Journal of Affective Disorders 276 (2020) 23–29

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Mindfulness-based intervention to decrease mood lability in at-risk youth: Preliminary evidence for changes in resting state functional connectivity

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ARTICLE INFO

Keywords:
Mindfulness
Bipolar disorder
Resting-state functional connectivity
Emotion regulation
Mood lability
Neuroimaging

ABSTRACT

Background: In youth at familial risk for bipolar disorder (BD), mood lability is an important precursor to BD onset. Previous work in adults indicates that mindfulness-based interventions (MBI) may improve emotion regulation, in part by increasing resting-state functional connectivity (rsFC) between posterior cingulate cortex (PCC) and executive control network (ECN). In this pilot study, we assessed effects of an MBI on PCC-ECN rsFC and mood lability in at-risk youth.

Methods: We recruited 35 youth (10–14 years old) with a first-degree family history of BD and mood lability, and 21 age-matched healthy controls. Eligible at-risk youth were scanned pre/post an 8-week MBI and assessed three months later. Healthy controls were scanned at matched timepoints but did not participate in the MBI. The MBI used age-appropriate strategies to promote non-judgmental, present-moment awareness. We assessed pre/post changes in PCC-ECN rsFC and how rsFC changes were related to mood outcomes.

Results: Twenty at-risk youth were scanned pre/post MBI; 16 had high-quality rsFC data. Following MBI, at-risk youth showed increased rsFC between PCC and left dorsolateral prefrontal cortex (DLPFC) (BA 9; $k = 28$; corrected $p = .006$); healthy controls did not show this increase. Following MBI, at-risk youth reported more mindfulness ($F = 7.15$, $p = .003$), less mood lability ($F = 7.2$, $p = .002$), and less suppression of negative emotions ($F = 5.05$, $p = .01$). PCC-DLPFC rsFC increases predicted less mood lability ($t = -2.25$, $p = .04$) and less emotion suppression ($t = -2.75$, $p = .02$) at follow-up.

Limitations: Small sample and lack of a control intervention.

Conclusions: PCC-DLPFC rsFC may be a clinically meaningful neural target of an MBI in at-risk youth, related to improvements in mood lability.

1. Introduction

Youth with a family history of bipolar disorder (BD) are at elevated risk for developing BD as well as other psychopathology (Duffy et al., 2014; Axelson et al., 2015; Mesman et al., 2013). In longitudinal studies of youth at familial risk for BD, mood lability (rapid and frequent switches in mood out of proportion to external stimuli) is associated with psychosocial impairment, and also predictive of subsequent BD onset (Hafeman et al., 2016; Akiskal et al., 1995). Thus, an early intervention to target this symptom, particularly in early adolescents who are just entering a period of elevated risk for mood disorder, may hold promise to improve psychosocial outcomes and alter risk trajectories.

One promising approach to targeting mood lability in these youth is a mindfulness-based intervention (MBI). Mindfulness is defined as intentionally paying attention in the present moment, with an attitude of openness and non-judgment (Kabat-Zinn, 1994). MBIs incorporate a range of practices to promote non-judgmental attention to the present moment. These approaches may increase present-moment acceptance of difficult circumstances and/or emotions, so that an individual can effectively respond as opposed to mindlessly react to stressful stimuli (Kabat-Zinn, 1990). Higher levels of mindfulness are associated with less suppression of difficult emotions and more resilience to stress (Galante et al., 2018; Nila et al., 2016; Pepping et al., 2016).

MBIs have been shown to be effective for the treatment and

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https://doi.org/10.1016/j.jad.2020.06.042
Received 6 April 2020; Received in revised form 1 June 2020; Accepted 16 June 2020
Available online 14 July 2020
0165-0327/

prevention of a wide range of psychopathology. In adults, MBIs have been shown in meta-analyses of randomized controlled trials (RCTs) to be effective for preventing relapse of depression in adults (Kuyken et al., 2016) and ameliorating mood and anxiety symptoms (Goldberg et al., 2018). A recent meta-analysis of RCTs also showed that MBIs led to decreased depression and anxiety/stress in children and adolescents and, in younger participants, an improvement in negative behaviors (Dunning et al., 2019). Beyond just treating mood disorders, MBIs may improve response to stressors or traumatic events (Creswell and Lindsay, 2014), and thus perhaps prevent mood disorder onset. This is consistent with an RCT of an MBI in a low-income middle school indicating that youth in the MBI group (vs. health education) showed fewer negative effects of stress (Sibinga et al., 2016). Regarding youth at familial risk, a small pilot study of ten offspring of parents with BD-I (ages 9–17 years old) found that, following the MBI, participants had less anxiety and better emotion regulation (Cotton et al., 2015). While to our knowledge there have been no interventions specifically targeting mood lability, an experience sampling study found that higher dispositional mindfulness was associated with less mood lability, as defined by mood switches throughout the day, in young adults (Hill and Updegraff, 2012).

