC might represent decoupling of the anterior-posterior axis of the DMN, an axis with pronounced atypicality in ASD that underpins deficits in self-awareness and Theory of Mind (Padmanabhan et al., 2017).

FUNCTIONAL CONNECTIVITY: NON-SPECIFIC EFFECTS

Both MBSR and SE groups showed a loss of preexisting FP-insula anticorrelations, suggesting common social factors, rather than mindfulness training, elicited DMN-SN connectivity alterations. While we predicted FP connectivity would be nonspecific to intervention group, we expected insula connectivity to be specific to MBSR. Thus, our hypothesis was partially supported. MBSR-induced increases in cortical thickness in the right FP, and in PFC-insula connectivity have been reported (Yu et al., 2021); but this study marks the first to report FP-insula connectivity changes. Whether these connectivity changes are unique to ASD is unclear, however they may be clinically relevant. The FP-insula pathway has been associated with greater self-regulation and resilience, and MDD (Lee et al., 2019). The negative correlation we

observed between FP-IC connectivity and depression symptomatology adds further support of the potential clinical significance of DMN-SN interactions. DMN-SN between-network changes are a primary effect of MBSR when compared to active controls (Rahrig et al., 2022), thus, our finding suggests a potential exception to MBSR's specificity for SN-DMN alterations in adults with ASD. Pronounced ASD-related difficulties in self-awareness and abnormal DMN and SN functional and structural organization may explain differences in MBSR's effects on ASD neurocircuitry relative to other populations (Lombardo et al., 2007a; Padmanabhan et al., 2017; Uddin & Menon, 2009b).

Our hypothesis of MBSR-specific alterations to SFG connectivity was not supported. Instead, both groups showed a transition from correlated to anticorrelated SFG and FP activity. In line with the non-specificity aspect, CBT and MBSR were compared head-to-head and both altered lateral and medial PFC activity in patients with social anxiety (Goldin et al., 2022). Previous work has established co-activation of SFG and mPFC during self-reflection in ASD, as well as hyperconnectivity accompanying self-centrism and excessive self-evaluation in patients with MDD (Lemogne et al., 2009; Nejad et al., 2013). Our finding suggests both MBSR and SE alter lateral-medial PFC connectivity during self-referential neural processing and warrant follow-up to evaluate clinical relevance.

The absence of cingulum (ACC and PCC) and MFC connectivity changes were unexpected, as the DMN and cortical midline structures generally are commonly reported therapeutic neural substrates of MBSR (Kral et al., 2019; Lutz et al., 2016). In a pilot study, we identified middle cingulate connectivity changes with the sensorimotor network that were not replicated in this larger sample (Pagni et al., 2020). While we did observe MBSR-specific and MBSR-nonspecific changes in the FP, the lack of effects in major DMN hubs – namely, the MFC and cingulum – may reflect a unique property of

mindfulness training or interventions more generally for adults with ASD. For example, aberrations in within- and between-network DMN connectivity in ASD may have impacted how the interventions were received and interacted with brain function (Padmanabhan et al., 2017). No behavioral intervention studies examining the DMN have been published in ASD, making conjecture difficult. Subsequent randomized clinical trials in adults with ASD are needed to determine if and to what extent cortical midline structures contribute to therapeutic outcomes.

Our hypothesis of intervention nonspecific alterations to amygdala connectivity was supported; however, we anticipated amygdala-PFC connectivity changes as reported in the context of emotion regulation (Gotink et al., 2016; Lin et al., 2018b; Opialla et al., 2014). Instead, both MBSR and SE showed amygdala-pre/postCG decoupling. We surmise social engagement akin to both interventions over the 8-week period reduced feelings of isolation and loneliness, an effect seen by other socially-oriented interventions, and diminished amygdala input to the sensorimotor system (Han et al., 2019; Hedley et al., 2017b). MBSR-induced attenuation of amygdala response is often interpreted as top-down inhibition, expressed neurobiologically as increased PFC-amygdala connectivity (see Gotink et al., 2016 for review). However, it is unclear if this effect is unique to mindfulness because similar effects have been observed with CBT (Goldin et al., 2022). While activation studies have found decreased signal in the amygdala and increased signal in sensorimotor regions, this is the first study to identify connectivity changes in this limbic-sensorimotor circuit.

Decreased connectivity between the amygdala and sensorimotor system correlated with alleviation of depressive symptoms across all participants, offering a shared neural correlate of MBSR and SE. MBSR-induced amygdala changes are suspected to be a key factor in improved emotional regulation (Gotink et al., 2016), with

amygdala dysfunction underlying anxiety and depression pathophysiology (Sehlmeyer et al., 2011; Siegle et al., 2007); functional pre/postCG connectivity changes have also been reported in adults with ASD after MBSR (Pagni et al., 2020). Our findings suggest limbic-sensorimotor decoupling may be a nonspecific metric of depression reduction in adults with ASD. Future work should seek to replicate and extend these findings using ROI-to-ROI and causal approaches.

Limitations

The greatest limitation to the present analysis is the modest sample size which may have been underpowered to detect small-to-medium effects. Nevertheless, this study is the largest of its kind in adults with ASD and was powered to detect medium-to-large effect sizes. Results yielded significant group by time interactions and main effects of time on behavioral measures and seed-to-voxel correlations at ROI's. Another potential limitation is fMRI analyses susceptibility to Type 1 errors. To reduce these concerns, we harnessed alpha inflation by employing rigorous statistical methods including FDR- and Bonferroni-correction. We also utilized a generalized psychophysiological interactions approach to elucidate task-specific modulation, a method that achieves improved model fit, specificity, and sensitivity compared to standard approaches (McLaren et al., 2012).

Other limitations pertain to generalizability, including the recruitment of intellectually-abled adults, which limits conclusions related to children and adolescents, and adults who experience intellectual challenges (IQ<70). To increase generalizability, we enrolled adults within a wide age range (18-80 years old), of all sex/gender orientations and handedness, and regardless of other co-morbidities common to ASD (epilepsy, Tourette's syndrome, hearing loss, etc). The present study also didn't evaluate the influence IQ, autism severity, age, or sex on outcomes. Additionally, self-report

measures are limited and future integration of objective cognitive and clinical measures in MBSR studies with autistic adults are warranted. Future research should seek to 1) characterize the complex interplay of demographic factors on clinical outcomes, 2) utilize clinician and performance-based assessments to confirm and extend these findings, and 3) employ mediation/moderation analyses to elucidate psychological and neural mediators of long-term therapeutic improvements(Pagni & Braden, 2021).

Conclusions

The current study contributes to a growing endeavor to treat mental health comorbidities and identify therapeutic biomarkers in ASD, and marks the first comprehensive investigation into the therapeutic neural correlates of MBSR in this population. In summary, we identified MBSR-specific and intervention nonspecific effects in behavior and brain connectivity patterns. MBSR demonstrated superior therapeutic outcomes compared to a social support active control intervention in the domains of working memory and mindfulness abilities. However, both MBSR and SE showed significant reductions in depression, anxiety, and autistic traits. These clinically meaningful changes suggest social support is similarly efficacious and sufficient to reduce psychiatric symptoms in adults with ASD. Additionally, this study elucidated mindfulness-specific and nonspecific neural mechanisms. MBSR-driven connectivity changes were found in: 1) insula and thalamus, corresponding with decreased trait anxiety and increased mindfulness; and 2) anterior-posterior DMN axis connectivity, corresponding with improved executive functioning. Nonspecific connectivity changes were found across all participants in: 1) SN-DMN between-network connectivity, corresponding with reductions in depression; 2) lateral-medial PFC axis; and 3) limbic-sensorimotor system, corresponding with reductions in depression. Overall, results suggest overlapping and nonoverlapping neural substrates of mindfulness meditation

and social support therapy in adults with ASD. Novel connectivity metrics provide critical information for the development of personalized medicine, causal connectivity analyses, and neurostimulation research.

CHAPTER 4

NEUROPHYSIOLOGICAL EEG SIGNATURES OF MBSR: PUTATIVE MECHANISM OF ANXIETY ALLEVIATION

INTRODUCTION

Autism spectrum disorder (ASD) is one of the most common neurodevelopmental disorders, affecting one in 54 children, with a projected cohort of 6 million autistic adults in the United States (Baio, 2012; Dietz et al., 2020). Adults with ASD face heightened risk of co-occurring psychiatric conditions, especially depression and anxiety disorders, which compound low rates of independence and employment (Howlin, 2000; Moss et al., 2017) and contribute to seven-fold higher suicide rates than the general population (Hedley et al., 2017b; Jokiranta-Olkoniemi et al., 2021). Together, a growing population of autistic adults with susceptibility to mental illness creates an urgent public health concern. Unfortunately, pharmacotherapies for co-occurring psychiatric conditions in ASD are limited due to poor efficacy, compliance issues, and adverse effects in adults with ASD, however mindfulness-based behavioral therapies mitigate these challenges and show promise for improving mental health (Beck, 2018; Coleman et al., 2019).

Evidence suggests Mindfulness-based stress reduction (MBSR), an intensive 8-week behavioral intervention that teaches various meditation practices aimed at reducing stress and enhancing present moment awareness, may alleviate psychiatric symptoms in ASD. Relative to waitlist and active controls, mindfulness therapy has been shown to improve depression, anxiety, emotion regulation, and quality of life in adults with ASD (Braden, Pagni et al., 2021; Pagni & Braden, 2021; Pagni et al., 2020; Spek et al., 2013). However, it remains unclear if improvements are mindfulness-specific or driven by other socio-cognitive factors. For example, Sizoo and colleagues (2017)

compared MBSR and Cognitive Behavioral Therapy (CBT) in a small sample of adults with ASD and found therapeutic improvements in the absence of a group interaction. Importantly, a comparison group controlling for the social support and educational constituents of MBSR, and brain-based characterization of how MBSR uniquely exerts therapeutic improvements, are critical to evaluating the "active ingredients" of mindfulness in the context of psychiatric co-morbidity in ASD.

Neuroimaging evidence suggests MBSR's mental health outcomes are mediated by alterations to the default mode network (DMN), a primary resting state network implicated in the etiology of depression and anxiety. Multimodal imaging studies utilizing simultaneous functional MRI (fMRI) and electroencephalography (EEG) recordings have laid the groundwork for a more comprehensive spatiotemporal understanding of DMN architecture and functioning, and have established EEG signatures of DMN activity (Das et al., 2022; Kilpatrick et al., 2011; Kral et al., 2019; Neuner et al., 2014; Ng et al., 2021; Wells et al., 2013). EEG spectral power accounts for ~70% of DMN functional connectivity variance, with beta power being positively correlated and explaining a significant portion of variance (Hlinka et al., 2010; Laufs et al., 2006); additionally, beta and gamma oscillations distinguish intra- and inter-network DMN connectivity (Das et al., 2022). Neuner and colleagues (2014) further elucidated this relationship, demonstrating connections between EEG beta-band power and fMRI signal in the PCC, a hub of the DMN, which has since been associated with trait anxiety and anxiety disorders (Imperatori et al., 2019; Jin et al., 2018; Pavlenko et al., 2009). Intracellular EEG and magnetoencephalography (EEG) work has also demonstrated positive relationships between gamma and DMN activity, particularly within the medial prefrontal cortex (mPFC) and PCC. Moreover, electroconvulsive therapy targeting beta-band activity reduces depressive symptoms (Takamiya et al.,

2019). Together, research suggests high-frequency EEG oscillations associated with DMN functioning may be a therapeutic neural target.

Mindfulness-related changes to beta-2 (high beta) and gamma-band power at midline electrodes have been established and linked to self-referential processing and DMN activity (Berkovich-ohana et al., 2014; Dor-Ziderman et al., 2013). For example, Ng and colleagues (2021) found MBSR-induced increases in beta-2 and gamma power during resting state and the mindfulness meditation practices 'Awareness of Breathing' and 'Body Scan' at electrodes FZ and PZ; in general, these metrics correlated with mindfulness traits and emotion regulation, suggesting midline neurophysiological signals reference psychological constructs relevant to MBSR. However, changes were relative to a waitlist control rather than an active control, limiting conclusions regarding the "active ingredients" of mindfulness. Meditation expertise has also been associated with lower trait gamma activity in frontal midline electrodes, associated with diminished self-referential processing, and higher trait and state gamma activity in posterior midline electrodes, associated with enhanced attention and sensory processing (Berkovich-Ohana et al., 2012). To date, no research has examined MBSR-elicited neurophysiological changes in adults with ASD, despite EEG data collection being cheaper, requiring lower participant burden, and holding potential to provide a practical objective measure of meditation progress relative to fMRI (Garrison et al., 2013).

The present study compared spectral power changes in beta-2 and gamma frequency bands at midline electrodes (FZ, CZ, and PZ) between MBSR and a social support/relaxation education (SE) active control group to isolate mindfulness-specific neurophysiological changes, as well as shared neurophysiological mechanisms among intervention groups. Pre-to-post symptoms of depression and anxiety were examined to identify mindfulness-specific neurophysiological correlates of depression and anxiety

symptom reduction. Based on prior mindfulness research demonstrating relations between high-frequency brain waves at cortical midline areas and the DMN, we hypothesized MBSR would alter midline high-beta and gamma power, specifically by attenuating power at frontal and central sites and enhancing power at posterior midline sites (Berkovich-Ohana et al., 2012; Berkovich-ohana et al., 2014; Ng et al., 2021). Additionally, we hypothesized mindfulness-induced changes in high-beta and gamma power would be associated with reductions in depression and anxiety, supported by a body of literature linking DMN hyperactivity to the etiology of psychiatric conditions (Lemogne et al., 2012).

METHODS

PARTICIPANTS

Ninety-six adults met autism diagnosis criteria comprised of 1) an ASD diagnosis confirmed with the Autism Diagnostic Observation Schedule-2 (ADOS-2; Lord et al., 2012) at the Southwest Autism Resource and Diagnostic Center and 2) meeting Diagnostic Statistical Manual-5 criteria performed by an experimental psychologist with 20 years of experience in ASD. Exclusion criteria consisted of an IQ score <70 on the Kaufman Brief Intelligence Test-2 (KBIT-2), active suicidality, and history of traumatic brain injury or substance abuse/dependence.

Power analysis was performed based on MBSR group by time EEG interactions reported by Kaunhoven & Dorjee (2021) indicated that a total sample of n=56 is sufficient to detect group by time interactions of small-to-moderate effect sizes (G*Power: ANOVA repeated measures, power=0.80, alpha=0.05; Faul et al., 2007; Kaunhoven & Dorjee, 2021).

SELF-REPORTED BEHAVIORAL MEASURES

Pre- and post-intervention questionnaires were collected during the EEG data collection visit within 1 month before and after the intervention assessing (i) depression via the Beck Depression Inventory-2 (BDI-II) and (ii) trait anxiety symptoms via the State-Trait Anxiety Inventory (STAI-2). An intention to treat approach was implemented, allowing participants with complete pre/post datasets to be included in the analysis, regardless of extent of participation in the intervention. Behavioral measures were incomplete – either due to missing pre/post questionnaires or <20% of the questions completed – for the following number of participants: BDI-II, n=2; STAI, n=4 (Figure 10). The protocol was approved by the University Institutional Review Board and all participants provided written consent.

