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Gamma neuromodulation improves episodic memory and its associated network in amnestic mild cognitive impairment: a pilot study

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ABSTRACT

Amnestic mild cognitive impairment (aMCI) is a predementia stage of Alzheimer's disease associated with dysfunctional episodic memory and limited treatment options. We aimed to characterize feasibility, clinical, and biomarker effects of noninvasive neurostimulation for aMCI. 13 individuals with aMCI received eight 60-minute sessions of 40-Hz (gamma) transcranial alternating current stimulation (tACS) targeting regions related to episodic memory processing. Feasibility, episodic memory, and plasma Alzheimer's disease biomarkers were assessed. Neuroplastic changes were characterized by resting-state functional connectivity (RSFC) and neuronal excitatory/inhibitory balance. Gamma tACS was feasible and aMCI participants demonstrated improvement in multiple metrics of episodic memory, but no changes in biomarkers. Improvements in episodic memory were most pronounced in participants who had the highest modeled tACS-induced electric fields and exhibited the greatest changes in RSFC. Increased RSFC was also associated with greater hippocampal excitability and higher baseline white matter integrity. This study highlights initial feasibility and the potential of gamma tACS to rescue episodic memory in an aMCI population by modulating connectivity and excitability within an episodic memory network.

1. Introduction

The adult aging population is rapidly growing with the Baby Boomer generation now between 57 and 75 years of age, totaling over 71 million adults in the United States alone. This rise in the population of seniors is also associated with increased incidence of cognitive decline and dementias (Anstey et al., 2019; Lopez et al., 2006), which will cause a significant burden on society unless the onset of dementia is delayed or prevented (Brookmeyer et al., 2016). Amnestic mild cognitive impairment (aMCI) is a predementia stage of Alzheimer's disease (AD) that is characterized by a decline in episodic memory (Christa Maree Stephan et al., 2013; Petersen, 1995). Not only does aMCI adversely affect quality of life, but it poses an increased risk for progression to AD (Alexopoulos et al., 2006; Forlenza et al., 2009; Tabert et al., 2006). By 2050, the population of adults over 65 is expected to double and those with AD are expected

Abbreviations: Aβ, beta amyloid; AD, Alzheimer's disease; AF, Arcuate Fasciculus; aMCI, amnestic mild cognitive impairment; CVLT, California Verbal Learning Test; DTI, diffusion tensor imaging; EF, electrical field; EPI, echoplanar imaging; FX, Fornix; GABA, gamma-aminobutyric acid; GFAP, glial acidic protein; Glx, glutamate/glutamine; E/I, excitatory/inhibitory ratio; Hipp, hippocampus; IADL, Instrumental Activities of Daily Living; LDI, lure discrimination index; IPL, inferior parietal lobe; LDFR, long-delay free recall; MDT, mnemonic discrimination task; MoCA, Montreal Cognitive Assessment; MRS, magnetic resonance spectroscopy; NfL, neurofilament light chain; ROAST, Realistic vOlumetric Approach to Simulate Transcranial Electric Stimulation; PAT, paired-associates task; Pars, pars triangularis; ROI, regions of interest; RSFC, resting-state functional connectivity; SDFR, short-delay free recall; SLF, Superior Longitudinal Fasciculus; tACS, transcranial alternating current stimulation; UN, Uncinate

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to quadruple (Brookmeyer et al., 2007). It is estimated that any intervention which slows down cognitive impairment in aging and increases independence and life expectancy, even by a single year, would save $367 trillion over 10 years (Scott et al., 2021). Indeed, successfully targeting cognitive decline in aging could lead to a larger economic impact than eradicating a disease (Scott et al., 2021). Given this looming public health crisis, any fruitful interventions that lead to prophylaxis of cognitive decline will result in a significant benefit to individuals, families, and society.

Currently, approaches to treating aMCI and AD often involve pharmaceutical interventions that only manage symptoms (Briggs et al., 2016; Yiannopoulou and Papageorgiou, 2020). These interventions do not prevent cognitive decline (Becker et al., 2008; Knopman et al., 2021). Emerging antiamyloid immunotherapies with disease-modifying effects have been recently approved for AD, but the clinical effects are marginal, they are associated with serious adverse effects, and they are costly. Therapeutic alternatives in AD are still a compelling need. One emerging approach to treating a variety of cognitive disorders is transcranial altering current stimulation (tACS), a noninvasive neuromodulatory technique that can entrain neuronal activity at a given frequency (Herrmann et al., 2013). When tACS is applied to improve cognition, it demonstrates efficacy in both healthy (Ambrus et al., 2015; Garside et al., 2014; Jaušovec et al., 2014; Jaušovec and Jaušovec, 2014; Jones et al., 2019; Joundi et al., 2012; Meiron and Lavidor, 2014; Polanía et al., 2012; Reinhart and Nguyen, 2019; Van Schouwenburg et al., 2017; Vosskuhl et al., 2015) and clinical populations (Kallel et al., 2016; Naros and Gharabaghi, 2017; Prehn-Kristensen et al., 2014). Importantly, tACS has notable advantages over pharmaceutical approaches, as it does not carry serious adverse side effects (Chaieb et al., 2014; Wassermann et al., 1996), may have a dual effect in boosting cognitive performance (Vossen et al., 2015) and is comparatively cost efficient.