A growing body of literature indicates that mindfulness is associated with more connectivity between the posterior cingulate cortex (PCC), an important node in the default mode network (DMN), and prefrontal regions important for executive function, i.e. executive control network (ECN) (Brewer et al., 2011; Creswell et al., 2016; King et al., 2016). Mindfulness-based increases in functional connectivity appear to be especially observed during “resting state”, perhaps reflecting a more effective intentional constraint (by the ECN) on mind-wandering and spontaneous thought (generated in the DMN) (Christoff et al., 2016). In particular, resting state functional connectivity (rsFC) between PCC and both the dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC), key nodes of the ECN, has been found to be higher in meditators vs. non-meditators (Brewer et al., 2011). In response to a mindfulness intervention, PCC-DLPFC rsFC has been found to increase in stressed, unemployed adults (Creswell et al., 2016), young adults with generalized anxiety disorder (Scult et al., 2019), and adults with post-traumatic stress disorder (King et al., 2016); and predictive of decreased inflammatory marker (IL-6) (Creswell et al., 2016). Collectively, these initial studies suggest that PCC-DLPFC connectivity is a promising brain-based biomarker for emotion regulation and stress resilience (Creswell et al., 2019), but no studies have evaluated this in youth, particularly those at risk for mood disorder.

We conducted a pilot study to assess whether an eight-week group MBI in youth at familial risk for BD would alter rsFC, particularly in networks shown previously to be impacted by an MBI (i.e. PCC-ECN); and, if present, whether this change would be associated with increased mindfulness and improvements in mood lability and other symptoms. We also compared the at-risk participants to healthy controls to determine the degree to which (1) any observed changes represented “normalizing” (i.e. made the at-risk appear closer to healthy controls) and (2) any observed changes were specific to the MBI rather than related to scanning a second time.

2. Methods and materials

2.1. Sample

We recruited 35 youth who were 10–14 years old who had a first-degree relative (parent or sibling) with BD, and also had elevated mood lability (based on the Child Affective Lability Scale, parent and child reports; CALS) (Birmaher et al., 2013). Youth were recruited primarily from a research registry through the University of Pittsburgh's Clinical and Translational Science Institute (Pitt + Me®) or advertisements ($n = 20$). Other participants were patients in a pediatric BD clinic (did not meet criteria for BD but had a first-degree relative with BD; $n = 5$); siblings of patients in a pediatric BD clinic ($n = 5$); or recruited from other clinics or studies ($n = 5$). At-risk youth were excluded if family history of BD could not be confirmed by clinical interview; if they met diagnostic criteria for BD, schizophrenia, schizoaffective disorder, and/or autism spectrum disorder; or if they had a contraindication for fMRI (e.g., metal in their body). For comparison purposes, we also scanned 21 healthy controls, recruited through the Pitt + Me® registry or advertisements. Healthy controls were excluded if they had a first- or second-degree relative with BD; met criteria for any present or lifetime psychiatric diagnosis; or had a contraindication for fMRI. All procedures were approved by the University of Pittsburgh Institutional Review Board.

2.2. Study protocol (at-risk)

2.2.1. Initial assessment (T1a)

At-risk youth who met study criteria based on an initial phone screen and a parent/guardian were invited to come for an assessment with a psychiatrist (DMH). After obtaining informed consent from the parent (and assent from the participant), we confirmed the family history of BD. This was done through a combination of record review (when available); in-person assessment via administration of the mania section of the Structured Clinical Interview for DSM-IV (SCID) (Spitzer et al., 1992); and, in a few cases, proxy assessment via the SCID (e.g. mother interviewed about a father with BD who died by suicide). We also assessed other first- and second-degree family history of BD using the Family History Screen (FHS) (Weissman et al., 2000), administered to the parent/guardian. To assess for mood lability, parent and child completed the CALS. The CALS scores range from 0 to 80 and values above 20 are consistent with significant psychopathology (Gerson et al., 1996). For this study, we included participants for whom parent and child scores averaged to ≥ 10. This number was chosen based on the Pittsburgh Bipolar Offspring Study, which showed that approximately half of the at-risk youth had at least this level of mood lability; thus, this strategy selected for symptomatic youth, while also optimizing feasibility of recruitment. Since this measure was a screen for inclusion, we did not include the CALS intake score in our analyses. Participants also completed questionnaires to assess dispositional mindfulness (Child and Adolescent Mindfulness Measure; CAMM) (Greco et al., 2011) and emotion regulation (Emotion Regulation Questionnaire; ERQ) (Gross and John, 2003). We next conducted a diagnostic assessment of the participant using the Kiddie Schedule for Affective Disorders – Present and Lifetime (K-SADS-PL) (Kaufman et al., 1997).

