Mindfulness Can Change Your Brain… For The Better!

A predictive analysis of anatomical MRI data using machine learning

A Major Qualifying Project Report submitted to the faculty of Worcester Polytechnic Institute Department of Biology and Biotechnology in partial fulfillment of the requirements for the Degree of Bachelor of Science.

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Submitted on April 25, 2024 to
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Acknowledgments

I would like to express my deepest gratitude to my advisor, Dr. Ben Nephew, whose guidance, support, and insightful critiques were invaluable throughout the research and writing of this project. Your expertise and encouragement were crucial to the completion of this project. What I discovered about the research process, enhanced in laboratory skills, applied to my courses, and more are invaluable and guaranteed to help me in my scientific career. I would also like to express my gratitude and thanks to Dr. Richard Lopez, whose initial vision and idea for this project lead to an amazing outcome. I am thankful to have worked under such a determined researcher whose passion for science I admire so much.
I want to say thank you to Bhaavin Jogeshwar and Senbao Lu for helping me with understanding what machine learning is. I would not have been able to learn how to code without your help. I am also immensely thankful to Matthew Scarpaci and Eric Loucks at the Brown University School of Public Health, who provided additional advice and resources that greatly enhanced my research.
A special thank you to Worcester Polytechnic Institute and the Department of Biology and Biotechnology, who provided me the opportunity to apply ***Lehr und Kunst*** to its fullest extent.

Abstract

In recent years, the U.S. Surgeon General declared a youth mental health crisis, characterized by a sharp increase in depression and anxiety among young adults. Emerging research has highlighted the potential of mindfulness-based interventions (MBIs) such as Mindfulness-Based Cognitive Therapy (MBCT), which integrates cognitive-behavioral techniques with mindfulness practices, in addressing these mental health challenges. This study seeks to explore the neurobiological impacts of MBIs on brain structures involved in depression, focusing on regions like the amygdala, hippocampus, and the prefrontal cortex, which are known to play pivotal roles in emotional processing and regulation. Using advanced machine learning techniques, this study analyzes MRI data to investigate structural brain changes and their correlation with improvements in emotional regulation, as measured by the Difficulty in Emotion Regulation Scale (DERS).

The results are poised to offer novel insights into the specific neurobiological pathways altered by MBIs, potentially guiding more effective treatments tailored to individual neurobiological profiles. The study not only contributes to a deeper understanding of depression’s underpinnings but also evaluates the long-term effectiveness of mindfulness practices in altering brain structures associated with mood regulation. This research underscores the necessity of further investigative efforts to substantiate MBIs as a viable and effective therapeutic option in the mental health arsenal, particularly for depression linked to neurobiological factors.

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Introduction

In 2021, the U.S. Surgeon General announced a youth mental health crisis highlighting a swift rise in depression and anxiety rates. This sudden rise in mental health issues among the young adult population could be related to social media but there hasn't been enough research to make that connection. Depression is a mood disorder that has been a leading driver of the Youth Mental Health crisis among young adults (Office of the Surgeon General, 2021). Levels of neurotransmitters like serotonin, dopamine, GABA, and others are reduced in depression and are the main points of treatment via medication. Neurotransmitters like GABA, in low concentrations reflect acute stress effects caused by depression. Evidence also points to the dysfunction in the glutamate neurotransmitter system in depression pathways as seen under fMRI screenings (Hassler 2010).

Research suggests that several structures in the brain have been implicated in the pathways for depression including the amygdala, the hippocampus, and the thalamus (Zhang et. al. 2018). The cortical and subcortical regions of the brain are also affected in depression (Pandya et. al. 2013). The cognitive model of depression put forth by Disner et. al. explains how negative cognition is increased under the influence of the subcortical emotional processing regions (Disner et. al. 2011). Disner explains that since individuals who experience depression are more likely to focus on negative stimuli which blocks out processing of other stimuli. This directly relates to a decrease of activity in the right ventrolateral prefrontal cortex (VLPFC) and the right dorsolateral prefrontal cortex (DLPFC). It is also seen that individuals with depression seem to have decreased activity of the anterior cingulate cortex (ACC) which is responsible for the ability to disengage from negative stimuli in comparison to healthy individuals. Decreased activity in the amygdala is also one of the main outcomes of depression. Amygdala activity in depressed individuals is heightened when presented with negative stimuli and this response is consistent with patients who show difficulties in emotion regulation (Ferri et. al., 2017).