Recent findings from animal models of AD show that 40 Hz (gamma) stimulation (e.g. through light, sound, magnetic, or electrical stimulation sources) improves episodic memory and learning, facilitates neurogenesis, and reduces biomarkers associated with AD pathology including beta amyloid (Aβ) and tau (Iaccarino et al., 2016; Jeong et al., 2014; Liu et al., 2020; Martorell et al., 2019; Singer et al., 2018; Zhen et al., 2017). In humans with MCI/AD, preliminary evidence suggests gamma tACS may also have positive effects on episodic memory (Benussi et al., 2022, 2021), particularly 1-month post treatment (Kehler et al., 2020). The effects of gamma tACS have been linked to increased cortical blood perfusion (Sprugnoli et al., 2021), indirect measures of cholinergic transmission (Benussi et al., 2021), and possibly reductions in tau (Dhaynaut et al., 2020), all of which are implicated in the progression to AD. Together, these studies provide evidence that gamma tACS may be used as a therapeutic intervention for AD.

In addition to understanding how tACS can improve aspects of cognitive functioning (i.e. episodic memory) and AD-related biomarkers (e.g. Aβ and tau), neuroimaging methods also serve as important diagnostic tools for detecting underlying neural changes in MCI and AD. First, MRI-based methods, such as diffusion tensor imaging (DTI) and resting-state functional connectivity (RSFC), can detect changes in both structural and functional brain network connectivity associated with AD progression, respectively. For example, prior work has shown lower white matter structural integrity in MCI and AD (Mayo et al., 2019, 2017). In addition, a large body of work has demonstrated lower RSFC between key regions involved in episodic memory processing (e.g. hippocampus [Hipp; Badhwar et al., 2017; Song et al., 2013]), inferior parietal lobe (IPL; Wang et al., 2015), and pars triangularis (Pars; Mascali et al., 2018). Importantly, these brain regions also exhibit changes in white matter integrity and regional structure (e.g. volume, cortical thickness). Such alterations are associated with episodic memory deficits in MCI (Goukasian et al., 2019; Hashimoto et al., 2016; O'Shea et al., 2016; Schaapsmeerders et al., 2015), progression to MCI from normal aging (Greene et al., 2010), and Aβ plaque deposition (Sheline and Raichle, 2013). Second, noninvasive proton magnetic resonance spectroscopy (MRS) can determine the concentration of brain metabolites such as gamma-aminobutyric acid (GABA) and glutamate/glutamine (Glx; Gujar et al., 2005), which are used as a measure of neuronal excitatory/inhibitory ratio (E/I). Importantly, prior research has identified a mechanistic connection between glucose metabolism and GABA receptor availability with RSFC measures (Rajkumar et al., 2021). These values also decrease in aging with accelerated cognitive decline in MCI (Oeltzschner et al., 2019) and AD (Huang et al., 2017). By additionally assessing tACS-related changes in neuroimaging measures, we can provide important preliminary insight regarding the underlying neural changes that may enable gamma tACS to remediate cognitive decline in aMCI, and the role of neuroimaging data as surrogate biomarkers of tACS target engagement.

Despite promising initial results, research on gamma stimulation is limited and additional preliminary work is needed to assess the feasibility and clinical efficacy of this intervention (Bréchet et al., 2021). Therefore, this preregistered study aimed to replicate and extend results from previous animal and human studies employing gamma tACS for therapeutic use. To achieve this, we conducted a single-arm assessment of gamma tACS, where aMCI participants received 60 min of gamma tACS for each of 8 sessions over 4 weeks. Specifically, stimulation targeted 3 regions of interest (ROIs) related to episodic memory processing: the Hipp, IPL, and Pars. Importantly, both the IPL and Pars are functionally connected with the Hipp during episodic memory tasks (Nilakantan et al., 2019; Wais et al., 2018), and therefore these 3 regions form an ideal target for network-level neuromodulation. Although precisely targeting deep cortical regions such as the Hipp with scalp electrodes is difficult, prior work has shown that noninvasive neuromodulation to IPL and Pars can affect Hipp activity through network effects (Nilakantan et al., 2019; Wais et al., 2018). Therefore, to affect this episodic memory network, we first generated electrical current models to identify optimal electrode positions. The results informed our approach as we broadly applied tACS bilaterally across electrodes spanning from frontal to parietal regions.