2.2.2. First scan visit (T1b)

Participants who satisfied inclusion/exclusion criteria were invited for an initial scan. At the scan visit, parents and children again completed the CALS; this additional data-point was collected since the intake CALS was a screen for study inclusion, so may have been inflated. They also completed questionnaires to assess depression (Moods and Feelings Questionnaire; MFQ, Daviss et al., 2006) and anxiety (Screen for Childhood Anxiety Related Disorders; SCARED, Birmaher et al., 1999). Parents completed the Child Mania Rating Scale (CMRS) (Pavuluri et al., 2006). The scan protocol consisted of a high-resolution T1-weighted structural scan; 8-minute resting state scan (eyes open, fixation cross); and a working memory and cognitive reappraisal task. We focus here on resting state analysis.

2.2.3. Mindfulness group

Eligible at-risk youth were then invited to attend a weekly mindfulness group for eight weeks. In some cases, groups started 1–2 months after the first scan, due to scheduling delays. The curriculum was based on concepts and practices from both the Mindfulness Based Stress Reduction (MBSR) and Mindfulness Based Cognitive Therapy (MBCT) programs, adapting publicly available practices and materials from the

Mindfulness in Schools Project (MiSP) .b program and Acceptance and Commitment Therapy for adolescents (Kuyken et al., 2013; Coyne et al., 2011); curriculum and practices can be found in the eSupplement. Groups consisted of 2–8 youth and were co-led by a child psychiatrist with training as a MiSP teacher (DMH) and a graduate student in counseling psychology and yoga instructor (ANO), both with ongoing daily mindfulness practices. The intention of the group activities was to develop a practice of bringing attention to the present moment (e.g. to the breath, body sensations) with an attitude of compassion and kindness. Participants were given small tokens to encourage home and in vivo practice, such as stickers with the practices and raisins for mindful eating. Participants were compensated for their time.

2.2.4. Second scan visit (T2)

Within three weeks of the final group, participants who attended at least half of the groups were again scanned using an identical protocol. Participants and parents again completed the CALS, MFQ, SCARED, CMRS, CAMM, and ERQ.

2.2.5. Three-month follow-up visit (T3)

Three months following the final group, participants were invited to return for a follow-up visit, at which time they completed the CALS, MFQ, SCARED, CMRS, CAMM, and ERQ; and provided additional feedback regarding their experience with the groups and mindfulness.

2.3. Study protocol (healthy controls)

2.3.1. Initial assessment (T1a)

Following the informed consent process, family history was assessed using the FHS. A KSADS-PL screen was used to assess for and rule out psychiatric diagnoses. Assessments were conducted by either a psychiatrist (DMH) or a trained research assistant who presented to the psychiatrist (DMH) for consensus ratings. Participants completed the CAMM and ERQ.

2.3.2. First scan visit (T1b)

Participants who met inclusion criteria were invited for a scan visit, identical to the at-risk protocol described above for the at-risk participants. Participants and parents completed the CALS, MFQ, SCARED, and CMRS.

2.3.3. Second scan visit (T2)

If the first scan was successfully completed (i.e. participant was able to remain relatively still; without excessive sleepiness; and completed the scanning protocol) (n = 18/21), participants were invited back for a second scan two to three months later. Sixteen participants returned for a second scan. Participants and parents again completed the CALS, MFQ, SCARED, CMRS, CAMM, and ERQ.

2.4. fMRI acquisition

Structural and functional images were acquired on a Siemens Verio 3T scanner at Carnegie Mellon University with a 32-channel head coil. High-resolution T1-weighted images (176 sagittal slices) were acquired using the following parameters: repetition time (TR) = 2.3 s, echo time = 1.97 ms, inversion time = 900 ms, flip angle = 9°, matrix size = 256 × 256, slice thickness = 1 mm. Functional imaging runs, including an eight minute resting state sequence, were acquired using echoplanar imaging (TR = 2 s, TE = 30 ms, flip angle = 79°, matrix size = 96. Number of slices = 69, multiband acceleration = 3, voxel size = 2 mm × 2 mm × 2 mm).

