PART B
STUDY DESCRIPTION

TITLE OF PROTOCOL	**EEG changes with meditation: A proposal to analyze EEG changes with a simple, online, guided meditative tool**
Principal Investigator	Balachundhar Subramaniam MD, MPH

B1. PURPOSE OF PROTOCOL

The purpose of this study is to assess:

a) the qualitative EEG measures associated with meditation
b) the observed difference in EEG changes between novice and experienced meditators
c) the observed difference in EEG changes between the start and end of 6 weeks of daily meditation

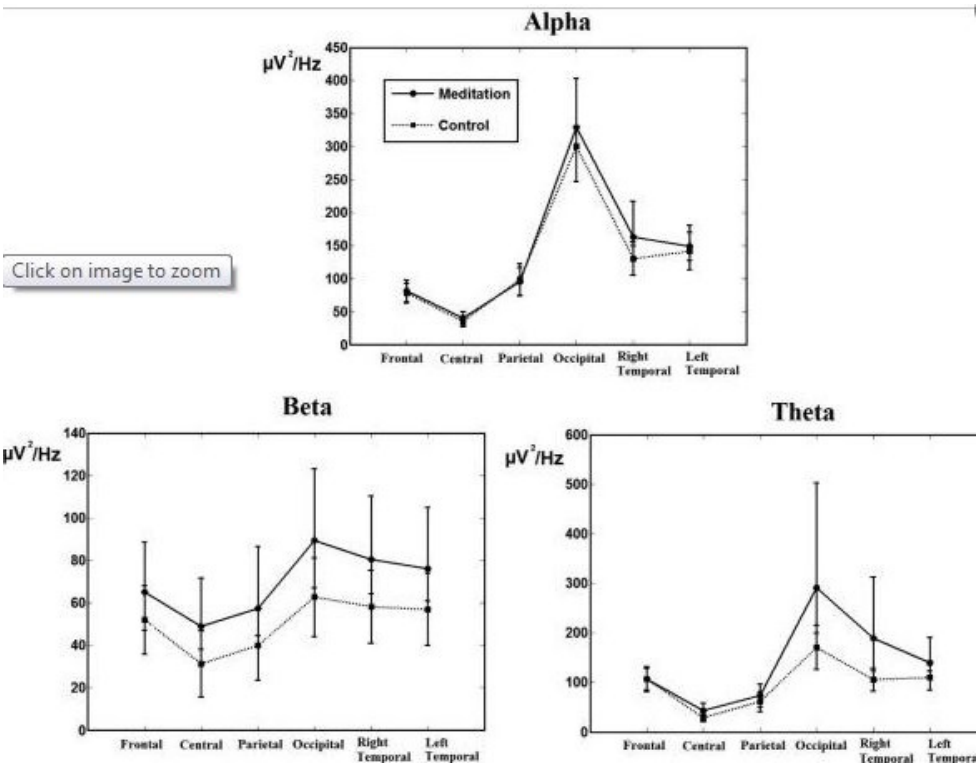
B2. SIGNIFICANCE AND BACKGROUND FOR THE STUDY

Meditation refers to a category of self-regulation practices which focus on training attention and awareness in order to bring mental processes under greater voluntary control. Meditation, as therapy, has the potential to improve mental well-being and development in specific capacities such as calmness, clarity, and concentration.[1] Mindfulness is defined in psychological terms as being characterized by paying total attention to the present moment with a nonjudgmental awareness of inner and outer experiences.[2]

Meditation and current literature:

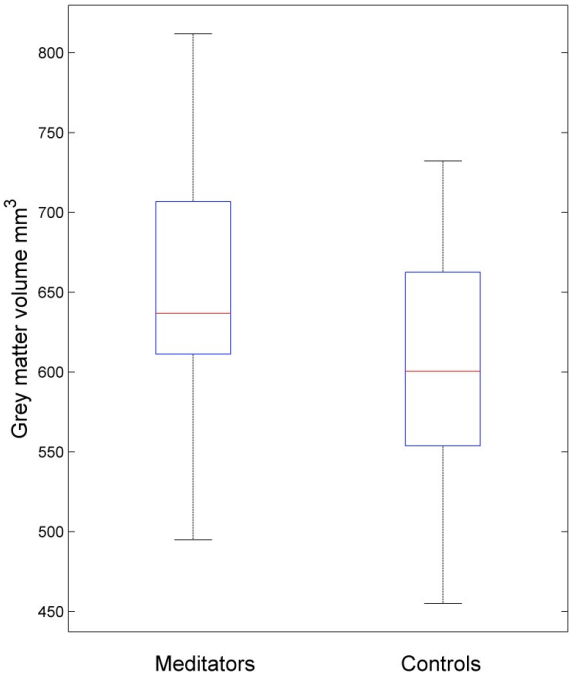
Studies have shown numerous benefits of meditation techniques. For example, Goyal et al. reported that meditation has a similar effect on anxiety and depression as compared to medication without the side effects.[3] Therefore, it is essential to assess the usefulness of incorporating meditation as an adjunctive therapy in perioperative patient care.

In order to study the benefits and efficacy of meditation intervention, it is important to have an objective measure that assesses the quality of meditation. Ahani et al. reported that EEG signals are sensitive to meditation using coherence and synchrony techniques as well as spectral analysis.[4] The overall effect of meditation is decreased electro-cortical arousal.[5] Meditators have shown to have higher alpha and theta activities in EEGs than non-meditators.[6] Focused-attention has shown to produce an increase of gamma activity in the brain. [7] Studies have also shown that meditation produces different activities at different locations such as increased alpha activity in frontal regions [8] and posterior regions.[9]



EEG spectral analysis of alpha, beta, and theta waves during meditation. Credits :Ahani et al[10]

A meta-analysis conducted in 2014 showed the most consistently altered brain regions were the left rostrolateral prefrontal cortex, anterior/mid cingulate cortex, anterior insula, primary/secondary somatomotor cortices inferior temporal gyrus, and hippocampus.[11] Insula is consistently linked to interoception-awareness of the body's internal and visceral states, including respiration, heart rate, emotional self-awareness, and potentially metacognitive awareness.[12,13] Somatosensory areas are also altered by meditation.



Neuroimaging studies have shown that there is increased cortical thickening in the left prefrontal lobe cluster as well as increased volume of insula, right temporal, and right angular gyrus.[14] Meditators have also shown to have increased grey matter volume.

Central box represents the value from the lower to upper quartile (25th to 75th percentile). The middle line represents the median. The vertical line extends from the minimum to the maximum value.[14]

Experienced and novice meditators:
A recent study has shown that after practicing 5-60 hours of meditation, novice meditators experience structural differences in 7 grey matters and 5 white matter tract regions.[15]

Number	Grey Matter areas	White matter areas
1)	Anterior cingulate cortices	Corpus callosum
2)	Posterior cingulate cortices	Superior longitudinal fasciculus
3)	Insular cortex	Sagital stratum
4)	Temporoparietal junction	Thalamic radiation
5)	Hippocampus	Corona radiata.
6)	Caudate nucleus	
7)	Cerebellum	

A recently published study reports that meditation resulted in effortless awareness in novice and experienced meditators and meditation was associated with lower activity in Posterior Cingulate Cortices (PCC).[15] A recent study has shown that meditation correlates with decreased activity of default mode network[16] as opposed to an increased activity of default mode network associated with mind wandering and self-referential processes.[17]

Network integration
A recent study has also assessed the network integration in EEG due to meditation and has found that meditation is associated with increased brain network integration.[15] Such studies demonstrate the possibility of application of real time EEG to associate an objective measure of brain activity with subjective mind states related to meditation. EEG has an excellent temporal resolution and is preferred over fMRI in this study since it is portable and less expensive.