Our primary goal in this study was to assess aspects of intervention feasibility in an aMCI population (i.e. compliance, tolerability). We secondarily examined stimulation-related changes in behavioral metrics of episodic memory functioning, such as verbal learning and memory recall, verbal fluency, and mnemonic discrimination as well as AD-related biomarkers Aβ and tau. As exploratory measures, we assessed neurofilament light chain (NfL) and glial acidic protein (GFAP), as they have been associated with axonal damage (Gaetani et al., 2019; Khalil et al., 2020, 2018; Preische et al., 2019) and astrogliosis (Chatterjee et al., 2021; Yang and Wang, 2015), respectively. In addition, we examined tACS-induced neural changes with MRI, focusing on RSFC and MRS-based metrics. Together, we aim to establish the feasibility and initial efficacy for gamma tACS to remediate cognitive decline in aMCI, alter biomarker status, and induce neuroplastic changes with the hope of gamma stimulation becoming a reliable therapeutic that can lead to prophylaxis of further decline.

2. Methods

2.1. Participants

This study was preregistered at ClinicalTrials.gov with identifier NCT04646499. The study protocol was approved by the University of California San Francisco (UCSF) Institutional Review Board and all participants signed informed consent documents prior to participating in the study. Participants received $20 per hour for participation and a

$50 bonus for completion of the study. To be eligible for this study, all participants were 60–80 years of age, fluent in English, had at least 12 years of education, and had normal or corrected-to-normal vision. In addition, participants had to have aMCI (see below for aMCI inclusion criteria) and be able to complete cognitive tasks and cooperate with all study procedures. The exclusion criteria were as follows: neurological or psychiatric disorders other than aMCI, receiving investigational medications or participated in a clinical trial with medications within the previous 30 days, family history of epilepsy, implanted electronic devices (e.g. pacemaker), prior serious head trauma, pregnant, or IQ under 80. In addition, participants were not on cholinesterase inhibitors, memantine, psychotropics, antidepressants, or antianxiety medications. Finally, participants did not have color vision deficiency, a history of substance abuse, glaucoma, macular degeneration, amblyopia, or strabismus.

Fourteen older adults with aMCI were enrolled, and 13 completed the entire intervention in a single-arm design (age mean: 73.62 years (SD: 5.44), Montreal Cognitive Assessment mean (MoCA; Nasreddine et al., 2005): 23.39 (SD: 3.66), Education years mean: 17.69 (SD: 2.78), 7 Male, 11 right-handed). Although there is no agreement on a single set of criteria for an MCI diagnosis (Petersen, 2004), participants were considered aMCI based on the presence of a self-reported memory complaint, a deterioration of memory skills as compared to other cognitive functioning, and intact activities of daily living (Petersen et al., 1999). More specifically, participants were considered aMCI by scoring between 27 and 16 on the MoCA and had a self-complaint of memory difficulty. In addition, participants needed an age-matched Z score of at least −1 on immediate memory or delayed memory (as measured by the California Verbal Learning Test, short version Delis et al., 2000) *and* at least −1 Z score on verbal fluency (D words), semantic fluency (animals), processing speed (digit symbol and number trails tasks), or task switching (number letter trails task). All participants scored as having intact activities of daily living by scoring as mostly independent on the Instrumental Activities of Daily Living (IADL) (see Section 5.4 below). One participant withdrew voluntarily prior to any cognitive assessment or tACS.

2.2. Study timeline

The study required 10 visits to UCSF over 5 weeks. During visit 1, participants completed baseline assessments of the IADL (Petersen, 2003) survey, cognitive tests assessing baseline episodic memory performance, and an MRI scan (Week 1, Fig. 1A). On the following week, participants received gamma tACS while engaged in the Stimulation Tasks (see details below) on 5 consecutive weekdays (Week 2, visits 2–6, Monday–Friday). On one day during each of the 3 following weeks, participants also completed the Stimulation Tasks while receiving gamma tACS (Weeks 3–5, visits 7–9). These sessions occurred on the same day of the week for each participant (e.g. consecutive Tuesdays), with a small number occurring ± one day. Finally, during the 5th week (visit 10), participants completed the same procedure as the baseline assessment (visit 1), which included the IADL survey, tests of episodic memory, and an MRI scan. All study activities took place at UCSF, except for one participant who completed the 8 tACS sessions in their home. For this participant, a researcher was present with the required tACS equipment during the at-home sessions, and the participant completed the MRI and outcome assessments at UCSF.