2.5. fMRI preprocessing

Data were analyzed using fmriprep 1.4.1rc1 and eXtensible Connectivity Pipeline (xcpengine), both implemented using a singularity container; for detailed preprocessing pipelines, see eMethods. Briefly, a reference volume and its skull-stripped version were generated; head-motion parameters with respect to the BOLD reference were estimated; susceptibility distortion was estimated based on a field map and used to calculate an unwarped BOLD reference; the BOLD reference was then aligned to the T1-weighted structural image using boundary-based registration; and then resampled in MNI space, concatenating all pertinent transformation (i.e. head-motion parameters, susceptibility distortion correction, BOLD-to-T1 and T1-to-MNI mappings). In addition, a file including nuisance regressors, including motion parameters, global signal, and framewise displacement (FD) was generated. Four (4/20; 20%) of at-risk participants were excluded due to excess motion during the pre and/or post resting state scan (mean FD > 0.5).

Output from fmriprep was used to generate a matrix of nuisance time series for confound regression, including (1) framewise motion estimates, white matter and cerebrospinal fluid mean signal, global signal, and quadratic and derivative expansions for these values (36P); and (2) spike regressors to censor volumes with high motion (FD > 0.5 mm) or signal change (DVARS > 2). Next, BOLD and nuisance time series were demeaned/detrended and temporally filtered (0.01–0.08 Hz; Butterworth filter); amplitude of large spikes in BOLD series was reduced (despiking); and multiple linear regression was executed to remove BOLD signal variance attributable to the above confound matrix. We utilized a combination of spike regression and despiking since this combination allowed for better subject retention and improved QC measures (see eFigures 1 and 2) compared to either approach alone in this high-motion sample. Using the xcpengine *seed* module, functional connectivity between a posterior cingulate (PCC) seed (MNI: 0, −62,24; 4 mm radius) and whole brain was extracted; and smoothed to 4 mm (susan).

2.6. Statistical analysis

Our primary fMRI analysis was a paired t-test to compare PCC rsFC during pre- vs. post-mindfulness scan in the at-risk group. For all included participants, PCC-rsFC maps (generated via xcpengine) were entered into a SPM12 second level mode (paired t-test), adjusting for motion (i.e. mean FD). A region-of-interest (ROI) analysis was conducted, including prefrontal ECN structures important to executive function. We defined anterior cingulate and bilateral middle frontal gyrus using WFU Pickatlas.

We next extracted regions with significant rsFC changes in at-risk to assess whether these changes were also observed in healthy controls; and assess group × time interactions. Similar to previous work (Creswell et al., 2016), we assessed a standard *group x time* interaction; we also tested whether the observed pattern of results was consistent with (1) “normalization” (differences between at-risk vs. healthy controls decreased following MBI) or “spreading interaction” (post-MBI at-risk showing unique differences).

Regarding clinical measures, we used repeated measures analysis of variance in SAS 9.41 (proc glm) to assess the degree to which clinical scales changed across pre, post, and 3-month follow-up visits. For each of the scales with both parent- and child-report (CALS, SCARED, MFQ), we used the average of parent and child reports; this was done to minimize multiple comparisons in this small pilot study. We next used paired t-tests to assess early (pre vs. post) and late (post vs. 3-month follow-up) changes in each symptom. We tested whether changes in mindfulness were correlated with or predicted decreases in symptomatology. Later decreases in symptomatology were operationalized as the symptoms score at 3-month follow-up, after adjusting for post-MBI values. Finally, we extracted connectivity values from significant clusters and tested whether early changes in rsFC was correlated with and/or predictive of clinical measures of interest. Given that this is a pilot study, we did not adjust for multiple comparisons for the clinical symptom data.

