COVER PAGE

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Mindfulness Based Stress Reduction and Post-Stroke Cognition

1. Abstract

Thrombectomy has significantly improved stroke outcomes. Nearly 80% of our clinic population now present with small strokes and low NIH Stroke Scale (NIHSS) scores. However, despite "good recoveries", greater than 40% endorse significant problems with higher-level cognitive functions, mood disorders, and fatigue. The natural history and pathophysiology of these deficits are not as well described as motor or language deficits; but they are equally debilitating, preventing previously high-functioning active individuals from returning to their prior workplace and social environments. This can be particularly difficult for the elderly, resulting in early retirement and loss of independence. The pathophysiology underlying these deficits remains unclear. Impairments in executive function and processing speed occur independent of stroke size, location, or depression. Using magnetoencephalography (MEG), a tool able to evaluate neurophysiologic processes in real time akin to EEG with better spatial resolution, *we have found that cerebral activation patterns are **slowed** and **more diffuse** during task completion in stroke patients compared to controls*; and at rest there is ***abnormal activity in the frontal lobes***, an area critical for executive function, processing speed, affect regulation, and decision making. Some patients improve over months; however, recovery is variable and by this time many have made critical life decisions. There is little data regarding effective treatment options. The ability to hasten improvement would significantly improve morbidity in a group with excellent recovery potential.

Mindfulness has been practiced since ancient times, but only recently gained popularity as an effective treatment for anxiety and depression both in normal individuals and those with chronic disease states. Mindfulness Based Stress Reduction (MBSR) has also been evaluated in a small series of patients with chronic stroke and traumatic brain injury and has *shown to improve performance during tasks of executive function*. A combination of meditation, body awareness, and yoga, MBSR is an active process thought to engage the frontal lobes. Based on our current understanding of pathophysiology, MBSR may serve as an attractive non-pharmacologic intervention to improve *subacute* post-stroke mood and cognitive dysfunction.

We will recruit a cohort of patients with minor stroke (NIHSS <8, modified Rankin score 0-2). Following baseline assessment of depression, fatigue, cognition, functional status, and patient satisfaction, individuals will be randomized to a standard 8 week MBSR course aimed at improving attention and concentration, and reducing anxiety and depression, or a bi-monthly standard Stroke Support Group (SSG). All patients will undergo reassessment post-intervention (~4-6 months post-infarct), along with MEG pre- and post-intervention. Participants will undergo neuroimaging pre- and post-intervention. We will evaluate differences in activation patterns and functional connectivity both at rest and during a visual cognitive task. We hypothesize that both groups will initially exhibit abnormal frontal lobe function compared to controls; however, after MBSR this will improve versus the SSG group.

Participants will also be administered a pre- and post-intervention Montreal Cognitive Assessment (MoCA), along with a battery of cognitive tasks to measure attention, concentration, processing speed, and executive function. Performance will be compared pre- and post-intervention, and for MBSR versus SSG participants. We hypothesize scores will be significantly better following MBSR compared to the SSG group. Finally, the PHQ9 and other measures of patient-reported outcomes (eg., mood) will be given to patients pre- and post-intervention and compared across groups at each time point. We hypothesize MBSR will improve rates of depression/anxiety compared to SSG. We will also evaluate patient satisfaction scores, measures of functional recovery: the modified Rankin scale (mRS) and Barthel Index (BI), and the likelihood of successful return to work. Individuals with minor stroke have tremendous potential to return to their baseline level of function, though often struggle. If effective in reducing post stroke mood and cognitive disorders for those with minor stroke, allowing them to return to work, MBSR will significantly reduce post-stroke morbidity and improve quality of life.

2. Objectives

Objective 1: To determine the effect of MBSR on abnormal cerebral activation patterns on MEG after stroke. Participants will undergo neuroimaging pre- and post-intervention. We will evaluate differences in activation patterns both at rest and during a visual cognitive task using cluster-based permutation tests. Patients in the MBSR and SSG groups will be compared to one another and to patients with no infarct

(previously collected cohort). T-tests and ANCOVA will be used to determine differences between groups at each time point. Functional connectivity studies will also be performed to evaluate differences between groups.