2.3. Surveys

Participants completed the IADL (Lawton and Brody, 1969) during the initial pre-tACS and post-tACS follow-up Cognitive Task sessions (Weeks 1 and 5, respectively). Additionally, following each tACS

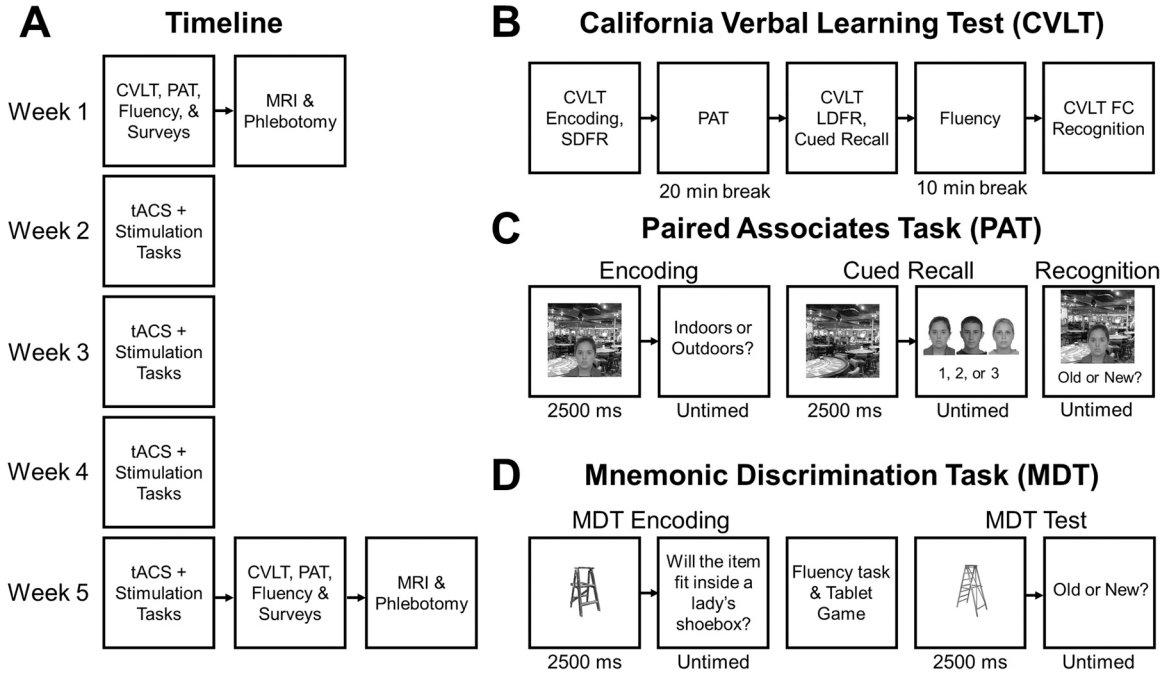

Fig. 1. (A) Weekly timeline for the study protocol. For Week 2, participants received tACS while completing the mnemonic discrimination task (MDT), fluency task, and a tablet game, collectively referred to as the 'Stimulation Tasks.' (B) The California Verbal Learning Test (CVLT) paradigm and timing. Following encoding of the words participants completed a distractor list and then the short-delay free recall (SDFR). Following a 20-minute break participant completed the long-delay free recall (LDFR). Following the next 10-minute break participants completed the forced-choice recognition section. (C) Paired Associated Task (PAT) paradigm and timing. Participants completed the PAT during the 20-minute break of the CVLT. (D) The Mnemonic Discrimination Task (MDT) paradigm and timing. Eight unique sets of stimuli were used during each MDT task conducted concurrently with each tACS session.

session, participants filled out a tolerability survey of the following 11 measures on a scale of 0 (not noticeable) to 10 (not tolerable): headache, neck pain, scalp pain, tingling, itching, burning sensation, increased alertness, increased sleepiness, trouble concentrating, acute mood change, and presence of phosphenes. Prior to the initial tACS session (Week 1) participants completed surveys that measure their anticipation, anxiety, and expected benefits on both memory and cognition following tACS on a scale of 1–10. Following the final tACS session (Week 5), participants were probed on the same categories for their perceived benefits of the tACS intervention.

2.4. Magnetic resonance imaging

Participants completed 2 MRI sessions with the same protocol prior to and following the tACS intervention (i.e. during the pre- and post-tACS phases, respectively; Fig. 1A). All data were collected by a Siemens 3 T MAGNETOM Trio MRI using a 64-channel head coil. First, high-resolution T1-weighted anatomical images were acquired ($1 \times 1 \times 1$ mm voxel size, FOV = $160 \times 240 \times 256$ mm, repetition time [TR] = 2300 ms, echo time [TE] = 3 ms, flip angle [FA] = 9°). For MRS, 2 voxels were placed in the left Pars, and left Hipp ($3 \times 3 \times 2$ cm each) based on the T1 structural scan. We then collected GABA-edited MEGA-PRESS scans (Mescher et al., 1998) (TR/TE = 2000/68 ms; Rothman et al., 1993), 128 averages, FA = 90°), with editing pulses at 1.9 edit-ON and 7.2 edit-OFF ppm (Mescher et al., 1998). The edit-ON and edit-OFF differences yield the peaks affected by the editing pulses.