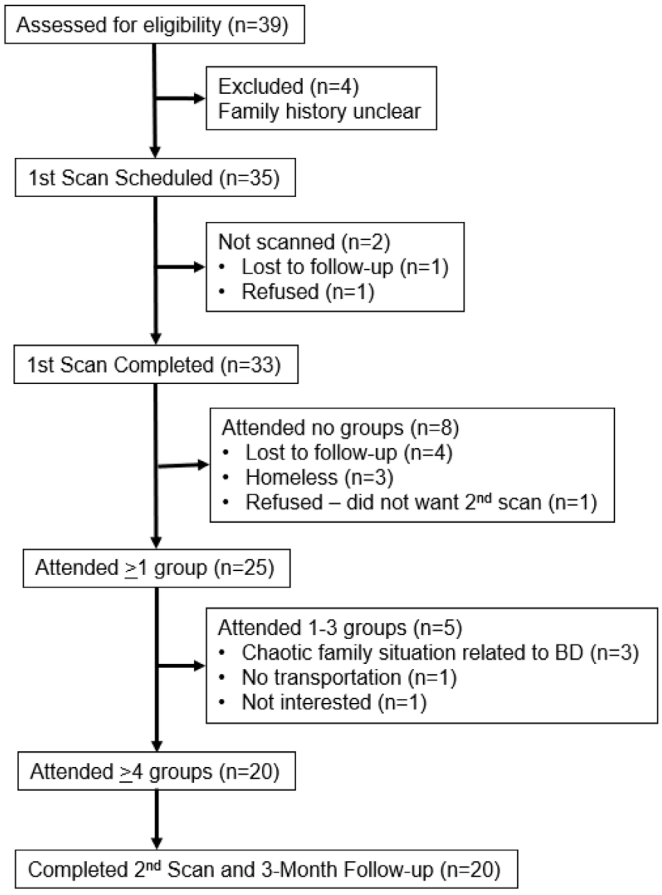


Fig. 1. Diagram for completers vs. non-completers (at-risk only).

3. Results

3.1. Sample

Fig. 1 shows the study protocol and reasons for drop-out. We consented 39 at-risk youth, of whom 35 met study criteria; 33/35 were scanned at T1. Eight scanned participants did not attend any group sessions, due to homelessness ($n = 3$), loss to follow-up (LTFU) ($n = 4$), and refusal ($n = 1$). Of the 25 participants who attended at least one group, 20 attended at least four; these participants were all scanned a second time (T2), and 100% came to the three-month follow-up. Sixteen at-risk participants and 15 healthy controls had good rsFC data for both T1 and T2 scans (i.e. mean FD < 0.5 mm). Table 1 shows the demographic characteristics of the at-risk youth (completers vs. non-completers) and healthy controls. Within at-risk participants, completers vs. non-completers did not show any differences in demographic or clinical characteristics at baseline. At-risk vs. healthy controls were more likely to be non-white and less likely to live with both parents. Most at-risk completers and non-completers met diagnostic criteria for lifetime ADHD (>85%); and a significant minority of at-risk youth had a lifetime history of depressive disorder. Over 80% of at-risk participants had a lifetime history of mental health treatment, including psychotherapy and/or medications.

3.2. fMRI analysis

We found that rsFC increased between PCC and the left dorsolateral prefrontal cortex (dlPFC) between pre- and post-scan ($k = 28$; MNI: −40,26,42; corrected $p = .006$; BA 9) (Fig. 2(a)). In extracted analyses, *group x time* interactions between at-risk vs. healthy controls was significant only at a trend level ($t = 1.76$, $p = .10$). However, unlike at-risk, healthy controls did not show an increase in PCC-dlPFC rsFC across scans (Fig. 2(b)). Prior to the MBI, there were no significant differences (even at a trend level) in PCC-dlPFC rsFC between at-risk vs. healthy controls; thus, this finding does not appear to be normalizing low PCC-dlPFC rsFC in these at-risk participants. Instead, the MBI appears to uniquely increase the PCC-dlPFC rsFC relative to the unexposed group (i.e. healthy controls, who did not attend mindfulness groups). This is consistent with a *group-by-time* "spreading interaction", such that PCC-DLPFC rsFC in the at-risk (MBI) post-scan is increased relative to PCC-DLPFC rsFC in the at-risk (MBI) pre-scan, control pre-scan, and control post-scans ($t = -2.87$, $p = .006$).

3.3. Clinical measures (Table 2)

Repeated measures analysis showed improvements across time in mood lability (CALSpc; $p = .002$) and anxiety (SCAREDpc; $p = .03$), and a decrease in suppression as an emotion regulation strategy (ERQ-supp; $p = .01$). Mindfulness (as measured by the CAMM), also increased over the course of the study, though this was attributable entirely to an increase between the second scan and three-month follow-up (T2 vs. T3; $p = .003$). There were no significant changes in self-reported depression or parent-reported manic symptoms. While there were no significant changes in reappraisal as an emotion regulation strategy across follow-up, there was an early increase in reappraisal (T1 vs. T2; ERQ-reapp; $p = .01$).

3.4. Changes in mindfulness and other clinical measures

Early individual-level changes in mindfulness (i.e. between scans; T1 vs. T2) were not correlated with or predictive of any of the other clinical measures. In contrast, later increases in mindfulness (between second scan and three-month-follow-up; T2 vs. T3) correlated with late decreases in many of the outcomes: SCAREDpc ($r = -0.47$, $p = .04$), CALSpc ($r = -0.52$, $p = .02$), ERQ-suppression ($r = -0.71$, $p = .002$), and MFQpc ($r = -0.48$, $p = .04$).