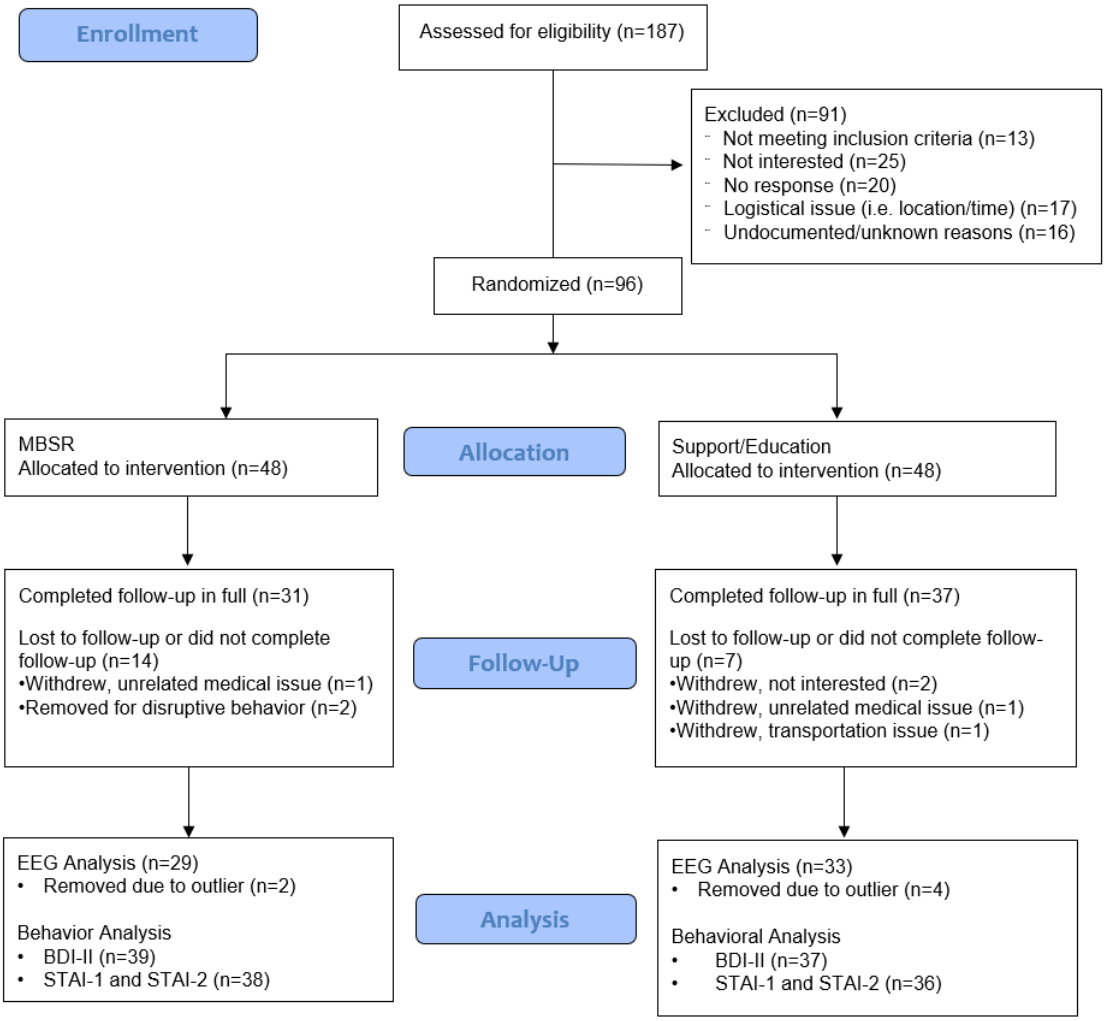


Figure 10. Participant flow chart

INTERVENTION GROUPS

Participants were randomly assigned to an 8-week MBSR group or a social support/relaxation education (SE) active control group. The standard MBSR protocol was minimally adapted for adults with ASD, and the SE intervention was developed to control for social interaction, discussion of relaxation techniques, and basic stress-related education (see Chapter 2 Methods for detailed description). Group demographics are displayed in Table 6.

EEG PROCEDURE AND DATA PREPROCESSING

Eyes-closed resting state EEG data were collected using Cognionics Quick-20 dry cap system (https://www.cgxsystems.com/quick-20m) and positioned according to the BESA 105 system. Participants were given the instructions: “Please close your eyes, relax, and remain as still as possible for 3 minutes”. The EEG recording was triggered by the experimenter to mark the beginning and ending of the 180 second recording session and trimmed according to these markers. Experimenter notes pertaining to bad electrodes, high impedances, and participant motion (i.e., movement, talking, opening eyes, etc.) were taken, as well as a video recording of participants to temporally cross-reference suspect EEG artifacts and experimenter notes.

Pre- and post-intervention EEG datasets were obtained from 68 (N_{MBSR}=31, N_{SE}=37) of the 74 participants who completed behavioral measures. Figure 11 shows the participant flow chart. Six participants' EEG data were not collected due to either equipment failure, experimenter error in data collection, or the participant not agreeing to EEG data collection. Another six participants were removed from the analysis during preprocessing due to bad channels or signal noise deemed significant outliers (Grubb’s test, $p<0.05$), providing a final sample of 62 (N_{MBSR} =29, N_{SE}=33).

Data were collected at a sampling rate of 500-Hz with impedances usually kept below the recommended 200 kΩ limit for signal accuracy and marked when impedances exceeded 200 kΩ (Ferree et al., 2001). Data preprocessing and analyses occurred using EEGLab version v 2022.1 (Delorme & Makeig, 2004) in Matlab 2021b (Mathworks, Natick, MA) in the following order: 1) bandpass filtered (0.2-40 Hz) using an IRR Butterworth filter, 2) artifact subspace reconstruction (ASR; see Plechawska-Wojcik et al., 2019), 3) spherical interpolation based on removed electrodes removed from step (2), 3) re-referencing to the averaged ear lobe electrodes, and 4) Independent Component Analysis (ICA; infomax algorithm) to identify and remove electrooculogram (EOG), electromyogram (EMG), and electrocardiogram (ECG) artifacts.

Artifact-free pre- and post-intervention EEG data were epoched into 1s segments and Fourier Transformed (nfft, non-uniform simple at 2000 steps) to compute mean spectral activities at each frequency band for electrodes of interest. Average EEG band power was calculated for high-beta and gamma (frequency ranges: 20-30 Hz and 30-40 Hz respectively), identically defined to Ng and colleagues (2021). Spectral data were visually examined using color scale plots and extracted for outlier detection using GraphPad's outlier calculator (Grubb's test, $p<0.05$; https://www.graphpad.com/quickcalcs/grubbs1/). Topographical scalp power distributions and spectral plots (1-40 Hz at ROI's) were generated via EEGLab for validation purposes; significant within-group power changes after FDR-correction were marked.

STATISTICS

Differences in intervention group demographics (sex, age, IQ, autism severity) were examined using Chi-squared and independent samples t-tests (Table 6). Mean spectral activity for pre- and post-intervention were extracted from FZ, CZ, and PZ for

beta-2 and entered into a repeated measures ANCOVA as within-subjects factor, with group as between-subject factor (MBSR and SE), and number of classes attended as covariate. Brain-behavior relationships were examined with depression and anxiety change scores (BDI-2 and STAI-2) via two-tailed Pearson product correlations with a significance threshold of $p<0.025$ to correct for multiple behavioral comparisons (BDI and STAI-2).

RESULTS

MBSR and SE groups did not differ with respect to sex, age, IQ, autism severity, or number of classes attended (Table 6). The percent of data retained for pre and post datasets did not differ between groups (Pre: $t(37.809)=1.386$, $p=0.174$; Post: $t(60)=-0.360$, $p=0.720$). Baseline and post-intervention group differences in spectral power were examined using independent samples t-tests (see footnote)[1].

[1] Baseline and post-intervention group differences in spectral power were examined using independent samples t-tests. Measures were nonsignificant with the exception of baseline beta-2 at FZ ($t(60)=-2.096$, $p=0.040$).

Table 6. Participant demographics and self-report mean, standard deviations, and ranges

	MBSR	SE	Baseline group differences
Sample size (Male/Female)	29 (18/11)	33 (19/14)	Chi^2 (62)= 0.127; p=0.798; j =0.045
Age, years	32.03 (13.55) Range: 18-67	34.34 (14.55) Range: 18-72	t(59)=-0.640; p=0.525; d=0.164
IQ[a]	105.39 (17.97) Range: 72-131	108.05 (17.82) Range: 70-142	t(55)=0.561; p=0.577; d=0.149
ADOS-2[b]	10.36 (3.97) Range: 7-23	10.54 (3.26) Range: 7-17	t(51)=0.177; p=0.860; d=0.050
Classes attended	6.10 (2.51) Range: 0-8	7.15 (1.35) Range: 3-8	t(41.652)=2.007; p=0.051; d=0.531 %

[a]Kaufman Brief Intelligence Test-2 Composite; [b]Autism Diagnostic Observation Schedule; MBSR = Mindfulness-based Stress Reductions, SE = social support/relaxation education; % Violation of Levene's homogeneity of variance, corrected values provided; *p<0.05

To examine intervention-specific changes in EEG signatures of default mode activity derived from resting state data, repeated measures ANCOVA's were performed at beta-2 and gamma frequency bands for midline electrodes FZ, CZ, and PZ. Intervention (MBSR versus SE) by Time (Pre versus Post) interactions were identified at FZ for beta-2 and gamma bands and at PZ for gamma band (Table 7; Figure 11a), in support of our primary hypothesis. Post-hoc independent paired samples t-tests at FZ revealed MBSR-elicited decreases in beta-2 ($t(28)=3.912$, $p=0.001$, Hedge's $g=0.517$ and gamma ($t(28)=3.469$, $p=0.002$, Hedge's $g=0.620$), which were nonsignificant for the SE group (beta-2: $t(32)=0.777$, $p=0.443$, Hedge's $g=0.126$; gamma: $t(32)=1.015$, $p=0.318$, Hedge's $g=0.183$). Post-hoc t-test at PZ revealed MBSR-elicited decreases in gamma ($t(28)=3.182$, $p=0.004$, Hedge's $g=0.622$) which were nonsignificant for the SE group ($t(32)=1.028$, $p=0.312$, Hedge's $g=0.194$). Beta power is predominately expressed fronto-centrally, with beta oscillations at CZ coined as Rolandic beta rhythms and at FZ coined as frontal beta rhythms (Engel & Fries, 2010; Kropotov, 2009); gamma may be less spatially confined, however, some work suggests posterior maximums, with peaks at PZ (Gruber & Müller, 2002). Overall, post-hoc analyses suggested interactions were driven by MBSR-elicited decreases in power. No Intervention by Time interactions were detected at CZ and PZ in the beta-2 band and at PZ in the gamma band (Table 7).

To examine nonspecific intervention changes in spectral power dynamics, main effects of time were examined at beta-2 and gamma frequency bands at midline electrodes FZ, CZ, and PZ. Main effects of time were detected at CZ for beta-2 and gamma frequency bands (Table 7, Figures 11b). Post-hoc paired samples t-tests at CZ revealed pre-to-post change in the MBSR group for beta-2 ($t(28)=3.941$, $p<0.001$, Hedge's $g=0.637$) and gamma ($t(28)=3.735$, $p=0.001$, Hedge's $g=0.621$), which were

nonsignificant in the SE group (Beta-2: t(32)=1.010, p=0.320, Hedge's g=0.186; gamma: t(32)=1.194, p=0.241, Hedge's g=0.227). Visual inspection shows both groups decreased beta-2 and gamma power, however decreases were steeper for the MBSR group. Main effects of Time were nonsignificant at FZ and PZ in the beta-2 band, and at PZ in the gamma band (Table 7).

Two validity checks were performed to ensure effects were region and frequency band specific: 1) visual inspection of topographical plots across frequency bands and 2) independent samples t-tests across 1-45 Hz range with multiple comparison FDR-correction. Topographical plots confirmed pre-to-post intervention changes in midline electrodes for the MBSR group, but not the SE group (Figure 12). Decreases in spectral power were restricted to beta-2 and gamma frequency bands as previously associated with mindfulness-related alterations to the DMN (Berkovich-Ohana et al., 2012; Ng et al., 2021; Figures 12-13). Topographical plots also suggested an MBSR-specific decrease in beta-2 and gamma power at electrode P8, however this was not an *a prior* hypothesis and therefore not further examined (Figure 12). Independent samples t-test confirmed an MBSR-specific effect in beta-2 and gamma frequency bands across all midline electrodes after FDR-correction (Figure 13). Some evidence for changes in other frequency bands (delta, theta, and low beta) at CZ were detected for the MBSR group, but these effects were not *a priori* hypotheses and therefore not examined (Figure 13).

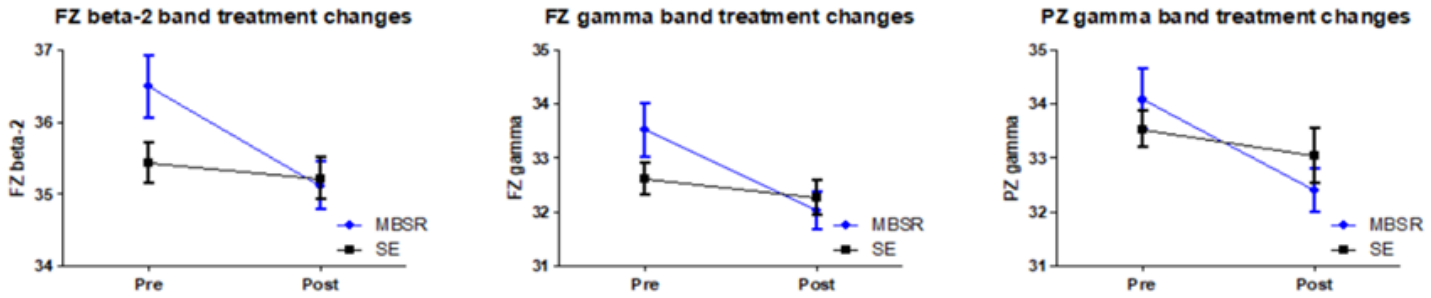
To examine group-specific brain-behavior relationships, correlations were performed with spectral power changes scores with depression (BDI) and anxiety (STAI-2) change scores (Supplemental table 1). Decreases in gamma at PZ was associated with anxiety reduction in the MBSR group (r=0.442, p=0.024, n=26; Figure 14), but not the SE group (r=-0.246, p=0.176, n=32). No correlations between gamma or beta-2 power at FZ and BDI and STAI-2 were found for the MBSR or SE groups.

Table 7. Group means, SD, ranges, and treatment effects

	MBSR		**Support/Education**			
	Pre mean (SD) range	**Post** mean (SD) range	**Pre** mean (SD) range	**Post** mean (SD) range	**Main effect of Time**	**Group by Time interaction**
Beta2-FZ	36.220 (2.329) 32.39-44.06	35.114 (1.798) 31.49-38.81	35.431 (1.621) 31.79-38.02	35.217 (1.705) 31.87-38.97	F(1,59)=0.543, p=0.464, ηp2=0.09	**F(1,59)=6.719, p=0.012*, ηp=0.102**
Beta2-CZ	37.296 (2.655) 33.19-44.77	35.525 (2.757) 31.41-44.30	36.318 (2.103) 31.71-40.94	35.888 (2.394) 31.44-40.40	**F(1,59)=6.216, p=0.015*, ηp2=0.095**	F(1,59)=2.932, p=0.092, ηp2=0.047
Beta2-PZ	36.859 (2.731) 32.95-43.96	35.417 (2.089) 30.72-39.17	36.232 (2.019) 32.22-40.59	35.729 (2.822) 31.64-45.62	F(1,59)=0.740, p=0.393, ηp2=0.012	F(1,59)=3.458, p=0.068, ηp2=0.055
Gamma-FZ	33.514 (2.702) 29.09-42.88	32.028 (1.893) 28.51-36.07	32.604 (1.722) 29.07-36.52	32.265 (1.896) 29.09-37.39	F(1,59)=0.618, p=0.435, ηp2=0.010	**F(1,59)=4.368, p=0.041*, ηp=0.069**
Gamma-CZ	34.461 (3.00) 29.78-43.66	32.582 (3.01) 27.74-41.45	33.630 (2.129) 29.14-38.16	33.105 (2.383) 28.64-37.97	**F(1,59)=6.420, p=0.014*, ηp2=0.098**	F(1,59)=2.501, p=0.119, ηp2=0.041
Gamma-PZ	34.074 (3.02) 29.88-42.85	32.396 (2.173) 27.35-37.17	33.528 (1.958) 29.08-38.26	33.031 (2.942) 28.96-43.34	F(1,59)=0.391, p=0.534, ηp2=0.007	**F(1,59)=4.075, p=0.048*, ηp2=0.065**

FZ, CZ, PZ = electrodes at medial frontal, central, and parietal sites; Beta-2=20-30 Hz; Gamma=30-40Hz; *p<0.05

A) **Group by Time interactions for FZ beta-2 and gamma and PZ gamma**



B) **Main effects of time for CZ beta-2 and gamma**

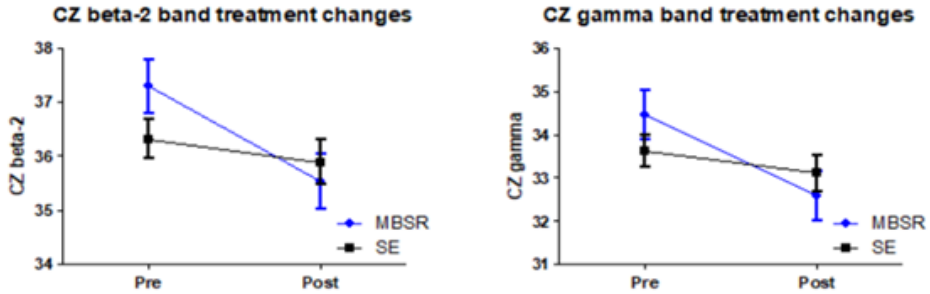


Figure 11. Significant pre-to-post treatment spectral power Group by Time interactions (A) and main effects of Time (B); $p<0.05$; y-axis=spectral power.