Next, participants completed approximately 6 minutes of eyes-closed resting-state functional MRI (rs-fMRI) using a T2*-weighted echoplanar imaging (EPI) sequence with the following parameters: 560 volumes, TR = 850 ms, TE = 32.8 ms, FA = 45°, in-plane resolution = 2.2 mm^2, 66 total 2.2 mm slices using a multiband acceleration factor of 6. Participants were instructed to close their eyes, remain awake, and be as still as possible. Last, DTI data were collected with 10 nondiffusion-weighted images ($b = 0$ s/mm^2) followed by 96 diffusion-weighted images ($b = 2500$ s/mm^2; TR = 2420 ms, TE = 72.2 ms, and FA = 85°). One participant did not have usable rs-fMRI at their post-tACS session due to imaging artifacts, resulting in usable datasets from 12 participants for these analyses. One participant did not have baseline DTI data due to time constraints in the MRI, resulting in usable datasets from 12 participants for these analyses.

2.5. Fluid biomarkers

Participants had 2 phlebotomy sessions immediately after their pre- and post-MRI sessions, on days with baseline behavioral assessments in Week 1 and the final tACS session in Week 5, respectively. Before both sessions, participants were instructed to fast from any food intake prior to arrival for a minimum of 4 h. Following the session, participants had an opportunity to rest and eat food. On both sessions, blood was collected by phlebotomy in EDTA tubes and centrifuged at 2000*g* for 10 min at 4 °C. Plasma was then aliquoted in 500 microliter polypropylene tubes, and stored at −80 °C until analyses, with an average needle-to-frozen storage time < 2 h. Plasma was analyzed according to vendor protocols, using commercially available kits Neuro 4-PLEX E [amyloid β_{1-42} (Aβ42), amyloid β_{1-40} (Aβ40), NfL, and GFAP] and pTau181 for single molecule arrays (Simoa) in an HD-X analyzer (Quanterix, Billerica, MA). Lowest level of quantification and average coefficient of variations were 0.378 pg/mL, 4.1% for Aβ42; 1.02 pg/mL, 3.5% for Aβ40; 0.4 pg/mL, 4.3% for NfL; 2.89 pg/mL, 4.6% for GFAP; and 0.4 pg/mL, 10.1% for pTau181. Analyzed samples underwent only one thaw cycle prior to use. Samples were run in duplicate, with kits from the same lot. At the end of data collection, the entire sample was gradually brought to room temperature for analysis. All analyses were conducted by a board-certified laboratory technician blinded to the hypotheses of our study. Although listed in our ClinicalTrials.gov registration, we were unable to assess neurogranin in the processing kit used. Following analysis, we were able to measure the picograms per milliliter (pg/mL) of each of the 4 AD biomarkers at both time points, to quantify stimulation-related changes in AD biomarker levels between the 2 time points.

2.6. Neuromodulation

Participants were fitted with a neoprene head cap with electrodes located at 8 locations bilaterally (F7, F8, FT7, FT8, T7, T8, P7, and P8; 10–20 EEG system; Supplementary Fig. 1). The tACS was delivered through an 8-channel mobile Starstim device (Neuroelectrics, Spain) with NG Pistim electrodes (contact area: 3.14 cm^2). On each session, the tACS current was ramped up slowly over 4 min to a total of 1.6 mA (0.4 mA per electrode baseline to peak, with (Liu et al., 2022) the 4 contralateral electrodes set to 180° offset), maintained full strength for 52 min, then ramp back down to 0 mA over 4 min. The electrode configuration was selected based on models of the tACS electric field (EF) distribution, where we sought to target multiple regions of the cortex known to be related to episodic memory processing: the Hipp, IPL, and Pars. Using NIC2 software (Neuroelectrics, Spain), we identified the electrode configuration that achieved a balanced EF distribution across our ROIs. The current intensity was selected based on our preliminary research in mouse models of AD (under review: Liu et al., 2022), which tested whether there was a dose-response curve between gamma stimulation strengths and efficacy. We observed that higher current intensities of gamma stimulation had the strongest effects. Therefore, we applied the highest dose of stimulation that we believed would be tolerable to adults with MCI, without inducing overly distracting side effects such as phosphenes or physical sensations that are more likely at higher stimulation doses. During each of the eight 60-minute tACS sessions, participants engaged in the Stimulation Tasks (see below for details). Following the end of each tACS session, participants filled out a survey of side effects (see Surveys above). During each of the eight 60-minute tACS sessions, participants engaged in the Stimulation Tasks (see below for details). Following the end of each tACS session, participants filled out a survey of side effects (see Surveys above).

2.7. Cognitive testing

During Week 1, prior to any tACS sessions (Fig. 1A), participants first completed the California Verbal Learning Test (CVLT; Delis et al., 2000) to assess aspects of episodic memory, including delayed free recall, and cued recall/recognition. The CVLT is a task known to positively correlate with hippocampal size (Aslaksen et al., 2018; Pohlack et al., 2014), act as an early detector of AD (Pozueta et al., 2011), and track disease progression such as demyelination in multiple sclerosis (Fink et al., 2010). Participants completed the standard and alternate versions of the CVLT during the initial cognitive testing session (Week 1; Fig. 1B) and the final Cognitive Testing session (Week 5), with the order counterbalanced across participants. The CVLT has a 20-minute and a 10-minute break period, with the former separating the short-delay free recall (SDFR) from the long-delay free recall (LDFR), and the latter break separating the LDFR from the force-choice recognition portion.