3.5. rsFC and clinical measures

Increases in PCC-dlPFC rsFC were predictive of lower mood lability at follow-up (T3), after adjusting for mood lability at second scan (T2) ($t = -2.25$, $p = .04$). In addition, rsFC increases were predictive of less emotion suppression at follow-up (T3), after adjusting for suppression at second scan (T2) ($t = -2.75$, $p = .02$). Finally, at a trend level, rsFC increases predicted greater self-reported mindfulness ($t = 2.12$, $p = .05$) and less anxiety ($t = -1.87$, $p = .08$) at follow-up (T3), after adjusting for levels at second scan (T2).

4. Discussion

In this initial feasibility study of mindfulness training for youth at risk for BD, we found that mindfulness training increased rsFC between posterior DMN (PCC) and left dlPFC. This is consistent with a growing body of work that indicates that PCC-dlPFC functional connectivity may be a marker of mindfulness program improvements in stress resilience and health. At-risk youth and healthy controls showed similar PCC-dlPFC at T1, but only the at-risk youth (who participated in the MBI) showed an increase at T2, consistent with a mindfulness-specific change in rsFC ("spreading interaction"). In addition, we found that our MBI was associated with increased self-reported mindfulness, as well as improvements in mood lability and anxiety, and less emotion suppression at follow-up. Furthermore, PCC-DLPFC predicted later decreases in mood lability and emotion suppression; and, on a trend level, decreases in anxiety and increases in mindfulness. Later increases in mindfulness were correlated with improvement in clinical symptoms, including mood lability, depression, anxiety, and emotion suppression.

These findings are consistent with previous work in adults that has

Table 1
Demographic characteristics of At-Risk Completers (AR (C)), At-Risk Non-Completers (AR(non-C), and Healthy Controls (HC).

	AR (C)(n = 20)	AR (Non-C)(n = 15)	HC (2 scans) (n = 15)	AR (C) vs. AR (Non-C)	AR (C) vs. HC
Age (S.D.)	12.1 (1.3)	11.6 (0.9)	12.4 (1.2)	p=.22	p=.55
Gender (% female)	12 (60%)	9 (60%)	10 (67%)	p = 1.0	p=.69
Race (% non-white)	12 (60%)	12 (80%)	4 (27%)	p=.21	p=.05
Living with both parents n (%)	3 (15%)	2 (15%)	9 (60%)	p=.89	p=.006
Family BD subtype				p=.48	
BD-I	4 (20%)	1 (7%)			
BD-II	9 (45%)	9 (60%)			
BD-NOS	7 (35%)	5 (33%)			
BD family member					
Parent	19 (95%)	13 (87%)		p=.38	
Sibling	3 (15%)	3 (13%)		p=.89	
Lifetime diagnoses					
ADHD	17 (85%)	13 (87%)		p=.89	
DBD	4 (20%)	7 (47%)		p=.09	
Anxiety	4 (20%)	6 (40%)		p=.19	
Depressive disorder	8 (40%)	7 (47%)		p=.69	
Current medications					
Stimulants	5 (25%)	4 (27%)		p=.91	
Non-stimulants	5 (25%)	1 (7%)		p=.15	
Antidepressants	5 (25%)	3 (20%)		p=.73	
Antipsychotics	4 (20%)	0 (0%)		p=.12	
Any medication	11 (55%)	6 (40%)		p=.38	
Lifetime treatment history: n (%)[a]	16 (80%)	13 (87%)		p=.60	

[a] Includes medication management and/or psychotherapy in outpatient, in-home, and/or inpatient setting.

Table 2
Change across time in clinical measures.

	n	F test	p-value	T1 vs. T2 (early)	T2 vs. T3 (late)
CALSpc	20	**7.20**	**.002**	**−9.8 (p=.03)**	−11.2 (p=.09)
SCAREDpc	20	**3.70**	**.03**	−2.9 (p=.51)	**−11.8 (p=.05)**
MFQpc	20	0.90	.41	−4.7(p=.37)	−3.5 (p=.53)
CMRS	19	3.10	.06	−3.4 (p=.07)	−1.9 (p=.40)
CAMM	18	**7.15**	**.003**	−0.14 (p=.89)	**3.4 (p=.003)**
ERQ-reappraisal	15	1.70	.20	**3.1 (p=.01)**	−2.3 (p=.25)
ERQ-suppression	15	**5.05**	**.01**	−1.0 (p=.29)	**−2.1 (p=.04)**