Aside from medication and standard behavioral therapies like CBT, there have been other methods used to treat depression like mindfulness based interventions. There has been some research on mindfulness based interventions as a potential therapeutic approach to treat depression as a non-invasive alternative to medication. In a study by Mesquita and colleagues, mindfulness based interventions have been effective in reducing depression symptoms in a range of participants and results have been comparable to Cognitive behavior Therapy (CBT) (Mequita et. al., 2023). A more widely accepted form of mindfulness based interventions is more formally known as 'Mindfulness-Based Cognitive Therapy' which is a type of psychotherapy that combines CBT, meditation, and mindfulness exercises. The overarching goal of these MBCTs' is practicing mindfulness to help the individual become more receptive to positive psychological thinking rather than a negative internal reflection. A study by Eisendrath et. al. (2018), showed MBCT reduced depressive symptoms in patients with treatment-resistant depression.

The problem is none of these studies can confidently conclude if these MBCTs affect the brain regions that have been implicated in depression. Understanding these neurobiological underpinnings of depression and MBCT would help to effectively target brain regions to alleviate and treat symptoms of depression. A huge part in predicting whether these mindfulness based interventions are going to work is to look at individual data collected from resting state analyses to identify the efficacy of mindfulness based treatments for depression. Predicting individual responses to these mindfulness based interventions still remains a challenge in the context of alleviating symptoms of depression. Research consistently supports the effectiveness of mindfulness-based interventions (MBIs) in reducing the severity of depression and anxiety symptoms (Collins, 2019; Hofmann, 2017;

Mesquita, 2023). These interventions, such as mindfulness-based stress reduction and mindfulness-based cognitive therapy, have been found to be particularly beneficial in preventing depressive relapse (Collins, 2019; Mason, 2001). The development of mindfulness skills, an attitude of acceptance, and living in the moment are key components of these interventions (Mason, 2001). However, further research is needed to fully understand the mechanisms of action and to establish guidelines for the use of MBIs in depression treatment (Collins, 2019; Mesquita, 2023).

Predictive models have been used to predict the outcomes of depression treatments in clinical trial settings (Coley et. al., 2021). These predictive models are useful in informing clinicians to cater treatments to patients' needs. These models could also be integrated in studying the effects of psychotherapies like MBCT against other more commonly known treatments of depression. Electronic Health Records (EHRs) are used in these predictive models to collect data like biomarkers and patient specific characteristics to be able to determine primary care for depression and identify points of treatment (Nemesure, 2021). The use of Artificial Intelligence (AI) in predictive modeling of clinical outcomes of depression and other mental health disorders has been increasing in recent years. Particularly in the case of depression and its underlying neural mechanisms, predictive modeling has been a big help to clinicians in determining the course of treatments for most patients. These predictive models can give insight into brain activity and neuroplasticity in specific regions that aren't specifically targeted in other forms of brain studies. There are several limitations when looking at predictive models used to understand the neural pathways of depression and the efficacy of mindfulness based interventions. Being able to accurately measure the therapeutic effects of mindfulness based interventions and changes in brain regions related to them requires its quantification in order to obtain measurable data. Predicting the long term effects of these interventions is also challenging because most of these models fail to capture these changes induced by mindfulness based interventions. Current predictive models fail to capture the individual variability in neural responses to psychological processes involved in mindfulness based therapies and treating depression. Current predictive models also fail to gauge how mindfulness based treatments may decrease depression from a behavioral perspective. Most depression studies were mainly region of interest (ROI) or network based. This limited researchers as they couldn't observe overall effects interventions and mindfulness based treatments would have on the brain. This allows researchers to only look at crude brain regions that are involved in depression pathways but not specific parts of the brain. This progress in methods of analysis also yielded means for multiple comparisons between parts of the brain.