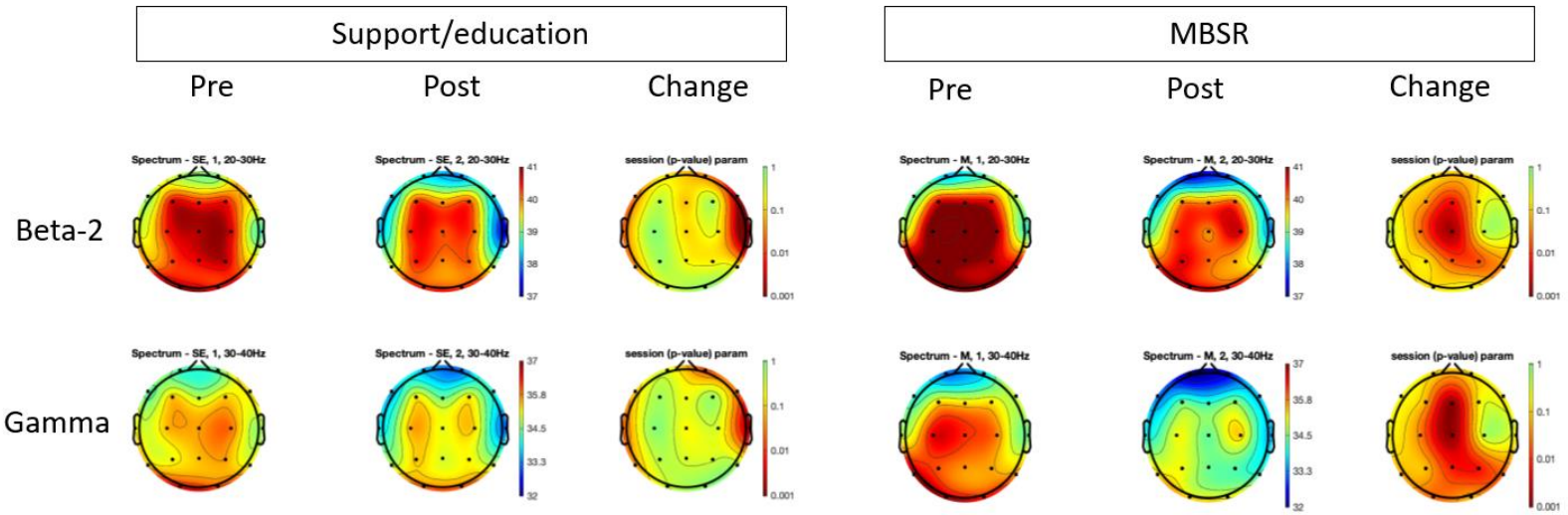


Figure 12. Topographical plots of pre- and post-treatment power at beta-2 and gamma frequency bands and p-value statistics for SE (left) and MBSR (right)

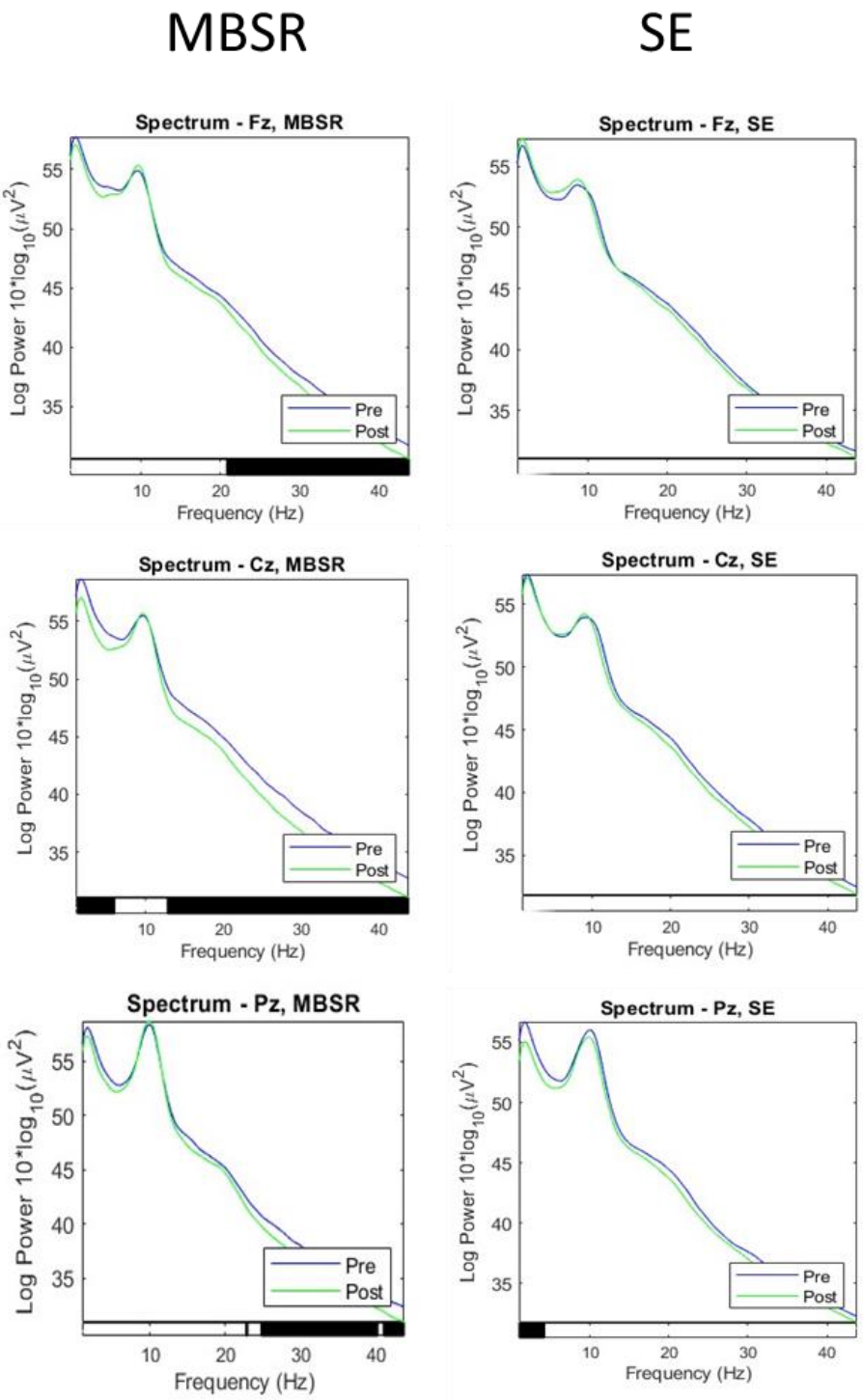


Figure 13. Spectrogram of pre- (blue) and post-treatment (green) power across 1-45 Hz frequency range for MBSR (right) and SE (left) at FZ (top), CZ (middle), and PZ (bottom). Independent samples t-test, p-FDR<0.05 = **BOLDED** bar

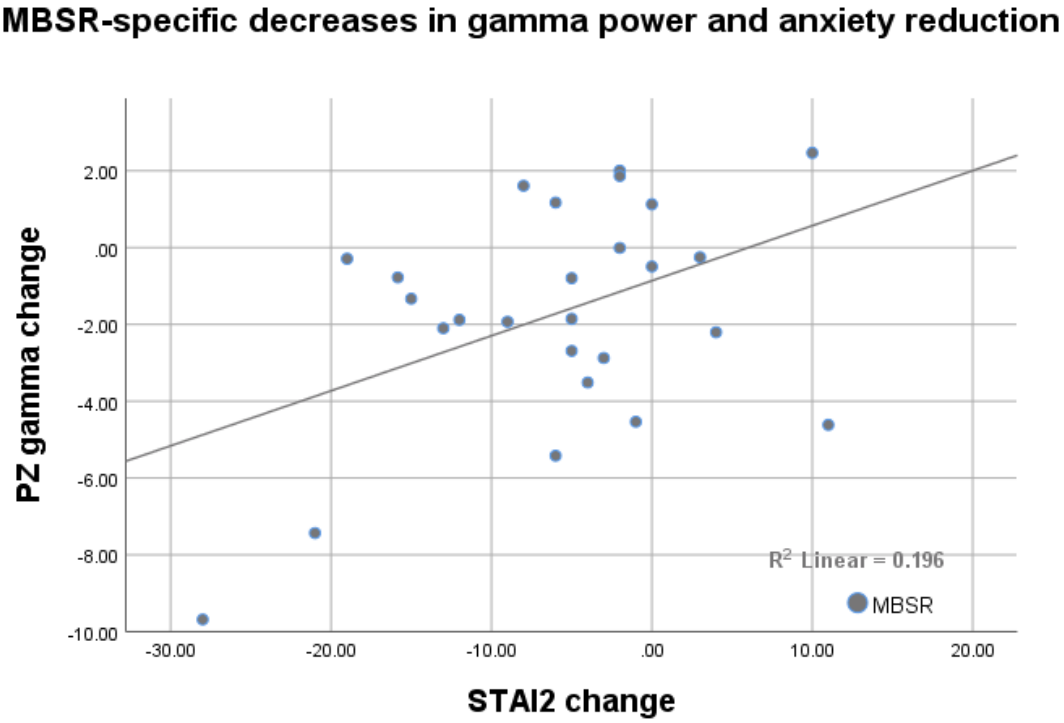


Figure 14. Associations between gamma power change at PZ (y-axis) and trait anxiety change (x-axis)

DISCUSSION

The present study identified changes to high-frequency brainwaves in the context of a randomized MBSR control trial with adults with ASD, and adds nuance to our growing understanding of the relationship between mindfulness, high-frequency brainwaves, and the DMN. This randomized clinical control trial sought to elucidate MBSR's effects on resting state spectral power dynamics in adults with ASD, and identify putative electrophysiological mechanisms of depression and anxiety alleviation. We found pre-to-post treatment decreases in high-beta and gamma power across ROI's, most of which were MBSR-driven. This is consistent with our hypotheses that meditation-induced decreases in high-frequency oscillations originating from cortical midline sources are thought to reflect reduced self-referential processing and DMN deactivation, and suggest dampening of DMN activity while at rest.

DMN activity has been associated with inter-hemispheric gamma in meditators (Berkovich-Ohana et al., 2014), with expert meditators exhibiting global gamma synchronization when achieving high meditative states (Berkovich-Ohana, 2017), and meditative states and traits generally correlating with gamma oscillations (although defined as 60-110 Hz; Braboszcz et al., 2017; Cahn et al., 2010). MEG studies have linked gamma band attenuation to decreased medial prefrontal cortex activity when transitioning from self-referential processing to present moment experience, which was accompanied by lower reports of negative emotions (Dor-Ziderman et al., 2016). EEG and fMRI studies corroborate this relationship, linking gamma attenuation with reduced DMN activity, and beta band attenuation with posterior medial parietal activity, further substantiating these brainwaves relationship to cortical midline structures (Jerbi et al., 2010; Ossandón et al., 2011). Specific to MBSR, high-beta and gamma power changes at central midline regions have been reported in novice, neurotypical practitioners (Ng et

al., 2021), during nonREM sleep in patients with insomnia, and associated with mindfulness traits (Goldstein et al., 2019). Together, these studies cohesively tie MEG, EEG, and fMRI findings to proposed models of the 'self' in the context of meditation and psychiatric conditions (see reviews by Nejad et al., 2013 and Northoff et al., 2006). Our findings extend this work, demonstrating MBSR-elicited beta and gamma attenuation in adults with ASD.

A few findings diverged from our original predictions and contrast other research. First, rather than MBSR-specific changes across all midline electrodes, both MBSR and SE groups combined showed decreased power at CZ at high-beta and gamma. However, post-hoc analyses revealed these effects were driven by the MBSR group. Further, group-by-time interactions at FZ and PZ provide overall support for our hypothesis of MBSR-specific effects. Second, we predicted *increased* gamma power at PZ, as found by Berkovich-Ohana and colleagues (2012) who proposed this as a marker of increased attention and sensory awareness; instead, we found MBSR-specific *decreases* in gamma power. These differences are likely design-related, since Berkovich-Ohana and colleagues (2012) contrasted resting state to a time production task among meditation practitioners of various expertise levels. Decreased gamma power at FZ and CZ were in line with their findings, and have been previously interpreted as diminished DMN activity.

Ng and colleagues (2012) also found MBSR *increased* beta and gamma at FZ and PZ during resting state relative to waitlist controls, and claimed these changes reflected less mind wandering and enhanced mindfulness. This interpretation conflicts with our results and Jerbi and colleagues (2010) seminal work showing DMN deactivation in mPFC and PCC correlates with gamma suppression using deep intracellular EEG recording techniques. In agreement with our findings, Ng and

colleagues (2012) found decreased power with meditation experience and within a subsample of experts, suggesting our sample may have successfully acquired mindfulness skills. This is evidenced by the objective marker of broadband EEG power decreases.

Interestingly, when resting state spectral power was contrasted with an active body scan meditation after MBSR, reductions in power were observed (Ng et al., 2021). Thus, we propose MBSR practitioners in the present study may have exhibited a meditative-like state at post-intervention; alternatively, in-line with foundational MEG and intracellular EEG studies investigating physiological correlates of the DMN, MBSR practitioners may have demonstrated a task-positive, rather than task-negative, physiological state (Dor-Ziderman et al., 2013; Jerbi et al., 2010). Both interpretations suggest DMN suppression. Since Ng and colleagues didn't observe the same gamma suppressing effect when contrasting resting state with breathing awareness, we hypothesize our effects may results from MBSR body scan practices, which have been shown to elicit stronger responses than breath awareness practices (Kok & Singer, 2017). Overall, our results suggest broad MBSR-induced decreases in resting state high-beta and gamma power across midline sites. The SE group showed slight decreases – albeit nonsignificant on their own – across these measures, too, suggesting a potentially partially overlapping therapeutic effect. However, MBSR effects were more robust and showed within-group time differences at the three ROI's for high-beta and gamma bands.

Mindfulness-based therapies are theorized to exert antidepressant and anxiolytic effects by altering brain processes underlying pathological forms of self-referential cognition, primary attributed to DMN dysregulation (Goldin et al., 2012; Lin et al., 2018b). Features of depression and anxiety – namely, negative attentional biases,

rumination, and inflexible cognition – have a well-established neural underpinning of hyperactivity and abnormal connectivity of the DMN and are attenuated by MBSR (Chiesa et al., 2014; Lemogne et al., 2012; Nejad et al., 2013). Our hypothesis of MBSR-induced changes in high frequency oscillations mediating antidepressant and anxiolytic outcomes was based on this body of literature, and partially supported. Specifically, we found gamma power at the midline parietal site correlated with the alleviation of anxiety symptoms in an MBSR-specific manner. Such changes may reflect attenuated activity in the posterior cingulate cortex (PCC), a key DMN region involved in autobiographical memory, mind wandering, and generalized anxiety disorder (Andreescu et al., 2014; Northoff & Bermpohl, 2004; Northoff et al., 2006b), and is in line with positive relationships described between gamma and DMN activity (Dor-Ziderman et al., 2013; Jerbi et al., 2010). Since PCC metrics predict treatment response in social anxiety disorder, PTSD, and OCD, irrespective of domains of treatment (behavioral or pharmacological), the PCC might be a candidate transdiagnostic therapeutic target (Faria et al., 2017; O'Neill et al., 2017; Sheynin et al., 2020). No other EEG measures correlated with depression or anxiety symptom change in this study. In sum, we propose central parietal gamma activity as a putative biomarker of mindfulness-induced anxiety symptom improvement. Future studies utilizing multimodal EEG and fMRI techniques are needed to elucidate these physiological interpretations of MBSR's impact on resting state neural activity in adults with ASD.