Objective 2: To determine the impact of mindfulness training on post-stroke cognitive impairment. Participants will be administered a pre- and post-intervention Montreal Cognitive Assessment (MoCA), along with a battery of cognitive tasks to measure attention, concentration, processing speed, and executive function. Performance will be compared pre- and post-intervention, and for MBSR versus SSG participants.

Objective 3: To determine the impact of mindfulness training on post-stroke depression. The PHQ9 will be given to patients pre- and post-intervention and compared across groups at each time point.

As secondary objectives we will also evaluate patient satisfaction scores, measures of functional recovery: the modified Rankin scale (mRS) and Barthel Index (BI), and the likelihood of successful return to work.

3. Background

Stroke is common, affecting nearly 800,000 individuals in the United States each year. It is debilitating, the leading cause of long-term disability and 4th leading cause of death. It is costly, resulting in an average of $36.5 billion dollars in healthcare expenditures and lost wages annually. Advances in treatment (intravenous tissue plasminogen activator and mechanical thrombectomy) have significantly reduced motor and language deficits, converting large hemispheric lesions into smaller infarcts with better overall long-term outcomes. Unfortunately, many patients arrive to the hospital too late to benefit from acute treatment, or continue to have symptoms despite intervention. Within our patient population, nearly 80% of individuals presenting for follow-up 4-6 weeks post-stroke report only "minor symptoms", with low severity measured by NIH Stroke Scale (NIHSS) and modified Rankin scores (mRS). Though these individuals lack dense hemiparesis or aphasia; over half endorse some degree of cognitive impairment, mood disorder, or fatigue that significantly impacts recovery. These symptoms appear independent of stroke size, location, or depression.

Post-stroke dementia has an established basis in the literature and is common, particularly in those over the age of 60. However, rather than confusion or frank memory impairment, in the subacute phase of stroke recovery many patients endorse an alternative syndrome: difficulty with executive function, focus, concentration, and other aspects of attention. These deficits can be hard for others to appreciate, especially in previously high-functioning active individuals, but are detectable on screening tests such as the Montreal Cognitive Assessment (MoCA), and are debilitating. For example, such deficits may prevent an executive from effectively leading a business meeting, or a nurse from returning to the rapid pace of patient care. This may result in early retirement, particularly when the patient is older. The interpersonal difficulties caused by depression or low energy can result in divorce and social isolation. Preliminary data generated from our current American Heart Association (AHA)-funded study using magnetoencephalography (MEG), a tool measuring neurophysiologic processes in real time akin to EEG, suggest that individuals with stroke display delayed activation patterns of low amplitude with increased dispersion of activity during task completion compared to controls, and abnormal frontal lobe activity at rest. The significance of this activity is uncertain; however, it is noteworthy given the reported deficits of our patients involve predominantly frontal lobe functions. Some patients improve over time; however, the rate and degree of recovery are varied and difficult to predict. Often, before individuals recover, they have already made critical decisions that impact the rest of their life. Frustratingly, their disease is often under-recognized, and patients find little benefit from common strategies that target more severe impairment.

Mindfulness training may provide an attractive therapeutic option. The practice of mindfulness is quickly gaining popularity as an effective treatment for anxiety and depression, though the practice itself dates back to ancient traditions focused on healing and the power of the mind. Mindfulness Based Stress Reduction (MBSR) is an 8 week program comprised of meditation, body awareness, and yoga that is currently the most evidence-based of the mindfulness practices. Studies using MBSR to decrease anxiety and depression have predominantly been conducted in normal individuals and those with chronic disease states such as migraine, pain, vascular disease, and diabetes. In 2014, Abbott and colleagues conducted a meta analysis on all randomized controlled clinical trials of individuals with vascular disease (n=9) including one with chronic stroke patients and found improvement in stress reduction, depression, and anxiety after MBSR. The practice of mindfulness is an active process thought to exercise the frontal lobes leading to improved function. Studies on patients with Alzheimer's disease have been promising, and in 2012, Johansson and colleagues showed that chronically after stroke or TBI, MBSR improved performance