To address the limitations in understanding how mindfulness based interventions affect brain regions implicated in depression, it is also important to understand emotional regulation and how that plays a part in the treatment of depression. Emotion regulation is often defined as a set of cognitive processes that influence how individuals process, express, and respond to emotions (Gross et. al., 1998). Emotion regulation has been known to affect how individuals react to their depression treatments like CBT and mindfulness based interventions. A dysfunctional emotion regulation strategy leads to an increase in the pathogenesis of depression (Compare et. al., 2014). Evidence also suggests that a dysfunctional emotion regulation strategy results in a negative effect on cognitive and neurobiological mechanisms like the overactivation of the HPA axis. The Difficulty in Emotion Regulation Scale (DERS) is a self report measure of 16 items that assess individuals ability to respond to situations that involve difficulty in emotion regulation. This scale is typically used to conceptualize emotion regulation and has psychological and clinical applications. It has 5 components used to assess emotion regulation: nonacceptance of emotional responses, difficulty in engaging in goal-directed behavior, difficulty in impulse control, limits in utilizing emotion regulation strategies, and lack of emotional clarity. A research gap lies between how different brain structures and the DERS can be used to better understand depression and mindfulness based interventions. This can be combated by using artificial intelligence (AI) and machine learning (ML). AI and ML methods have been used to identify patterns in behavioral data that could be used to predict the efficacy of interventions used to treat various mental health problems. These methods allow for the consideration of various hypotheses and help to examine the complex relationship between various structures of the brain and the mechanisms they are implicated in the pathways of depression. The aim of this project is to leverage MRI data gathered in a resting state functional connectivity study to understand the relationship between depression and interoception measures and changes in functional connectivity in the brain. The objective of this project is to examine the links between structural measures in the brain like volumes of cortical and subcortical regions implicated in the pathways for depression and the symptoms of depression and the effectiveness of mindfulness based interventions. Evaluating relationships between changes in brain structures over time and depression and interoception measures would help in identifying the positive effects of mindfulness based interventions. Research suggests that glucocorticoid neurotoxicity, glutamatergic toxicity, decreased neurotrophic factors, and decreased neurogenesis have been said to reduce brain volume in pathways of depression (Hasler, 2010). Similarly there is also consistent evidence of volume loss in the hippocampus and other brain regions because of the duration of untreated depression. Predictive modeling and ML tools are specifically helpful when looking at volume loss and changes in brain regions that cannot be targeted using conventional methods of looking at mental health disorders like MRIs.

The overarching research question for this project is to analyze brain data from anatomical MRI scans to identify structural differences involved in changes induced by psychological factors in individuals with depression symptoms. These MRI scans will be analyzed to identify specific brain structures that are implicated in the pathways for depression. This analysis will also help in understanding the role mindfulness based interventions have in improving emotion regulation. In a paper by Polcari et. al. neural correlates of mindfulness based blood pressure (MB-BP) interventions were identified using diffusor tensor imaging (DTI). Changes in structural connectivity were associated with depression symptoms, mindfulness, and emotion regulation. Using resting state data, MRI scans will be processed in the Free Surfer software to further identify the specific volumes of brain structures and their correlations to DERS.

Research Questions and Hypotheses

This study explores the hypothesis that mindfulness based interventions may be associated with structural changes in brain regions responsible for depression like the prefrontal cortex, amygdala, and the hippocampus and changes in these might correlate with emotion regulation among individuals. The independent variable would be the mindfulness based interventions which include mindfulness meditations and alternatives to common treatments for depression. The dependent variable would be the changes in volumes in brain regions. The brain regions that will be analyzed in this study will be the amygdala, the prefrontal cortex, and structures of the limbic system. These regions are most prominently implicated in the pathways to depression and emotion regulation. This study will also explore the planned hypothesis that mindfulness based interventions lead to significant changes in structures of the brain associated with depression and emotion regulation like decreased volume in the amygdala identified using data from anatomical MRI scans. These structural measures will be correlated with improved emotion regulation as measured against the DERS using the Free Surfer software. The independent variable will be the mindfulness based intervention and the dependent variable would be the volume changes in the brain in the amygdala and prefrontal cortex. The Free Surfer software will be used to conduct analysis of anatomical MRI data gathered in a resting state functional connectivity study to establish a connection between volume changes in the brain and emotion regulation. The hypotheses will aim at answering the research question of how mindfulness based interventions influence structural changes in brain regions associated with depression pathways. This analysis will also aim at answering if there is an impact on emotion regulation abilities in individuals.