LIMITATIONS

Important limitations should be considered. First and foremost is the modest sample size which warrants replication with larger samples. Despite this limitation, the sample size was sufficiently powered to detect group by time interactions, as indicated by our a priori power analysis and results. However, trending group by time interactions

suggest the study may have been underpowered to detect smaller effect sizes. Second, the low-density dry cap EEG system prevented source localization analyses, reduced the effectiveness of channel interpolation and ICA artifact rejection, and overall has reduced signal-to-noise ratio relative to high-density, low impedance systems. Further, issues with high impedances and bad channels caused data loss which reduced power and increased variance in the final dataset. To overcome these challenges, we employed ASR and visual inspection to identify and remove artifacts and bad channels; inspection of individual-level EEG traces in combination with outlier detection and validation checks (Figure 4 and 5) provided assurance of data integrity. Moreover, ICA was applied to identify non-neural physiological noise (i.e. lateral and horizontal eye movements, cardiovascular signals, electrical system activity) and removed. Regardless, studies using high-density, low-impedance systems are needed to confirm and further elucidate the spatial-temporal electrophysiological signature of MBSR in adults with ASD.

Other limitations concern the generalizability of findings. Adults with ASD were excluded on the basis of intellectual disability, substance use/abuse, and personal history of concussion resulting in loss of consciousness. These criteria sought to mitigate the influence of confounding variables on EEG recording and MBSR/SE compliance, however limit generalizability to these individuals on the autism spectrum. Attempts to improve generalizability were taken by including a wide age range of adults (18-75 years old) and individuals with co-occurring conditions (Bipolar, epilepsy, hearing lose, and Tourette's syndrome).

CONCLUSIONS

Treatments for co-occurring depression and anxiety in adults with ASD are limited, yet critical to reducing heightened suicide rates and maintaining long-term independence and employment throughout the adult lifespan (Howlin, 2000; Jokiranta-

Olkoniemi et al., 2021). While MBSR has shown efficacy, this study elucidated neurophysiological correlates with an active control comparison group. In short, MBSR appears to influence high-frequency brainwave attenuation across cortical midline sites associated with DMN dysfunction and psychiatric conditions. In the MBSR group, decreases in gamma-band oscillations at a posterior midline site corresponded with anxiety reduction. Future studies are warranted to characterize the complex spatiotemporal correlates of MBSR in adults with ASD through the use of multimodal imaging and personalized medicine approaches.

CHAPTER 5

THERAPEUTIC NEURAL MECHANISMS OF MINDFULNESS IN AUTISM: INSIGHTS, IMPLICATIONS, AND FUTURE DIRECTIONS

OVERVIEW OF FINDINGS

These studies contribute to the early characterization of mindfulness-specific and nonspecific therapeutic neural correlates in adults with ASD, and to a growing pursuit to treat co-occurring psychiatric conditions in a population facing exceptional challenges (Ghaziddin & Zafar, 2008; Maddox & Gaus, 2018). The fMRI neurocircuitry and EEG spectral power techniques employed successfully captured MBSR-induced changes among multiple neural networks, as extensively documented in other clinical populations (Gotink et al., 2016; Hatchard et al., 2017). Specifically, functional activity and connectivity and neurophysiological changes were identified in hubs of the DMN, SN, and CEN.

Study 1 identified MBSR-specific increases in dorsal anterior cingulate cortex (dACC/MCC) activity which correlated with the alleviation of depressive symptoms. Hypoactivation of the dACC has been found in ASD during self-reflection relative to health controls, suggesting MBSR effects were in a normalizing direction (Lombardo et al., 2010). Moreover, the MBSR group demonstrated increased dACC-sensorimotor and decreased dACC-mPFC connectivity, which may be interpreted as enhanced attention on present moment experience (ascribed to sensorimotor activity) and diminished attention on the self (ascribed to mPFC activity; Farb et al., 2007b). Hyperconnectivity between the dACC and mPFC in MDD also suggests decreases in this circuit may reflect normalization in adults with ASD in the context of depression (Lemogne et al., 2012). Findings provide preliminary insight into MBSR's effects on ASD-specific deficits, particularly within the DMN and SN, during self-referential processing.

Study 2 sought to elucidate mindfulness-specific and nonspecific behavioral and functional connectivity (self-reflection fMRI) changes in a randomized clinical trial consisting of an adequately powered sample (n=78). Behaviorally, both MBSR and SE interventions demonstrated efficacy for depression, anxiety, and autistic traits; however, the MBSR intervention evidenced additional efficacy for mindfulness traits and working memory. Both MBSR and SE interventions elicited decreases in amygdala-sensorimotor (SN-SMN) and frontal pole-insula (DMN-SN) connectivity, which correlated with depression alleviation. Connectivity changes may represent attenuated amygdala input to the sensorimotor system, resulting in a diminished flight-or-flight response to psychologically perceived threats, as well as attenuated salience toward internal stimuli (DMN-SN).

MBSR-specific insular-thalamus (intra-SN) decoupling correlated with anxiolytic effects and increased mindfulness, and frontal pole-posterior cingulate cortex (intra-DMN) decoupling correlated with improved working memory. Intra-SN connectivity changes may represent altered bottom-up processing or top-down regulation of ascending sensory information that warrant causal connectivity analyses (Farb et al., 2015). Intra-DMN connectivity change may represent compartmentalization of distinct aspects of self-referential processing, wherein autobiographical memory, served by the PCC, is accessed independently of valence attribution, served by medial PFC regions (Northoff & Bermpohl, 2004). Using a gPPI approach to elucidate functional connectivity changes in self-reflection neurocircuitry, this study characterized distinct and shared therapeutic mechanisms of mindfulness meditation and social support therapy in adults with ASD.

Study 3 identified MBSR-specific and nonspecific alterations to high-frequency EEG brainwaves across midline electrodes. Specifically, decreases in beta and gamma

frequency bands power were generally found for both MBSR and SE, however effects were largely driven by mindfulness training. Results support Berkovich-Ohana and colleagues (2014) theory of mindfulness-attributed DMN alterations to neurophysiology. Additionally, MBSR-specific reductions in gamma power at the posterior midline correlated with anxiolytic effects. Overall, findings suggest mindfulness training alters neurophysiological signatures of the DMN, and offer a putative therapeutic neural correlate of anxiety reduction.

The characterization of distinct and shared therapeutic mechanisms of mindfulness meditation and social support therapy marks a critical first step toward improving clinical treatment for adults with ASD. Findings corroborate MBSR's effects in other populations implicating the DMN, SN, and ECN, suggesting common biomarkers in adults with ASD (Gotink et al., 2016). Notably, while findings in ASD were generally consistent with previous research, nuances in behavioral and brain-related discoveries warrant emphasis and consideration for future research.

First, nonspecific behavioral and connectivity changes suggest SE is sufficient to improve mental health and autistic traits and that overlapping neural mechanisms of mindfulness and social support are responsible for therapeutic improvements – namely, the amygdala and insula. MBSR's non-superior clinical efficacy for depression, anxiety, and autism traits relative to social support therapy aligns with previous work comparing MBSR and CBT (Sizoo & Kuiper, 2017). Benefits of the SE intervention on depression and anxiety in ASD align with previous work showing loneliness and satisfaction with social support predict depressive symptoms (Hedley et al., 2018); moreover, perceived support in the form of tangible materials rather than belonging and appraisal has been linked to depression/suicidality over belonging and appraisal (Hedley et al., 2017b).

Future research utilizing meditation/moderation analyses are needed to identify psychological factors underlying SE's therapeutic outcomes and circuit-based changes.

Non-overlapping behavioral and neural changes suggest mindfulness meditation induces unique neural adaptations that contribute to the enhancement of mindfulness abilities and working memory. Such distinction of MBSR-specific effects in adults with ASD may assist clinician-informed patient care and the mindfulness field more generally. Shared and distinct neurocircuit changes (ROI's and their respective targets) have been reported individually in activation studies (Gotink et al., 2016), but scantly mentioned jointly in connectivity analyses. Such novelty merits caution, yet offers novel connectivity metrics to be further probed using advanced neuroimaging methods and sophisticated analyses techniques (i.e. dynamic causal modeling, graph theory, and Bayesian statistical approaches). Future research should seek to replicate and extend these findings in adults with ASD.

IMPLICATIONS FOR PERSONALIZED MEDICINE

Personalized medicine marks the next frontier of psychiatry and is ushered in with the advent of machine learning and rapidly developing technology to optimize predictive power and clinical outcomes. The acquisition of big data spanning genetics, epigenetic, neurobiology, neural network dynamics, and behavior is critical to these endeavors. Behavioral and brain-related findings from these studies provide information that may inform the development of personalized medicine approaches to treat psychiatric co-morbidity in ASD. For example, behavioral and neuroimaging metrics may assist in 1) selecting appropriate psychosocial treatments on an individual basis, 2) predicting treatment response, 3) objectively tracking improvement throughout treatment, and 4) dynamically targeting neurocircuits with neurostimulation technology.

Intervention nonspecific behavioral and connectivity changes from this clinical trial suggest SE is sufficient to reduce depression, anxiety, and autistic traits. Moreover, antidepressant effects, at least in part, share common neural pathways between MBSR and SE. Applied practically, patients seeking treatment for depression, anxiety, or autism-related challenges may be referred to social support-based therapy, which can be administered by community leaders at lower cost, without the need for a specialist or insurance. This model of therapy can be implemented long-term with potentially enduring benefits that should be explored in future investigations. Additionally, connectivity metrics (amygdala-sensorimotor system and frontal pole-PCC) may be useful for predicting and tracking treatment response if depression remission is the primary clinical goal. However, if patients are seeking additional benefits in mindfulness abilities and working memory, MBSR is likely the preferred treatment.

fMRI and EEG findings suggest distinct neural substrates of mindfulness training underlie therapeutic gains, which may be harnessed in an additive manner to optimize efficacy. For example, MBSR-specific decreases in insula-thalamus connectivity and posterior gamma power were associated with improvements in anxiety; but SE also elicited reductions in anxiety, suggesting an unidentified mechanism may be involved. If this is the case, both interventions may be prescribed to bolster therapeutic gains. This neural circuit was also associated with increased mindfulness traits, including 'nonjudgment toward experience', which are considered primary psychological mediators of improved mental health and quality of life (Chiesa et al., 2014). Moreover, age-related decline in cognitive functioning, especially working memory, may also motivate MBSR therapy over alternative treatment options (Powell et al., 2017). MBSR uniquely elicited decoupling of the anterior-posterior axis of the DMN which accompanied working memory improvements. Therefore, the DMN axis may be further

examined for its link to working memory. If substantiated, integrity of this neural pathway could be assessed before treatment to determine if it predicts poor or declining working memory in ASD. Additionally, this pathway might be assessed throughout the MBSR intervention to predict treatment response. Although these neural metrics are preliminary, they encourage ROI-to-ROI approaches to investigate behavioral treatments for the development of personalized medicine for adults with ASD. Such clinical utility is speculative and requires replication and extension. Additionally, personalized medicine will likely not be guided by neuroimaging metrics alone, but by the combination of genetic, epigenetic, neurobiological, systems-level, and behavioral information; thus, these findings are a stepping stone for informed patient care.

IMPLICATIONS FOR NEUROSTIMULATION RESEARCH

Neurostimulation methods such as targeted focused ultrasound (tFUS) are emerging, noninvasive techniques holding enormous potential for treating conditions like depression by modulating neural activity with spatiotemporal precision (George et al., 2021). tFUS stimulation has been applied to DMN regions and shown to produce changes in mood and cognition, and alter large-scale functional connectivity (Fini & Tyler, 2020; Kim et al., 2022; Sanguinetti et al., 2020). Preliminary neurostimulation findings are encouraging and offer promise as next generation of treatment options for ASD and neuropsychiatric treatments (Khaleghi et al., 2020; Sanguinetti et al., 2014).

Self-reflection neurocircuitry elucidated in Studies 1 and 2 provides novel neural pathways underlying therapeutic effects in ASD. Neurostimulation research may seek to dynamically target these pathways within normal physiological parameters to facilitate the acquisition of mindfulness traits and optimize clinical outcomes. Such applications require substantial research prior to being tested in clinical domains. First, effective connectivity analyses must be performed at ROI's and their respective targets to

determine the input-output architecture and temporal signaling dynamics underlying mindfulness-induced functional connectivity changes. Next, greater spatial resolution must be obtained using smaller voxel sizes with MRI/fMRI data to hone in on circuits of interest. Together, this complementary spatiotemporal information enables the development of precise tFUS protocols for dynamic modulation of neurocircuits, seeking to either strengthen or attenuate neural pathways. The addition of EEG recordings before, during, and after neurostimulation offers an easy and affordable objective measure to track the effects of tFUS and determine their relations with therapeutic changes (Fini & Tyler, 2020). These studies lay the groundwork for this work by identifying neurocircuit-based changes underpinning therapeutic improvements.

CONCLUSIONS

Findings from these studies assist in characterizing MBSR's effects on behavior and fMRI/EEG brain measures in adults with ASD, and highlight the importance of randomized clinical trials for discerning the "active ingredients" of mindfulness. The methodologies applied - namely, self-reflection fMRI and resting state EEG - successfully identified neural mechanisms specific to mindfulness mental training, as well as those shared with social support-based therapy. Functional activity and connectivity changes in the DMN, SN, and ECN, and neurophysiological changes associated with the DMN, contributed to therapeutic improvements in depression, anxiety, mindfulness abilities, and working memory. While these network-based changes require replication and extension in larger cohorts, other networks should also be explored in data-driven approaches. Through the use of multimodal neuroimaging, future research is needed to further characterize the neural underpinnings of mindfulness therapy in pursuit of personalized medicine and neurostimulation paradigms to optimize ASD treatments.

REFERENCES

Abbott, R. A., Whear, R., Rodgers, L. R., Bethel, A., Thompson Coon, J., Kuyken, W., … Dickens, C. (2014). Effectiveness of mindfulness-based stress reduction and mindfulness based cognitive therapy in vascular disease: A systematic review and meta-analysis of randomised controlled trials. *Journal of Psychosomatic Research*, *76*(5), 341–351. https://doi.org/10.1016/j.jpsychores.2014.02.012

Andreescu, C., Sheu, L. K., Tudorascu, D., Walker, S., & Aizenstein, H. (2014). The ages of anxiety - Differences across the lifespan in the default mode network functional connectivity in generalized anxiety disorder. *International Journal of Geriatric Psychiatry*, *29*(7), 704–712. https://doi.org/10.1002/gps.4051

Avery, J. A., Drevets, W. C., Moseman, S. E., Bodurka, J., Barcalow, J. C., & Simmons, W. K. (2014). Major depressive disorder is associated with abnormal interoceptive activity and functional connectivity in the insula. *Biological Psychiatry*, *76*(3), 258–266. https://doi.org/10.1016/j.biopsych.2013.11.027

Baio, J. (2012). Prevalence of Autism spectrum disorders - Autism and Developmental Disabilities Monitoring Network, 14 Sites, United States, 2008. *Morbidity and Mortality Weekly Report*, *61*(SS-3), 1–19.

