Brain Energy Metabolism and Sleep in Adults.

Title of the Protocol: Brain Energy Metabolism and Sleep in Adults

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Abbreviations

AD: Alzheimer's disease
MCI: Mild Cognitive Impairment
ATP: Adenosine Tri-Phosphate
pH : Potential of Hydrogen
Mg2+: Magnesium
PET: Positron Emission Tomography
SPECT: Single-photon emission computed tomography
MRS: Magnetic Resonance Spectroscopy
1H MRS: Proton Magnetic Resonance Spectroscopy
31P MRS: Phosphorus Magnetic Resonance Spectroscopy
NAA: N-acetyl aspartate
PMEs: Phosphomonoesters
PDEs: Phosphodiesters
Pcr: Phosphocreatine
Pi: Inorganic phosphate
NTPs: Nucleotide Triphosphate
NDPs: Nucleotide Diphosphate
MMSE: Mini-Mental Status Examination
CVLT: California Verbal Learning Task
DKEFS: Delis- Kaplan Executive Function System
CDR: Clinical Dementia Rating Scale
WAIS: Wechsler Adult Intelligence Scale
TOSL: Test of strategic learning
COWAT: Controlled Oral Word Association Test
BNT: Boston Naming Test
DSFB: Digit Span Forward and Backward
APOE Apolipoprotein
ABCA7 ATP binding cassette-A7

Contents

1. Introduction and Purpose

The main purpose of this study is to understand the impact of brain energy metabolites (BEM), sleep patterns and specific genes on the performance of neurocognitive measures of memory, attention, language and complex executive functions in cognitively normal adults, in preclinical stages of Alzheimer's disease (AD) i.e., mild cognitive impairment (MCI), and Alzheimer's disease. The secondary goal is to investigate if sleep and cognition could be improved in the three cohorts with dental intervention to correct the airway.

The three primary goals of this pilot will be followed by a secondary goal to test if dental intervention improves brain health in terms of brain's metabolic rate and cognition. The primary and secondary goals are

1. Explore the ratios of brain energy (ATP/PCr, Pi/PCr) and phospholipids (PME/PDE) metabolites as measured by magnetic resonance spectroscopy at 7 Tesla, and compare the differences in them with the performance of episodic memory, attention, language, and executive functions (abstraction, reasoning, verbal fluency, working memory) in three groups: cognitively normal adults, MCI and AD.

2. Investigate the differences in sleep patterns measured by the ratio sleep quality index (Stable/ Unstable sleep) in cognitively normal adults, MCI and AD and its relation to the performance of episodic memory, attention, language, and executive functions (abstraction, reasoning, verbal fluency, working memory) in three groups.

3. Investigate the differences in the variations of two genes, APOE-E4 and ABCA7, in relationship to the changes in the brain energy metabolites and its relation to the performance of episodic memory, attention, language, and executive functions (abstraction, reasoning, verbal fluency, working memory) in those with cognitively normal adults, MCI and AD.

4. Investigate if dental intervention improves sleep patterns and overall cognitive behavior in the three cohorts.

2. Background

Alzheimer's disease (AD) is rapidly progressing in the elder population and the pathophysiological changes in the brain starts at least 1-2 decades before the disease onset. During this period of slow progression individuals may notice subtle changes in the memory and this subset of population are termed as Mild Cognitive Impairment (MCI). MCI is a pre-clinical stage of Alzheimer's disease (AD) in which individuals have memory complaints but are functionally independent and not yet clinically diagnosed with dementia[39]. New modalities for potential identification of the progression of the disease, includes different biomarkers, state-of-the-art technologies like sleep tracking and magnetic resonance spectroscopy (MRS) may provide an additional, important tools to facilitate early detection of disease, which may allow for earlier intervention and provide a potential gauge for response to treatment.

