The Effects of Mindfulness Meditation on Resting-State Functional Connectivity and Executive Function in Adults with Autism Spectrum Disorder

by

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ABSTRACT

Individuals with autism spectrum disorder (ASD) are known to show impairments in various domains of executive function (EF) such as behavioral flexibility or inhibitory control. Research suggests that EF impairment in adults with ASD may relate to ASD core symptoms, restrictive behaviors and social communication deficits. Mindfulness-based stress reduction (MBSR) has shown promise for improving EF abilities in neurotypical adults, but research has not explored its efficacy or neural mechanisms in adults with ASD. This pilot study examines the effects of an 8-week MBSR intervention on self-report measures of EF and resting-state functional connectivity in a sample of adults with ASD. Fifty-four participants were assigned either to an MBSR group (n = 29) or a social support group (n = 25). Executive function was measured using the BRIEF-2 before and after the intervention for the twenty-seven participants in the second cohort. MBSR-specific improvements in EF were found for BRIEF measures of initiation, inhibition, and working-memory. Resting-state fMRI data was analyzed using independent component analysis (ICA), and group by time resting-state functional connectivity differences were observed between the cerebellar network and frontal regions including the right frontal pole (rFP), medial frontal cortex (MFC) and left and right superior frontal gyri (SFG). The MBSR group showed increases in functional connectivity between the cerebellum and EF regions which correlated with improvements in BRIEF-2 measures. These findings suggest that MBSR may improve EF domains in adults with ASD, and that increases in functional connectivity between the cerebellum and frontal regions while at rest may be a mechanism for such improvements.

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INTRODUCTION

In 1943, Leo Kanner described the unusual behaviors he observed as follows: "All of the children's activities and utterances are governed rigidly and consistently by the powerful desire for aloneness and sameness" (Kanner, 1943). The first of the DSM-V's two core criteria for diagnosing *Autism Spectrum Disorder (ASD)* is the symptom of restrictive and repetitive behaviors and interests (Association, 2013). Cognitive flexibility, behavioral inhibition and an ability to adapt and approach situations in novel ways are important aspects of executive function (EF) (Banich & Compton, 2018). For decades, researchers have explored how EF domains such as working memory, planning, inhibitory control, and flexibility may function differently among individuals with ASD (Hill, 2004a, 2004b; Hughes et al., 1994; Ozonoff et al., 1991). Recent research has attempted to characterize the neural correlates of EF differences in ASD by examining associations between behavioral measures of EF and brain differences, using functional MRI. Our group has linked poorer set-shifting and working memory performance in adults with ASD to decreased cortico-striatal-thalamic-cortical (CSTC) network recruitment during a working memory task (Braden et al., 2017). Given the behavioral and neural findings suggestive of impaired flexibility, it is plausible that the restrictive and repetitive behaviors present in ASD, and the rigidity and desire for sameness observed by Kanner in 1943, are symptoms of impairments of metacognitive domains of EF.

The other core impairment present in ASD is a deficit in social communication abilities (Association, 2013). Emerging research over the past decade suggests that impaired EF is also related to poorer social communication abilities in ASD. One theory proposes that EF and prefrontal activity are directly involved in compensatory mechanisms which individuals with ASD may use to mask or camouflage their social symptoms (Johnson, 2012; Johnson et al., 2015; Livingston & Happé, 2017). In children, certain self-regulatory processes such as inhibition and flexibility are predictive of social functioning among those with ASD, but not for neurotypical children (Leung et al., 2016). Our group has contributed to this body of knowledge in older adults with ASD by showing that lower functional connectivity between the right dorsolateral prefrontal cortex and the Frontoparietal Network (FPN), a functional network of regions which support EF, correlated with greater social difficulties (Walsh et al., 2019). Given the associations between EF and symptom severity in ASD, there is a critical need for targeted interventions that may bolster EF among adults with ASD, in order to improve quality of life and preserve cognitive function during aging.

Mindfulness

Mindfulness meditation is a practice in which one observes moment-to-moment experiences with intention, without judgment and with a welcoming acceptance of whatever arises (Kabat-Zinn & Hanh, 2009). Mindfulness-Based Stress Reduction (MBSR) is a mindfulness program originally developed by Jon Kabat-Zinn in order to treat patients with chronic pain through the deliberate training of self-regulation abilities via mindfulness awareness (Kabat-Zinn, 1982). MBSR has grown considerably in popularity in recent decades, and a recent meta-analysis of MBSR studies concluded that current evidence suggests it is effective for reducing stress, depression, anxiety, and improving overall quality of life in healthy subjects (Khoury et al., 2015). Studies have shown that mindfulness also significantly improves EF both in older adults (Moynihan et al., 2013) as well as younger children and adolescents (Mak et al., 2018).

Little research to date has examined behavioral changes associated with an MBSR intervention for adults with ASD. One study found that a 9-week mindfulness-based therapy reduced depression, anxiety and rumination among adults with ASD (Spek et al., 2013), though the findings could have been due to the effects of social support rather than the mindfulness practices per se. Pilot findings from our lab have validated that MBSR is beneficial for reducing depression symptoms in adults with ASD, and found that symptom improvements correlated with increased activity in the middle cingulate cortex, a region involved in self-referential processing, during a self-reflection task (Pagni et al., 2020).