Basso, J. C., McHale, A., Ende, V., Oberlin, D. J., & Suzuki, W. A. (2019). Brief, daily meditation enhances attention, memory, mood, and emotional regulation in non-experienced meditators. *Behavioural Brain Research*, *356*, 208–220. https://doi.org/10.1016/j.bbr.2018.08.023

Beck, K. B., Greco, C. M., Terhorst, L. A., Skidmore, E. R., Kulzer, J. L., & McCue, M. P. (2020). Mindfulness-Based Stress Reduction for Adults with Autism Spectrum Disorder: Feasibility and Estimated Effects. *Mindfulness*, *11*(5), 1286–1297. https://doi.org/10.1007/s12671-020-01345-2

Berkovich-Ohana, A. (2017). A case study of a meditation-induced altered state: increased overall gamma synchronization. *Phenomenology and the Cognitive Sciences*, *16*(1), 91–106. https://doi.org/10.1007/s11097-015-9435-x

Berkovich-Ohana, A., Glicksohn, J., & Goldstein, A. (2012). Mindfulness-induced changes in gamma band activity - Implications for the default mode network, self-reference and attention. *Clinical Neurophysiology*, *123*(4), 700–710. https://doi.org/10.1016/j.clinph.2011.07.048

Berkovich-ohana, A., Glicksohn, J., Goldstein, A., & Israel, R. G. (2014). *Studying the default mode and its mindfulness-induced changes using EEG functional connectivity*. 1616–1624. https://doi.org/10.1093/scan/nst153

Biegel, G. M., Brown, K. W., Shapiro, S. L., & Schubert, C. M. (2009). Mindfulness-

Based Stress Reduction for the Treatment of Adolescent Psychiatric Outpatients: A Randomized Clinical Trial. *Journal of Consulting and Clinical Psychology*, *77*(5), 855–866. https://doi.org/10.1037/a0016241

Bonnelle, V., Smith, W. J., Mason, N. L., Cavarra, M., Kryskow, P., Kuypers, K. P. C., … Feilding, A. (n.d.). Analgesic potential of macrodoses and microdoses of classical psychedelics in chronic pain sufferers: a population survey. *British Journal of Pain*, *0*(0), 20494637221114960. https://doi.org/10.1177/20494637221114962

Braboszcz, C., Rael Cahn, B., Levy, J., Fernandez, M., & Delorme, A. (2017). Increased gamma brainwave amplitude compared to control in three different meditation traditions. *PLoS ONE*, *12*(1), 1–27. https://doi.org/10.1371/journal.pone.0170647

Braden, B. B., Pagni, B. A., Monahan, L., Walsh, M. J. M., Dixon, M. V., Delaney, S., … Ware, J. E. (2021). Quality of life in adults with autism spectrum disorder: influence of age, sex, and a controlled, randomized mindfulness-based stress reduction pilot intervention. *Quality of Life Research*, (0123456789). https://doi.org/10.1007/s11136-021-03013-x

Braden, B. B., Pipe, T. B., Smith, R., Glaspy, T. K., Deatherage, B. R., & Baxter, L. C. (2016). Brain and behavior changes associated with an abbreviated 4-week mindfulness-based stress reduction course in back pain patients. *Brain and Behavior*, *6*(3), 1–13. https://doi.org/10.1002/brb3.443

Bremer, B., Wu, Q., Guadalupe, M., Álvarez, M., Hölzel, B. K., Wilhelm, M., … Torske, A. (2022). Mindfulness meditation increases default mode , salience , and central executive network connectivity. *Scientific Reports*, 1–15. https://doi.org/10.1038/s41598-022-17325-6

Brereton, A. V, Tonge, B. J., & Einfeld, S. L. (2006). Psychopathology in children and adolescents with autism compared to young people with intellectual disability. *Journal of Autism and Developmental Disorders*, *36*(7), 863–870. https://doi.org/10.1007/s10803-006-0125-y

Brewer, J. A., & Garrison, K. A. (2014). The posterior cingulate cortex as a plausible mechanistic target of meditation: Findings from neuroimaging. *Annals of the New York Academy of Sciences*, *1307*(1), 19–27. https://doi.org/10.1111/nyas.12246

Brewer, J. A., Worhunsky, P. D., Gray, J. R., Tang, Y. Y., Weber, J., & Kober, H. (2011). Meditation experience is associated with differences in default mode network activity and connectivity. *Proceedings of the National Academy of Sciences of the United States of America*, *108*(50), 20254–20259. https://doi.org/10.1073/pnas.1112029108

Brugha, T. S. (2010). *Anxiety and Depression in Adults with Autism Spectrum Disorder: A Systematic Review and Meta-analysis*. *395*(2005), 311905.

Burns, A., Irvine, M., & Woodcock, K. (2019). Self-Focused Attention and Depressive Symptoms in Adults with Autistic Spectrum Disorder (ASD). *Journal of Autism and Developmental Disorders*, *49*(2). https://doi.org/10.1007/s10803-018-3732-5

Burrows, C. A., Laird, A. R., & Uddin, L. Q. (2016). Functional connectivity of brain regions for self- and other-evaluation in children, adolescents and adults with autism. *Developmental Science*, *19*(4), 564–580. https://doi.org/10.1111/desc.12400

Philipi C.l,, & Koenigs, M. (2014). The neuropsychology of self-reflection in psychiatric illness. *Journal of Psychiatric Research*, 55–63. https://doi.org/10.1016/j.jpsychires.2014.03.004.The

Cachia, R. L., Anderson, A., & Moore, D. W. (2016a). Mindfulness in Individuals with Autism Spectrum Disorder: a Systematic Review and Narrative Analysis. *Review Journal of Autism and Developmental Disorders*, *3*(2), 165–178. https://doi.org/10.1007/s40489-016-0074-0

Cachia, R. L., Anderson, A., & Moore, D. W. (2016b). Mindfulness in Individuals with Autism Spectrum Disorder: a Systematic Review and Narrative Analysis. *Review Journal of Autism and Developmental Disorders*, *3*(2), 165–178. https://doi.org/10.1007/s40489-016-0074-0

Cahn, B. R., Delorme, A., & Polich, J. (2010). Occipital gamma activation during Vipassana meditation. *Cognitive Processing*, *11*(1), 39–56. https://doi.org/10.1007/s10339-009-0352-1

Carmody, J., & Baer, R. A. (2008). Relationships between mindfulness practice and levels of mindfulness, medical and psychological symptoms and well-being in a mindfulness-based stress reduction program. *Journal of Behavioral Medicine*, *31*(1), 23–33. https://doi.org/10.1007/s10865-007-9130-7

Casartelli, L., Molteni, M., & Ronconi, L. (2016). So close yet so far: Motor anomalies impacting on social functioning in autism spectrum disorder. *Neuroscience and Biobehavioral Reviews*, *63*, 98–105. https://doi.org/10.1016/j.neubiorev.2016.02.001

Cassidy, S., & Rodgers, J. (2017). Understanding and autism. *The Lancet Psychiatry*, *4*(6), e11. https://doi.org/10.1016/S2215-0366(17)30162-1

Che, X., Zhang, Q., Zhao, J., Wei, D., Li, B., Guo, Y., … Liu, Y. (2014). Synchronous activation within the default mode network correlates with perceived social support. *Neuropsychologia*, *63*(1), 26–33. https://doi.org/10.1016/j.neuropsychologia.2014.07.035

Chiesa, A., & Serretti, A. (2010). A systematic review of neurobiological and clinical features of mindfulness meditations. *Psychological Medicine*, *40*(8), 1239–1252. https://doi.org/10.1017/S0033291709991747

Chiesa, Alberto, Anselmi, R., & Serretti, A. (2014). Psychological mechanisms of mindfulness-based interventions: What do we know? *Holistic Nursing Practice*, *28*(2), 124–148. https://doi.org/10.1097/HNP.0000000000000017

Christensen, H., & Marck, D. (2017). *The Efficacy of Mindfulness Based Stress Reduction (MBSR) for Decreasing Anxiety and Depression among Breast Cancer Survivors*. Retrieved from http://commons.pacificu.edu/pa%0Ahttp://commons.pacificu.edu/pa/613%0Ahttp://commons.pacificu.edu/pa/613/

Coleman, D. M., Adams, J. B., Anderson, A. L., & Frye, R. E. (2019a). Rating of the Effectiveness of 26 Psychiatric and Seizure Medications for Autism Spectrum Disorder: Results of a National Survey. *Journal of Child and Adolescent Psychopharmacology*, *29*(2), 107–123. https://doi.org/10.1089/cap.2018.0121

Coleman, D. M., Adams, J. B., Anderson, A. L., & Frye, R. E. (2019b). Rating of the Effectiveness of 26 Psychiatric and Seizure Medications for Autism Spectrum Disorder: Results of a National Survey. *Journal of Child and Adolescent Psychopharmacology*, *29*(2), 107–123. https://doi.org/10.1089/cap.2018.0121

Critchley, H. D., & Garfinkel, S. N. (2018). The influence of physiological signals on cognition. *Current Opinion in Behavioral Sciences*, *19*, 13–18. https://doi.org/10.1016/j.cobeha.2017.08.014

Dane, S., & Balci, N. (2007). Handedness, eyedness and nasal cycle in children with autism. *International Journal of Developmental Neuroscience*, *25*(4), 223–226. https://doi.org/10.1016/j.ijdevneu.2007.03.005

Das, A., de los Angeles, C., & Menon, V. (2022). Electrophysiological foundations of the human default-mode network revealed by intracranial-EEG recordings during resting-state and cognition. *NeuroImage*, *250*(January), 118927. https://doi.org/10.1016/j.neuroimage.2022.118927

de Vibe, M., Bjørndal, A., Fattah, S., Dyrdal, G. M., Halland, E., & Tanner-Smith, E. E. (2017). Mindfulness-based stress reduction (MBSR) for improving health, quality of life and social functioning in adults: A systematic review and meta-analysis. *Campbell Systematic Reviews*, *11*(November 2015), 1–267. https://doi.org/10.4073/csr.2017.11

Delorme, A., & Makeig, S. (2004). EEGLAB: An open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *Journal of Neuroscience Methods*, *134*(1), 9–21. https://doi.org/10.1016/j.jneumeth.2003.10.009

Demetriou, E. A., Lampit, A., Quintana, D. S., Naismith, S. L., Song, Y. J. C., Pye, J. E., … Guastella, A. J. (2018). Autism spectrum disorders: A meta-analysis of executive

function. *Molecular Psychiatry*, *23*(5), 1198–1204. https://doi.org/10.1038/mp.2017.75

Desaunay, P., Briant, A. R., Bowler, D. M., Ring, M., Gérardin, P., Baleyte, J. M., … Guillery-Girard, B. (2020). Memory in autism spectrum disorder: A meta-analysis of experimental studies. *Psychological Bulletin*, *146*(5), 377–410. https://doi.org/10.1037/bul0000225

Desikan RS, Ségonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, Buckner RL, Dale AM, Maguire RP, Hyman BT, Albert MS, K. R. (2006). An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage.*, *31*(3), 968–980.

Dietz, P. M., Rose, C. E., McArthur, D., & Maenner, M. (2020). National and State Estimates of Adults with Autism Spectrum Disorder. *Journal of Autism and Developmental Disorders*, (0123456789). https://doi.org/10.1007/s10803-020-04494-4

Dor-Ziderman, Y., Ataria, Y., Fulder, S., Goldstein, A., & Berkovich-Ohana, A. (2016). Self-specific processing in the meditating brain: a MEG neurophenomenology study. *Neuroscience of Consciousness*, *2016*(1). https://doi.org/10.1093/nc/niw019

Dor-Ziderman, Y., Berkovich-Ohana, A., Glicksohn, J., & Goldstein, A. (2013). Mindfulness-induced selflessness: A MEG neurophenomenological study. *Frontiers in Human Neuroscience*, *7*(SEP), 1–17. https://doi.org/10.3389/fnhum.2013.00582

Dziuk, M. A., Larson, J. C. G., Apostu, A., Mahone, E. M., Denckla, M. B., & Mostofsky, S. H. (2007). Dyspraxia in autism: Association with motor, social, and communicative deficits. *Developmental Medicine and Child Neurology*, *49*(10), 734–739. https://doi.org/10.1111/j.1469-8749.2007.00734.x

Engel, A. K., & Fries, P. (2010). Beta-band oscillations—signalling the status quo? *Current Opinion in Neurobiology*, *20*(2), 156–165. https://doi.org/https://doi.org/10.1016/j.conb.2010.02.015

Shapiro, L. *EMBODIED COGNITION by Lawrence Shapiro When*.

Farb, N. A. S. (2014). *To which of thine selves be true? Changes in viscerosomatic neural activity with mindfulness meditation training reflect improved present-moment self-awareness. 75*(6-B(E)), No-Pagination Specified.

Farb, N. A. S., Segal, Z. V., & Anderson, A. K. (2013). Mindfulness meditation training alters cortical representations of interoceptive attention. *Social Cognitive and Affective Neuroscience*, *8*(1), 15–26. https://doi.org/10.1093/scan/nss066

Farb, N. A. S., Segal, Z. V., Mayberg, H., Bean, J., Mckeon, D., Fatima, Z., & Anderson,

A. K. (2007a). Attending to the present: Mindfulness meditation reveals distinct neural modes of self-reference. *Social Cognitive and Affective Neuroscience*, *2*(4), 313–322. https://doi.org/10.1093/scan/nsm030

Farb, N. A. S., Segal, Z. V., Mayberg, H., Bean, J., Mckeon, D., Fatima, Z., & Anderson, A. K. (2007b). Attending to the present: Mindfulness meditation reveals distinct neural modes of self-reference. *Social Cognitive and Affective Neuroscience*, *2*(4), 313–322. https://doi.org/10.1093/scan/nsm030

Farb, N., Daubenmier, J., Price, C. J., Gard, T., Kerr, C., Dunn, B. D., … Mehling, W. E. (2015). Interoception, contemplative practice, and health. *Frontiers in Psychology*, *6*(JUN), 1–26. https://doi.org/10.3389/fpsyg.2015.00763

Faria, V., Gingnell, M., Hoppe, J. M., Hjorth, O., Alaie, I., Frick, A., … Furmark, T. (2017). Do You Believe It? Verbal Suggestions Influence the Clinical and Neural Effects of Escitalopram in Social Anxiety Disorder: A Randomized Trial. *EBioMedicine*, *24*, 179–188. https://doi.org/10.1016/j.ebiom.2017.09.031

Faul, F., Erdfelder, E., Lang, A.-G., & Buchner, A. (2007). G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods*, *39*(2), 175–191. https://doi.org/10.3758/bf03193146

Ferree, T. C., Luu, P., Russell, G. S., & Tucker, D. M. (2001). Scalp electrode impedance, infection risk, and EEG data quality. *Clinical Neurophysiology : Official Journal of the International Federation of Clinical Neurophysiology*, *112*(3), 536–544. https://doi.org/10.1016/s1388-2457(00)00533-2

Fini, M., & Tyler, W. J. (2020). Emotional Processing , Physiology , and Performance I : Dorsal Anterior Cingulate Cortex Targeting . *MedRxiv*, 1–29.