found mindfulness to be associated with increased rsFC between PCC and dlPFC (Brewer et al., 2011; Creswell et al., 2016; King et al., 2016), extending this work to a sample of youth at-risk for mood disorder. The PCC is a key node in the DMN, a network involved in mind-wandering and self-referential processing (Sheline et al., 2009; Mason et al., 2007). Others have postulated that increased connectivity between this node and the dlPFC may decrease mind-wandering and facilitate a more focused attention to the present moment (Brewer et al., 2011). This is supported in our study by the finding that PCC-dlPFC rsFC increases predicted increases in self-reported mindfulness. Interestingly, this rsFC increase is not associated with symptom changes at the time of scan, but rather predicts the changes over the next three months. Thus, these neural changes are perhaps an early indication of increased mindfulness, which then subsequently lead to self-reported increases in mindfulness, improvements in emotion regulation (e.g. decreased emotion suppression) and decreases in mood lability.

Contrary to our hypotheses, mindfulness did not increase during the group, but rather increased during the three-month period following group. While mood lability (our target symptom) decreased during the group (T2-T1), other symptoms that showed changes across time (i.e. emotion suppression and anxiety) did not improve significantly during group, but rather between the last group and three-month follow-up (T3–T2). One possibility is that skills learned in the MBI took time to incorporate, leading to changes only after the groups had ended. This is interestingly similar to neurofeedback, where many of the clinical changes are observed weeks to months after the neurofeedback intervention (Rance et al., 2018). If replicated, this time course is quite promising, as it indicates that changes in mindfulness, mood lability, and anxiety may be durable and sustained. Given that most of our participants were in treatment, a second possibility is that the MBI led to greater engagement in subsequent treatment (psychotherapy or medication management), which then may have resulted in sustained improvements. While we do not have sufficient data regarding treatment engagement in the current pilot study to evaluate this possible mechanism, it will be tested in future studies.

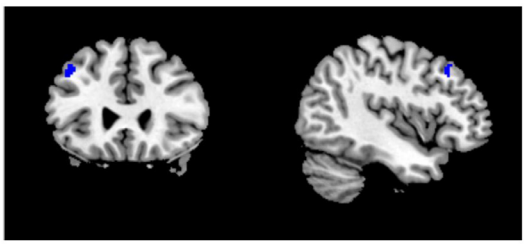
We note that this sample was not recruited exclusively from a clinic, but the majority had enough symptoms and impairment to warrant treatment at some point in time. Most participants met criteria for ADHD, while a significant minority had a lifetime history of depression, anxiety, and disruptive behavior disorders. Interestingly, there are several studies that have found MBIs to be helpful for ADHD, although this work is in early stages with primarily pilot studies and wait-list controls (Evans et al., 2018; Cairncross and Miller, 2016). Approximately half of our participants were on at least one medication. The characteristics of this sample are related to the inclusion criteria, which included a family history of bipolar disorder and elevated mood lability. Also, the time commitment required for these groups selected for participants who were symptomatic and generally had some functional impairment.

5. Limitations

Our study has many limitations that need to be considered when interpreting these results. First, this is a pilot study with a limited sample size and no (at-risk) comparison group. We note that small sample sizes increase the likelihood that observed associations are due to chance. In addition, we do not know whether these changes are related to mindfulness or another non-specific component of the MBI (e.g. social interaction and support). However, we do note that the consistency with previous work, as well as the very interesting relationships with clinical variables, are less consistent with chance or non-specific group effects. Second, many participants had concurrent treatment, which may also have confounded our findings. While we assessed overall level of care (e.g. outpatient), we did not assess specific type of therapy or level of engagement; it is possible that individual changes in these factors could have led to observed neural or clinical changes, though it is unlikely that this would lead to systematic bias.

Third, youth did not all participate in the same group, but rather

a. Left DLPFC region showing increased PCC rsFC following MBI in the at-risk youth



b. Group x Time interaction within extracted cluster (p=.10). Compared to all other scans (Healthy Controls; At-Risk Scan 1), At-Risk Scan 2 showed increased PCC-DLPFC rsFC (p=.006); this pattern is consistent with a “spreading interaction” model.

