Exploring the Potential Benefits of the Use of Acupuncture to Reduce Agitation, Irritability and Anxiety in Alzheimer's Disease and Alzheimer's Disease Related Dementias Utilizing Non-Invasive Measures of Autonomic Nervous System Physiology and Actigraphy as Biomarkers

Alison McManus DNP, FNP-BC
Principal Investigator
Massachusetts General Hospital

Jessica Gerber, MS, Lic.Ac.
Co-Investigator
Massachusetts General Hospital

Victoria Williams, PHD
Co-Investigator
Massachusetts General Hospital

Steven E. Arnold, MD
Co-Investigator
Massachusetts General Hospital

Jennifer Gatchel MD, PHD
Co-Investigator
Massachusetts General Hospital

Kathleen Monahan, BS
Clinical Research Coordinator
Massachusetts General Hospital

Version Date: December 7th, 2018

Abbreviations:

AE- Adverse Event
AIA- Anxiety, Irritability, Agitation
AD- Alzheimer's Disease
ADRD- Alzheimer's Disease Related Dementias
ANS- Autonomic Nervous System
CFR- Code of Federal Regulations
CU- Cognitively Unimpaired
DLB- Dementia with Lewy Bodies
EDC- Electronic Data Capture
ER-SCR- Event-Related Skin Conductance Response
FTD- Frontotemporal Dementia
HF- High Frequency
HRC- Human Research Committee
HRV- Heart Rate Variance
IRB- Institutional Review Board
LF- Low Frequency
MADRC-LC- The Massachusetts Alzheimer's Disease Research Center Longitudinal Cohort
MGH- Massachusetts General Hospital
NN- N-N interval- equivalent to R-R interval
NN50- N-N intervals differing more than 50ms
NPI-Q- Neuropsychiatric Inventory Questionnaire
NS-SCR- Non-Specific Skin Conductance Response
PI- Principle Investigator
POMS- Profile of Mood States
RMSSD- Root Mean Square of Successive RR Interval Differences
RR- R-R Interval
SC- Skin Conductance
SDNN- Standard Deviation of N-N Interval

I. BACKGROUND AND SIGNIFICANCE

Studies have revealed the benefits of acupuncture for numerous disorders including, but not limited to, sleep disorders, anxiety, cardiovascular disease, and epilepsy.[1] While previous research seems to support the use of acupuncture as a possible treatment for anxiety and related disorders[1,6] little research has focused on anxiety, irritability, and agitation (AIA) symptoms in patients with Alzheimer's Disease and Alzheimer's Disease Related Dementias (AD/ADRD). This is not to say that this population has not been a source of interest in previous acupuncture literature, as research has already demonstrated that it is a tolerable and safe procedure for this patient subset.[2] However, most studies have focused on its effect on cognitive symptoms, as opposed to neuropsychiatric symptoms.

Anxiety, irritability, and agitation symptoms are extremely prevalent, occurring in 40-100% of AD patients.[3] These symptoms lead to increased morbidity and mortality, accelerated nursing home placement, decreased quality of life and increased health costs for the patient. They also cause additional stress and cost for the caregiver and family members.[4] Pharmaceutical options are sparse, and the few that ameliorate even a small subset of these symptoms also significantly increase the risk of cerebrovascular events and death.[5] The prevalence of these symptoms, their subsequent effects, and the scant treatment options are forcing researchers to consider more holistic alternatives, such as acupuncture.

The autonomic nervous system (ANS) plays a primary role in AIA symptoms. It is responsible for our "fight or flight" emergency response and our eventual relaxation. Therefore, when the ANS does not perform correctly, AIA symptoms can result. When the ANS initiates the sympathetic nervous system, heart rate increases as it prepares the body for action. Conversely, when the parasympathetic system engages, heart rate slows and calms the body down. Much of this is controlled by the vagal nerve. As a result, heart rate variability (HRV) becomes a reliable measure of autonomic function or dysfunction.[11] More specifically, when the ANS is functioning properly, the vagal nerve has more control over heart rate and this leads to greater variability, as the nerve is constantly reacting to and adapting to external stimuli. If the ANS is dysfunctional, the vagal nerve will not have as much control and, instead, the heart will beat in a steadier, more metronome-like fashion. Skin conductance (SC) will also be utilized in this sub-study. Skin conductance measures the activation of sweat glands. Sweat is an arousal response controlled by the ANS and is therefore another reliable measure of ANS function or dysfunction.[8]