on tests of executive function including the Symbol Digit Test and Trail Making Test. To date, mindfulness has not been evaluated in the subacute phase of stroke recovery, though this is a critical time when patients are making decisions that impact the rest of their lives. We believe that improving anxiety/depression and cognition during this time period would have significant impact on the success of an individual's reintegration into society, considerably improving post-stroke morbidity and reducing the burden of healthcare costs and lost wages.

4. Study Procedures

a. This is a prospective, randomized, controlled, longitudinal clinical trial that will make use of the following protocol:

- Patients are admitted to the hospital for acute stroke and undergo work-up including MRI; they are entered into our Clinical Outcomes Database (routine clinical care, database is HIPAA compliant and has prior IRB approval). At this point, or at their first follow-up clinic visit, they will be identified and approached about participation in the study.
- All patients are scheduled for an appointment in the Bayview Stroke Intervention Clinc (BaSIC) approximately 4-6 weeks +/- 4 weeks post-stroke
- Seen at 4-6 weeks (routine care)- consented and tested if enrolled (per research protocol, as part of a prior approved study on Stroke Recovery)
- Those meeting inclusion criteria for the Mindfulness and MEG study will be consented, randomized, and undergo the following additional procedures:
    - 1 month MEG visit at the University of Maryland (UMD, our current partner for our ongoing MEG study)- brain activity will be measured at rest and during cognitive tasks
    - EITHER 8 weeks of either MBSR Training and guided meditation using provided resources or participation in our bi-monthly Stroke Support Group
    - Repeat MEG following intervention (approximately 4-6 months post-stroke)
        - UMD MEG Protocol:
            - Magnetic fields will be recorded using a 275-channel whole-head MEG system (KIT System)

The MEG System non- invasively measures the magnetoencephalographic (MEG) signals produced by electrically active tissue of the brain. These signals are recorded by a computerized data acquisition system, displayed, and may then be interpreted by trained physicians to help localize these active areas. The location may then be correlated with anatomical information of the brain. MEG is routinely used to identify the locations of visual, auditory, somatosensory, and motor cortex in the brain. * MEG is also used to non-invasively locate regions of epileptic activity within the brain. The localization information provided by MEG may be used, in conjunction with other diagnostic data, in neurosurgical planning.

Indications used in this study

The MEG System will non-invasively measure the MEG signals produced by electrically active tissue of the brain. These signals will be recorded by a computerized data acquisition system, displayed, and then be interpreted by trained *scientists* to help *characterize* and to localize these active areas *while the subjects are resting but awake, and while they perform several cognitive tasks*. The location will then be correlated with anatomical information of a *standard* brain *model or the subject's head MRI*. MEG will be used to identify the locations of visual, auditory, somatosensory, and motor cortex in the brain.

- The total length of the MEG recordings will depend on the length of the tasks (an estimate of 60 min has been used).

- Finally, patients will return for their 2nd post-stroke follow-up in BaSIC (routine care) and testing (if part of the Mindfulness or Recovery Study) following intervention (approximately 4-6 months post-stroke)

b. We currently follow patients with minor stroke for 12 months post-infarct. They undergo additional testing as part of the study at their 1, 6, and 12 month follow-up visits. For this study, we will use MEG to map brain activity in individuals at the 1 and 6 month follow-up time points. This will require 2 visits to clinic at which time they will undergo testing, intervention with MBSR versus a Stroke Support Group, and 2 trips to the University of Maryland for MEG.

c. The study is not formally blinded, as all patients who undergo imaging and intervention will have a stroke. However, the team at UMD will be initially blinded to stroke location, clinical symptoms, and

intervention. A control population for comparison already exists and for this pilot study we are interested in imaging affected individuals to determine differences.