The first goal of this research project aims to understand the variations in the brain energy and phospholipid metabolites as measured by magnetic resonance spectroscopy at 7 Tesla across three groups: cognitively normal adults, MCI, and AD. The brain requires a lot of energy in the form of adenosine triphosphate (ATP) to support the neuronal activity and it has a rich source of phospholipids to maintain biological functions. Therefore, abnormalities in the mechanism of energy supply and phospholipids can affect a wide range of function in the neuronal cells. Previous literature using 18FDG PET scan has showed impairments in brain glucose metabolism associated with cognitive decline in MCI even before the individual presents with clinically apparent cognitive dysfunction [19, 27]. Thus, measuring the ratio of energy metabolites ATP-to-PCr (ATP/PCr) and Pi-to-PCr (Pi/PCr) offers a promising way to predict energetic status of resting brain. Additionally, the levels of phospholipids start to decrease by the age of twenty (20) and more pronounced decline is noticed after the age of 80 years [10,47]. Thus, aging and diseased brains are more susceptible to the changes in the levels of phospholipids metabolites which can lead to neurodegenerative disorders. Two classes of phospholipid metabolites that can be studied using 31P MRS are phosphomonoesters (PMEs) and phosphodiesterase (PDEs) [1]. PMEs are the essential building blocks for cell/neuronal membrane synthesis whereas PDEs are the metabolites from the breakdown of the cell/neuronal phospholipids membrane. A higher ratio of PMEs-to-PDEs can, therefore, reflect as an improvement in brain health leading to neurogenesis, with the opposite suggesting neurodegeneration. Thus, 31P MRS has opened a window to measure various neurochemical metabolites non-invasively, which could provide detailed information about important high-energy phosphate metabolites, as well as phospholipid metabolites in real time. 7T Ultra-high magnetic field MRI scanner, which is now increasingly accessible worldwide and enables fast and accurate BEM measurement, may provide a comprehensive approach for aiding in the diagnosis of the neurodegenerative process from cognitively normal adults to MCI and AD and also monitoring the treatment responses to newer drugs.

Secondly, disturbance in sleep patterns can impact the brain's energy metabolism by altering the ratio of brain energy and phospholipid metabolites, thereby causing impaired brain cognitive functions. Aging, is an important moderator of sleep quality, and may affect non-REM slow wave sleep (SWS), which facilitates the clearance of toxic material like amyloid protein. Stable sleep helps restore the neurobiological and neurophysiological responses in relation to energy requirements impacting the changes in the concentration of brain energy and phospholipid metabolism. Currently, data are lacking regarding the relationship between sleep, brain energy requirement and its effect on the performance of cognitive domains in relation to normal aging, MCI, and AD.

Thirdly, BEM is regulated by specific genes that support the continuous energy requirements for the electrical activity of the brain. Hence in this research, we are interested in investigating the effect of two genes APOE ε4 and ABCA7 on brain energy and phospholipids metabolites in the three groups. It is important to understand this connection as genes regulate the synthesis of appropriate protein/enzymes like ABCA7 transporter protein for glucose metabolism leading to energy production.

Finally, based on an "improving sleep first hypothesis", a dental intervention (MyTAP; midline traction oral appliance (OA) therapy) will be offered to participants presenting with abnormal sleep and upper airway obstruction parameters. Therapeutic intervention to attenuate upper airway obstruction in sleep by using continuous positive airway pressure (CPAP) was shown to also improve cognitive functioning in AD patients with OSA(Cooke et al. 2009). In most cases, upper airway obstruction can also be acutely corrected using a simple fitted, clinically proven, FDA-cleared midline traction design oral appliance to restore sleep quality and possibly improve cognition and 'normalize' BEM. There are currently no reports on the efficacy of oral appliance therapy to improve daytime sleepiness, objective sleep measures and cognitive function in patients with MCI or AD. The MyTAP is similar to other midline traction design oral appliances which has been in clinical use for over 20 years without any serious adverse effects in treating patients with primary snoring to severe sleep apnea. (Gershman 2002; Hoekema et al. 2008) The MyTAP oral appliance will be used in accordance with its indications for use and FDA-approved labeling. The safety and efficacy of the midline traction oral appliance has already been published. (Thornton & Roberts 1996) As per FDA cleared label MyTAP® OA family of intra-oral appliances are intended for the treatment of night-time snoring and mild to moderate obstructive sleep apnea in patients 18 years or age or older.