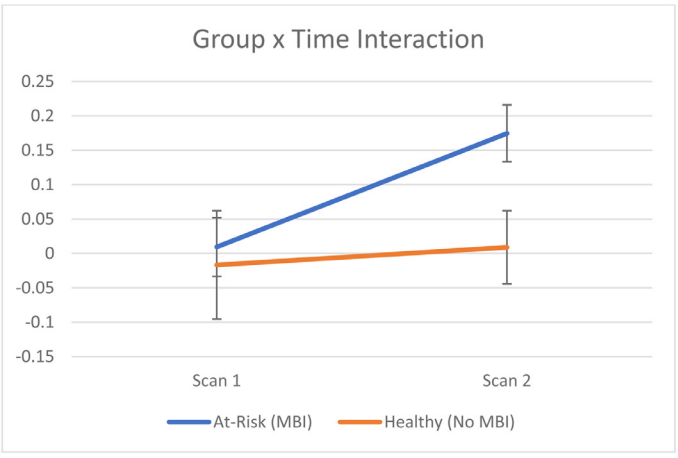


Fig. 2. (a) Left DLPFC region showing increased PCC rsFC following MBI in the at-risk youth. (b) Group × Time interaction within extracted cluster ($p = .10$). Compared to all other scans (Healthy Controls; At-Risk Scan 1), At-Risk Scan 2 showed increased PCC-DLPFC rsFC ($p = .006$); this pattern is consistent with a “spreading interaction” model.

participated in four groups over the course of two years. There are likely group-specific effects that we were not able to assess in this analysis due to limited power; here, we assess the overall pre-post MBI differences. Fourth, we recruited 35 at-risk participants, while only 20 completed the protocol. Ten participants did not attend any groups, reflecting primarily the stressors among families coping with severe mental illness. Of those who attended at least one group, 80% attended at least five; this points to the acceptability of the groups to both participants and their parents. While it is possible that completers vs. non-completers were different, which would impact the generalizability of our findings, we did not find any demographic or clinical differences between these groups. Future work will explore ways to increase accessibility of these groups for families with severe mental illness (e.g. use of videoconferencing technology).

6. Conclusions

In conclusion, we find that an MBI in youth at-risk for bipolar disorder is associated with increased PCC-dlPFC rsFC, which is in turn predictive of decreases in mood lability. While this study did not have a control arm, we did have healthy controls who did not undergo the MBI and did not show an increase in PCC-dlPFC rsFC. Comparison with healthy controls indicates that MBI-related changes were not “normalizing”. Thus, effects of the MBI appear to be mindfulness-specific, perhaps reflecting increased resilience, as opposed to addressing brain abnormalities in the at-risk participants. An important next step is to assess these neural markers and effects in a larger randomized controlled trial. With an MBI-specific marker identified, a future direction will be to assess whether we can enhance this increase in rsFC in more targeted ways (e.g. neurofeedback). Finally, given that this intervention appears to increase PCC-dlPFC rsFC, which in turn predicts less mood lability, future work may also assess other populations for whom emotion dysregulation is problematic, such as youth at risk for depression.

Contributors

Dr. Hafeman obtained funding, designed the study, co-designed and co-led the mindfulness groups, conducted or supervised all assessments, conducted all statistical analyses, and wrote and revised the manuscript. Ms. Ostroff co-designed and co-led the mindfulness groups and provided critical revisions on the manuscript. Ms. Feldman was involved in data collection and data management and provided critical revisions on the manuscript. Ms. Hickey was involved in data management and provided critical revisions on the manuscript. Dr. Phillips provided important feedback regarding study design, analysis, and manuscript. Dr. Creswell provided guidance regarding study design, design of mindfulness groups, and analysis. Dr. Birmaher provided consultation regarding study design, assessment, and analysis; and provided important feedback on the current manuscript. Dr. Goldstein was involved in study design, provided guidance regarding implementation of mindfulness groups, and gave feedback on analysis and final manuscript.

Role of the funding source

Our funding sources did not have any role in determining study design; the collection, analysis, or interpretation of data; and no involvement in the decision to submit results for publication.

Acknowledgments

We would like to acknowledge our participants and families. We would like to acknowledge our funding sources from the Klingenstein Third Generation Foundation and K23MH110421.

Disclosures

Dr. Hafeman has received funding from the National Institutes of Mental Health, the Klingenstein Third Generation Foundation, and the Brain and Behavior Research Foundation. Dr. Goldstein has received funding from the National Institutes of Mental Health and the American Foundation for Suicide Prevention, University of Pittsburgh CTSI, and Brain and Behavior Foundation; and royalties from Guilford Press. Dr. Birmaher receives funding from the National Institutes of Mental Health; and has or will receive royalties for publications from Random House, Inc., Lippincott Williams & Wilkins, and Wolters Kluwer. Dr. Phillips has received funding from the National Institutes of Mental Health. Dr. Creswell has received research funding from Headspace Inc. Ms. Ostroff, Ms. Feldman, and Ms. Hickey do not have any financial disclosures.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2020.06.042.

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