During the CVLT 20-minute break, participants completed the Paired-Associates Task (PAT). The PAT assesses episodic memory via recall and recognition of pairs of face and scene stimuli and, therefore, was selected so that the stimuli would not interfere with the verbal words encoded during the CVLT (Fig. 1C). We used a modified version of the PAT, where the stimulus presentation timing was increased by 500–2500 ms; however, the trial count and task demands were the same as the PAT in Voskontas et al. (Viskontas et al., 2016). The task begins with an encoding period consisting of 10 face-scene pairs.

After the presentation of each face-scene pair (2500 ms), participants judged whether the person was in an indoor ('D' key) or outdoor scene ('K' key). The 10 face-scene pairs were presented randomly 6 times each. Immediately following the PAT encoding period, participants were tested in the recall period where they were presented with one face or scene (2500 ms) followed by 3 items of the other category (scenes or faces, respectively). Participants then responded (untimed) with which of the 3 items they believed was paired with the initial stimulus presented during the encoding phase. Each face and scene item pair were used as the probe 3 times resulting in 60 total recall trials. Following the end of the PAT recall period, participants were presented with a recognition task where they were shown either correctly matched or incorrectly matched face-scene pairs (untimed). Correct face-scene pairs were presented 3 times in random order each, and incorrect pairs were presented 60 times resulting in 90 trials. An alternate version of the PAT task was used during the final cognitive testing session with unique stimuli (Week 5), and these 2 versions were counterbalanced between participants.

During the CVLT 10-minute break, participants completed a verbal and semantic fluency task where they had 60 s to say as many words as possible that begin with the given letter or fit the category (excluding proper nouns). During the pre- and post-tACS intervention (visits 1 and 10) participants completed the categories F, A, S (Thurstone, 1938), and animals (Goodglass and Kaplan, 1983). The cognitive testing always occurred at the beginning of the day, so that no fatigue effects lowered participant performance and to ensure that participants could successfully complete both standardized memory tests (CVLT) as well as the computerized memory test (PAT).

2.8. Stimulation tasks

Once the tACS began, participants completed a series of Stimulation Tasks designed to engage episodic memory. First, they completed the Mnemonic Discrimination Task (MDT; Stark et al., 2013; P. E. Wais et al., 2021), which assesses high-fidelity long-term memory. The MDT was adapted from established behavioral pattern separation tasks that are thought to be dependent on the hippocampus (Bakker et al., 2008; Wais et al., 2017; Yassa et al., 2011). During each tACS session, participants completed the MDT with unique stimuli consisting of common real-world items (Brady et al., 2013; P. E. Wais et al., 2021). This resulted in 8 versions of the MDT, which were counterbalanced in order between participants (forwards or backwards order). Immediately after the tACS began, participants completed the encoding portion of the MDT task. During encoding, participants were cued first with "will the object fit inside a lady's shoe box?" Following the prompt, participants viewed 39 items in a random order and responded to the question for each item with an untimed button press (Fig. 1D). Next, participants were presented with a second cue "can you carry the object across the room using only one hand?" Participants then responded to this question following a random presentation of the same 39 items. All items were presented for 2500 ms followed by a screen that listed the button press responses ("D" for yes, "K" for no). A fixation cross was presented on the screen for 1000 ms between trials. The MDT encoding portion of the task is timed to last 8–10 min. All versions of the MDT task were created using PsychoPy (Peirce et al., 2019).

Following the MDT encoding period, participants completed 20 min of a commercially available tablet game, Spot the Difference. This game was chosen so that participants are mentally engaged in a visual search task that has no interference with recently encoded items from the MDT task and not a task that would evoke stress due to task difficulty. Participants completed this task at their own pace and advanced to new images without any score being kept. Next, participants completed the semantic fluency task (Goodglass and Kaplan, 1983; Thurstone, 1938) with 3 letters and a category similar to the cognitive testing with F, A, S, and animals (see above). Here, we created 8 unique sets each consisting of 3 letter prompts and one semantic category. Thus, the fluency task was not repeated across any of the tACS sessions and was different from the fluency tasks used as our Cognitive Tasks outcome measures. Participants were instructed to name as many items as possible.

During the final 10 min, participants completed 3 MDT test blocks where they viewed 13 items seen during encoding, 13 items that were an alternate (similar) version of the encoded items, and 5 novel lures. For each item, participants responded as to whether they were the same exact item from the encoding task from the beginning of stimulation. Each item was viewed for 2500 ms and followed by a screen where participants would respond whether the item was definitely old ("D" key), maybe old ("F" key), maybe new ("J" key), or definitely new ("K" key). A fixation cross was presented on the screen for 1000 ms between trials. The order of the target, lure, and novel items was random within each of the 3 testing blocks. In total, the tasks for the participant to complete during stimulation are equal to the length of the tACS session (1 h).