The study will be concluded in two phases. In Phase-1, eligible participant will complete a set of neurocognitive testing, genetic sample collection, sleep assessment, and MRS scan. If participant is interested in dental intervention they will progress to Phase-2. In Phase-2 of the study, subjects will complete the dental intervention for 3 months followed by neurocognitive testing and sleep assessment.

3. Summary of the Project

This study will investigate:

1. Brain energy metabolites ratio (energy and phospholipids metabolites)

2. Sleep quality index and its relationship with the performance of episodic memory, attention, language, and executive functions (abstraction, reasoning, verbal fluency, working memory) in three groups: cognitively normal adults, MCI, and AD.

3. Genetic components of APOE ε4 and ABCA7

4. Effects of dental intervention in individuals with abnormal sleep parameters and cognition.

We will recruit up to 60 individuals in three groups of twenty each (20, Cognitively normal, 20 with MCI, and 20 AD) between the ages 55-85 years old. The individuals will be recruited from Dallas- Fort Worth areas through advertisements, flyers, social media, word of mouth, and those from the Center for BrainHealth who had expressed interest in future studies. Interested individuals will complete a study screen for medical history, demographics and memory questionnaire called Clinical Dementia Rating (CDR) scale.

A waiver of consent is being requested to cover potential subjects with a diagnosis of Alzheimer's disease as they participate in the phone screen (including an MRI safety screen) and an initial Clinical Dementia Rating (CDR) scale to assess their ability to provide written informed consent for study participation. If they receive a score of 1 or less, they will be deemed competent to provide their own written informed consent and will proceed to the second part of the competency screen. The potential subject will then be provided a summary of the study and will have their understanding assessed via a short quiz using the competency questionnaire .They have to answer all the questions on this questionnaire appropriately to

deemed competency. They will also undergo an initial Mini Mental Status Exam. If they receive a score of 20 or above on the MMSE, they will be deemed competent to provide independent informed consent, and will continue the consent process to provide full written informed consent for study participation.

An alteration of consent and a waiver of documentation of consent are being requested to cover potential subject with normal cognition or mild cognitive impairment, and the phone screen (including an MRI safety screen) for eligibility purposes. If these individuals are deemed eligible to participate in the study, they will be invited to the study site to provide full written informed consent to participate in the study.

After completing the phone screen, the eligible participants will visit the Center for BrainHealth for consent and neuropsychological assessment lasting for approximately three hours. Later, either the same day or at another date they will complete the MRS scan at the AIRC (approximately 90 minutes). Third, the participant will complete an in home sleep study for four (4) consecutive nights with a brief self-assessment sleep questionnaire for each night. Finally, the participant with upper airway obstruction and high snore count from sleep analysis will be offered dental intervention. The dental intervention will be performed at Center for BrainHealth, UTD by one of the dentist from Texas A&M Dental University i.e., Dr. Jason Hui, or Dr. Philip Wilson, Dr. Amrittej Virk, and Dr. Pollyana Marques de Moura. Upon completion of dental intervention, participant will be reassessed on their neurocognitive behavior, and sleep assessment.

4. Study procedures

Phase-1 will include phone screen, neuropsychological assessment, genetic sampling, sleep assessment, and MRS scan. Phase-2 will include dental intervention for 1 month followed by post-intervention testing using neuropsychological and sleep assessments.

The detailed protocol that will be used for recruitment and completing both phase-1 and phase-2 of the study is as follows:

a. Phone screen- During the initial phone call, potential participants will undergo will undergo a brief phone screen to assess inclusion and exclusion criteria, as well as MRI suitability followed by a memory questionnaire called clinical dementia rating (CDR)scale. CDR will be completed on the phone with the potential participant's family member first and then completed with the participant. It covers six (6) cognitive domains such as memory, judgment, and problem solving, community affairs, orientation, personal care and hobbies.

b. Neuropsychological assessment and Genetic testing: A clinician from the Center for BrainHealth will review the consent form with the participant. If the participant understands and agrees to sign and proceed, the form will be signed. After consenting, a buccal swab for genetic testing and vital signs (weight, height, blood pressure and heart rate) will be acquired. Then clinician will administer a group of standardized and experimental tests to each participant on neuropsychological testing. The assessment may last up to 3 hours, depending on the pace of the participant's response times. The intent of the tasks is to assess higher-level thinking skills, memory, attention, language, working memory, and selective learning. The assessment will be done at the Center for BrainHealth at 2200 W. Mockingbird Lane, Dallas, Texas.