Resting-State

The discovery that baseline activity in the brain - that is, while a person is doing nothing in particular, produces reliable activation in certain areas and not others (Raichle et al., 2001) has sparked interest in the nature of resting-state functional connectivity in the brain, and in what factors may influence it. Some initial research in ASD suggested that it may be characterized by under-connectivity, or decreased synchronization between specific neural regions, while at rest (Cherkassky et al., 2006). A more recent review highlights mixed findings of resting-state functional connectivity in ASD, with some showing under-connectivity between regions and others showing overconnectivity between regions (Hull et al., 2017). We have shown that decreased resting-state functional connectivity between the FPN and dorsolateral prefrontal cortex is associated with poorer EF abilities in adults with ASD (Walsh et al., 2019). Resting-state functional connectivity is of particular interest in the context of a mindfulness-intervention such as MBSR, given that mindfulness practices involve an awareness and acceptance of experiences at rest. They do not involve cognitively engaging with any external task, but rather the individual simply observes how experience unfolds when left alone, unperturbed, or at rest.

The current study examined resting-state functional connectivity changes associated with an 8-week MBSR intervention in adults with ASD. Given that MBSR has been shown to improve EF in neurotypical adults, and that underconnectivity within the FPN at rest in ASD is associated with poorer behavioral measures of EF, we hypothesize that: a) MBSR will improve self-reported measures of EF in adults with ASD, and b) improvements in EF as a result of MBSR may be driven by increases in functional connectivity between large-scale networks containing pre-frontal regions while at rest.

METHODS

The study included two cohort groups in which the effects of an 8-week MBSR intervention were compared to the effects of an 8-week social support/relaxation education (SE) intervention. Participants from both groups met weekly; the MBSR participants engaged in mindfulness practices whereas the SE participants discussed relaxation-based stress-reduction strategies. Male and female adults with ASD were randomly assigned to either group at baseline. A total of 27 participants participated in the first cohort [MBSR group, n = 16, SE group, n = 11] and 27 participants in the second cohort [MBSR group, n = 13, SE group, n = 14]. All participants had confirmed ASD diagnoses based on administration of the Autism Diagnostic Observation Schedule, Second Edition (Lord et al., 2012) at the Southwest Autism Research and Resource Center.

Both groups met once per week, for 2-hour sessions, over a period of 8 weeks. The MBSR intervention followed mindfulness techniques standardized by Jon Kabat-Zinn; sessions were led by a certified MBSR instructor with more than 10 years of experience as well as a speech-language pathologist who had more than 20 years of experience working with individuals with ASD. MBSR group participants were instructed to practice at home for a total of 45 minutes per week. The mindfulness techniques taught participants to non-judgmentally observe the nature of moment-to-moment experiences. Practices consisted of paying attention to the breath, slowly scanning one's attention over sensations in the body, observing tastes, smells, sights, sounds and physical sensations of objects, as well as noticing how emotions and thoughts manifested within the body and mind. SE group participants met for the same amount of time as the MBSR group and learned about stress-reduction and relaxation techniques provided by the National Center for Complementary and Integrative Health (NCCIH): https://www-nccih-nih-gov.ezproxy1.lib.asu.edu/health/relaxation-techniques-for-health. Sessions were led by the principal investigator of the study and another lab member. Participants were also encouraged to practice the stress-reduction techniques at home between in-person sessions.

Baseline and follow-up functional and structural MRIs were collected at Barrow Neurological Institute in Phoenix, AZ using a 3 Tesla Philips Ingenia scanner with a maximum gradient strength of 45 mT/m. T1-weighted structural scans were acquired using the following parameters: field of view = 240 mm, 170 sagittally-acquired slices, thickness = 1.2mm per slice, and 256 x 256 in-plane resolution. T_2^*-weighted images were acquired as participants lay awake at rest using the following parameters: field of view = 240 mm, slice thickness = 3 mm, TR = 3000 ms, TE = 30ms, voxel size = 3 mm x 3mm, flip angle = 90^0, and in-plane resolution = 64 x 64. During the 6-minute resting-state functional scans, participants were told to close their eyes, to think of nothing in particular, and to try not to fall asleep. During both the baseline and follow-up visits at Barrow Neurological Institute, participants completed a series of self-report questionnaires assessing symptoms of mood and cognitive function. In order to assess various domains of executive function, the Behavior Rating Inventory of Executive Function, Second Edition (BRIEF-2) was used (Gioia et al., 2015). The BRIEF survey was not administered for first cohort participants.

All neuroimaging data was preprocessed using Statistical Parametric Mapping, Twelfth Edition (SPM12; https://www.fil.ion.ucl.ac.uk/spm/software/spm12/). Pre-processing steps consisted of slice-timing correction, realignment, co-registration with anatomical skull-stripped T1-weighted image, normalization to MNI space and spatial smoothing using an 8mm full width half maximum Gaussian kernel. Fully preprocessed pre- and post- intervention images were loaded into CONN toolbox (https://www.nitrc.org/projects/conn) for functional-connectivity analyses. Denoising steps included linear regression to limit the confounding effects of 6 parameters for both white matter and CSF, 18 parameters for realignment and 2nd-order derivatives as added confound dimensions, and 76 parameters for motion scrubbing. A band pass filter of [0.009 0.08] was used, and an additional step included cubic detrending. Quality assurance plots indicated that excessive motion rendered resting-state data inadequate for a total of 9 subjects, and thus these 9 subjects [MBSR group, n = 4; SE group, n = 5] were excluded from the analysis. A total of 25 MBSR participants' and 20 SE participants' functional connectivity data was included in the 1st and 2nd level analyses in CONN. Quality assurance reports indicated no significant associations between quality control parameters (i.e., Mean Motion, Max Motion, etc.) and functional connectivity.