3. Data processing and statistical analysis

Given the relatively small number of participants in this study, we used nonparametric tests for all statistical analyses to reduce influence from potential extreme values. Changes in outcome metrics were assessed with nonparametric Wilcoxon sign-ranked tests. We also report rank-biserial correlations (r_{rb}) to represent effect sizes of these changes, similar to Cohen's d. We set a significance threshold of $p < 0.05$ and report nonsignificant 'trends' at $p < 0.10$. As this is a hypothesis-generating pilot study, we did not correct for multiple comparisons for each test conducted. Fig. 2 indicates the amount of data included in the analyses for each outcome measure.

3.1. Primary Outcomes

Our primary outcome measures were feasibility and tolerability of 8 sessions of gamma tACS. To assess these, we measured dropout rate of participants and the reported side effects collected following

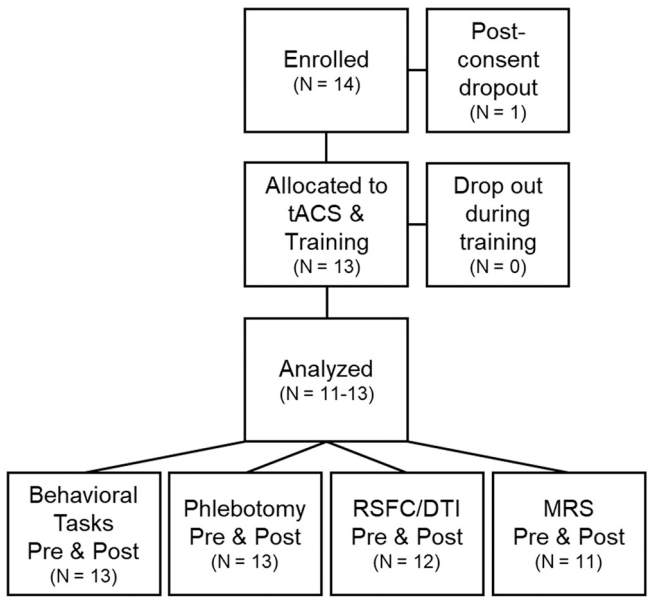

Fig. 2. Flow chart of participant enrollment, data collection, and analysis stages. One participant withdrew prior to completing any tasks. One participant had excessive movement during the RSFC at follow-up. One participant had no DTI scan due to time constraints at baseline. Two participants had an error in the MRS protocol at

each stimulation session. Analysis of the side effects collected following the end of tACS consists of the average across all 8 sessions for the 11 potential categories. These metrics were rated on a scale of 0 (not noticeable) to 10 (not tolerable). As this was a single-arm design, we compared side effect ratings from this study to those from a recently completed a multisession tACS intervention in healthy older adults of the same age range (Zanto et al., 2021), in which we administered 1 mA of 6 Hz tACS to the prefrontal cortex (F3–F4, 10–20 EEG system). This allows for an age-matched comparison between prior stimulation protocols and one that is higher in dose (1.0 mA, 1.6 mA), frequency (6 Hz, 40 Hz), and duration (~20 min, 60 min) as employed in the current study. Given that side effect ratings from the previous tACS protocol (6 Hz, 1 mA, 20 min) were not statistically different from other duration or frequency control groups, this comparison provides additional insight regarding the perceptual experience and may help guide future researchers when designing gamma stimulation protocols. As both studies included the same side-effects questionnaire categories, we conducted a nonparametric Mann-Whitney U test to assess differences in the average ratings for each metric between the 2 studies.

3.2. Secondary Behavioral Outcomes

Secondary outcome measures assessed changes in performance on the memory and fluency tasks (CVLT, PAT, fluency). The CVLT is a standardized cognitive test with different task demands at each stage. For CVLT, we focused on the correct items named during the SDFR and LDFR sections. For the PAT, we measured accuracy for both the recall and recognition portions. For the semantic (animals) and verbal (F, A, S) fluency task, we measured the number of correct nonrepeated words.

3.3. Secondary Fluid Biomarker Outcomes

Secondary biomarker measures were assessed by analyzing change in each fluid biomarker. This pre- and post-tACS analyses of the blood draw samples allow for changes in measures of amyloid (Cullen et al., 2021; Nakamura et al., 2018; Schindler et al., 2019), tau (Cullen et al., 2021), NfL (Kaeser et al., 2021), and GFAP (Chatterjee et al., 2021; Gaetani et al., 2019; Khalil et al., 2020, 2018; Preische et al., 2019; Yang and Wang, 2015). In addition, we measured the ratio of Aβ42 to Aβ40, as this ratio is believed to be a better metric for identifying AD individuals than individual Aβ values (Janelidze et al., 2016; Lehmann et al., 2018; Risacher et al., 2019). Changes in these biomarkers from pre-tACS to post-tACS were assessed with Wilcoxon sign-ranked tests.