Fox, K. C. R., Nijeboer, S., Dixon, M. L., Floman, J. L., Ellamil, M., Rumak, S. P., … Christoff, K. (2014). Is meditation associated with altered brain structure? A systematic review and meta-analysis of morphometric neuroimaging in meditation practitioners. *Neuroscience and Biobehavioral Reviews*, *43*, 48–73. https://doi.org/10.1016/j.neubiorev.2014.03.016

Frith, U., & Happe, F. (2003). Theory of Mind and Self-Consciousness: What Is It Like to Be Autistic? *Mind and Language*, *14*(1), 82–89. https://doi.org/10.1111/1468-0017.00100

Fuentes, J. J., Fonseca, F., Elices, M., Farré, M., & Torrens, M. (2020). Therapeutic Use of LSD in Psychiatry: A Systematic Review of Randomized-Controlled Clinical Trials. *Frontiers in Psychiatry*, *10*(January), 1–14. https://doi.org/10.3389/fpsyt.2019.00943

Simon, G.E., Revicki, D., Heiligenstein, J., Grothaus, L., VonKorff, M., Katon, W.J., & Hylan, T.R. (2000). Recovery from depression, work productivity, and health care costs among primary care patients. *General Hospital Psychiatry*, *22*(3), 153–162. https://doi.org/10.1016/S0163-8343(00)00072-4

Gaigg, S. B., Flaxman, P. E., McLaven, G., Shah, R., Bowler, D. M., Meyer, B., … South, M. (2020). Self-guided mindfulness and cognitive behavioural practices reduce anxiety in autistic adults: A pilot 8-month waitlist-controlled trial of widely available online tools. *Autism*, *24*(4), 867–883. https://doi.org/10.1177/1362361320909184

Garfinkel, S. N., & Critchley, H. D. (2013). Interoception, emotion and brain: new insights link internal physiology to social behaviour. Commentary on:: "Anterior insular cortex mediates bodily sensibility and social anxiety" by Terasawa et al. (2012). *Social Cognitive and Affective Neuroscience*, *8*(3), 231–234. https://doi.org/10.1093/scan/nss140

Garrison, K. A., Santoyo, J. F., Davis, J. H., Thornhill IV, T. A., Kerr, C. E., & Brewer, J. A. (2013). Effortless awareness: Using real time neurofeedback to investigate correlates of posterior cingulate cortex activity in meditators' self-report. *Frontiers in Human Neuroscience*, *7*(JUL), 1–9. https://doi.org/10.3389/fnhum.2013.00440

George, M., Badran, B., Caulfield, K., Summers, P., & Li, X. (2021). Is transcranial focused ultrasound stimulation (tFUS) the next holy grail for treating depression? *Brain Stimulation*, *14*(6), 1746. https://doi.org/10.1016/j.brs.2021.10.531

Ghaziddin, M., & Zafar, S. (2008). Psychiatric Comorbidity Of Adults With ASD. *Clinical Neuropsychiatry*, *5*(1), 9–12. Retrieved from http://www.clinicalneuropsychiatry.org/pdf/02_ghaziuddin.pdf

Gold, E., Smith, A., Hopper, I., Herne, D., Tansey, G., & Hulland, C. (2010). Mindfulness-based stress reduction (MBSR) for primary school teachers. *Journal of Child and Family Studies*, *19*(2), 184–189. https://doi.org/10.1007/s10826-009-9344-0

Goldberg, S. B., Tucker, R. P., Greene, P. A., Davidson, R. J., Wampold, B. E., Kearney, D. J., & Simpson, T. L. (2018). Mindfulness-based interventions for psychiatric disorders: A systematic review and meta-analysis. *Clinical Psychology Review*, *59*(August 2017), 52–60. https://doi.org/10.1016/j.cpr.2017.10.011

Goldin, P. R., Thurston, M., Allende, S., Moodie, C., Dixon, M. L., Heimberg, R. G., & Gross, J. J. (2022). *Evaluation of Cognitive Behavioral Therapy vs Mindfulness Meditation in Brain Changes During Reappraisal and Acceptance Among Patients With Social Anxiety Disorder A Randomized Clinical Trial*. *95817*. https://doi.org/10.1001/jamapsychiatry.2021.1862

Goldin, P., Ziv, M., Jazaieri, H., & Gross, J. J. (2012). Randomized Controlled Trial of Mindfulness-Based Stress Reduction Versus Aerobic Exercise: Effects on the Self-Referential Brain Network in Social Anxiety Disorder. *Frontiers in Human Neuroscience*, *6*(November), 1–16. https://doi.org/10.3389/fnhum.2012.00295

Goldsmith, R. E., Gerhart, J. I., Chesney, S. A., Burns, J. W., Kleinman, B., & Hood, M. M. (2014). Mindfulness-Based Stress Reduction for Posttraumatic Stress Symptoms: Building Acceptance and Decreasing Shame. *Journal of Evidence-Based Complementary and Alternative Medicine*, *19*(4), 227–234. https://doi.org/10.1177/2156587214533703

Goldstein, M. R., Turner, A. D., Dawson, S. C., Segal, Z. V., Shapiro, S. L., Wyatt, J. K., … Ong, J. C. (2019). Increased high-frequency NREM EEG power associated with mindfulness-based interventions for chronic insomnia: Preliminary findings from spectral analysis. *Journal of Psychosomatic Research*, *120*(October 2018), 12–19. https://doi.org/10.1016/j.jpsychores.2019.02.012

Gotink, R. A., Meijboom, R., Vernooij, M. W., Smits, M., & Hunink, M. G. M. (2016). 8-week Mindfulness Based Stress Reduction induces brain changes similar to traditional long-term meditation practice – A systematic review. *Brain and Cognition*, *108*, 32–41. https://doi.org/10.1016/j.bandc.2016.07.001

Gruber, T., & Müller, M. M. (2002). Effects of picture repetition on induced gamma band responses, evoked potentials, and phase synchrony in the human EEG. *Cognitive Brain Research*, *13*(3), 377–392. https://doi.org/10.1016/S0926-6410(01)00130-6

Gu, J., Strauss, C., Bond, R., & Cavanagh, K. (2015). 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. *Clinical Psychology Review*, *37*, 1–12. https://doi.org/10.1016/j.cpr.2015.01.006

Joo, H.M., Lee, S.J., Chung, Y.G., & Shin, I.Y. (2010). Effects of mindfulness based stress reduction program on depression, anxiety and stress in patients with aneurysmal subarachnoid hemorrhage. *Journal of Korean Neurosurgical Society*, *47*(5), 345–351. https://doi.org/10.3340/jkns.2010.47.5.345 LK -

Haase, L., May, A. C., Falahpour, M., Isakovic, S., Simmons, A. N., Hickman, S. D., … Paulus, M. P. (2015). A pilot study investigating changes in neural processing after mindfulness training in elite athletes. *Frontiers in Behavioral Neuroscience*, *9*(AUGUST), 1–12. https://doi.org/10.3389/fnbeh.2015.00229

Han, Gloria, Tomarken, Andrew, Gotham, K. (2019). Social and non-social reward moderate the relation between autism symptoms and loneliness in adults with ASD, depression, and controls. *Autism Research*, *12*(6), 884–896. https://doi.org/10.1002/aur.2088.Social

Hatchard, T., Mioduszewski, O., Zambrana, A., O'Farrell, E., Caluyong, M., Poulin, P. A., & Smith, A. M. (2017). Neural changes associated with mindfulness-based stress reduction (MBSR): Current knowledge, limitations, and future directions. *Psychology and Neuroscience*, *10*(1), 41–56. https://doi.org/10.1037/pne0000073

Hedley, D., Uljarević, M., Foley, K. R., Richdale, A., & Trollor, J. (2018). Risk and protective factors underlying depression and suicidal ideation in Autism Spectrum Disorder. *Depression and Anxiety*, *35*(7), 648–657. https://doi.org/10.1002/da.22759

Hedley, D., Uljarević, M., Wilmot, M., Richdale, A., & Dissanayake, C. (2017a). Brief Report: Social Support, Depression and Suicidal Ideation in Adults with Autism Spectrum Disorder. *Journal of Autism and Developmental Disorders*, *47*(11), 3669–3677. https://doi.org/10.1007/s10803-017-3274-2

Hedley, D., Uljarević, M., Wilmot, M., Richdale, A., & Dissanayake, C. (2017b). Brief Report: Social Support, Depression and Suicidal Ideation in Adults with Autism Spectrum Disorder. *Journal of Autism and Developmental Disorders*, *47*(11), 3669–3677. https://doi.org/10.1007/s10803-017-3274-2

Heilbronner, S. R., & Hayden, B. Y. (2016). Dorsal Anterior Cingulate Cortex: A Bottom-Up View. *Annual Review of Neuroscience*, *39*(1), 149–170. https://doi.org/10.1146/annurev-neuro-070815-013952

Hilton, C., Graver, K., & LaVesser, P. (2007). Relationship between social competence and sensory processing in children with high functioning autism spectrum disorders. *Research in Autism Spectrum Disorders*, *1*(2), 164–173. https://doi.org/10.1016/j.rasd.2006.10.002

Hirvikoski, T., Mittendorfer-rutz, E., Boman, M., Larsson, H., Lichtenstein, P., & Bo, S. (2016). *Premature mortality in autism spectrum disorder*. 232–238. https://doi.org/10.1192/bjp.bp.114.160192

Hlinka, J., Alexakis, C., Diukova, A., Liddle, P. F., & Auer, D. P. (2010). Slow EEG pattern predicts reduced intrinsic functional connectivity in the default mode network: An inter-subject analysis. *NeuroImage*, *53*(1), 239–246. https://doi.org/10.1016/j.neuroimage.2010.06.002

Hofmann, S. G., Sawyer, A. T., Witt, A. a, & Oh, D. (2010). Mindfulness for depression and anxiety. A metaanalisys. *Journal Consulting Clinical Psychology*, *78*(2), 169–183. https://doi.org/10.1037/a0018555.The

Hollocks, M. J., Jones, C. R. G., Pickles, A., Baird, G., Happé, F., Charman, T., & Simonoff, E. (2014). The Association Between Social Cognition and Executive Functioning and Symptoms of Anxiety and Depression in Adolescents With Autism Spectrum Disorders. *Autism Research*, *7*(2), 216–228. https://doi.org/10.1002/aur.1361

Hölzel, B. K., Hoge, E. A., Greve, D. N., Gard, T., Creswell, J. D., Brown, K. W., … Lazar, S. W. (2013). Neural mechanisms of symptom improvements in generalized anxiety disorder following mindfulness training. *NeuroImage: Clinical*, *2*(1), 448–458. https://doi.org/10.1016/j.nicl.2013.03.011

Howlin, P. (2000). Outcome in adult life for more able individuals with autism or Asperger syndrome. *Autism*, *4*(1), 63–83. https://doi.org/10.1177/1362361300004001005

Hudson, C. C., Hall, L., & Harkness, K. L. (2019). Prevalence of Depressive Disorders in Individuals with Autism Spectrum Disorder: a Meta-Analysis. *Journal of Abnormal Child Psychology*, *47*(1), 165–175. https://doi.org/10.1007/s10802-018-0402-1

Hughes, J. W., Fresco, D. M., Myerscough, R., Van Dulmen, M. H. M., Carlson, L. E., & Josephson, R. (2013). Randomized controlled trial of mindfulness-based stress reduction for prehypertension. *Psychosomatic Medicine*, *75*(8), 721–728. https://doi.org/10.1097/PSY.0b013e3182a3e4e5

Hyde, L. W., Gorka, A., Manuck, S. B., & Hariri, A. R. (2011). Perceived social support moderates the link between threat-related amygdala reactivity and trait anxiety. *Neuropsychologia*, *49*(4), 651–656. https://doi.org/10.1016/j.neuropsychologia.2010.08.025

Imperatori, C., Farina, B., Adenzato, M., Valenti, E. M., Murgia, C., Marca, G. Della, … Ardito, R. B. (2019). Default mode network alterations in individuals with high-trait-anxiety: An EEG functional connectivity study. *Journal of Affective Disorders*, *246*(November 2018), 611–618. https://doi.org/10.1016/j.jad.2018.12.071

Jain, S., Shapiro, S. L., Swanick, S., Roesch, S. C., Mills, P. J., Bell, I., & Schwartz, G. E. R. (2007). A randomized controlled trial of mindfulness meditation versus relaxation training: Effects on distress, positive states of mind, rumination, and distraction. *Annals of Behavioral Medicine*. https://doi.org/10.1207/s15324796abm3301_2

Jerbi, K., Vidal, J. R., Ossandon, T., Dalal, S. S., Jung, J., Hoffmann, D., … Lachaux, J. P. (2010). Exploring the electrophysiological correlates of the default-mode network with intracerebral EEG. *Frontiers in Systems Neuroscience*, *4*(June), 1–9. https://doi.org/10.3389/fnsys.2010.00027

Jha, A. P., Stanley, E. A., Kiyonaga, A., Wong, L., & Gelfand, L. (2010). Examining the Protective Effects of Mindfulness Training on Working Memory Capacity and Affective Experience. *Emotion*, *10*(1), 54–64. https://doi.org/10.1037/a0018438

Jin, M. J., Kim, J. S., Kim, S., Hyun, M. H., & Lee, S. H. (2018). An integrated model of emotional problems, beta power of electroencephalography, and low frequency of heart rate variability after childhood trauma in a non-clinical sample: A path analysis study. *Frontiers in Psychiatry*, *8*(JAN). https://doi.org/10.3389/fpsyt.2017.00314

Johnson, S. C., Baxter, L. C., Wilder, L. S., Pipe, J. G., Heiserman, J. E., & Prigatano, G. P. (2002). Neural correlates of self-reflection. *Brain*, *125*(8), 1808–1814. https://doi.org/10.1093/brain/awf181

Jokiranta-Olkoniemi, E., Gyllenberg, D., Sucksdorff, D., Suominen, A., Kronström, K., Chudal, R., & Sourander, A. (2021). Risk for Premature Mortality and Intentional Self-harm in Autism Spectrum Disorders. *Journal of Autism and Developmental Disorders*, *51*(9), 3098–3108. https://doi.org/10.1007/s10803-020-04768-x

Kabat-Zinn, J. (2003). Mindfulness-based interventions in context: Past, present, and future. *Clinical Psychology: Science and Practice*, *10*(2), 144–156. https://doi.org/10.1093/clipsy/bpg016

Kaufman, K. No Title. *1990*.

Kaunhoven, R. J., & Dorjee, D. (2021). Mindfulness Versus Cognitive Reappraisal: the Impact of Mindfulness-Based Stress Reduction (MBSR) on the Early and Late Brain Potential Markers of Emotion Regulation. *Mindfulness*, *12*(9), 2266–2280. https://doi.org/10.1007/s12671-021-01692-8

Kazemi, R., Rostami, R., Khomami, S., Baghdadi, G., Rezaei, M., Hata, M., … Fitzgerald, P. B. (2018). Bilateral transcranial magnetic stimulation on DLPFC changes resting state networks and cognitive function in patients with bipolar depression. *Frontiers in Human Neuroscience*, *12*(September), 1–10. https://doi.org/10.3389/fnhum.2018.00356

Khaleghi, A., Zarafshan, H., Vand, S. R., & Mohammadi, M. R. (2020). Effects of Non-invasive Neurostimulation on Autism Spectrum Disorder: A Systematic Review. *Clinical Psychopharmacology and Neuroscience*, *18*(4), 527–552. https://doi.org/10.9758/CPN.2020.18.4.527

Khoury, B., Sharma, M., Rush, S. E., & Fournier, C. (2015). Mindfulness-based stress reduction for healthy individuals: A meta-analysis. *Journal of Psychosomatic Research*, *78*(6), 519–528. https://doi.org/10.1016/j.jpsychores.2015.03.009

Kiep, M., Spek, A. A., & Hoeben, L. (2015). Mindfulness-Based Therapy in Adults with an Autism Spectrum Disorder: Do Treatment Effects Last? *Mindfulness*, *6*(3), 637–644. https://doi.org/10.1007/s12671-014-0299-x

Kilpatrick, L. A., Suyenobu, B. Y., Smith, S. R., Bueller, J. A., Goodman, T., Creswell, J. D., … Naliboff, B. D. (2011). Impact of mindfulness-based stress reduction training on intrinsic brain connectivity. *NeuroImage*, *56*(1), 290–298. https://doi.org/10.1016/j.neuroimage.2011.02.034

Kim, Y. G., Kim, S. E., Lee, J., Hwang, S., Yoo, S., & Lee, H. W. (2022). *Neuromodulation Using Transcranial Focused Ultrasound on the Bilateral Medial*

Prefrontal Cortex.