A Group Independent Component Analysis (ICA) was used in order to isolate 30 separate component sources of functional connectivity signals across the 45 participants. A within-subjects Post > Pre contrast was combined with a between-subjects MBSR Group > SE Group contrast in order to isolate mindfulness-specific changes in functional connectivity as a result of the intervention. Using these contrasts, a whole-brain analysis tested for significant ICA-cluster interactions using a significance threshold of $p < 0.05$ for cluster sizes and Family-Wise Error (FWE)-correction for multiple-comparisons. Significant ICA-cluster interactions for MBSR > SE, Post > Pre contrasts were exported from CONN and inputted as variables in SPSS for a subsequent correlational analysis with behavioral self-report measures. Pearson correlations tested for associations between significant ICA-Cluster functional connectivity changes [MBSR > SE; Post > Pre] and changes in self-reported mood and cognitive symptoms. SPSS was used to test for Group by Time Interactions for self-reported behavioral measures using repeated-measures analysis of variance (ANOVA).

RESULTS

Demographics

Table 1 shows demographic variables for the participants included in this analysis. No significant differences were present between groups for sex, age, IQ, or ADOS scores.

Table 1: *Participant demographics*

	MBSR	Support/Education (SE)	Baseline Comparison
Participants (M/F)	29 (18/11)	25 (17/8)	
Age in years	29.21 (11.84 Range: 18 - 64	33.16 (15.26) Range: 18 - 72	t (52) = 1.07; p = 0.29; d = 0.29
IQ	101.18 (16.51) Range: 70 - 131	106.08 (17.14 Range: 70 - 139	t (51) = 1.06; p = 0.29; d = 0.29
ADOS	11.66 (3.15) Range: 8 - 20	10.72 (3.35) Range: 7 - 17	t (52) = -1.06; p = 0.30; d = -0.29

Executive Function Measures:

BRIEF Global scores are divided into two indexes: *Behavior Regulation* Index and *Metacognition* Index. A significant group by time interaction was observed specifically for the *Behavior Regulation* Index (p = 0.047), and a trending group by time interaction was observed for the *Metacognition* Index (p = 0.082). A main effect of time was observed for BRIEF *Initiation* (p = 0.01), though the effect was primarily driven by changes in the MBSR group. Significant group by time interactions were found for the following subscales: *BRIEF Inhibition* (p = 0.005), *BRIEF Initiation* (p = 0.03), and *BRIEF Working Memory* (p = 0.017).

Table 2: *Repeated Measures ANOVA of Executive Function: BRIEF-II*

		F	Significance	Effect size
BRIEF_BehRegIndex	Main effect of time	2.19	0.154	0.094
	Group by time Interaction	4.44	**0.047***	0.174
BRIEF_MetaCogIndex	Main effect of time	1.13	0.300	0.051
	Group by time Interaction	3.33	0.082	0.137
BRIEF_Inhibit	Main effect of time	1.42	0.247	0.063
	Group by time Interaction	10.00	**0.005***	0.322
BRIEF_Shift	Main effect of time	3.11	0.092	0.129
	Group by time Interaction	0.001	0.973	0.000
BRIEF_Emo	Main effect of time	0.69	0.417	0.032
	Group by time Interaction	3.82	0.064	0.154
BRIEF_Selfmon	Main effect of time	1.58	0.222	0.070
	Group by time Interaction	1.20	0.286	0.054
BRIEF_ini	Main effect of time	8.05	**0.010***	0.277
	Group by time Interaction	5.38	**0.030***	0.204
BRIEF_WM	Main effect of time	0.49	0.492	0.023
	Group by time Interaction	6.78	**0.017***	0.244
BRIEF_Plan	Main effect of time	0.03	0.859	0.002
	Group by time Interaction	1.71	0.205	0.075
BRIEF_Task	Main effect of time	0.17	0.682	0.008
	Group by time Interaction	0.67	0.424	0.031
BRIEF_Org	Main effect of time	1.48	0.238	0.066
	Group by time Interaction	0.18	0.674	0.009