Methods

Participants and Data Acquisition

Participants for this analytical study were recruited pre COVID in 2018 to 2020. Participants were recruited via flyers/recruitments cards throughout Rhode Island and Massachusetts, referrals from friends, family members, coworkers, or from a primary or other health care practitioner. Participants were only included in the randomized control trial if they had hypertension or elevated blood pressure, were able to speak, read, and write English, and were adults (≥18 years of age). Participants were excluded if they regularly meditated, had a serious medical illness which would interfere with their class attendance, had active substance abuse, suicidal ideation, or eating disorder, and a have a history of bipolar or psychotic disorders or self-injurious behavior. The protocol was approved by an institutional review board at Brown University and participants signed a written informed consent. Clinical, Mindfulness, and MRI data was obtained from baseline, 10 weeks, and 6 months following completion of MB-BP or active control protocol.

Data Analysis

To convert PAR/REC files to NIfTI format using FreeSurfer, an intermediary tool or software needs to be used, as FreeSurfer itself does not directly handle PAR/REC to NIfTI conversion. However, other tools can be used to perform the conversion before processing the images in FreeSurfer. One commonly used tool for this purpose is "dcm2niix," which is capable of converting various DICOM files to NIfTI format and can handle some non-DICOM formats as well.

Step 1: Convert PAR/REC to NIfTI

First convert the PAR/REC files to NIfTI format. If "dcm2niix" does not support PAR/REC directly (support can vary based on the version and build), you might need to use a tool specifically designed for PAR/REC files, such as "parrec2nii" from the "nibabel" Python package or other similar utilities.

Using `dcm2nii` (if compatible):

1. Install `dcm2nii` on your system. It's available for Linux, macOS, and Windows.
2. Open a terminal or command prompt.
3. Navigate to the folder containing your PAR/REC files.
4. Run `dcm2nii` with the appropriate options. For example:

```bash
dcm2niix -o output_directory path_to_PARREC_files
```

This command tells `dcm2niix` to convert the files in `path_to_PARREC_files` and place the output NIfTI files in `output_directory`.

Using `parrec2nii` from `nibabel`:

1. Ensure you have Python and `nibabel` installed.
2. Use the `parrec2nii` command-line interface or write a small Python script to convert the files:

```python
import nibabel as nib
pr = nib.load('path_to_your_file.PAR')
nib.save(pr, 'output_file.nii')
```

Step 2: Process NIfTI Files in FreeSurfer

Once the NIfTI files have been converted, process them in FreeSurfer using its various tools and pipelines, such as `recon-all` for cortical reconstruction and volumetric segmentation.

After the images have been processed and opened in FreeSurfer, they need to be segmented into each individual image to analyze volume and structural connectivity changes. Use the following code to segment volumetric and thickness from the anatomical MRI data.

```
#!/bin/bash
# Path to the FastSurfer script
FASTSURFER_SCRIPT="/path/to/run_fastsurfer.sh"
# Path to your subject directories (only needed if using subject IDs)
DATA_DIR="/path/to/data"
# Path to your subject list
SUBJECT_LIST="subject_list.txt"
# Read each line in the subject list
while IFS= read -r subject
do
  echo "Processing $subject"
  # Run FastSurfer for each subject
  bash "$FASTSURFER_SCRIPT" --fs_license /path/to/license.txt --t1
"$DATA_DIR/$subject/mri/orig.mgz" --sid $subject --sd /output/path --parallel
done < "$SUBJECT_LIST"
"Run_fastsurfer.sh  --t1 $directory/of/.nii/file
--sid try1fastsurfer --sid directory
--parallel
--threads 16
--device cuda
--no_cereb"
```

This will output volumetric data for each MRI scan and store it in a .txt file.

The DKT atlas was used to compare and analyze brain regions to the anatomical MRI data. Using this atlas the volumetric data was extracted and calculated.

Results

In total 27 participants' data was used in this analysis because they completed both pre- and post FMRI imaging. All of these participants were administered the MAIA (for interoceptive awareness), DERS (for emotional regulation), and the CESD-R (for depression). Using the predictive analyses model described above, that uses ML, changes overtime were investigated from baseline and 6 months. DTI MRI data was also used from these scans to investigate variables in white matter neural tracts at baseline and 6 months follow up.

Group Differences in Clinical Outcomes

Table 1: Changes in clinical variables over time

Clinical Variable	Group	Baseline Mean	6 Month Mean	Mean Change Over Time
DERS Full Score	Control	75.12	76.47	1.35
	Intervention	78.1	68.3	-9.8
Interoceptive Awareness	Control	14.88	13.82	-1.05
	Intervention	19.6	14.9	-4.7
Emotional Regulation	Control	9.88	10.53	0.65
	Intervention	10.6	9.4	-1.2

No significant differences were observed in baseline values for either control or the intervention conditions. A significant interaction was seen between intervention condition and time with respect to MAIA scores. There was a statistically significant ($p<0.05$) difference between MAIA scores of participants who participated in the intervention versus those who didn't participate in the intervention. No statistically significant effects were seen on the DERS scores either.