Kok, B. E., & Singer, T. (2017). Phenomenological Fingerprints of Four Meditations: Differential State Changes in Affect, Mind-Wandering, Meta-Cognition, and Interoception Before and After Daily Practice Across 9 Months of Training. *Mindfulness*, *8*(1), 218–231. https://doi.org/10.1007/s12671-016-0594-9

Kral, T. R. A., Imhoff-Smith, T., Dean, D. C., Grupe, D., Adluru, N., Patsenko, E., … Davidson, R. J. (2019). Mindfulness-Based Stress Reduction-related changes in posterior cingulate resting brain connectivity. *Social Cognitive and Affective Neuroscience*, *14*(7), 777–787. https://doi.org/10.1093/scan/nsz050

Kropotov, J. D. (2009). Chapter 3 - Beta Rhythms. In J. D. Kropotov (Ed.), *Quantitative EEG, Event-Related Potentials and Neurotherapy* (pp. 59–76). https://doi.org/https://doi.org/10.1016/B978-0-12-374512-5.00003-7

Lao, S. A., Kissane, D., & Meadows, G. (2016). Cognitive effects of MBSR/MBCT: A systematic review of neuropsychological outcomes. *Consciousness and Cognition*, Vol. 45. https://doi.org/10.1016/j.concog.2016.08.017

Laufs, H., Holt, J. L., Elfont, R., Krams, M., Paul, J. S., Krakow, K., & Kleinschmidt, A. (2006). Where the BOLD signal goes when alpha EEG leaves. *NeuroImage*, *31*(4), 1408–1418. https://doi.org/10.1016/j.neuroimage.2006.02.002

Lee, J., Pavuluri, M. N., Kim, J. H., Suh, S., Kim, I., & Lee, M. S. (2019). Resting-state functional connectivity in medication-naïve adolescents with major depressive disorder. *Psychiatry Research - Neuroimaging*, *288*(April), 37–43. https://doi.org/10.1016/j.pscychresns.2019.04.008

Lemogne, C., Delaveau, P., Freton, M., Guionnet, S., & Fossati, P. (2012). Medial prefrontal cortex and the self in major depression. *Journal of Affective Disorders*, *136*(1–2), e1–e11. https://doi.org/10.1016/j.jad.2010.11.034

Lemogne, C., le Bastard, G., Mayberg, H., Volle, E., Bergouignan, L., Lehé;ricy, S., … Fossati, P. (2009). In search of the depressive self: Extended medial prefrontal network during self-referential processing in major depression. *Social Cognitive and Affective Neuroscience*, *4*(3), 305–312. https://doi.org/10.1093/scan/nsp008

Lerner, D., & Henke, R. M. (2008). What does research tell us about depression, job performance, and work productivity? *Journal of Occupational and Environmental Medicine*, *50*(4), 401–410. https://doi.org/10.1097/JOM.0b013e31816bae50

Lin, Y., Callahan, C. P., & Moser, J. S. (2018a). A mind full of self: Self-referential processing as a mechanism underlying the therapeutic effects of mindfulness training on internalizing disorders. *Neuroscience and Biobehavioral Reviews*, *92*(May), 172–186. https://doi.org/10.1016/j.neubiorev.2018.06.007

Lin, Y., Callahan, C. P., & Moser, J. S. (2018b). A mind full of self: Self-referential processing as a mechanism underlying the therapeutic effects of mindfulness training on internalizing disorders. *Neuroscience and Biobehavioral Reviews*, *92*(June), 172–186. https://doi.org/10.1016/j.neubiorev.2018.06.007

Liu, X., Chen, W., Hou, H., Chen, X., Zhang, J., Liu, J., … Bai, G. (2017). Decreased functional connectivity between the dorsal anterior cingulate cortex and lingual gyrus in Alzheimer's disease patients with depression. *Behavioural Brain Research*, *326*, 132–138. https://doi.org/10.1016/j.bbr.2017.01.037

Lombardo, M. V., Barnes, J. L., Wheelwright, S. J., & Baron-Cohen, S. (2007a). Self-referential cognition and empathy in austism. *PLoS ONE*, *2*(9). https://doi.org/10.1371/journal.pone.0000883

Lombardo, M. V., Chakrabarti, B., Bullmore, E. T., Sadek, S. A., Pasco, G., Wheelwright, S. J., … Baron-Cohen, S. (2010). Atypical neural self-representation in autism. *Brain*, *133*(2), 611–624. https://doi.org/10.1093/brain/awp306

Lombardo, M. V., Pierce, K., Eyler, L. T., CarterBarnes, C., Ahrens-Barbeau, C., Solso, S., … Courchesne, E. (2015). Different functional neural substrates for good and poor language outcome in autism. *Neuron*, *86*(2), 567–577. https://doi.org/10.1016/j.neuron.2015.03.023

Lombardo, M. V, Barnes, J. L., Wheelwright, S. J., & Baron-Cohen, S. (2007b). Self-referential cognition and empathy in austism. *PLoS ONE*, *2*(9). https://doi.org/10.1371/journal.pone.0000883

Lord, C., Rutter, M., DiLavore, P., Risi, S., Gotham, K., & Bishop, S. (2012). Autism diagnostic observation schedule–2nd edition (ADOS-2). *Western Psychological Corporation*.

Luberto, C. M., Shinday, N., Song, R., Philpotts, L. L., Park, E. R., Fricchione, G. L., & Yeh, G. Y. (2018). A Systematic Review and Meta-analysis of the Effects of Meditation on Empathy, Compassion, and Prosocial Behaviors. *Mindfulness*, Vol. 9. https://doi.org/10.1007/s12671-017-0841-8

Lutz, J., Brühl, A. B., Scheerer, H., Jäncke, L., & Herwig, U. (2016). Neural correlates of mindful self-awareness in mindfulness meditators and meditation-naïve subjects revisited. *Biological Psychology*, *119*, 21–30. https://doi.org/10.1016/j.biopsycho.2016.06.010

Lykins, E. L. B., Baer, R. A., & Gottlob, L. R. (2012). Performance-based tests of attention and memory in long-term mindfulness meditators and demographically matched nonmeditators. *Cognitive Therapy and Research*, *36*(1), 103–114. https://doi.org/10.1007/s10608-010-9318-y

Maddox, B. B., & Gaus, V. L. (2018). Community Mental Health Services for Autistic Adults: Good News and Bad News. *Autism in Adulthood*, *1*(1), 15–19. https://doi.org/10.1089/aut.2018.0006

Maddox, B. B., Kang-Yi, C. D., Brodkin, E. S., & Mandell, D. S. (2018). Treatment utilization by adults with autism and co-occurring anxiety or depression. *Research in Autism Spectrum Disorders*, *51*(March), 32–37. https://doi.org/10.1016/j.rasd.2018.03.009

Marchand, W. R. (2012). Mindfulness-based stress reduction, mindfulness-based cognitive therapy, and zen meditation for depression, anxiety, pain, and psychological distress. *Journal of Psychiatric Practice*, *18*(4), 233–252. https://doi.org/10.1097/01.pra.0000416014.53215.86

Marchand, W. R. (2014). Neural mechanisms of mindfulness and meditation: Evidence from neuroimaging studies. *World Journal of Radiology*, *6*(7), 471. https://doi.org/10.4329/wjr.v6.i7.471

Mazefsky, C. A., Herrington, J., Siegel, M., Scarpa, A., Maddox, B. B., Scahill, L., & White, S. W. (2013). The role of emotion regulation in autism spectrum disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, *52*(7), 679–688. https://doi.org/10.1016/j.jaac.2013.05.006

McLaren, D. G., Ries, M. L., Xu, G., & Johnson, S. C. (2012). A Generalized Form of Context-Dependent Psychophysiological Interactions (gPPI): A Comparison to Standard Approaches. *Neuroimage*, *61*(4), 1277–1286. https://doi.org/10.1016/j.neuroimage.2012.03.068.A

Menezes, M., Harkins, C., Robinson, M. F., & Mazurek, M. O. (2020). Treatment of Depression in Individuals with Autism Spectrum Disorder: A Systematic Review. *Research in Autism Spectrum Disorders*, *78*(August), 101639. https://doi.org/10.1016/j.rasd.2020.101639

Menon, V. (2011). Large-scale brain networks and psychopathology: A unifying triple network model. *Trends in Cognitive Sciences*, *15*(10), 483–506. https://doi.org/10.1016/j.tics.2011.08.003

Menon, V., & Uddin, L. Q. (2010). Saliency, switching, attention and control: a network model of insula function. *Brain Structure & Function*, *214*(5–6), 655–667. https://doi.org/10.1007/s00429-010-0262-0

Modinos, G., Ormel, J., & Aleman, A. (2009). Activation of anterior insula during self-reflection. *PLoS ONE*, *4*(2), 1–8. https://doi.org/10.1371/journal.pone.0004618

Mori, M., & Tanno, Y. (2015). Mediating Role of Decentering in the Associations between Self-Reflection, Self-Rumination, and Depressive Symptoms. *Psychology*,

06(05), 613–621. https://doi.org/10.4236/psych.2015.65059

Moss, P., Mandy, W., & Howlin, P. (2017). Child and adult factors related to quality of life in adults with autism. *Journal of Autism and Developmental Disorders*, *47*(6), 1830–1837. https://doi.org/10.1007/s10803-017-3105-5

Müller, F., Lenz, C., Dolder, P., Lang, U., Schmidt, A., Liechti, M., & Borgwardt, S. (2017). Increased thalamic resting-state connectivity as a core driver of LSD-induced hallucinations. *Acta Psychiatrica Scandinavica*, *136*(6), 648–657. https://doi.org/10.1111/acps.12818

Nakata, H., Sakamoto, K., & Kakigi, R. (2014). Meditation reduces pain-related neural activity in the anterior cingulate cortex, insula, secondary somatosensory cortex, and thalamus. *Frontiers in Psychology*, *5*(DEC), 1–12. https://doi.org/10.3389/fpsyg.2014.01489

Nejad, A. B., Fossati, P., & Lemogne, C. (2013). Self-Referential Processing, Rumination, and Cortical Midline Structures in Major Depression. *Frontiers in Human Neuroscience*, *7*(October), 1–9. https://doi.org/10.3389/fnhum.2013.00666

Neuner, I., Arrubla, J., Werner, C. J., Hitz, K., Boers, F., Kawohl, W., & Shah, N. J. (2014). The default mode network and EEG regional spectral power: A simultaneous fMRI-EEG study. *PLoS ONE*, *9*(2). https://doi.org/10.1371/journal.pone.0088214

Neuromorphometrics, I. (n.d.). *No Title*.

Ng, H. Y. H., Wu, C. W., Huang, F. Y., Cheng, Y. T., Guu, S. F., Huang, C. M., … Chuang, C. H. (2021). Mindfulness Training Associated With Resting-State Electroencephalograms Dynamics in Novice Practitioners via Mindful Breathing and Body-Scan. *Frontiers in Psychology*, *12*(521), 1–38. https://doi.org/10.3389/fpsyg.2021.748584

Northoff, G., & Bermpohl, F. (2004). Cortical midline structures and the self. *Trends in Cognitive Sciences*, *8*(3), 102–107. https://doi.org/10.1016/j.tics.2004.01.004

Northoff, G., Heinzel, A., de Greck, M., Bermpohl, F., Dobrowolny, H., & Panksepp, J. (2006a). Self-referential processing in our brain-A meta-analysis of imaging studies on the self. *NeuroImage*, *31*(1), 440–457. https://doi.org/10.1016/j.neuroimage.2005.12.002

Northoff, G., Heinzel, A., de Greck, M., Bermpohl, F., Dobrowolny, H., & Panksepp, J. (2006b). Self-referential processing in our brain-A meta-analysis of imaging studies on the self. *NeuroImage*, *31*(1), 440–457. https://doi.org/10.1016/j.neuroimage.2005.12.002

O'Neill, J., Piacentini, J., Chang, S., Ly, R., Lai, T. M., Armstrong, C. C., … Nurmi, E. L. (2017). Glutamate in pediatric obsessive-compulsive disorder and response to cognitive-behavioral therapy: Randomized clinical trial. *Neuropsychopharmacology*, *42*(12), 2414–2422. https://doi.org/10.1038/npp.2017.77

Oakley, B. F. M., Tillmann, J., Ahmad, J., Crawley, D., San José Cáceres, A., Holt, R., … Loth, E. (2021). How do core autism traits and associated symptoms relate to quality of life? Findings from the Longitudinal European Autism Project. *Autism*, *25*(2), 389–404. https://doi.org/10.1177/1362361320959959

Opialla, S., Lutz, J., Scherpiet, S., Hittmeyer, A., Jäncke, L., Rufer, M., … Brühl, A. B. (2014). Neural circuits of emotion regulation: a comparison of mindfulness-based and cognitive reappraisal strategies. *European Archives of Psychiatry and Clinical Neuroscience*, *265*(1), 45–55. https://doi.org/10.1007/s00406-014-0510-z

Ossandón, T., Jerbi, K., Vidal, J. R., Bayle, D. J., Henaff, M. A., Jung, J., … Lachaux, J. P. (2011). Transient suppression of broadband gamma power in the default-mode network is correlated with task complexity and subject performance. *Journal of Neuroscience*, *31*(41), 14521–14530. https://doi.org/10.1523/JNEUROSCI.2483-11.2011

Padmanabhan, A., Lynch, C. J., Schaer, M., & Menon, V. (2017). The Default Mode Network in Autism. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, *2*(6), 476–486. https://doi.org/10.1016/j.bpsc.2017.04.004

Pagni, B. A., & Braden, B. B. (2021). Early Reflections on the Therapeutic Effects of Mindfulness-Based Therapies in Adults with Autism and Suggestions for Future Research. *Journal of Psychiatry and Brain Science*. https://doi.org/10.20900/jpbs20210013

Pagni, B. A., Walsh, M. J. M., Foldes, E., Sebren, A., Dixon, M. V., Guerithault, N., & Braden, B. B. (2020). The neural correlates of mindfulness-induced depression reduction in adults with autism spectrum disorder: A pilot study. *Journal of Neuroscience Research*, *98*(6), 1150–1161. https://doi.org/10.1002/jnr.24600

Parkinson, T. D., Kornelsen, J., & Smith, S. D. (2019). Trait Mindfulness and Functional Connectivity in Cognitive and Attentional Resting State Networks. *Frontiers in Human Neuroscience*, *13*(April), 1–16. https://doi.org/10.3389/fnhum.2019.00112

Paulus, M. P., & Stein, M. B. (2010). Interoception in anxiety and depression. *Brain Structure & Function*, *214*(5–6), 451–463. https://doi.org/10.1007/s00429-010-0258-9

Pavlenko, V. B., Chernyi, S. V., & Goubkina, D. G. (2009). Eeg correlates of anxiety and emotional stability in adult healthy subjects. *Neurophysiology*, *41*(5), 337–345. https://doi.org/10.1007/s11062-010-9111-2

Pickut, B. A., Van Hecke, W., Kerckhofs, E., Mariën, P., Vanneste, S., Cras, P., & Parizel, P. M. (2013). Mindfulness based intervention in Parkinson's disease leads to structural brain changes on MRI: A randomized controlled longitudinal trial. *Clinical Neurology and Neurosurgery*, *115*(12), 2419–2425. https://doi.org/https://doi.org/10.1016/j.clineuro.2013.10.002

Plechawska-Wojcik, M., Kaczorowska, M., & Zapala, D. (2019). The Artifact Subspace Reconstruction (ASR) for EEG Signal Correction. A Comparative Study. In J. Świ\katek, L. Borzemski, & Z. Wilimowska (Eds.), *Information Systems Architecture and Technology: Proceedings of 39th International Conference on Information Systems Architecture and Technology -- ISAT 2018* (pp. 125–135). Cham: Springer International Publishing.

Pollatos, O., Gramann, K., & Schandry, R. (2007). Neural systems connecting interoceptive awareness and feelings. *Human Brain Mapping*, *28*(1), 9–18. https://doi.org/10.1002/hbm.20258

Powell, P. S., Klinger, L. G., & Klinger, M. R. (2017). Patterns of Age-Related Cognitive Differences in Adults with Autism Spectrum Disorder. *Journal of Autism and Developmental Disorders*, *47*(10), 3204–3219. https://doi.org/10.1007/s10803-017-3238-6

Preller, K. H., Burt, J. B., Ji, J. L., Schleifer, C. H., Adkinson, B. D., Stämpfli, P., … Anticevic, A. (2018). Changes in global and thalamic brain connectivity in LSD-induced altered states of consciousness are attributable to the 5-HT2A receptor. *ELife*, *7*, 1–31. https://doi.org/10.7554/eLife.35082

Quach, D., Jastrowski Mano, K. E., & Alexander, K. (2016). A Randomized Controlled Trial Examining the Effect of Mindfulness Meditation on Working Memory Capacity in Adolescents. *Journal of Adolescent Health*, *58*(5), 489–496. https://doi.org/https://doi.org/10.1016/j.jadohealth.2015.09.024

Rahrig, H., Vago, D. R., Passarelli, M. A., Auten, A., Lynn, N. A., & Brown, K. W. (2022). Meta - analytic evidence that mindfulness training alters resting state default mode network connectivity. *Scientific Reports*, (0123456789), 1–13. https://doi.org/10.1038/s41598-022-15195-6

Reed, P. (2019). Mechanisms of Mindfulness in Those with Higher and Lower Levels of Autism Traits. *Mindfulness*, *10*(2), 234–244. https://doi.org/10.1007/s12671-018-0964-6

Hofmann, S.G., & Gomez, A.F. (2017). Mindfulness-Based Interventions for Anxiety and Depression. *Psychiatric Clinics of North America*, *40*(4), 739–749. https://doi.org/10.1016/j.psc.2017.08.008

Saggar, M., King, B. G., Zanesco, A. P., MacLean, K. A., Aichele, S. R., Jacobs, T. L.,

… Saron, C. D. (2012). Intensive training induces longitudinal changes in meditation state-related EEG oscillatory activity. *Frontiers in Human Neuroscience*, *6*(SEPTEMBER), 1–14. https://doi.org/10.3389/fnhum.2012.00256

Sanguinetti, J. L., Hameroff, S., Smith, E. E., Sato, T., Daft, C. M. W., Tyler, W. J., & Allen, J. J. B. (2020). Transcranial Focused Ultrasound to the Right Prefrontal Cortex Improves Mood and Alters Functional Connectivity in Humans. *Frontiers in Human Neuroscience*, *14*(February), 1–13. https://doi.org/10.3389/fnhum.2020.00052

Sanguinetti, J. L., Smith, E. E., Allen, J. J. B., & Hameroff, S. R. (2014). *Human brain stimulation with transcranial ultrasound: Potential applications for mental health*.