It is suggested that acupuncture aids in restoring balance between sympathetic and parasympathetic activity.[1] Specifically, it has been shown to affect the hypothalamus, medulla oblongata, dorsomedial prefrontal cortex, and the ventrolateral periaqueductal gray, among others[1]. These brain areas encompass a large portion of the regions involved in autonomic regulation. Previous research has revealed that acupuncture influences autonomic activity as measured by HRV and SC.[7,9] This study aims to understand the effects of acupuncture on AIA symptoms in AD/ADRD as they are presented in outward behavior, HRV and motor restlessness as measured by the BioStamp nPoint, and SC. The location of needle points were selected based on commonly used points in other research studies involving anxiety, agitation, and irritability in persons with and without dementia.[10]

II. SPECIFIC AIMS

The purpose of this study is to discover whether acupuncture has an influence on HRV, SC, motor restlessness, and self-reported or rated behavioral expression of symptoms in individuals with AD/ADRD. This will identify any possible potential for a new, nonpharmacological therapy for treating AIA symptoms in this complicated population.

We hypothesize the following:

1.) Acupuncture will acutely benefit autonomic dysregulation in AD/ADRD subjects with AIA as indexed by reduced HRV and SC during treatment compared to pre-treatment rest.
2.) There will be a short-term benefit of acupuncture treatment on autonomic regulation as indicated by increased mean HRV and less motor restlessness on actigraphy and on behavioral symptoms as indicated by lower reported score on the Profile of Mood States (POMS)-abbreviated and fewer AIA symptoms documented by the subject or study partner during the observation period following the treatment compared to the pre-treatment observational day.
3.) Individuals without AIA, both CU and AD/ADRD, will reap similar benefits on autonomic regulation and behavioral symptoms as those with AIA.

III. SUBJECT SELECTION

Inclusion: Study subjects should meet all the inclusion criteria during screening evaluations to be entered into the study.

- Ages 55-95 inclusive, male or female.
- Diagnosis of CU, or probable AD, FTD or DLB as determined by established clinical criteria at screening[14].
- For the AIA symptomatic groups, a score of > 2 for Severity on at least 1 of the AIA-relevant items on the NPI-Q, i.e., Anxiety, Irritability/Lability, Agitation or Aggression.
- For the CU and no neuropsychiatric symptoms group, NPI-Q score must be 0 for AIA-relevant items, i.e., Anxiety, Irritability/Lability, Agitation or Aggression.
- No concurrent use of therapies with prohibitive effects on interpretation of HRV and SC measurements, e.g., those with major direct adrenergic or anticholinergic activities.
- Stable doses (>2 weeks) of concurrent dementia or psychiatric drugs for those applicable.

Exclusion: Study subjects should not meet any exclusion criteria during screening evaluations or they will be excluded from entry into the study.

- Atrial or junctional arrhythmias or other cardiac conditions, including pacemakers or other implantable devices that affect RR intervals or their measurement.
- AIA symptoms or dementia so severe that subject cannot assent and cooperate with all study procedures or requires immediate rescue medication for behavioral control.
- Seizure disorders or other potentially confounding medical, neurological or longstanding psychiatric illnesses.

Subjects will be recruited from the parent AIA study. The parent study, "A Test-Retest Reliability Study of Non-Invasive Measures of Autonomic Nervous System Physiology and

Actigraphy as Biomarkers of Agitation, Irritability and Anxiety in Alzheimer's Disease and Alzheimer's Disease Related Dementias" (protocol: 2018P000817), is an ongoing study that is investigating autonomic dysfunction as it relates to AIA in individuals with and without dementia. The parent AIA study will be recruiting from The Massachusetts Alzheimer's Disease Research Center Longitudinal Cohort (MADRC-LC), which undergoes annual in-person assessments with standardized clinical and neuropsychological rating instruments and all have expressed an interest in participating in additional research. The parent study will also be recruiting from other MGH neurology subspecialty clinics along with the Principal Investigator's (treating physician) clinic. Finally, individuals may be recruited for the parent study through internet trial postings through MGH and Brigham and Women's Hospital, along with fliers at approved MGH locations.