d. All participants will receive routine care. Intervention with MBSR/Support Group, and MEG testing will be performed above and beyond typical care and does not otherwise alter the treatment or monitoring course.
e. There is a control group of patients of similar age without stroke who have already undergone MEG imaging and will be used as non-stroke control group; though the Stroke Support Group will allow for adjustment for socialization and activity as confounding factors (as the alternative intervention to MBSR)
f. There is no concrete definition of treatment failure or removal criteria. We will use an intention-to-treat analysis; however also perform a per-protocol analysis. Attendance at 75% of MBSR or Support Group sessions will constitute full participation.
g. There will be no change to the patient's care when the study ends. Participants may choose to leave the study at any time. Though they will not be fully compensated (see below) for an early drop-out, their data up to that point will be analyzed, and there will be no alteration in their care.

5. Inclusion/Exclusion Criteria

Inclusion Criteria:

1. Adults (≥18 years) presenting with neurological symptoms due to acute ischemic stroke (onset within the week).
2. Evidence on brain MRI of acute ischemic stroke (imaging negative strokes and TIAs will be excluded).
3. Native English speaker (by self-report) prior to stroke.
4. NIHSS <8 at initial follow-up visit (~30 days post).
5. mRS 0-2 at initial follow-up visit.

Exclusion Criteria:

1. Primary intracerebral hemorrhage- blood on imaging.
2. Presence of proximal large vessel occlusion.
3. Cortical exam findings including aphasia or neglect.
4. Prior history of dementia or undertreated psychiatric illness.
5. Uncorrected hearing or visual loss.
6. Inability to attend weekly MBSR or support group sessions.
7. Inability to travel to College Park, Maryland for 2 MEG recording sessions
8. Presence of any of the following that would lead to significant artifact on MEG: cardiac pacemaker, intracranial clips, metal implants or external clips within 10mm of the head.
9. Claustrophobia, obesity, and/or any other reason leading to difficulty staying in the MEG machine.

6. Drugs/ Substances/ Devices

a. No drugs or substances will be administered.
b. We will be using magnetoencephalography (MEG), as above.

7. Study Statistics

a. Primary outcome variables include: MEG- changes in spectral properties and an estimate of the localization of spontaneous brain activity during resting state, functional connectivity during resting state. Clinical- performance on the MOCA and other cognitive measures (as part of the Recovery Study), patient-reported outcomes: fatigue, depression, satisfaction, quality of life.
b. Secondary outcome variables include: changes in spectral properties, spontaneous brain activity, and functional connectivity during completion of various cognitive tasks.
c. We will use an intention-to-treat analysis; however, we will adjust for degree of participation and consider an additional exploratory per-protocol analysis. For those lost-to-follow-up, data will be censored at the time they are lost. In addition to the proposed analyses, if there is evidence for an uneven distribution of confounding factors across treatment and control groups, we will perform multivariable linear regression to adjust for confounders *(eg. degree of participation, age, sex, level of education, antidepressant use, and major medical co-morbidities (Charlson Comorbidity Index))*.

To determine the effect of MBSR on abnormal cerebral activation patterns on MEG after stroke:

- Participants will undergo neuroimaging at 1 and 6 months post-stroke. Participants in the MBSR and SSG will be compared to a previously collected group of controls with no infarct. Source localized whole brain activation will be assessed to determine overall differences in space and time between each group (MBSR v SSG) versus controls for each time point. Cluster-based permutation tests (based on independent measures t values) will then be performed to evaluate mean differences in activation for ROIs between groups at each time point. Paired t values will allow for evaluation of changes over time within each group. Amplitude of peak activation and spike latency will be assessed. ANCOVA will allow for adjustment of potential confounders.
- *Sample Size.* We have been able to demonstrate results at or approaching statistical significance for our current cohort of patients with minor stroke versus controls after enrolling only 9 participants. This number is similar to many other published studies evaluating differences in activation patterns on MEG. We do anticipate less of a difference when comparing stroke patients to other stroke patients, and will therefore increase our sample size to at least 20 individuals in each group. There remains a chance given the potential for improvement in both groups, that we may still be inadequately powered to detect long-term outcomes in this pilot study; however results will also allow treatment effect estimates that will inform a larger clinical trial.