Seeley, W. W. (2019). The salience network: A neural system for perceiving and responding to homeostatic demands. *Journal of Neuroscience*, *39*(50), 9878–9882. https://doi.org/10.1523/JNEUROSCI.1138-17.2019

Sehlmeyer, C., Dannlowski, U., Schöning, S., Kugel, H., Pyka, M., Pfleiderer, B., … Konrad, C. (2011). Neural correlates of trait anxiety in fear extinction. *Psychological Medicine*, *41*(4), 789–798. https://doi.org/DOI: 10.1017/S0033291710001248

Sevinc, G., Hölzel, B. K., Hashmi, J., Greenberg, J., McCallister, A., Treadway, M., … Lazar, S. W. (2018). Common and dissociable neural activity after mindfulness-based stress reduction and relaxation response programs. *Psychosomatic Medicine*, *80*(5), 439–451. https://doi.org/10.1097/PSY.0000000000000590

Sevinc, G., Rusche, J., Wong, B., Datta, T., Kaufman, R., Gutz, S. E., … Lazar, S. W. (2021). Mindfulness Training Improves Cognition and Strengthens Intrinsic Connectivity Between the Hippocampus and Posteromedial Cortex in Healthy Older Adults. *Frontiers in Aging Neuroscience*, *13*(August), 1–13. https://doi.org/10.3389/fnagi.2021.702796

Shapiro, S. L. (2007). How Is Mindfulness Helpful? *The Art of Science and Mindfulness*, 93–104. https://doi.org/http://dx.doi.org/10.1037/11885-007

Shattuck, P. T., Narendorf, S. C., Cooper, B., Sterzing, P. R., Wagner, M., & Taylor, J. L. (2012). Postsecondary education and employment among youth with an autism spectrum disorder. *Pediatrics*, *129*(6), 1042–1049. https://doi.org/10.1542/peds.2011-2864

Sheynin, J., Duval, E. R., King, A. P., Angstadt, M., Phan, K. L., Simon, N. M., … Liberzon, I. (2020). Associations between resting-state functional connectivity and treatment response in a randomized clinical trial for posttraumatic stress disorder. *Depression and Anxiety*, *37*(10), 1037–1046. https://doi.org/10.1002/da.23075

Siegle, G. J., Thompson, W., Carter, C. S., Steinhauer, S. R., & Thase, M. E. (2007). Increased amygdala and decreased dorsolateral prefrontal BOLD responses in unipolar depression: related and independent features. *Biological Psychiatry, 61*(2), 198–209. https://doi.org/10.1016/j.biopsych.2006.05.048

Sizoo, B. B., & Kuiper, E. (2017). Cognitive behavioural therapy and mindfulness based stress reduction may be equally effective in reducing anxiety and depression in adults with autism spectrum disorders. *Research in Developmental Disabilities, 64*, 47–55. https://doi.org/10.1016/j.ridd.2017.03.004

Song, Y., & Lindquist, R. (2015). Effects of mindfulness-based stress reduction on depression, anxiety, stress and mindfulness in Korean nursing students. *Nurse Education Today, 35*(1), 86–90. https://doi.org/10.1016/j.nedt.2014.06.010

Spek, A. A., Ham, N. C. Van, & Nyklíček, I. (2013). Research in Developmental Disabilities Mindfulness-based therapy in adults with an autism spectrum disorder : A randomized controlled trial. *Research in Developmental Disabilities*, *34*(1), 246–253. https://doi.org/10.1016/j.ridd.2012.08.009

Sterling, L., Dawson, G., Estes, A., & Greenson, J. (2008). Characteristics associated with presence of depressive symptoms in adults with autism spectrum disorder. *Journal of Autism and Developmental Disorders*, *38*(6), 1011–1018. https://doi.org/10.1007/s10803-007-0477-y

Szatmari, P., Bryson, S. E., Streiner, D. L., Kim, J. A., & Wilson, F. J. (2003). The Prevalence of Anxiety and Mood Problems among Children with Autism and Asperger Syndrome. *Autism*, *4*(2), 117–132. https://doi.org/10.1177/1362361300004002002

Takamiya, A., Hirano, J., Yamagata, B., Takei, S., Kishimoto, T., & Mimura, M. (2019). Electroconvulsive therapy modulates resting-state EEG oscillatory pattern and phase synchronization in nodes of the default mode network in patients with depressive disorder. *Frontiers in Human Neuroscience*, *13*(February), 1–9. https://doi.org/10.3389/fnhum.2019.00001

Tang, Y. Y., Hölzel, B. K., & Posner, M. I. (2015). The neuroscience of mindfulness meditation. *Nature Reviews Neuroscience*, *16*(4), 213–225. https://doi.org/10.1038/nrn3916

Toichi, M., Kamio, Y., Okada, T., Sakihama, M., Youngstrom, E. A., Findling, R. L., & Yamamoto, K. (2002). A lack of self-consciousness in autism. *American Journal of Psychiatry, 159*(8), 1422–1424. https://doi.org/10.1176/appi.ajp.159.8.1422

Turner, J. A., Anderson, M. L., Balderson, B. H., Cook, A. J., Sherman, K. J., & Cherkin. (2016). Mindfulness-based stress reduction and cog itive-behavioral therapy for CLBP: simiTurner, J. A.,lar effects on mindfulness.... *Pain*, *157*(11), 2434–2444.

https://doi.org/10.1097/j.pain.0000000000000635.Mindfulness-based

Uddin, L. Q., & Menon, V. (2009a). The anterior insula in autism: Under-connected and under-examined. *Neuroscience and Biobehavioral Reviews*, *33*(8), 1198–1203. https://doi.org/10.1016/j.neubiorev.2009.06.002

Uddin, L. Q., & Menon, V. (2009b). The anterior insula in autism: Under-connected and under-examined. *Neuroscience and Biobehavioral Reviews*, *33*(8), 1198–1203. https://doi.org/10.1016/j.neubiorev.2009.06.002

van der Velden, A. M., Scholl, J., Elmholdt, E.-M., Fjorback, L. O., Hamer, C. J., Lazar, S. W., … Kuyken, W. (2022). Mindfulness training changes brain dynamics during depressive rumination: A randomized controlled trial. *Biological Psychiatry*. https://doi.org/https://doi.org/10.1016/j.biopsych.2022.06.038

van Steensel, F. J. A., Bögels, S. M., & Perrin, S. (2011a). Anxiety Disorders in Children and Adolescents with Autistic Spectrum Disorders: A Meta-Analysis. *Clinical Child and Family Psychology Review*, *14*(3), 302–317. https://doi.org/10.1007/s10567-011-0097-0

van Steensel, F. J. A., Bögels, S. M., & Perrin, S. (2011b). Anxiety Disorders in Children and Adolescents with Autistic Spectrum Disorders: A Meta-Analysis. *Clinical Child and Family Psychology Review*, *14*(3), 302–317. https://doi.org/10.1007/s10567-011-0097-0

Wallace, G. L., Kenworthy, L., Pugliese, C. E., Popal, H. S., White, E. I., Brodsky, E., & Martin, A. (2016). Real-World Executive Functions in Adults with Autism Spectrum Disorder: Profiles of Impairment and Associations with Adaptive Functioning and Co-morbid Anxiety and Depression. *Journal of Autism and Developmental Disorders*, *46*(3), 1071–1083. https://doi.org/10.1007/s10803-015-2655-7

Way, B. M., Creswell, J. D., Eisenberger, N. I., & Lieberman, M. D. (2010). Dispositional Mindfulness and Depressive Symptomatology: Correlations With Limbic and Self-Referential Neural Activity During Rest. *Emotion*, *10*(1), 12–24. https://doi.org/10.1037/a0018312

Weber-goericke, F., & Muehlhan, M. (2019). Review article A quantitative meta-analysis of fMRI studies investigating emotional processing in excessive worriers : Application of activation likelihood estimation analysis ☆. *Journal of Affective Disorders*, *243*(July 2018), 348–359. https://doi.org/10.1016/j.jad.2018.09.049

Wells, R. E., Yeh, G. Y., Kerr, C. E., Wolkin, J., Davis, R. B., Tan, Y., … Kong, J. (2013). Meditation's impact on default mode network and hippocampus in mild cognitive impairment: Pilot study. *Neuroscience Letters*, *556*, 15–19. https://doi.org/10.1016/j.neulet.2013.10.001

Whyatt, C., & Craig, C. (2013). Sensory-motor problems in Autism. *Frontiers in Integrative Neuroscience*, *7*(July), 1–12. https://doi.org/10.3389/fnint.2013.00051

Williams, D. (2010). Theory of own mind in autism: Evidence of a specific deficit in self-awareness? *Autism*, *14*(5), 474–494. https://doi.org/10.1177/1362361310366314

Wilson, M. (2002). *Wilson2002_Article_SixViewsOfEmbodiedCognition*. *9*(4), 625–636.

Yu, J., Rawtaer, I., Feng, L., Fam, J., Kumar, A. P., Kee-Mun Cheah, I., … Mahendran, R. (2021). Mindfulness intervention for mild cognitive impairment led to attention-related improvements and neuroplastic changes: Results from a 9-month randomized control trial. *Journal of Psychiatric Research*, *135*(December 2020), 203–211. https://doi.org/10.1016/j.jpsychires.2021.01.032

Zeidan, F., Martucci, K. T., Kraft, R. A., Gordon, N. S., Mchaffie, J. G., & Coghill, R. C. (2011). Brain mechanisms supporting the modulation of pain by mindfulness meditation. *Journal of Neuroscience*, *31*(14), 5540–5548. https://doi.org/10.1523/JNEUROSCI.5791-10.2011

APPENDIX A

CO-AUTHOR PERMISSIONS

CHAPTER 2

CHAPTER 3

CHAPTER 4

APPENDIX B

SUPPLEMENTAL MATERIAL FOR CHAPTER 2

Supplemental Information

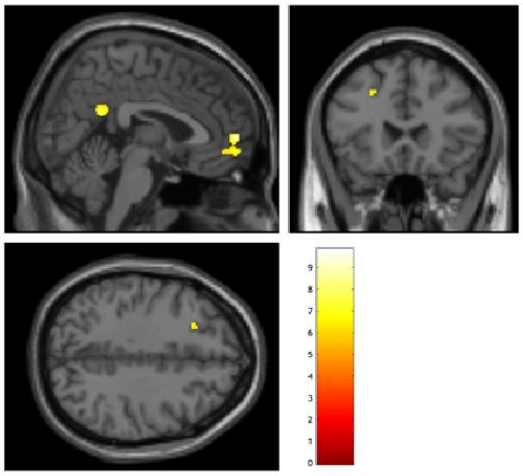
Supp. Table 1. Behavioral data during self-reflection fMRI task

	MBSR			Support/ Education			
	Pre	Post	Paired t-test	Pre	Post	Paired t-test	Baseline group difference
Percent Responded	98.15 (1.74)	98.81 (1.41)	t(13)=-1.59; p=0.136; d=0.42	98.46 (1.12)	96.92 (7.39)	t(12)=0.75; p=0.469;d=0.29	t(25)=0.54; p=0.590;d=0.21
Accuracy (%)	88.34 (3.40)	76.64 (24.89)	t(13)=1.70; p=0.114; d=0.66	82.23 (21.52)	84.25 (9.60)	t(12)=0.30; p=0.770;d=0.12	t(25)=1.05; p=0.298;d=0.40
Reaction Time (ms)	1641 (202)	1637 (238)	t(13)=0.081; p=0.937; d=0.018	1588 (305)	1598 (36)	t(12)=0.180; p=0.856;d=0.03	t(25)=0.54; p=0.592;d=0.20

Supp. Table 2. Self-reflection task activation

	Brodmann Area	Peak Voxel Coordinate	Cluster Size (K_E)	Peak Significance (FWE-corrected)	Z-Score	T-Score	Cluster-Level (FWE-corrected)
ACC, mPFC	10, 32	(3, 57, 3)	784	p<0.001*	6.24	9.84	p<0.001*
PCC, Precuneus	23, 31	(0, -50, 24)	463	p<0.001*	5.87	8.76	p<0.001*
MFG	10	(-24, 24, 39)	27	p=0.014*	4.97	6.59	p=0.007*

anterior cingulate cortex (ACC); medial prefrontal cortex (mPFC); posterior cingulate cortex (PCC); middle frontal gyrus (MFG); *p<0.05



SUPP. FIGURE S1 Neural activation during self-reflection, collapsed across groups at pre-intervention, Self > Word contrast, reveals clusters in medial prefrontal cortex, anterior cingulate cortex, posterior cingulate cortex, precuneus, and left middle frontal gyrus

APPENDIX C

SUPPLEMENTAL MATERIAL FOR CHAPTER 4

Supplemental information

	MBSR		Support/Education	
	Pre Mean (SD) Range	**Post** Mean (SD) Range	**Pre** Mean (SD) Range	**Post** Mean (SD) Range
BDI-II	17.88 (11.55) 0-48	12.92 (10.89)0-33	15.43 (11.52) 0-43	10.03 (9.15) 0-35
STAI-2	49.76 (11.10) 34-76	43.85 (10.17) 27-67	45.13 (14.41) 22-72	41.56 (12.47) 22-66

Pre- and post-intervention means, standard deviations (SD), and ranges for MBSR and SE groups; BDI-II=Beck Depression Inventory-II; STAI-2= State and Trait Anxiety Inventory – Trait Scale.

APPENDIX D

IRB APPROVAL

APPROVAL: EXPEDITED REVIEW

Dear Brittany Braden,

On 12/9/2017 the ASU IRB approved the protocol from 12/9/2017 to 12/8/2018 inclusive. Three weeks before 12/8/2018 you are to submit a completed Continuing Review application and required attachments to request continuing approval or closure.

If continuing review approval is not granted before the expiration date of 12/8/2018 approval of this protocol expires on that date. When consent is appropriate, you must use final, watermarked versions available under the "Documents" tab in ERA-IRB.

In conducting this protocol you are required to follow the requirements listed in the INVESTIGATOR MANUAL (HRP-103).

Sincerely,

IRB Administrator

cc:
Melissa Walsh
Nicole Roberts
Jocelyn Alvar
Rachelle Jones
Leah Doane
Cory Riecken
Caleb Haynes
Leah Randolph
Teri Pipe
Maria Dixon
Christopher Blais
Christen Webb
Emily Foldes
Mary Burleson
Ashlyn Gonzales
Brittany Braden

Type of Review:	Initial Study
Title:	The Neural Changes Associated with a Mindfulness Intervention for Adults with Autism Spectrum Disorder
Investigator:	Brittany Braden
IRB ID:	STUDY00007227
Category of review:	(6) Voice, video, digital, or image recordings, (4) Noninvasive procedures, (7)(a) Behavioral research
Funding:	Name: Arizona State University (ASU)
Grant Title:	
Grant ID:	