The neuropsychological test battery will include standardized and experimental measures tests like Mini-Mental State Examination (MMSE),Wechsler Memory Scale (WMS-III) Logical Memory (LM) subtest, California Verbal Learning Task (CVLT), Controlled Oral Word Association Test (COWAT), Boston Naming Test (BNT), Digit Span Forward and Backward (DSFB), Delis-Kaplan Executive Function System Card Sorting , Trails A & B, Test of Strategic Learning (TOSL), Wechsler Adult Intelligence Scale (WAIS) Similarities subtest, selective auditory learning task, memory of intention test, Montreal cognitive assessment (MoCA) and neuromotor index (Altoida app) . The following questionnaires will also be administered: Lawton instrumental activities of daily living scale, medical questionnaires, activity questionnaires, met analysis memory questionnaire (MMQ), geriatric depression scale, Cognitive Reserve Index Questionnaire (CRIq) to measure cognitive reserve, Epworth Sleepiness Scale, a Pittsburg Sleep Quality Index (PSQI), a sleepio-internet based questionnaire, and sleep dairy to measure sleep habits.

c. Magnetic resonance spectroscopy (MRS): On the same or separate days, the participants will have MRS at 7Tesla at one point of time during which they will lie in the scanner while images of their brain will be recorded for one and half (1.5) hours. In the scanner the participants will be asked to be awake in the scanner, with head placed in a pad-cushioned coil. The volume coil $^{1}H/^{31}P$ MRS imaging data will be acquired using the 7Tesla human MRI scanner at UT Southwestern Medical Center (UTSW). During the MRS data acquisition, subjects will be positioned head-first and supine in the MRI scanner, with the back of the head positioned to rest in the head coil. After preparatory imaging scans, which will be is mainly for localization and shimming, the ^{31}P MRS data acquisition will be followed, which will include two surveying scans for evaluation of shimming quality on ^{31}P spectra and of ^{31}P excitation profiles along HF direction, then a six-slice 2D Chemical Shift Imaging(CSI) scan over the whole brain. For survey MRS scans, standard pulse-acquire technique will be used. Typical parameters are TR 4 s, sampling points 4 K, zero-filled to 8 K prior to FT, post-pulse delay 0.5 ms to filter out the broad phospholipids ^{31}P signal. For CSI, slice-thickness will be 2 cm along LR direction, 4-6 slices, TR = 1 sec, NA = 4, sample points 2 K in-plane resolution $2x2cm^2$, scan time ~45 min. After ^{31}P MRSI data acquisition, voxel-by-voxel data analysis will be carried out to compare the regional difference in relative concentration of the phosphoryl metabolites; and all the measurements will be calculated from these values.

d. Sleep quality assessment (Figure 1, 2) SleepImage (MyCardio, LLC, Broomfield, CO) recorder collects data on electrocardiogram (ECG), actigraphy, body position, snore, ECG-derived respiration, HRV, HR. The SleepImage system includes a sleep recorder that is clinically validated and FDA cleared to allow the non-intrusive collection of objective measures of sleep quality. The participant will complete the sleep study for four (4) consecutive nights using the device along with self-assessment of sleep by answering the PSQI questionnaire for each night.

The sleep data will be analyzed by Dr. Preetam Schramm and Dr. Emet Schneiderman.

Figure 1: SleepImage sleep device in recording position.

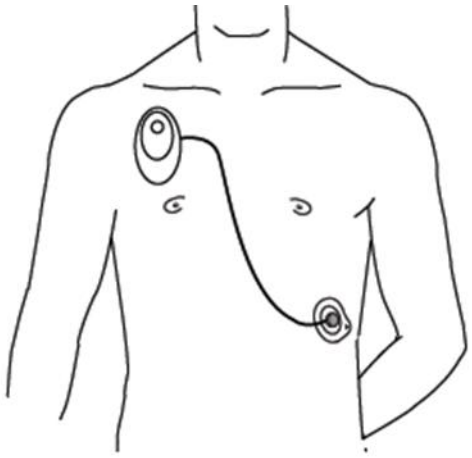

Figure 2: SleepImage sleep device actual size.