To determine the impact of mindfulness on post-stroke cognitive impairment:

- The MoCA and cognitive battery will be administered at 1 and 6 months post-stroke. T-tests and chi square analysis will compare cognitive performance (MoCA, global cognitive score, and individual cognitive tests) pre- and post-intervention for each group (MoCA cutoff <26), and MBSR v SSG participants at each time point.

To determine the impact of mindfulness on post-stroke depression:

- Participants will be administered the PHQ-9 pre- and post-intervention. Paired t-tests will be used to evaluate for significant differences in scores between time points using each score as a continuous variable. Chi square analysis will be used to evaluate presence or absence of moderate depression (PHQ9 score >9). Independent t-tests and chi square analysis will compare scores of MBSR versus SSG participants for each time point.
- *Sample Size.* Based on prior MBSR studies, we anticipate that this will show a greater clinical effect than change in MoCA, giving us more than adequate power to detect differences with this sample size.

To determine the functional significance of the treatment, patient perception and satisfaction with recovery

- Along with degree of successful reintegration will be evaluated using Likert scores. Regression models will be created to evaluate the effect of mindfulness on perception of recovery and patient satisfaction at each time point. Within regression models, we will include traditional markers of recovery (mRS and BI) to determine the independent effect of mindfulness training on satisfaction and quality of life.

d. Early stopping rules: the study will be stopped if the participant is unable to tolerate the MEG or MBSR.

8. Risks

a. Participants have had minor strokes and are recovering well without severe neurological deficits but we acknowledge the following relative risks:
   - MEG- there are few to no medical risks with MEG. We will not be imaging pregnant women. The major risk is claustrophobia, though the machine is relatively open and in a large room, and boredom. MEG personnel will show the MEG, explain that it is only a recording device, does not make noise, and carefully describe the testing procedure to each subject before recording the head shape, applying the fiducial markers and initiating MEG recording. MEG personnel will be in audio contact with the subject during the recording and be able to see them through a video link. If any subject experiences stress or discomfort the study can be stopped at any time. In addition, the MEG scanner uses helium. It is truly a remote possibility that the liquid helium may boil off rapidly and fill the recording room with extremely cold dense gaseous helium, which can be dangerous if breathed for more than a few minutes. The MEG operator will clearly notice the quench and immediately provide assistance to anyone inside the recording room. This has never happened in the center's long history of imaging.
   - Travel- Given their relatively good function and outpatient status, there is less risk to travel, despite their relatively recent stroke. In order to take part in the MEG portion of the study patients must be fully functionally independent and able to travel unaccompanied to the University of Maryland.

- MBSR- Mindfulness training is a combination of meditation and yoga and is well tolerated among many groups with chronic medical problems, including physical limitations. However, given the low stroke severity of our patients, we do not anticipate any additional risks above what would be seen in a population without stroke. We will monitor for fatigue, embarrassment, or other unanticipated issues, and adjustments will be made if needed.
- SSG- Support groups can be therapeutic to patients and their families. The major risk is embarrassment; however, while attendance is required and participation will be encouraged, no patient will be forced to share or participate if it makes them uncomfortable.
- Loss of Confidentiality- The potential legal and social risks to the participants relate to the question of confidentiality of information. It is possible that information obtained may adversely affect the subject's legal or social position if not kept strictly confidential. However, subjects will be identified by number, and other measures will be put in place to minimize the risk of loss of confidentiality including but not limited to keeping data on a password protected computer accessible only to the study team.

b. Unanticipated problems or study deviations will be reported to the IRB by the PI and an action plan will be created to remedy the situation.

c. All protocol events or deviations will be reported to the PI regardless of the location of their occurrence (JHMI or UMD), in real time. Members of the study team at JHH and UMD will be in communication regularly to discuss any issues, often in real-time as they arise (either in person or by phone on the day of study participation). Monthly, any event and the formulated action plan (as above) will be reviewed by a study team consisting of co-investigators at both campuses through a teleconference.

d. As outlined below, there will be no direct cost to the patient for participating in the study, and they will be compensated for their time and participation.

