Phase 1 - The Use of Rhythmic Light Therapy to Entrain Gamma Oscillations and the Circadian System in Patients With Alzheimer's Disease
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Statistical Design and Power

Goal	Variables	Instruments	Outcome Measures
Aims 1: Demonstrate, in a mixed design, that RL affects brain activity, subjective sleep and cognition in MCI and HC. Aim 2: Investigate long-term impact of the combined intervention (TLI + RL) on sleep (actigraphy and questionnaires) and cognition (standardized tests). Aim 3: Explore the impact of RL alone on circadian entrainment.	Aim 1: EEG, subjective sleep, cognition. Aims 2: Sleep quality and quantity, cognition, QoL, acceptance of intervention, circadian light exposure. Aim 3: Outcome measures from Aim 2.	Daysimeter (pendant) – 7 days at baseline, wks 9, 14) Actigraph (wrist) 7 days at baseline, wks 9, 14) Ambulatory EEG – Aim 1 only Questionnaires WPA task WM task IPT task	**Aim 1**: Cognition (WM task), Subjective sleepiness (KSS), Brain activities (EEG) **Aim 2**: • Biomarker (urine melatonin) at baseline, wk 9 • Light exposures during study (CS, lux) • Rest-activity rhythms (IS, IV, RA) • Sleep quantity (efficiency, latency, duration) • Sleep quality (PSQI) at baseline, wk 9,14 • Cognition (WPA, WM, IPT, ADAS-Cog) – at baseline, weekly (wks 1-9), wk 14 • QoL (DQoL) - at baseline, weekly (wks 1-9), wk 14 • Acceptance of TLI and RL – wk 9 only • Cognition (MoCA, CDR-SOB) at baseline, wk 9, 14

Variables and Measures. Rest-activity rhythms before and after the TLI and RL will be measured using **the actigraph (rest-activity) data**. The following measures will be calculated: (1) interdaily stability (IS), a ratio indicating the strength of coupling between the light-dark cycle and rest-activity rhythm over a 24-hour period; (2) intradaily variability (IV), an indication of the fragmentation of the rest-activity rhythm (i.e., the frequency of the transitions between rest and activity); (3) RA of the rest-activity rhythm, calculated as the difference between the means of the most active 10-hour period (M_{10}) and the least active 5-hour period (L_5) in the 24-hour pattern; and (4) measures of nighttime sleep (minutes of sleep, sleep onset latency, and sleep efficiency).[118] Photopic light levels (lux) and CS values will be calculated from the light-dark data collected with the Daysimeter. Increases in IS and RA and a decrease in IV will be considered an improvement in rest-activity patterns. We will evaluate the change in these variables from baseline to the end of intervention period and the post intervention period to assess carryover effects. Questionnaires will allow us to evaluate QoL and sleep quality. For the **EEG data**, the power at 40 Hz, 4–8 Hz (theta), and 30–55 Hz (low gamma) frequency ranges will be calculated at each electrode position (i.e., Fz, Cz, Pz, and Oz). 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). [90]

Sample Size and Estimated Statistical Power: Studies for each aim will have enough power to detect the impact of the active intervention on the study measures. Based on our pilot study, a planned sample size of 20 in each group (including 30% attrition rate) will provide 95% power, using 2-sided alpha = 0.05 significance tests, to detect statistically significant differences in the means between 2 paired treatment conditions in Aim 1.

Statistical Analyses: Analyses will include (1) evaluation to determine data quality, (2) creation of constructed variables and determination of variable distributions, (3) testing of parametric statistical assumptions wherever appropriate, (4) preliminary (generally bivariate) testing of hypotheses, (5) consideration of potential covariates to build into the statistical models to increase the probability of detecting treatment effects if they exist, and (6) development and elaboration of multivariate models. Aim 1: For all outcome measures, data obtained during T2 will be first normalized to the data obtained during T1 to obtain the relative change over time within each condition (i.e., RL and Placebo RL) in each group (i.e., HC and MCI). A linear mixed-effects models (LMEM) will be used to test for significant effects for all outcome measures with group and condition are entered as fixed factors, and participant entered as a random factor. Determinations of significance (p <0.05) in the LMEM results will employ 2-tailed t tests with Sidak correction.