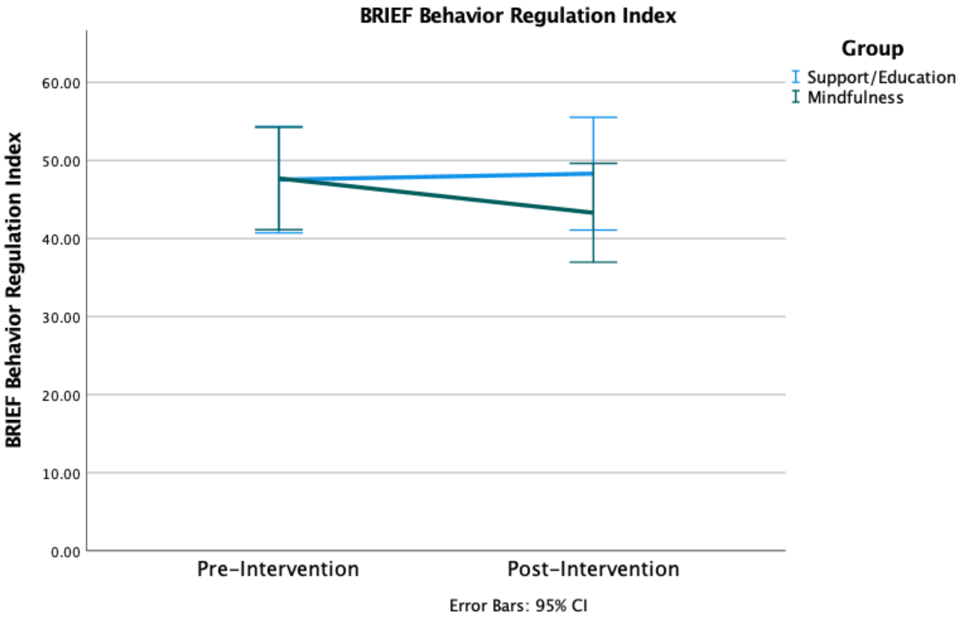


Figure 1. Plot of pre- to post- changes in BRIEF Behavior Regulation Index scores for each group. Significant group-by-time interaction: F = 4.44; p = 0.047.

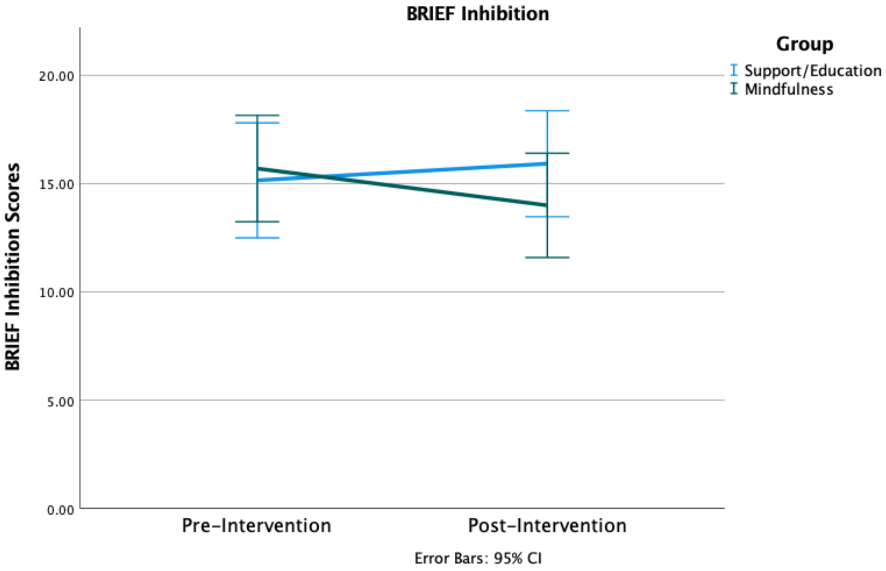


Figure 2: Plot of pre- to post- changes in BRIEF Inhibition Subscale scores for each group. Significant group-by-time interaction: F = 10.00; p = 0.005.

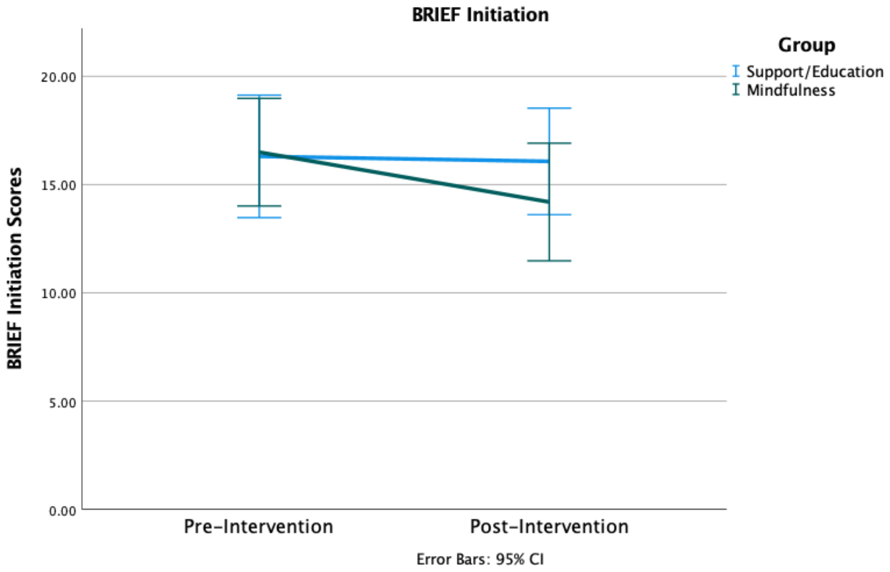


Figure 3: Plot of pre- to post- changes in BRIEF Initiation subscale scores for each group. Significant group-by-time interaction: F = 5.38; p = 0.03.