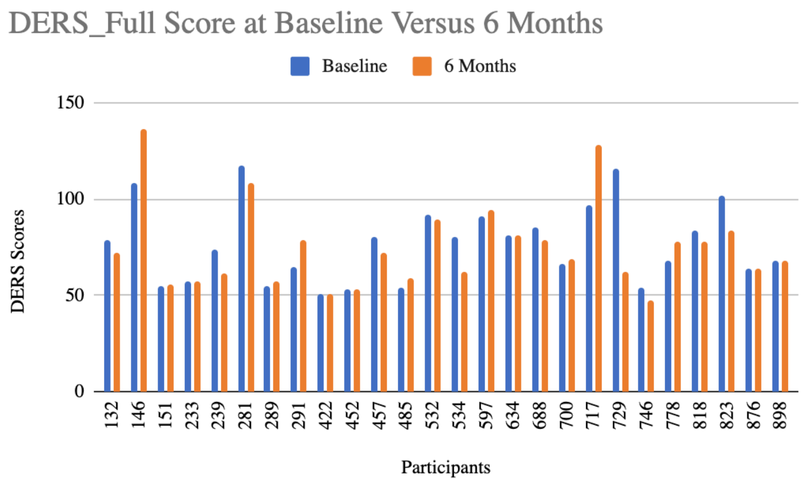

Figure 1: DERS_Full Scores for each participant at baseline versus 6 months

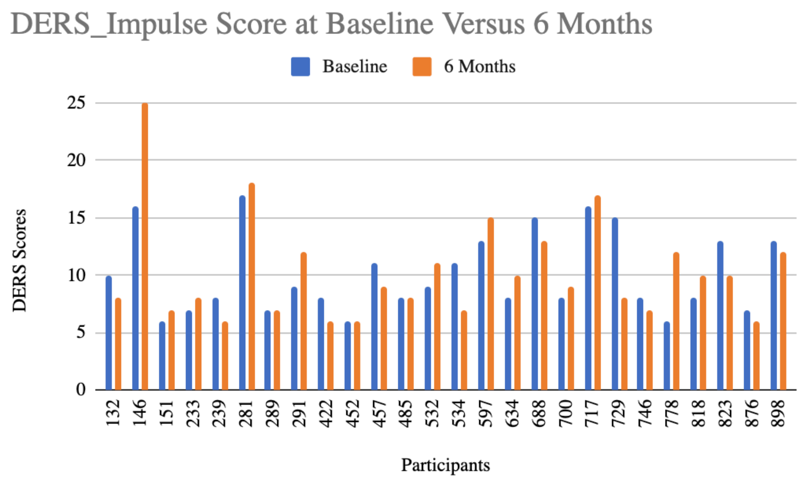

Figure 2: DERS_Impulse Scores for each participant at baseline versus 6 months

Group Differences in MRI Metrics

From the table above significant differences are seen between MB-BP and control over time when looking at volumetric changes in the brain. 5 brain regions were selected a priori to analyze using ML pipeline and Random Forest (RF) pipeline. No effect was seen on the left cerebral white matter whereas significant changes were seen in the right cerebral white matter, hippocampus, amygdala, and the insulae. This shows significant effects of the MB-BP intervention on depression pathways specifically in the amygdala, hippocampus, and insulae.

Table 2: Volumes in mm^3 for control and MB-BP

	Group 1	Group 1	Group 2 (MB-BP)	Group 2 (MB-BP)
	Baseline	6 Months	Baseline	6 Months
Left Cerebral White Matter	104.46	104.54	104.45	104.54
Right Cerebral White Matter	106.01	105.40	105.04	**106.24**
Hippocampus	149.38	149.59	148.17	**151.05**
Amygdala	151.79	152.35	151.40	**153.08**
Left and Right Insulae	134.78	134.20	134.99	**136.30**