Eligible subjects scheduled for in-person visits in the parent study will be informed of the sub-study option during the consenting process on day one of parent study activities. They will be informed that this is completely voluntary and independent of their participation and eligibility in the parent study.

IV. SUBJECT ENROLLMENT

Subjects will be informed of the acupuncture sub-study during the consenting process on day one of the parent AIA study. Should a subject not want to partake in the sub-study, their participation in the parent study will not be affected. Subjects who are interested will be given ample time to review the study procedures and ask any questions they may have. If they wish to speak with the licensed acupuncturist who would be performing the procedure, they will be given that opportunity. Dr. McManus, Dr. Arnold, Dr. Gatchel, or Jessica Gerber, the licensed managing acupuncturist will obtain written informed consent from each participant, at the start of the screening visit. The consenting discussion of the sub-study will include all of the required elements of informed consent, including the purpose of the research, the procedures to be followed, the risks and discomforts, as well as potential benefits associated with participation. This discussion will also make very clear that this is a completely optional sub-study and will not affect participation in the parent AIA study.

Should a subject agree to participate in the acupuncture sub-study, sign consent, but subsequently change their mind, they will not be punished. Signing consent for the sub-study will not bind the participant into receiving acupuncture treatment. Repealing consent will not affect participation in the parent study in any way. Similarly, should a subject wish to terminate the acupuncture treatment mid-session, the licensed acupuncturist will immediately remove the needles and ensure the subject is safe to return home.

This study will be conducted in compliance with Title 21 Part 50 of the United States of America Code of Federal Regulations (CFR), Federal Regulations, and ICH Guidance Documents pertaining to informed consent.

V. STUDY PROCEDURES

The sub-study will be introduced to subjects during the consenting process for the AIA parent study. It will be emphasized that participation in the acupuncture portion as a sub-study is strictly voluntary and will in no way affect participation or eligibility in the parent study.

After the second day of participation in the parent study, individuals who would like to participate in the sub-study will receive a 20-minute acupuncture session. Before beginning, participants will be asked to complete the POMS-abbreviated mood questionnaire. We will employ a modified standardized acupuncture protocol with points used in previous research studies[10] to effectively reduce symptoms of anxiety and depression in individuals with dementia. The treatment will include commonly used acupuncture points for a total of 9 needles located on the top of the head, forehead, hand, wrist, lower leg, ankle and top of foot at approximately 0.5 – 1 cm depth. Needles will be placed at acupoints GV20 (x1), Yintang (x1) and left HT-7 (x1), left LI-4 (x1), right PC-6 (x1), bilateral ST- 36 (x2), right KD- 3 (x1) and left LV-3 (x1). A licensed acupuncturist credentialed by MGH will perform all acupuncture treatments. Upon insertion, the study acupuncturist will manipulate the needles to elicit the "de qi" sensation common in acupuncture treatments. Participants will then repeat the POMS-abbreviated shortly following the removal of acupuncture needles. Finally, participants will repeat the POMS a third time before removing the BioStamp nPoint the following day, roughly 20 ±4 hours after treatment.

The data collected for this sub-study will consist of observed behavioral expression and reported AIA symptoms and mood, HRV, SC, and motor restlessness and actigraphy as measured by the BioStamp nPoint. Upon completing the parent study's activities, subjects will remain connected to the SC measuring device, which will record SC throughout the acupuncture session. Additionally, subjects will wear the BioStamps home after completing the treatment. These will provide roughly 22 hours of HRV and actigraphy recordings post-acupuncture session. Finally, CU subjects or AD/ADRD study partners will be asked to complete a behavior diary. This will provide us with an understanding of the subjects' behavior and symptoms for a day following acupuncture treatment. This diary will be returned via mail with the BioStamps and third POMS. Once these are received, data will be entered into the EDC and the participant will have completed the study.

VI. BIOSTATISTICAL ANALYSIS

General Considerations: Statistical analyses will begin with scatterplot inspection, and descriptive statistics. All variables will be checked for normality and other parametric assumptions, with appropriate transformation applied if necessary for parametric analyses. If normality assumptions cannot be met, non-parametric test equivalents will be used. Missing data, if any, will be characterized, with scrutiny towards identification of any patterns of missingness. Demographic and clinical characteristics of the sample will be evaluated and potentially important differences in these characteristics (e.g., age, sex, education, non-psychiatric medication class) by diagnoses will be assessed using X^2 tests or Student t-tests (and/or ANOVA) for categorical and quantitative variables, respectively. Demographic or clinical variables that differ between groups will be included as covariates. $P<0.05$ will be considered significant. This study is a pilot study, largely descriptive and exploratory. Multiple comparison corrections will not be applied in the primary analyses.