Total time committed towards research will be around 37 hours excluding the time for transit.

Dental Intervention:

Participants whose sleep recordings (Figure 1) show the presence of clinically significant snoring (≥4 snores/hour of sleep) will be referred for dental intervention. If the participant chooses dental intervention, the attending dentist will determine if the individual is eligible for oral appliance therapy (OA). OAs are the recommended first line therapy for snoring, obstructive sleep apnea with mild to moderate obstruction, and also those seeking an alternative to CPAP therapy.

The OA device (Figure 2) will be used per manufacturers' recommendations. The device has a thermal acrylic liner to ensure a very accurate fit. Each subject will also be custom fitted with a mandibular positioner ("AM Aligner" or "Morning Positioner") to use for up to 20 minutes after awakening. This will assist in returning the subject to his/her normal occlusion. Appliance Acclimation: the OA will be adjusted / titrated to the awake patient's maximal comfortable protrusive position by a study dentist.

1. Fitting of an OA: The MyTAP (Airway Management Inc., Dallas, TX) custom-fitted dental OA will be applied chair-side by a trained dentist. The starting position will be determined by the patient at a comfortable position but not less than 60% as determined by the Pro Gauge measurement tool. "Comfortable" is defined as the advanced mandibular position that permits the subject to sleep for ≥5 hours per night for at least 6 nights of the week. [Completion time: 30 minutes)
2. Participants are expected to wear the appliance nightly during sleep. Participants will be allowed to advance the jaw 0.5 mm every 2 nights (less frequently if needed to minimize transient discomfort) without causing discomfort at the temporal mandibular joint, masticatory muscles or teeth that lasts more than 1 hour after removing the appliance in the morning.
3. Subjects will use diaries to record appliance settings and hours of sleep on each sleep recorded or non-recorded night.

The dental intervention will be performed at Center for BrainHealth, The University of Texas at Dallas by one of the dentists from Texas A&M Dental University i.e., either Dr. Jason Hui, Dr. Philip Wilson, or Dr. Amrittej Virk, or Dr. Pollyanna Marques de Moura.

Safety
The MyTAP OA and sleep recorder to be used are FDA cleared. The OA is in wide use by dental patients throughout the US, Europe and Australia. Both have demonstrated efficacy so that their use in the proposed research is consistent with what is done in routine clinical care and involves no more than minimal risk. All of the proposed tests are noninvasive.

Figure 2. MyTAP Oral Appliance

5. Criteria for inclusion and exclusion of Subjects:

Eligible participants will be:

- Ages 55-85 years
- At least 12 years of education
- Right hand dominant
- With or without minor memory complaints, (those with a diagnosis of Alzheimer's disease are also eligible for the study),
- Participants who can safely have an MRS scan
- Have motor abilities including the use of the right arm and hand for neuropsychological testing.
- Able to speak, read, and comprehend English fluently
- Non-pregnant, and not on Hormone replacement therapy

Exclusion criteria will be:

- Pregnancy
- Use of Hormone Replacement therapy
- Less than 12 years of education
- Left hand dominant
- Unable to speak, read and write English fluently (Testing and training material are validated in English).
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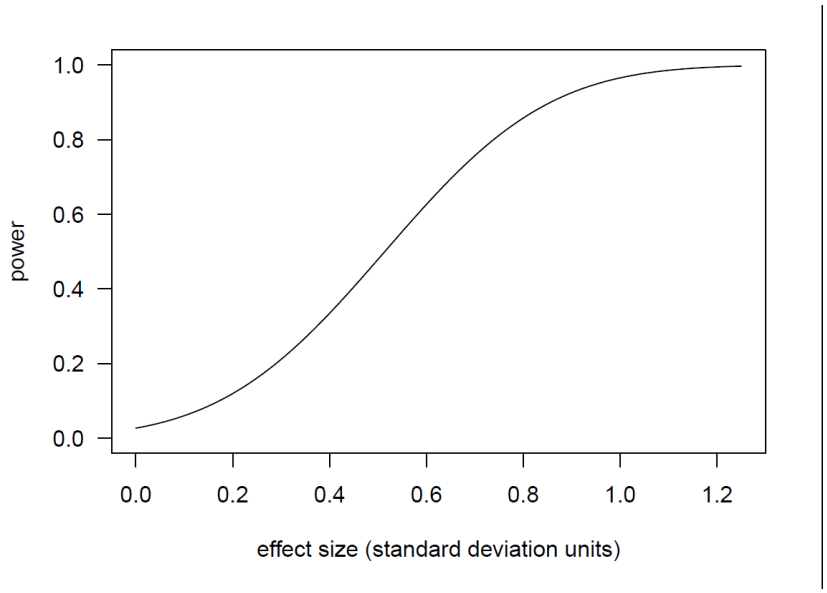
- Neurological Disorders, e.g., stroke, brain tumor, cerebral hemorrhage.

- Autoimmune disorders like fibromyalgia, systemic lupus erythematosus (SLE), Multiple sclerosis and rheumatoid arthritis.
- Metabolic diseases such as diabetes mellitus, thyroid disorders that are not currently managed by a physician
- Psychiatric disorders such as bipolar disorder, major depressive disorder, pervasive developmental disorder, schizophrenia, anxiety disorder.
- Current drug or alcohol abuse
- Head injuries with an Ohio State University TBI Identification (Short Form) score greater than 3.
- Cancer treated with radiation and/or chemotherapy
- General anesthesia within the prior six months
- Uncorrected vision and hearing problems.
- Active pain requiring treatment
- BMI ≥35
- Previously treated for diagnosed sleep disorders
- Known chronic obstructive pulmonary disease(COPD)
- Exclusion for imaging criteria (includes the following, or any other concerns by the AIRC staff)
    - Permanent Makeup.
    - Exclusions for metal safety include questionable ferrous implants, bullets, BB's, shrapnel,
    - Medical devices which are unsafe in MRI.
    - Hearing aid that cannot be removed.

6. Sample Size

In pilot data we tested 12 variables for mean change following training and estimated effect sizes for the set of variables that were significant at a 10% false discovery rate (FDR). The equivalent alpha level for a 10% FDR in our set of pilot data was estimated to be 0.055to account for the potential increase in false positives due to the multiple tests, and the minimum effect size for the set of variables that satisfied the FDR level was 0.6 standard units. Using the pilot data estimate of an FDR-equivalent alpha level we calculated power for a range of effect sizes and for a sample size of N=60 (shown in figure below).



Given the parameters specified above, the figure shows a power level of at least 0.60 when the effect size is at least 0.7 standard units. Based on our pilot data we expect to be sufficiently powered, with multiple testing accommodation, using N=60 subjects for tests of mean change.

7. Sources of Research Material

Materials obtained for research purposes include demographic information, survey/questionnaire data, neuropsychological testing battery, brain imaging MRS 7T data, genetic data and sleep data in cognitively normal adults and mild cognitive impairment. A swab of the cheek/saliva will be collected for a DNA sample. All of the data will be obtained for research purposes.

8. Potential Risks:

Neuropsychological assessment risk: There are no known risks associated with the neuropsychological testing other than possible fatigue and frustration. If the participants feel tired they will be allowed to rest. If they become frustrated, they can rest or stop participation at any time.

