Phase 1 - The Use of Rhythmic Light Therapy to Entrain Gamma Oscillations and the Circadian System in Patients With Alzheimer's Disease
PI: Mariana Figueiro
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A. Specific Aims

Data suggest that approximately 40% of the estimated 5.5 million older (65+) Americans with Alzheimer's disease (AD) suffer from severe dysfunction of sleep-wake and circadian systems, manifesting clinically as sundowning, excessive daytime sleepiness, nocturnal wandering, agitation, and day-night reversal, which substantially increases the burden of caregivers. [1, 2] In people with mild cognitive impairment (MCI), an “at risk” or potential prodromal stage of dementia, sleep-wake disturbance is evident in up to 60% of patients. [3, 4] It has also been shown that coherent 40 Hz neural oscillation is a fundamental frequency of healthy brain activity [5] and it is believed to play a role in attentional selection and memory operations. [6] ADRD patients in particular, have reduced gamma oscillations. Animal studies showed that exposing mice to flickering lights at 40 Hz reduces Aβ42 levels in cortical regions of the brain.

Our team has published various studies showing the positive impact of a tailored lighting intervention (TLI) designed to promote circadian entrainment in persons with ADRD. In addition, we recently collected and published on exciting pilot data showing that light modulating at 40 Hz increases gamma power and gamma/theta coupling, both associated with increase in memory and cognition. **In Aim 1, we will investigate how the light delivering 40 Hz to promote gamma wave entrainment (rhythmic light [RL]), affects subjective sleep and cognition in a controlled laboratory study. A lab study will allow us to collect electroencephalogram (EEG), perform cognitive tests, and observe the response in those with MCI compared to a healthy control group (HC).**

Aim 1: In a randomized, placebo-controlled, mixed-design laboratory study, we will demonstrate the effect of 40 Hz RL on: 1) brain response (EEG), 2) cognitive performance (working memory task), and 3) subjective sleepiness (questionnaires). We will recruit 20 adult MCI and 20 healthy, age-matched controls (HC) to participate in this study. It is hypothesized that compared to the placebo intervention (i.e., random flicker): 1) 40 Hz RL will increase gamma (40 Hz) neural oscillation and increase theta-gamma coupling, 2) improve cognitive performance and 3) reduce subjective sleepiness. We also hypothesize that gamma power will be reduced in MCI participants and the effect size of the intervention will be greater in MCI participants than in the HC.

We will, for the first time, demonstrate that a practical, effective, tailored, nonpharmacological intervention using light that promotes circadian entrainment (TLI) and deliver neurostimulation (40 Hz RL) can be used to improve sleep and cognition in older adults with MCI and mild AD living at home or in inde- pendent or assisted living facilities, thereby possibly mitigating significant financial and social burdens, including decreasing cognitive deterioration in this population. Moreover, given recent evidence linking the importance of sleep in the development of AD, the proposed studies can have a significant impact on the progression of the disease MCI and mild AD.

Aim 1: Participant Recruitment. Population/Sample: Community Persons Living with Mild Cognitive Impairment (MCI) or mild Alzheimer’s disease (AD) and Healthy Age-matched Controls (HC).

a. Study sites: Participants will be recruited from the Capital District and NYC area in conjunction with physicians who have access to the clinical population. Our team have demonstrated the ability to recruit older adults, including those with AD and their caregivers, in 3 recent NIH-funded trials. As in prior successful trials, recruitment methods will include: (1) provider referral, (2) on-site (in assisted living) by research staff, (3) flyers placed in participating sites or through advertising in the community, and (4) social media. We plan to collect equal numbers of participants in winter and summer to account for a possible effect of season and equal number of males and females.

b. Procedures: Dr. Figueiro’s team, with referrals from local physicians already working with her, will enroll 40 participants (20 controls) for **Aim 1**. Participants must be diagnosed with amnestic MCI or mild AD, as defined by a Montreal Cognitive Assessment (MoCA)[87] score between 17 and 25. For the healthy controls, the inclusion criteria are: must not be diagnosed with MCI or ADRD (MOCA score above 25). All participants must not be taking sleeping medication or oral melatonin, those taking antidepressants will be included, but type of medicine and dosage intake will be monitored, must score a 5 or less in the Pittsburgh Sleep Quality Index (PSQI) and must not have any of the exclusion criteria below. Study participants who meet the inclusion and exclusion criteria will discuss informed consent for study participation, using procedures and consent forms approved by the Institutional Review Board.