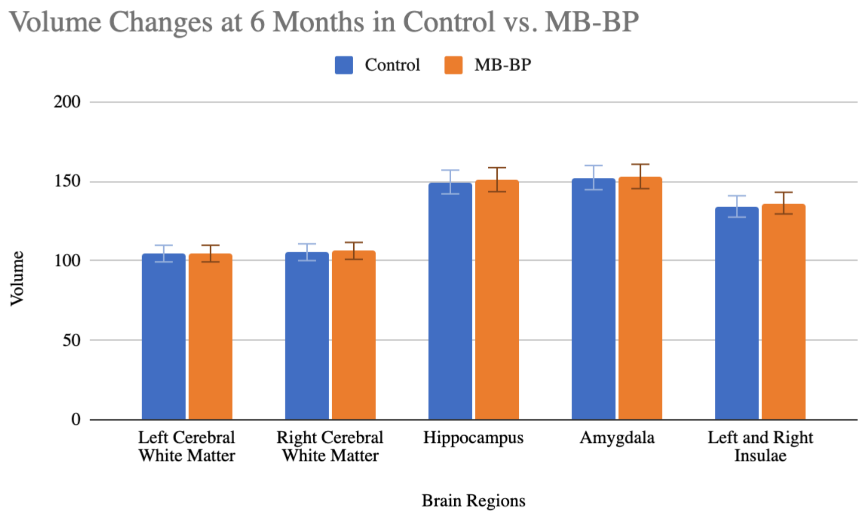

Figure 3: Volume changes between control and MB-BP in brain regions

Clinical Outcome and MRI Metric Correlations

Table 3: Correlations between changes over time in Interoception and DERS scores and MRI metrics

	MRI Metric		
	Hippocampus	**Amygdala**	**Left and Right Insulae**
Interoceptive Awareness	R^2= 0.276 p=0.008	R^2= 0.15 p=0.351	R^2= 0.188 p=0.151
DERS	R^2= 0.175 p=0.078	R^2= 0.041 p=0.166	R^2= 0.331 p=0.107

The table above shows correlations between interoceptive awareness and depression symptoms with MRI metrics over time. Changes in the hippocampus, amygdala, and insulae were positively correlated with interoceptive awareness and DERS scores. These changes were negatively correlated with MAIA scores.

Discussion

This predictive analysis was conducted using data that was used in a stage 1 clinical trial of MB-BP (Loucks et. al., 2019). This study was a predictive analysis that aimed at identifying volumetric changes in brain regions that are implicated in depression pathways using anatomical MRIs. This analysis provided insight into structural connectivity and volume changes influenced by MBIs. Increases in interoceptive awareness and decreases in depression symptoms were observed. Changes over time in interoceptive awareness and emotion regulation were observed within control and intervention conditions. STructural connectivity and volumetric changes were observed when the MB-BP control participants were compared to controls. From this analysis, it can be said that MB-BP and MBIs influence volumetric changes in brain regions leading to increased structural connectivity between brain regions in the depression pathway.

There were significant correlations between key outcomes and MRI change over time. These changes in MRI metrics in the hippocampus and amygdala are associated with increased mindfulness and decreased depressive symptoms. Similar research using fMRI has identified specific brain regions involved in mindfulness, including the midline cortical structures associated with interoception, such as the anterior insula, ventral anterior cingulate cortex, medial prefrontal cortex, and precuneus (Ives-Deliperi, 2011). These regions are also implicated in depression, with changes in cerebral blood flow and metabolism observed in the frontal-temporal cortex and caudate nucleus (Cummings, 1993). Furthermore, mindfulness meditation has been found to induce gray matter changes in the right anterior ventral insula, left and right insulae, and the anterior cingulate gyrus (Pernet, 2020, 2021). These findings align with the findings of this study in that mindfulness and depression symptoms may be seen in overlapping brain regions, particularly those involved in interoception and emotional processing. The findings of this study are consistent with previous research on mindfulness and depression symptoms. A meta-analysis on MBCTs also yielded similar results where it was concluded that it is an effective treatment for depression (Goldberg et. al., 2019).