MRI Risk: The magnetism of the MRI scanner will attract certain metal objects and could cause serious harm. Subjects will be asked to fill out an MRI screening form which has questions about their health, previous surgeries and the presence of metal or implanted devices in their body. People with metal or device implants such as pacemakers, infusion pumps, aneurysm clips, shunts, clips, metal plates, rods, joints or screws, certain IUD implants, shrapnel or metal in the eyes, and permanent eyeliner or eyebrows may be excluded from participation in this study. Subjects are encouraged to please tell the researchers if there is any possibility of metal in their body. Researchers will carefully screen subjects to determine if it is safe for them to have an MRI. There are no known risks from exposure to magnetic fields. Subjects may experience nervousness and/or anxiety due to the loud banging made by the machine while it is taking pictures and from confinement in a tight space (claustrophobia). If they become anxious, they can

stop the procedure at any time. They may also experience some discomfort and fatigue from lying still during imaging. If they have any metal clips or plates in their body, they are encouraged to tell the investigator. MRI may not be appropriate if subjects are pregnant or are trying to become pregnant.

MRI may not be appropriate if subjects have permanent eyeliner or eyebrows or any pieces of metal in their body, such as the following:

- heart pacemaker, heart valve replacement, or aortic clips
- metal fragments in your eyes, skin, or elsewhere in the body
- brain clips or pieces of metal used in aneurysm surgery or intracranial bypass
- venous umbrella
- pieces of metal in the body resulting from work as a sheet-metal worker or welder
- clips placed in an internal organ
- prosthetic devices, such as middle ear, eye, joint, or penile implants
- joint replacement.
- hearing aid that cannot be removed
- neurostimulator
- insulin pump
- intrauterine device (IUD)
- shunts or stents
- metal mesh or coil implants
- metal plate, pin, screws, or wires, or any other metal implants

Women who are pregnant or suspect pregnancy may not participate in this study. Women of childbearing potential will have a urine pregnancy test.

Loss of Confidentiality: Any time information is collected; there is a potential risk of loss of confidentiality. Every effort will be made to keep subject's information confidential; however, this cannot be guaranteed.

Risks to an Embryo, Fetus or Breast-fed Infant Females: If females are part of this study while pregnant or breast-feeding an infant, it is possible that they may expose the unborn child or infant to risks. For that reason, pregnant and breast-feeding females cannot participate in the study. If subjects can become pregnant, a pregnancy test will be done (from a urine sample), and it must be negative before they can be a part of this study. If subjects do become pregnant during this study, they must tell the researchers immediately.

Other Risks: There may possibly be other side effects that are unknown at this time. If subjects are concerned about other, unknown side effects, they are encouraged to please discuss this with the researchers.

7T Magnet Potential Risks: This procedure is experimental and the long-term risks of the high magnetic field are unknown. Exposure to high magnetic fields may have effects on the normal electrical activity of the body including changes in nerve and heart function. Changes in the heart rate or rhythm could occur. Blood pressure, temperature, and pulse rate may change. Studies with an 8 Tesla MRI have not shown any significant effects. A subject may feel dizzy when moving the head quickly while in the magnetic field. This is a relatively frequent sensation, perhaps occurring in 30% or more of subjects. In studies at 8 Tesla, 1 subject out of 200 has vomited as the result of being in the

magnet. A relatively common sensation is a metallic taste in the mouth while entering or exiting the scanner. A subject might see tiny light flashes similar to those that occur when you rub your eyes in the dark. This is less common and has no known harmful effects. Claustrophobia (uneasiness at being in a confined space) is a common contraindication in any MRI procedure at any magnetic field strength (tesla). Exposure to the rapidly changing magnetic fields could cause twitching of the subject's muscles. This effect, known as peripheral nerve stimulation (PNS), is temporary. It is possible that radio frequency energy in a 7 Tesla MRI system may be absorbed in an unexpected manner by human subjects. Local heating of the leg may occur. Studies with an 8 Tesla MRI have not shown any significant effects in studies of the head. As with all MRI, any metal in the body or in clothing represents a risk. Metallic objects can be accelerated by the magnetic field and become dangerous. A metal implant or foreign object in the body could be displaced by the magnetic field. There can be increased heating near metal structures.

Sleep recorder risk: The minor physical risk associated with the sleep-monitoring aspects of this study are no more than those involved with standard tests of bodily (physiological) functions, for example wearing a heart monitor or polysomnography. We do not anticipate any significant physical risk to subjects from using the sleep recorder while participating in this study. It is not anticipated that the 2 hypoallergenic adhesive electrodes used with the recorder will cause itching or rashes. The adhesive used to attach the electrodes is medical grade meant for use on human skin similar to a bandage and is disposed and replaced with new adhesive electrodes with each use.