9. Benefits

a. Participants taking part in either MBSR or SSG may derive benefit from the intervention. In addition, they will be advancing the field so that future patients with minor stroke will recover faster and more fully.

10. Payment and Remuneration

a. Participants will be recompensed for travel (see below) and also be compensated for their time and participation. They will receive a total of $400 for full participation in study ($100 after their first MEG (1 month), $100 after completion of the intervention (with completion of at least 75% of sessions, $100 after their second MEG (4-6 months, post-treatment), and $100 for successful full completion: intervention, pre- and post-MEG, and pre- and post-cognitive testing).

11. Costs

- MEG- cost for image acquisition as well as data processing and interpretation will be paid for through research funding by the PI (approximately $500 per MEG).
- Travel costs- travel costs including travel to and from The University of Maryland will also be paid for by the PI using study funds. Patients may choose to arrive at the facility using a service such as Uber (trip paid for by the study team) or arrive to the facility themselves where they will be reimbursed for gas and parking.
- MBSR- the 8 week program will be provided at no cost to the patient as part of the study protocol.
- Stroke Support Group- SSG occurs bi-monthly and is run by the team at our Comprehensive Stroke Center. No additional funding is required.

Changes to the Protocol to Continue Research Without In-Person Visits (in the setting of worsening pandemic)

Consent- We will expand consent to include remote consent facilitated by video conferencing if needed during their video televisit follow-up. The consent will be reviewed with the patient as previously described either by phone or video. Verbal consent will be obtained. They will be provided with a copy of the consent form via email/fax/mail and will send back in their signed copy (following verbal consent).

Clinic Visits/Testing- We have adapted the cognitive tasks and testing batteries so that they can be performed remotely via video conferencing and we can see them remotely via telehealth visits for their clinical/research follow-up visits (participants will need a laptop with a camera for remote/telehealth visits).

When remote assessment/therapy is not feasible, we will conduct in-person visits. In that case, prior to each scheduled visit, we will call participants and screen for COVID-19 symptoms and exposure. If a participant reports symptoms or exposure, the in-person visit will be cancelled. In-person visits will be rescheduled pending medical evaluation of signs/symptoms or after 14-day self-quarantine if there was exposure or potential exposure. The research team will reference JHU policies for self-screening and will defer any in-person or on-campus activities if they report COVID-19 symptoms and another member of the team will conduct the visit if possible. During each visit, participants and the research team will wear masks. If they do not provide their own mask, we will provide a disposable mask for them and practice social distancing whenever possible along with proper hand hygiene practices. All assessment/therapy materials and work surfaces (tables, doorknobs) will be disinfected after each session.

Interventions- Currently, both the weekly Stroke Support Group and Mindfulness Based Stress Reduction group are in person. If it is safe for in-person encounters, for the added potential benefit of socialization, we will continue to hold them in small groups. We will take all of the necessary safety precautions described above.

In addition, have adapted both interventions so that they can be available over telecommunication platforms (eg. Zoom) depending on the severity of the pandemic over the study period.

MEG- The safety steps described above will be implemented for these in-person visits as well. Scanning is limited to the participant and a tech within the large imaging center in a free-standing imaging center on the University of Maryland Campus. If necessary, we will temporarily discontinue MEG scanning should Johns Hopkins (or the University of Maryland) determine it is unsafe to continue given progression of the pandemic and will use cognitive outcomes alone as our outcome measure in these participants in that case.