We hypothesize that the acupuncture will acutely benefit autonomic dysregulation in AD/ADRD subjects with AIA as indexed by reduced HRV and SC during treatment compared to pre-treatment rest. Therefore, we will explore any differences in HRV/SC after during/after treatment compared to pre-treatment rest.

In HRV analysis, more than 70 variables can be calculated in time- and frequency-domains,[12] including those mentioned previously: mean RR interval, SDNN, RMSSD, NN50 counts and three spectral frequency bands (very low, low and high) as well as total spectral power. In the time domain, SDNN reflects all the cyclic components responsible for variability in the recording epoch, so represents total variability. RMSSD is thought to reflect vagal tone and is relatively free of respiratory influences. In the frequency domain, low frequency (LF) band is thought to reflect a mix of sympathetic and vagal activity, while the high frequency (HF) band reflects vagal tone. The ratio LF/HF is often used as an index of overall sympathovagal balance. In SC analyses, resting tonic SC levels, non-specific skin conductance response (NS-SCR) amplitudes and frequencies occurring during tonic recording, and event-related skin conductance response ("ER-SCR", as with acoustic startle or an emotional stimulus) are the common measures. NS-SCR frequency is often interpreted as reflecting background sympathetic arousal and startle ER-SCR as the event-related sympathetic arousal responsiveness. Our analysis will explore any differences in post-treatment HRV/SC compared to pre-treatment.

We also hypothesize that there will be a short-term benefit of acupuncture treatment on autonomic regulation and behavioral symptoms as indicated by increased mean HRV, less motor restlessness on actigraphy, lower reported score on the POMS-abbreviated, and fewer observational AIA symptoms documented by subject or study partner during the observation period following the treatment compared to the pre-treatment observational day. Therefore, any changes in these measurements will be explored.

VII.. RISKS AND DISCOMFORTS

The risks associated with acupuncture are like any procedure that involves the insertion of needles through the skin. These include but are not limited to fainting, bleeding, infection, increased pain, nerve and tissue damage, needle breakage. None of these risks are common. The acupuncturists are fully trained and licensed and will take every precautionary measure to avoid any adverse effects.

VIII. POTENTIAL BENEFITS

It is possible that some of the patients will derive direct benefit from participation in the acupuncture. If any patient wishes to continue acupuncture, the licensed managing acupuncturist will provide them with a list of competent and validated practitioners in their community.

Moreover, it is anticipated that findings from these studies will help advance brain research generally, and in understanding the possible benefits of acupuncture on AIA symptoms in AD/ADRD.

IX. MONITORING AND QUALITY ASSURANCE

The PI, Dr. McManus, will ultimately be responsible for the validity and integrity of the data collected at the MGH site, and for ensuring that the study is conducted in accordance with the IRB-approved protocol. After data is collected and recorded on forms, the study coordinator may input the data into the Partners approved REDCap. Entries will be reviewed for accuracy and completeness by a second study coordinator. Finally, the PI or her designee (Co-I) will conduct monthly reviews to check that data in REDCap accurately reflects the data collected on the original data capture forms. The research team (PI, Co-I, research coordinators) will subsequently meet to discuss the results of this review, as well as case report forms and source documentation.

All electronic documentation will be stored on password-protected devices in locked cabinets located in secured areas. Paper forms will be stored in locked cabinets located in secured areas. Dr. McManus will ultimately be responsible for the accuracy of the data.

Subjects will be monitored for adverse events from the time they sign consent until completion of their participation in the study. For the purposes of this study, an adverse event (AE) will be defined as any unfavorable or unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the study. Stable chronic conditions (e.g. arthritis) that are present prior to the start of the study and do not worsen during the trial will NOT be considered adverse events. Chronic conditions that occur more frequently (for intermittent conditions) or with greater severity are considered as worsened and therefore would be recorded as adverse events.

In the event of either an adverse event or a serious adverse event, whether associated with study or not, the Investigator will notify the Partners IRB per the current guidelines. The study procedures and the well-being of all participants will be monitored closely by the MGH principal investigator, Alison McManus, DNP.