Genetic data risk: Finally, there is no associated risk with genetic testing other than potential loss of confidentiality which will be guarded against. The results of the genetic testing will not be shared with the participants.

Dental Intervention Risk: The minor physical risk associated with the sleep-monitoring aspects of this study are no more than those involved with standard tests of bodily (physiological) functions, for example wearing a heart monitor. The OA may cause pain in the jaw joint and teeth, and difficulty in opening or closing the jaw; these conditions are usually temporary. In the long term, the OA may cause changes in tooth position and in the bite (occlusion), as well as damage to the teeth and gums.
We do not anticipate any significant physical risk from participating in this study. Though not impossible, we do not expect the adhesive hypoallergenic electrodes of the SleepImage device to cause itching or rashes. By wearing an OA, a subject may experience some discomfort and/or reduced function of the jaw joint (temporomandibular joint) and muscles of the jaw (chewing muscles) and of the face during and after treatment. Subjects may also experience some reduction in sleep quality due to discomfort while acclimating to wearing the OA. Other minor risks include temporary irritation of the mouth and oral cavity due to contact with the OA, and excessive salivation or dry mouth from mouth breathing. Repositioning of the lower jaw and tooth movement may also occur, but are typically minor and reversible. Also highly unlikely, a subject could swallow or aspirate part of an OA should it break. Participants will be carefully monitored for all of these risks by one or more of the study dentists. A telephone number and email address will be given to participants in case of questions and emergencies.

Data Storage: All data from questionnaires and cognitive tasks will be stored on a password-protected computer with the participant's study number. A master link linking participant numbers to names and other contact information will be stored on a different computer that is also password protected. All data will be stored without any identifying participant information linked to the data itself. All data will be stored without any identifying participant information – only the participant's study number will appear on the sample.

Procedures to Maintain Confidentiality: We have taken a number of measures to ensure the confidentiality of the data and the safety of the participants. As we describe in the sections above, all data from the proposed study will be identified by a numerical ID code only. The information linking the numerical ID code to identifying information will be maintained separately and securely from the data themselves.

Every effort will be made to maintain the confidentiality of study records. Only the researchers will have access to any personally identifying information, that is, contact information for each participant (i.e., an email address or phone number). This information will not be stored with the participant data. An identification number will be assigned to each participant so that it will be possible to identify information to be shared with other researchers as described in the HIPAA. In data analysis, each participant will be identified by this number. All research materials with identifiable data, consisting of detailed health questionnaires, neuropsychological testing, and consent and HIPAA forms, will be kept in locked cabinets in the Center for BrainHealth at UTD. Imaging data at UTSW will be stored following HIPAA-compliant protocol. The data from the study may be published, but all information will be deidentified and HIPAA compliant. The confidentiality of the data will be maintained within the legal limits. Only associates listed on this study will have access to identifying data. The Research Coordinator, the Principal Investigator, and co-investigators will have access to the data and to the codes, along with designated research associates. The researchers will destroy the personal identifiers upon completion of data collection for the study.

9. Participant Safety and Data Safety Monitoring Plan

Dr. Chapman, PI will closely monitor the following at least on a monthly basis:

Study accrual rate
Experience of study participants
Study attrition including participant withdrawals/dropouts
Patterns of AEs and/or unanticipated events
Patterns of protocol deviations and/or violations
Changes in risk/benefit

10. Potential Benefits

Benefit to participant:

The only benefit participant can have in this study is from dental intervention to improve sleep quality. Other benefits related to MRS and genetic data are not anticipated from this study.

Benefit to society:

We hope the information learned from this study will help our understanding of early changes in the brain in individuals with normal cognitive functioning, mild cognitive impairment, and Alzheimer's Disease, in the areas of neuropsychological assessment, magnetic resonance spectroscopy imaging (MRS), genetic sample and sleep analysis. We also are interested in learning if correction of airway through dental intervention will improve sleep and cognition in three cohorts.

11. Incentive

The participant will be paid $30 on successful completion of all the study parameters.

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