Aim 1 - Screening Assessments

a. Cognitive screening utilizing the MoCA: The MoCA[87] is a one-page, 30-point test that can be administered in 10 minutes. It assesses short-term memory, visuospatial abilities, executive functions, attention, concentration and working memory, language, and orientation to time and place. In a validation study, it was shown to be a promising tool for detecting mild cognitive impairment and early AD onset compared to the MMSE. According to Nasreddine et al.,[87] the sensitivity and specificity of the MoCA for detecting MCI (n = 94 participants) were 90% and 87%, respectively, compared to 18% and 100%, respectively, for the MMSE. The sensitivity and specificity of the MoCA for detecting early AD (n = 93 participants) were 100% and 87%, respectively, compared to 78% and 100%, respectively, for the MMSE. MCI/mild AD participants must have a MOCA score between 17 and 25. The control group participants must have a MOCA of 25 or greater.

b. The Clinical Dementia Rating Scale Sum of Boxes (CDR-SOB). CDR will be obtained through semi-structured interviews of patients and informants, and cognitive functioning will be rated in 6 domains of functioning: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. Each domain is rated on a 5-point scale of functioning as follows: 0, no impairment; 0.5, questionable impairment; 1, mild impairment; 2, moderate impairment; and 3, severe impairment (personal care is scored on a 4-point scale without a 0.5 rating available). The global CDR score will be computed using online algorithm (www.biostat.wustl.edu/~adrc/cdrpgm/index.html). The CDR-SOB score is obtained by summing each of the domain box scores, with scores ranging from 0 to 18. We will include those in boxes 0.5-4.0 (Questionable cognitive impairment to very mild dementia) and 4.5-9.0 (mild dementia). The CDR demonstrates good reliability[88, 89]and has been validated against neuropathologic finding.[90-92]

c. Sleep disturbance using the PSQI: The PSQI is a tool that can be used to measure sleep quality in clinical populations, composed of 19 items that generate 7 component scores (subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction).[93] The sum of the 7 component scores yields a single global score. A global score >5 is considered to indicate sleep disturbances. For Aim 1, we will include those who have scores <5 (no sleep disturbances).

Aim 1 - Study Assessments

a. Electroencephalogram (EEG). EEG recordings will be taken 2 times per experimental session using a BioSemi ActiveTwo system (BioSemi, Amsterdam, NL). Prior to each session, electrodes will be applied to the participants' scalps according to the international 10–20 system. [94] Four electrodes will be placed along the midline of participants' crania at locations Fz (frontal), Cz (central), Pz (parietal), and Oz (occipital). Reference electrodes will be placed on the earlobes at locations A1 and A2. To record blinking, an electrode will be placed under each participant's right eye for electrooculographic (EOG) measurements. The power at 40 Hz, 4–8 Hz (theta), and 30–55 Hz (low gamma) frequency ranges will be calculated at each electrode site. Entrainment to the 40 Hz rhythmic stimulation will be assessed in terms of increases in power at 40 Hz. Theta-gamma coupling will be assessed using the modulation index (MI), [95] wherein each phase of theta (0–360° interval) was binned into eighteen 20° intervals. The standard Hilbert transform will be applied to obtain time series of theta phases and amplitude envelope of low gamma. The composite time series will then be constructed, which will yield the amplitude of low gamma oscillation at each phase of the theta rhythm. The mean amplitude of gamma at each theta bin will be calculated and normalized by dividing each bin value by the sum over the bins, resulting in the phase-amplitude distribution function. The gamma amplitude MI by theta phase will be calculated by measuring the divergence of the observed amplitude distribution from a uniform distribution.

b. Subjective Sleepiness. Participants will be asked to report a Karolinska Sleepiness Scale (KSS) [96] score 2 times per experimental session. The KSS outcome prompts participants to rate how sleepy or alert they are feeling on a scale ranging from 1 to 9, where 1 = "very alert," 3 = "rather alert," 5 = "neither alert nor sleepy," 7 = "sleepy, but no difficulty remaining awake," and 9 = "very sleepy, fighting sleep, an effort to remain awake."

c. Working Memory (WM) Task: This complex operation span task has been used to examine WM in MCI, AD, [97] and healthy older adults. [98] The WM task contains 9 practice (not included in final score) and 20 test trials. Participants view a serial visual display of letters and math problems. They are asked to hold the letters in memory while simultaneously determining if the simple math problems are correct (e.g., 7+5=13). The letter strings are 4-8 letters long + 4 repetitions of each. Each of the simple math equation is on the screen for 3000 ms and each letter is presented for 1000 ms. Participants are instructed to press the "M" key with their right hand if the simple math equation is correct and press the "V" key with their left hand if the equation is not correct. Math performance is measured in percent correct. Similar to Unsworth et al., [99] we will only include data in the analysis if participants can performed equal and/or greater than 75% correct on the math equations. After each trial, a

question mark appears on the screen to signal the response period. Participants are asked to enter the letters in the same order they were presented. The recall part of the task will not be timed, and participants are not able to go to the next trial until the correct number of letters is entered. Then, a “Ready?” prompt appears on the screen and participants will press the space bar to start the next trial. Four breaks are inserted throughout the task. Participants are tested in the WM task before and after each experimental condition. Performance is as- sessed by calculating Accuracy and Reaction Time (RT).

d. **Questionnaires to assess Fatigue, pain and depressive symptoms:** Four questionnaires will be collected one time at the first session.