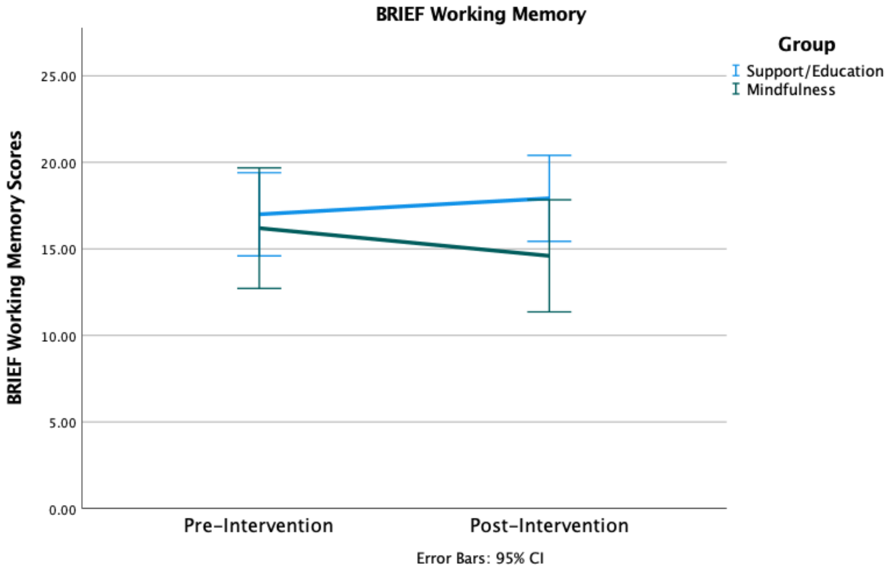


Figure 4: Plot of pre- to post- changes in BRIEF Working Memory subscale scores for each group. Significant group-by-time interaction: F = 6.78; p = 0.017.

Functional Connectivity Analysis

Spatial correlations between the isolated ICA components and canonical networks revealed strong matches for the Cerebellar, Dorsal Attention, and Visual Networks. Moderate correlations were found with the Default Mode and Sensorimotor Networks, and weak correlations were found for the Frontoparietal, Language and Salience Networks. Only one ICA component - the Cerebellar Network, showed a group by time functional connectivity change, and it involved two frontal clusters.

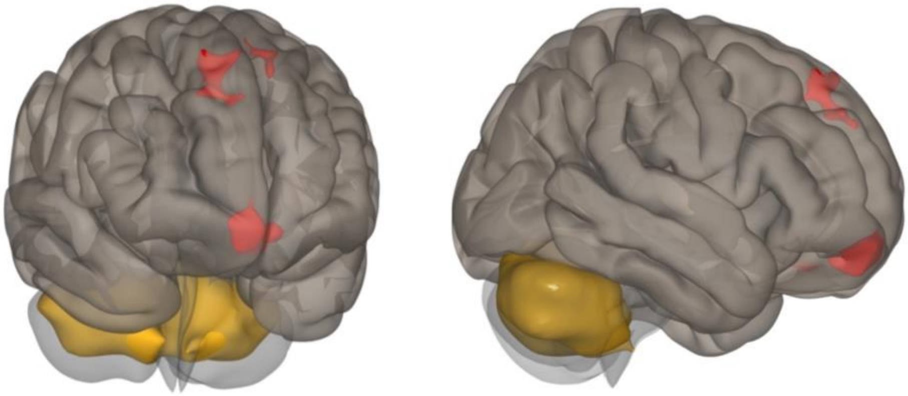
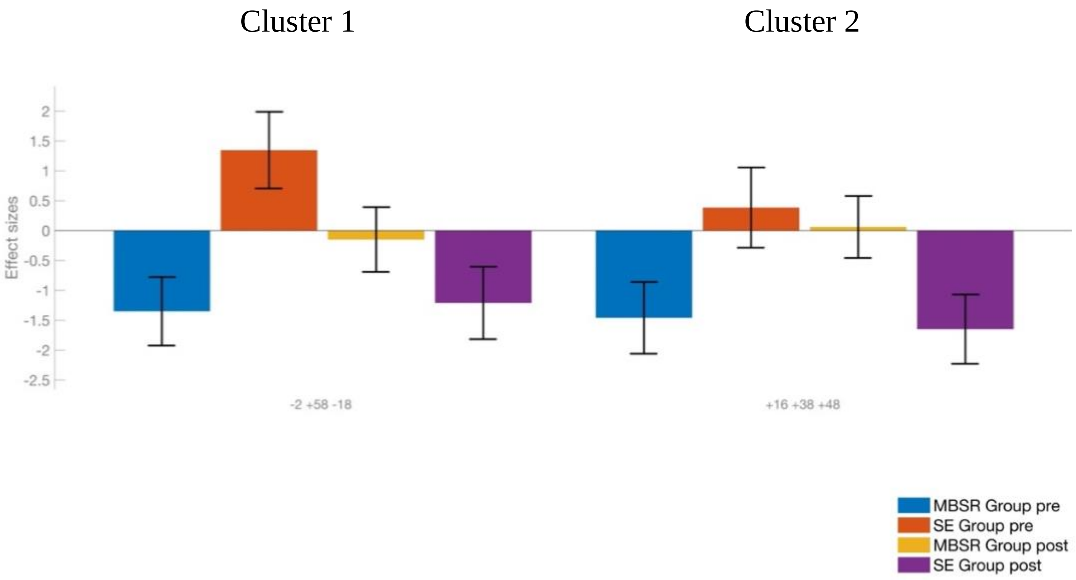


Figure 5: Two different views of a 3-D Brain generated in CONN Toolbox showing ICA Component 1 as a strong match with the Cerebellar Network (yellow), and two clusters (red) with which the Cerebellar Network showed significant group by time functional connectivity changes: Cluster 1 encompassed regions of the Medial Frontal Cortex (MFC) and Right Frontal Pole (rFP). Cluster 2 encompassed regions of the rFP and, to a lesser extent, the left and right Superior Frontal Gyrus (SFG).