Meditation encompasses a family of complex practices that include yoga meditation, mindfulness meditation, mantra meditation, tai chi, etc. However, the training requirements for these types of meditation are variable including training from a trained teacher. Isha Kriya is a type of meditation that does not involve complicated trainings, rituals or mantras and can be performed anywhere at any time. Isha Kriya is a meditation technique that regulates breathing and produces a positive effect on the mind and body as endorsed by millions of people worldwide.[18] At this time, no studies have been done regarding the EEG changes in the brain during Isha Kriya.

This study will investigate if Isha Kriya produces EEG changes comparable to that of established literature and will look at the differences between the start and the end of a 6 week cycle. This study will also explore the difference in EEG changes between experienced and novice meditators.

B3. DESCRIPTION OF RESEARCH PROTOCOL

A. Study Design – Overview, Methods, Procedures

Study design:

This is a prospective trial enrolling healthy volunteers, including novice meditators and experienced meditators. Subjects will undergo an EEG at baseline and again after 6 weeks. During the 6 weeks, subjects will be asked to meditate twice a day, 12 minutes each time.

Recruitment:

Recruitment will occur via flyers posted at BIDMC and flyers emailed to mediation listservs.

Study procedures:

1) EEG

Subjects will undergo an EEG at baseline and again after 6 weeks (+/- 1 week). During the EEGs, the subjects will be asked to meditate.

The ENOBIO 32 EEG device is an investigational device under US federal law which is a 24-bit EEG data reader at the rate of 500 S/s which comes as a wearable wireless electrophysiology sensor system. It includes spectrogram and 3D visualization in real time of spectral features. It also collects triaxial acclereometer data. These data are stored in microSD offline in Holter mode.[19] This EEG communicates via wireless allowing the subjects to be in a comfortable position and also can reduce the effects of electrical interference. EEG measures brain waves by the following processes:

Pre-processing Signal
Down sampling will be done to eliminate interference from unexpected signals.
After down sampling, Band Pass Filter (BPF) will be used to filter the signals.

Ensemble Average
In this step, signal acquired from every selected channel would be averaged. There are fifteen signals from the instruction that are averaged into one signal representing the instruction.

Short Time Fourier Transform (STFT)
STFT will be used to determine a dominant frequency from the signal of an ensemble average result when the event occurs.

Event Related Desynchronization/Event Related Synchronization
ERD/ERS during event is calculated with the above data.

2) Meditation

Subjects will be introduced to Isha Kriya (IK) meditation. IK is a meditation that can be learned quickly and requires approximately 12 minutes, twice a day of practice. This regimen was chosen because of its simplicity making it an excellent way to introduce meditation to beginners. IK does not incorporate a spiritual or religious focus. Dr. Subramaniam, the principal investigator of the study, was trained to be an instructor by the Isha Institute of Inner Sciences, a nonprofit foundation located at McMinnville, Tennessee.

At the time of enrollment, Dr. Subramaniam, or a trained research team member, will provide a brief introduction to IK meditation and review a handout of the meditation instructions. The subjects can utilize the online-guided meditation or follow the instructions on their own.

Preparation:	Sit in a cross-legged posture or sit in a chair, spine comfortably erect, hands upon thighs, palms facing up, face slightly upturned, eyes closed, keeping a mild focus between the eyebrows.
Meditation:	Slow inhaling and exhaling while mentally focusing on the words “I am not the body” and “I am not even the mind” for 7 minutes; uttering a long “Ahh” sound seven times; sitting for 5 minutes with eyes closed.

Subjects will be asked to practice the meditation twice daily for 12 minutes each session, for approximately 6 weeks. They will be given a meditation diary to complete daily.