The results from the MAIA scores were negatively correlated with changes in brain regions over time. On the other hand, the DERS scores were positively correlated with changes in brain regions over time. These findings are consistent with other studies that have investigated changes in neural tracts related to depression pathways. Research has consistently shown a correlation between DERS and volume changes in the hippocampus and amygdala. In individuals with major depressive disorder, larger amygdala volumes are associated with worse memory performance and higher anxiety scores (Weniger, 2006). Similarly, smaller hippocampal volumes are related to higher anxiety scores (Weniger, 2006). In adolescents at ultra-high risk for psychosis, amygdala volume is positively correlated with sadness emotion recognition, particularly in females (Bartholomeusz, 2014). In children with and without a history of preschool onset MDD, smaller hippocampal volumes are associated with greater cortico-limbic activation to sad or negative faces (Suzuki, 2013). Furthermore, there is a sex difference in the correlation between emotional control and amygdala volumes, with smaller left amygdala volumes being associated with better emotional control in girls and larger left amygdala volumes being associated with better emotional control in boys (Blanton, 2010). All of this evidence points to the beneficial effects of MBIs in increasing and promoting structural connectivity in brain regions implicated in depression pathways. These findings create opportunities for further exploration using ML pipelines to analyze anatomical MRIs and identify markers for treatments and potential onset of depressive episodes.

Conclusion

For a predictive analysis study analyzing brain volume changes in depression pathways with respect to MBIs using ML tools, there are several promising future directions that could enhance the understanding and efficacy of these interventions. Future studies could incorporate a broader range of data types, including genetic, epigenetic, and biochemical markers, alongside anatomical MRI data. Integrating these diverse data streams could improve the predictive power of ML models and offer a more comprehensive understanding of how MBIs influence brain structure and function in the context of depression. Implementing longitudinal designs that track changes over longer periods can help in understanding the long-term effects of MBIs on brain structure and function. This would allow researchers to assess the sustainability of benefits from MBIs and observe potential delayed effects on brain plasticity and depressive symptoms. Future research could focus on including a more diverse sample population in terms of ethnicity, age, severity of depression, and other mental health conditions. This diversity would help in generalizing the findings and tailoring interventions to specific subgroups within the population. Utilizing more advanced machine learning algorithms such as Deep Learning (DL) could enhance the analysis of complex interactions within brain imaging data. Techniques like convolutional neural networks (CNNs) could be particularly useful in automatically detecting patterns and features in brain images that relate to the effectiveness of MBIs. Developing systems that use real-time brain imaging and machine learning to provide feedback during MBIs could help in customizing and optimizing interventions for individual patients based on their specific brain activity patterns. Conducting studies that compare the effectiveness of different types of MBIs (e.g., Mindfulness-Based Cognitive Therapy vs. Mindfulness-Based Stress Reduction) could elucidate which aspects of mindfulness practices are most beneficial for brain health and depression alleviation. Further research into the mechanisms by which MBIs affect brain structure and function could provide deeper insights into the biological pathways influenced by mindfulness practices. This could involve exploring the role of stress reduction, inflammation reduction, and enhancement of neuroplasticity. Exploring how MBIs can be effectively combined with traditional therapeutic approaches like CBT or pharmacotherapy could provide a holistic approach to treating depression, leveraging the strengths of both traditional and alternative therapies. These directions not only aim to refine the predictive analytics capabilities but also seek to deepen the understanding of how mindfulness interventions can be tailored and optimized to better treat depression, ultimately improving patient outcomes.

While MBIs are effective and can be used in tandem with more traditionally established treatments for depression, there is more to be explored in terms of increased neural plasticity and structural connectivity over time. The current study has demonstrated the potential of mindfulness-based interventions (MBIs) to influence brain structure changes in individuals with depression, utilizing advanced machine learning tools to analyze MRI data. Despite these promising findings, several limitations must be acknowledged. The sample size was relatively small, which might limit the generalizability of the results. Furthermore, the study focused on short-term effects without assessing the long-term sustainability of the brain changes and improvements in depressive symptoms.

Additionally, the study used a homogeneous participant pool that might not reflect the broader population affected by depression. Future research should aim to include a more diverse demographic to ensure the findings are applicable across different ages, ethnicities, and severities of depression. Moreover, integrating multimodal data sources and employing longitudinal designs could provide more comprehensive insights into how MBIs affect brain structure and depression over time.

Despite these limitations, the study contributes significantly to our understanding of the neurobiological impacts of MBIs and paves the way for further exploration into personalized mindfulness practices as a therapeutic approach for mental health disorders, particularly depression. The integration of machine learning offers a novel approach to identifying and predicting the effectiveness of MBIs, which could lead to more targeted and effective treatments. As research continues to evolve, these findings hold the potential to inform clinical practices and improve outcomes for individuals struggling with depression.

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