Table 3: *Group by time functional connectivity changes with Cerebellar Network*

Cluster	x,y,z	Size	Size p-FWE	Peak p-FWE	Peak p-unc
1	-02 +58 -18	654	0.000000	0.103894	0.000001
2	+16 +38 +48	490	0.000009	0.312370	0.000005


Cluster 1

Cluster 2

Figure 6: Plots of pre- to post- functional connectivity effect sizes for the two clusters showing significant group by time functional connectivity changes for both.

Correlations Between Functional Connectivity and BRIEF Changes

Functional connectivity changes between the Cerebellar Network and regions of the MFC and rFP (Cluster 1) showed significant correlations with several Executive Function Changes measured by the BRIEF-2 within the MBSR group. Significant correlations involved the BRIEF *Behavior Regulation* Index, as well as the following subscales: BRIEF Initiation, BRIEF Emotional Control, and BRIEF Self-Monitoring. Correlations were trending for the BRIEF *Metacognition* Index, as well as for the BRIEF Inhibition Subscale.

Table 4: *Correlations Between Functional Connectivity and BRIEF Changes for MBSR*

	Cerebellar Network - MFC / right FP Functional Connectivity Change
BRIEF Behavior Regulation Index	**r (7) = -0.866; p = 0.003***
BRIEF Inhibition	r (7) = -0.615; p = 0.078
BRIEF Shift	r (7) = -0.564; p = 0.114
BRIEF Emotional Control	**r (7) = -0.913; p < 0.001****
BRIEF Metacognition Index	r (7) = -0.585; p = 0.098
BRIEF Initiation	**r (7) = -0.822; p = 0.007****
BRIEF Working Memory	r (7) = -0.544; p = 0.130
BRIEF Plan	r (7) = -0.397; p = 0.290
BRIEF Organization	r (7) = -0.332; p = 0.383
BRIEF Self-Monitoring	**r (7) = -0.677; p = 0.045***

*Significance p < 0.05
**Significance p < 0.01

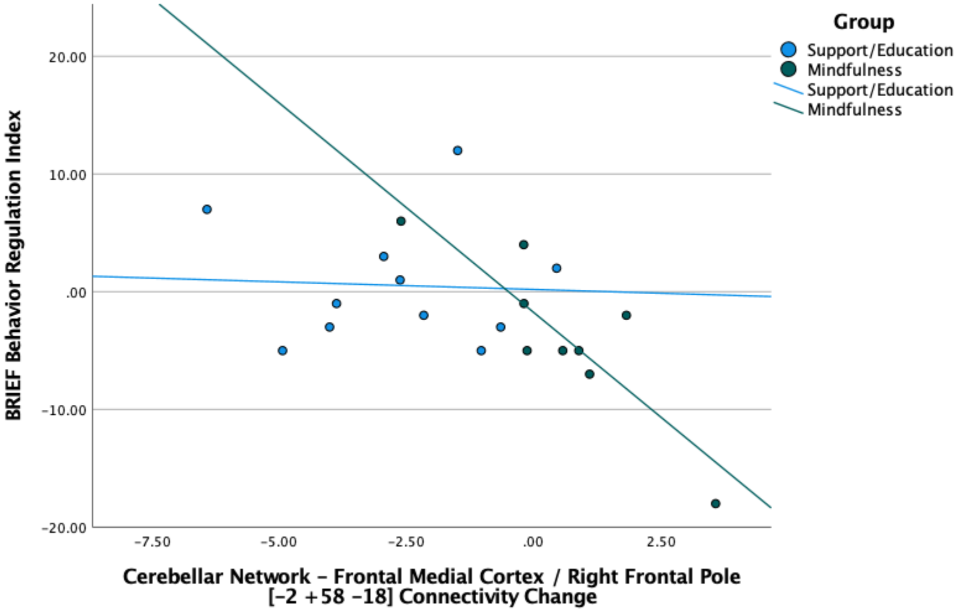


Figure 7: Scatterplot of BRIEF Behavior Regulation Index Change Scores and functional connectivity changes between Cerebellar Network and MFC/rFP. Functional connectivity changes correlated significantly with BRIEF Behavior Regulation Index scores (r (7) = -0.866; p = 0.003) for MBSR group only.