All adverse events will be reviewed by the Principal Investigator, Dr. Alison McManus, and will be reported to the Human Research Committee (HRC) in accordance with HRC Guidelines.

X. REFERENCES

1. Qian-Qian Li et al., "Acupuncture Effect and Central Autonomic Regulation," *Evidence-Based Complementary and Alternative Medicine : ECAM* 2013 (2013), https://doi.org/10.1155/2013/267959.

2. Jing Zhou et al., "The Effectiveness and Safety of Acupuncture for Patients With Alzheimer Disease," *Medicine* 94, no. 22 (June 5, 2015), https://doi.org/10.1097/MD.0000000000000933.

3. Qing-Fei Zhao et al., "The Prevalence of Neuropsychiatric Symptoms in Alzheimer's Disease: Systematic Review and Meta-Analysis," *Journal of Affective Disorders* 190 (January 15, 2016): 264–71, https://doi.org/10.1016/j.jad.2015.09.069.

4. Helen C. Kales, Laura N. Gitlin, and Constantine G. Lyketsos, "Management of Neuropsychiatric Symptoms of Dementia in Clinical Settings: Recommendations from a Multidisciplinary Expert Panel," *Journal of the American Geriatrics Society* 62, no. 4 (April 2014): 762–69, https://doi.org/10.1111/jgs.12730.

5. Martin Steinberg and Constantine G. Lyketsos, "ATYPICAL ANTIPSYCHOTIC USE IN PATIENTS WITH DEMENTIA: MANAGING SAFETY CONCERNS," *The American Journal of Psychiatry* 169, no. 9 (September 2012): 900–906, https://doi.org/10.1176/appi.ajp.2012.12030342.

6. Diogo Amorim et al., "Acupuncture and Electroacupuncture for Anxiety Disorders: A Systematic Review of the Clinical Research," *Complementary Therapies in Clinical Practice* 31 (May 2018): 31–37, https://doi.org/10.1016/j.ctcp.2018.01.008.

7. Kaoru Sakatani et al., "Effects of Acupuncture on Autonomic Nervous Function and Prefrontal Cortex Activity," *Advances in Experimental Medicine and Biology* 662 (2010): 455–60, https://doi.org/10.1007/978-1-4419-1241-1_65.

8. Soafara Andrianome et al., "An Assessment of the Autonomic Nervous System in the Electrohypersensitive Population: A Heart Rate Variability and Skin Conductance Study," *Journal of Applied Physiology (Bethesda, Md.: 1985)* 123, no. 5 (November 1, 2017): 1055–62, https://doi.org/10.1152/japplphysiol.00229.2017.

9. Chih-Chieh Hsu et al., "Effects of Electrical Acupuncture on Acupoint BL15 Evaluated in Terms of Heart Rate Variability, Pulse Rate Variability and Skin Conductance Response," *The American Journal of Chinese Medicine* 34, no. 01 (January 1, 2006): 23–36, https://doi.org/10.1142/S0192415X06003606.

10. Nancy B. Emerson Lombardo et al., "Acupuncture as Treatment for Anxiety and Depression in Persons with Dementia: Results of a Feasibility and Effectiveness Study," *Alzheimer's Care Today* 2, no. 4 (Fall 2001): 28.

11. Juan Sztajzel, "Heart Rate Variability: A Noninvasive Electrocardiographic Method to Measure the Autonomic Nervous System," *SWISS MED WKLY*, n.d., 10.

12. Laborde S, Mosley E, Thayer JF. Heart Rate Variability and Cardiac Vagal Tone in Psychophysiological Research - Recommendations for Experiment Planning, Data Analysis, and Data Reporting. Front Psychol. 2017;8:213. doi: 10.3389/fpsyg.2017.00213. PubMed PMID: 28265249; PMCID: PMC5316555.

13. Walter, S.D., Eliasziw, M. Donner, A. Sample size and optimal designs for reliability studies. Statistics in Medicine, 1998; 17:101-110.

14. McKhann, G. M., Knopman, D. S., Chertkow, H., Hyman, B. T., Jack Jr, C. R., Kawas, C. H.,...& Mohs, R. C. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & dementia*. 2011 May *7*(3), 263-269. doi: 10.1016/j.jalz/2011.03.005.