	Baseline	**After 6 weeks**
Group 1 - Novice meditators	Meditation with EEG monitoring	Meditation with EEG monitoring
Group 2 - Experienced meditators	Meditation with EEG monitoring	Meditation with EEG monitoring

Study Monitoring / Adverse Events:
The study interventions are non-invasive and minimal risk. Therefore, we will limit the scope of AE monitoring and reporting to the following:

- All Serious Adverse Events believed to be related to the study procedures
- Unexpected, non-serious Adverse Events believed to be related to the study procedures

B. Statistical Considerations

a. ***Sample Size Justification:*** In this pilot study, atleast10 patients who complete both EEGs are required for analysis. In order to achieve this target accrual of 10 patients and also to account for potential dropouts, a total of 15 volunteers will be recruited.

b. ***Data Analysis:*** Continuous data will be reported as means ± standard deviation or median (quartile 1, quartile 3) depending on distribution. Normality will be assessed with the Shapiro-Wilk test. Categorical data will be reported as frequencies and proportions and assessed with a chi-square of Fisher's Exact test as appropriate. SAS 9.4 (SAS Institute Inc., Cary, NC) will be used for all analyses, with two-sided p-values < 0.05 considered statistically significant.
The primary aim of the study is to study the effect of guided meditation on EEG. This will be a descriptive study noting the EEG changes (alpha vs beta), differences in the waveform signals between novices and experienced meditators, and at the beginning and the end of the 6-week period. Secondary analysis is being conducted with collaborators outside of BIDMC. Professor Contreras Vidal, Jose & his subordinate Sujatha Ravindran, Akshay from The University of Houston; will be assisting in the analysis of the EEG data collected. They will be provided with limited de-identified dataset in accordance to the terms of specific Data Use Agreements. No PHI will be shared between the institutions and all data will be completely de-identified before secure transfer to the co-investigators.

Primary endpoint:

1) Examine the qualitative EEG measures associated with Isha Kriya meditation
   - Event related potential fields in EEG: amplitude in fT and latency in ms
   - Oscillations: power spectral density and time-frequency oscillations in fT^2/Hz

Secondary endpoints:

1) Investigate the difference in EEG changes between novice and experienced meditators
2) Investigate the difference in EEG changes between the start and end of 6 weeks of daily meditation

C. Subject Selection

This is a descriptive study of healthy volunteers, including novices and expert meditators.

Inclusion criteria:

1) 18 years or older
2) Novice or expert meditator

Novice meditator: No meditation practice in the previous year and < 20 entire lifetime hours

Expert meditator: Meditation ≥ 30 min per day for at least 5 days per week over the past 1 year

Exclusion criteria:

1) History of any neurological condition (i.e. Parkinson's disease, Alzheimer's disease, Huntington's disease, brain tumors, brain surgery, or multiple sclerosis)
2) History of depression, currently being treated with antidepressants
3) History of any psychiatric disorder, within last 5 years (i.e. anxiety, psychosis, posttraumatic stress disorder, attention deficit hyperactive disorder)
4) Current use of cognition enhancing medications
5) Active history (within the last 5 years) of alcohol or drug abuse (> 10 drinks per week)
6) History (within the last 5 years) of stroke/aneurysm
7) Recent history (< 3 months) of seizures
8) Non-English speaking

Subject Protection
Subjects will not be recruited on the basis of race, ethnicity, or gender. However, it is not clear whether the final study sample will contain a representative spread of the racial and gender makeup. There is no reason to exclude pregnant women from this protocol.

B4. POSSIBLE BENEFITS

We do not anticipate any direct benefit to be gained by the individual subject. Insights gained from this trial may allow us to better understand and interpret results and potentially provide information about the association between meditation and structural and functional brain changes.

B5. POSSIBLE RISKS AND ANALYSIS OF RISK/BENEFIT RATIO

Since this is a feasibility study on healthy individuals, and the intervention is non-invasive EEG, the risks expected to be associated with this study are minimum.

EEG:
Noninvasive EEG monitoring is considered a safe procedure. It has no discomfort and produces no sensation. In addition, there is no risk of electric shock. In rare instances, EEG can precipitate seizures in individuals with a seizure disorder due to flashing of lights or deep breathing.[20] EEG will be performed by trained study staff.

Meditation:
The meditation intervention only involves thought and mindful breathing. We do not anticipate any physical risk. The meditation program has not been used in this arena prior to this study. Therefore, there is no published information regarding psychological risk. Additional counseling regarding any psychological or emotional distress stemming from this will be provided by the principal investigator at the request of the subject or family.