- The Fatigue Severity Scale (FSS) uses contains nine statements that rate the severity of fatigue symptoms on a rating from 1 to 7, which measures the severity of fatigue and its effect on a person's activities and lifestyle.
- Self-Description Inventory measures levels of self-evaluative behavior in terms of favorable and unfavorable personality attributes.
- The Beck Depression Inventory (BDI) is a 21-item, self-report rating inventory that measures characteristic attitudes and symptoms of depression.
- The Short-form McGill Pain Questionnaire (SF-MPQ-2) assesses the major symptoms of both neuropathic and nonneuropathic pain. Previous research has demonstrated its reliability, validity, and responsiveness in diverse samples of patients with chronic pain.

Aim 1 - Experimental Protocol

a. Allocation. HC and MCI participants will be randomly assigned to one of the 2 experimental conditions (40 Hz RL and Placebo RL) in a counterbalanced order (Fig. 5). All subjects will experience both conditions.

b. Data collection. The experimental protocol for the study is shown in Fig. 6. Participants will complete a sleep–wake diary during all weeks of the experiment, starting 1 week prior to beginning the study. These diaries will document bedtimes, rising times, caffeine consumption, and quality of sleep. The experimental sessions will start at 14:00 on each experimental day which will be separated by 1 week. Sessions will initiate with a 10-minute adaptation period to a low-level ambient light (e.g., 3000K) providing illuminance of 15 lux at participants’ eye level on a vertical plane,

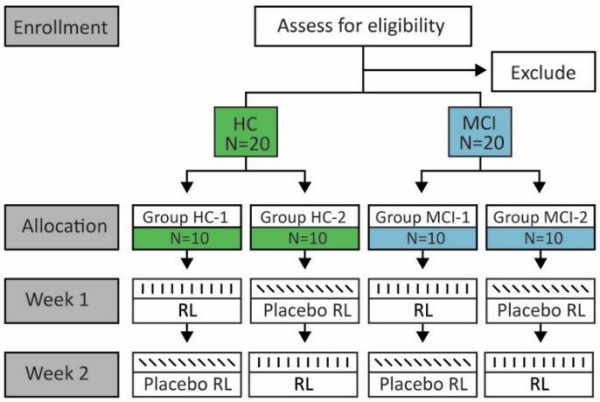

Fig. 5. Diagram of proposed flow for the participants in Aim 1. N: no. of participants; HC: healthy control; MCI: mild cognitive impairment; RL: rhythmic light

followed by a pre-exposure data collection period (T1), including KSS, EEG, and WM task. Based on their groupings participants will experience either 40 Hz RL, or Placebo RL conditions for a duration of 1 h, followed by the second data collection period (T2) (see Fig. 6).

Description of the lighting interventions is below. Participants will be asked to remain awake and keep their eyes open during the entire session. They will also be asked to refrain from body movement and excessive blinking during EEG recordings, which should be 3 minutes, to avoid the occurrence of EOG artifacts in the EEG data.

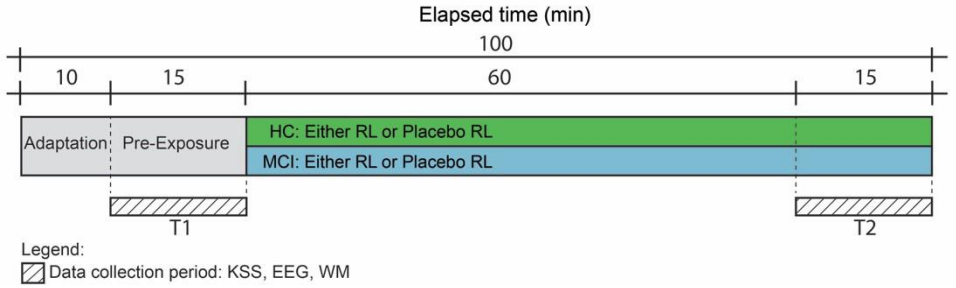

Fig. 6. The experimental protocol for the study. KSS: Karolinska Sleepiness Scale; EEG: electroencephalogram; HC: healthy control; MCI: mild cognitive impairment; WM: Working Memory task, RL: rhythmic light; T1 and T2: data collection periods.

Aim 1: 40 Hz RL Device Description

The flicker frequency of the 40 Hz RL used in Aim 1 will be 40 Hz and the stimulation will be a square wave with a 50 % duty cycle (i.e., 12.5 ms light- on and 12.5 ms light-off). In the Placebo RL condition, the duty cycle will be delivered with a random interval determined by a Poisson process with an average interval of 40 Hz. Both RL and Placebo RL conditions will provide a 30 lux of red light on a vertical plane at the eye level. The red light will be used because it does not affect the circadian system; therefore, we will be able to attribute observed effect to the flicker frequency utilized. We hypothesize that the improvement in cognition and subjective sleepiness will be greater in the 40 Hz RL compared to the random RL and the effect will be larger in persons with MCI.