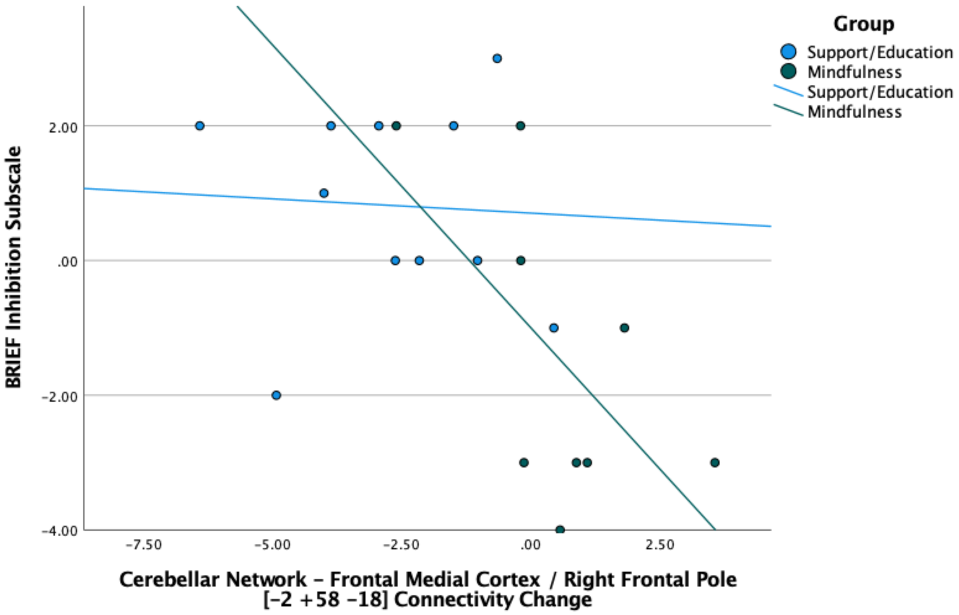


Figure 8: Scatterplot of BRIEF Inhibition subscale scores and functional connectivity changes between Cerebellar Network and MFC/rFP. Functional connectivity changes showed a trending correlation with BRIEF Inhibition subscale scores (r (7) = -0.615; p = 0.078) for MBSR group only.

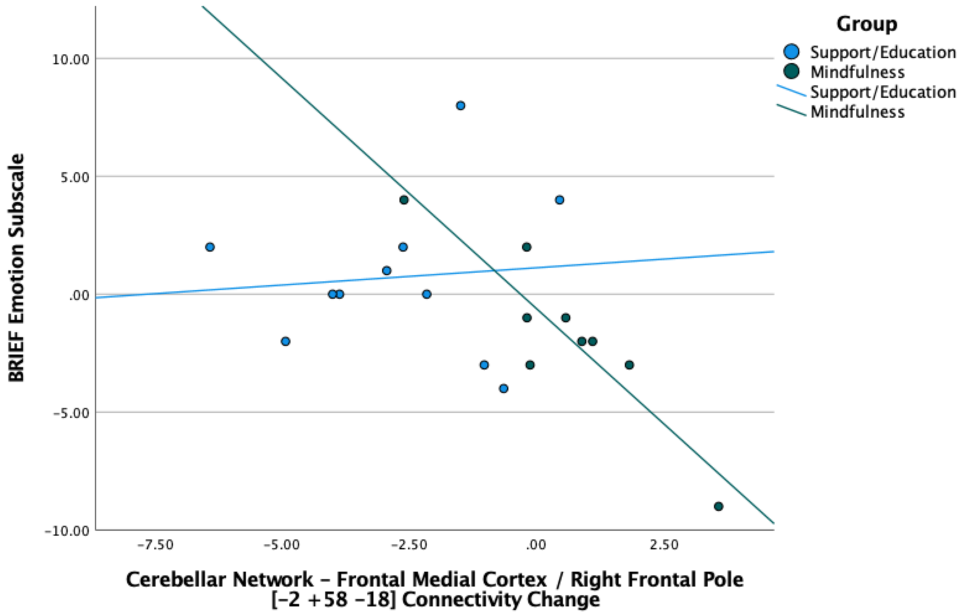


Figure 9: Scatterplot of BRIEF Emotional Control subscale scores and functional connectivity changes between Cerebellar Network and MFC/rFP. Functional connectivity changes correlated significantly with BRIEF Emotional Control subscale scores (r (7) = -0.913; $p < 0.001$) for MBSR group only.

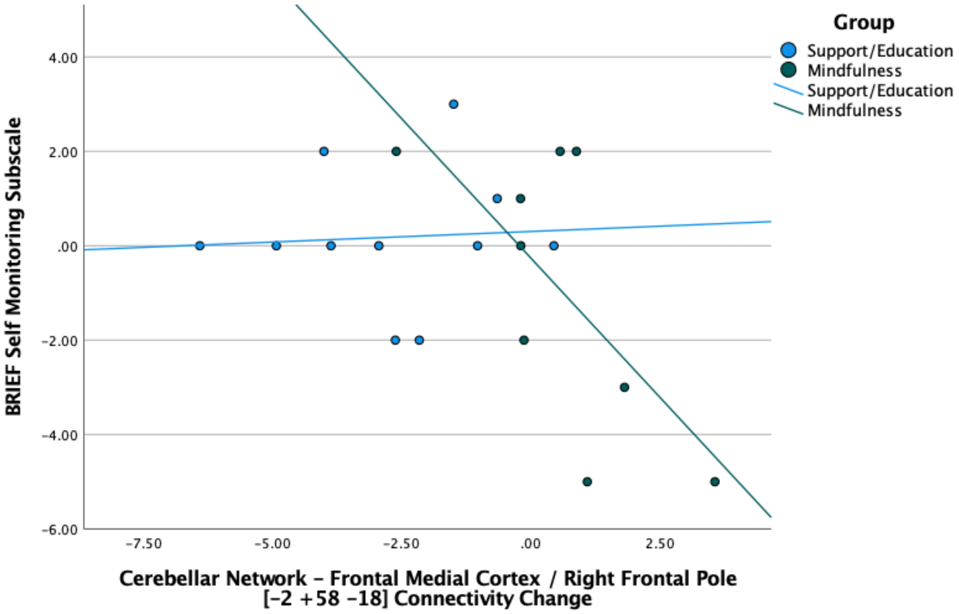


Figure 10: Scatterplot of BRIEF Self-Monitoring subscale scores and functional connectivity changes between Cerebellar Network and MFC/rFP. Functional connectivity changes correlated significantly with BRIEF Self-Monitoring subscale scores (r (7) = -0.677; p = 0.045) for MBSR group only.