Risk of breach of confidentiality: As with any research study, there is a small risk associated with a breach of confidentiality. All research staff for this trial has been extensively trained in how to handle confidential data and how to minimize the possibility of this risk. Data will be completely de-identified and transferred in a secure manner.

Risk/Benefit Ratio: The meditation intervention has no expected risks and the knowledge gained could provide information about the association between meditation and structural and functional brain changes. Research team members will attempt to mitigate any of the possible risks described above.

B6. RECRUITMENT AND CONSENT PROCEDURES

Recruitment

Subjects will be identified by the study team via response to study flyers seeking volunteers. Flyers will be posted throughout the Beth Israel Deaconess Medical Center. Flyers will also be sent to meditation listservs such as Isha.

When interested subjects contact the study team, the study will be discussed and the subject will undergo prescreening for eligibility via phone. If the subject meets eligibility criteria, an appointment for the first EEG will be scheduled.

Consent

When the subject arrives at BIDMC for the first EEG, the study will be discussed and the consent form reviewed with a research team member. The subjects will have the opportunity to ask any and all questions, and are free to decline participation at any time. Written informed consent will be obtained prior to any research procedures. A copy of the signed consent will be provided to the subject and the original will be kept in the research files.

The research team undergoes standardized, rigorous training regarding the informed consent process for research. Within the Center for Anesthesia Research Excellence (CARE) at BIDMC, this training is personally overseen by the Clinical Research Administrator and includes: didactic sessions, mandated attendance at CCI/HSPO seminars related to the informed consent process, shadowing of informed consent in a variety of contexts, trainee-led informed consent conversations with the aid of consenting checklists and accompanied by senior staff member and/or PI, robust feedback sessions, and clear communication when the team member is skilled enough to engage in informed consent discussions without direct supervision. All CARE members, including non-physicians, undergo this training.

Subject Protection

This meditation regimen was chosen because it excels in simplicity and is a great way to introduce meditation to beginners. It does not incorporate a spiritual or religious focus**.** Subjects who are unable to consent for themselves will be excluded from this study.

B7. STUDY LOCATION

Privacy
Study interactions and procedures will take place in private clinical settings with curtains/doors closed so as to provide privacy and comfort. Every effort will be made to protect the privacy of the participant.

Physical Setting
Subjects will be enrolled at BIDMC. Prescreening will occur via phone. Consent and EEGs will be performed in either the Clinical Research Center (CRC) or Pre-admission Testing (PAT) clinic. Electronic data will be maintained on password-protected computers behind the institutional firewall. Paper records will be maintained in locked file cabinets and secure research offices.

B8. DATA SECURITY

All electronic data will be stored in REDCap and/or on password-protected servers behind the BIDMC firewall. Any data collected on paper will be stored in locked file cabinets or in secure offices. Each subject will be assigned a study-specific ID number. A crosswalk between the participants and their study IDs will be maintained on password-protected computers by members of the research team. Limited information will be retained on patients who are prescreened and do not qualify, or who are approached and declined, for the purposes of generating a CONSORT diagram.
Any transfer of data to outside collaborators will be done by sending Limited Data Sets with date-shifting, using Secure File Transfer. Data will be completely de-identified and transferred in a secure manner. The de-identified data will be loaded in memory drive and/or DVD and send via trackable FedEx or using a Secure File Transfer online. Recipients will work with the data on their secure institutional computers, behind a firewall. All data sharing will be done in accordance to the terms of BIDMC-issued Data Use Agreements.

B9 Multi-Site Studies

N/A – not a multi-site study

Is the BIDMC the coordinating site? ☐ Yes ☐ No
Is the BIDMC PI the lead investigator of the multi-site study? ☐ Yes ☐ No

B10 Dissemination of Research Results

Participants will be thanked for their time throughout the study. There is no plan to share the results at the conclusion of this trial.

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