DISCUSSION

The results from this study suggest that MBSR may improve certain domains of EF in adults with ASD, and that this effect may be mediated in part by increases in resting-state functional connectivity between the cerebellar network and frontal regions such as the medial frontal cortex and frontal pole. MBSR significantly improved domains of EF which are implicated in behavioral regulation and control, whereas improvements in metacognitive domains of EF only trended toward significance. Our lab has previously found that decreased resting-state functional connectivity between the frontoparietal network and dorsolateral prefrontal cortex may contribute to EF impairments in adults with ASD. We therefore expected that a possible mechanism of EF improvements as a result of MBSR would be increased resting-state functional connectivity across large scale networks containing prefrontal regions. The finding of MBSR-specific increases in functional connectivity involving EF regions such as the right frontal pole and medial frontal cortex is congruent with this expectation. The frontal pole is involved in evaluating possible outcomes of a scenario (Koechlin, 2011), and the MFC has been shown both to mediate behavioral adaptation in order to improve task-performance (Ridderinkhof et al., 2004), and to play a role in social cognition (Amodio & Frith, 2006). Given that ASD is characterized by impairments in behavioral flexibility and social behavior, it is promising that an intervention such as MBSR may increase functional connectivity changes with a region such as the MFC, which is known to play a role in such functions.

The finding that functional connectivity differences would involve the Cerebellar

Network was not expected based on our hypotheses, though it is a region whose function has been implicated both in ASD and in EF processes. Contrary to what was once believed, the cerebellum's role extends beyond motor coordination and planning, and a number of recent studies provide strong evidence that the cerebellum is core among affected regions in ASD (Becker & Stoodley, 2013; D'Mello & Stoodley, 2015; Khan et al., 2015). Reduced grey matter volume in the right Crus II of the cerebellum was shown in adults with ASD and linked to ASD traits, and a subsequent seed-based analysis involving the right Crus II showed decreases in resting-state functional connectivity with a number of frontal areas, among which were contralateral regions of the frontal pole and superior frontal gyrus (Olivito et al., 2018). The frontal pole and superior frontal gyri were two of the regions which show increased functional connectivity with the Cerebellar Network as a result of MBSR in this study. Furthermore, it has been demonstrated in neurotypical adults that functional connectivity between Crus I & II of the cerebellum and the right frontoparietal network at rest is predictive of individual differences in EF (Reineberg et al., 2015). The above findings in adults with ASD and neurotypical adults lend credence to the possibility that resting-state functional connectivity between the cerebellum and prefrontal regions supports a range of EF abilities.

The specific subscales of the BRIEF which showed significant group by time interactions were the *Inhibition, Initiation,* and *Working Memory* subscales. There was also a significant group by time interaction for the *Behavior Regulation Index*, and trending group by time interactions for the *Metacognition Index*, and the *Emotional Control* subscale. MBSR-specific correlations with resting-state functional connectivity changes were observed for the *Initiation* subscale, *Emotional Control* subscale, and *Self-Monitoring* subscale; a trending correlation with the *Inhibition* subscale was also observed. While only the *Behavior Regulation Index* showed a significant correlation with functional connectivity changes, the *Metacognition Index* showed a trending correlation. Improvements in self-regulatory abilities such as inhibitory control are expected outcomes of mindfulness-based practices, given that mindfulness allows for the recognition of habits and intentions which in turn may allow for better behavioral control. Improved regulation of one's emotions is also a skill which is expected to develop through mindfulness training, as one may become more accepting and less reactive toward emotional experiences.

LIMITATIONS

While the total sample for the study was 54 participants, the BRIEF survey was only administered for the second cohort, which consisted of 27 participants. Furthermore, 3 of the 9 participants who were excluded from the neuroimaging analysis due to excessive motion were part of the second cohort. As a result, only 9 MBSR participants had both resting-state fMRI and BRIEF self-report data, thereby limiting our sample size and statistical power considerably. Among the group by time functional connectivity changes provided by CONN, there are evident differences in baseline connectivity between the groups. A larger sample is necessary in order to attain similar baseline values for resting-state connectivity across groups; this would provide greater confidence as to the neural mechanisms involved in MBSR-specific EF improvements. Finally, the behavioral results of the study are limited due to the subjective nature of participants' self-assessment, and the results could be strengthened by an objective assessment of EF through neurocognitive assessments.

CONCLUSION

Given that impairments in EF may contribute to the two core symptoms of repetitive / restrictive behaviors and social communication impairment in ASD, there is a critical need for interventions which may improve EF in adults with ASD. Our preliminary findings show support for mindfulness practices as a means of improving EF in adults with ASD. Increases in resting-state functional connectivity between the Cerebellar Network and frontal regions including the rFP and MFC may in part explain the effects of MBSR on improvements in behavioral regulatory domains of EF in adults with ASD. Future studies should incorporate larger samples to explore the effects of mindfulness-based interventions on measures of EF in adults with ASD, and resting-state functional connectivity analyses should be used to better understand the mechanisms underlying symptom improvements.

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