3.4. Exploratory Behavioral Outcomes

We examined changes in MDT task performance as a non-registered exploratory measure, focusing on the changes in the lure discrimination index (LDI, proportion lure correct rejection—proportion novel false alarm; Wais et al., 2021) between the initial tACS session and final tACS session. Changes in performance were assessed with a Wilcoxon sign-rank test. As the MDT task was completed concurrently with the tACS, it is important to note that changes in MDT performance reflect gains during tACS from repeated test performance, rather than transfer to an untrained task, as with our secondary outcomes. In addition to examining changes in this study population, however, we also compared initial and final LDI performance in these MCI participants to a placebo training control group of healthy older adults from a previous study, where no training-related MDT gains were expected (Wais et al., 2021). For this analysis, we compared both initial and final performance between these groups using nonparametric Mann-Whitney U tests (Wais et al., 2021).

Further, we examined changes in IADL from pre-tACS to post-tACS as an exploratory measure on each of the categories: bathing, dressing, grooming, mouth care, toileting, transferring bed/chair, walking, climbing stairs, eating, shopping, cooking, managing medications, phone use, housework, driving/transport, and managing finances. Specifically, we measured change in the IADL metrics from the pre-tACS to post-tACS session by measuring the average rating across all IADL categories and comparing these in nonparametric Wilcoxon signed-rank tests between the pre-tACS baseline and post-tACS follow-up sessions.

4. Exploratory neural outcomes

4.1. Resting-state functional MRI

We conducted exploratory analyses on the rs-fMRI data collected during the pre- and post-tACS scans. Standard preprocessing of MRI data for functional connectivity analyses was carried out with AFNI (Cox, 1996) and FreeSurfer (Fischl, 2012). First, participants' T1-weighted anatomical images were skull-stripped and segmented into gray matter, white matter, and cerebrospinal fluid (CSF) using FreeSurfer. Next, EPI data were preprocessed using afni_proc.py in AFNI. First, the despike option was applied to interpolate extreme outlier time points from the BOLD signal intensity time courses. Next, the EPI data were motion corrected (aligning each EPI volume to the volume with the minimum outlier fraction), coregistered to the T1-weighted anatomical image, warped to MNI space, and resampled to an isotropic resolution of 2 mm^3. Further, we implemented noise reduction by regressing out several 'nuisance' variables: (1) 12 motion regressors (6 realignment parameters and their derivatives), (2) voxel-wise local white matter regressors using AFNI's fast ANTATICOR method, and (3) the top 3 principal components from lateral ventricle voxels. EPI data were also bandpass filtered (0.01–0.10 Hz), and volumes with excessive motion (> 1 mm root mean square motion) and the volume prior were censored. Nuisance regression, bandpass filtering, and censoring were performed in a single step.

To measure functional connectivity, we quantified Pearson's correlations (and applied a Fisher z-transform) between ROI time-series from Pars, IPL, and Hipp (left and right) during the baseline and follow-up MRI sessions. Pars and Hipp ROIs were automatically output from the MRS scan (see below), and we generated an additional IPL ROI in FSL (Jenkinson et al., 2012). We copied each left hemisphere mask to the right hemisphere to generate masks for all 6 regions. We calculated functional connectivity as the average connectivity between each ROI pair between and within hemispheres (e.g. IPL-Hipp connectivity calculated as the average of right IPL-Hipp, left IPL-Hipp, right IPL – left Hipp, and left IPL – right Hipp). We note that RSFC for one participant had relatively high values at baseline for each ROI pairing (average RSFC: 0.64) compared to the other participants (Table 2), despite having no visible artifacts or excessive motion. Although our statistical analyses use nonparametric tests to reduce influence from such extreme values, we also report all RSFC analyses with and without this participant and indicate whether the results differ (Supplementary Table 2). Importantly, due to technical issues, this participant did not have baseline MRS or DTI measures and therefore did not overly influence correlation results with those metrics.

4.2. MRS

Proton 1H MRS data were collected in 2 ROIs (left Pars and left Hipp). MRS data from our third ROI (IPL) were not collected due to time constraints in the scanner. During the second MRI session, we duplicated voxel placement based on images from the first MRI

session (Bai et al., 2017). All GABA and Glx concentrations were analyzed using GANNET 3.1 (Edden et al., 2014), which is a specialized toolbox for Matlab (The Mathworks Inc., 2016) designed to analyze GABA by calculating the area under the curve. The E/I ratio of Glx to GABA within ROIs was calculated (Glx/GABA+, both CSF-corrected with a water reference file). This ratio measured the excitatory/inhibitory balance within the ROI at both the pre-tACS and post-tACS MRI sessions. Two participants had poor shimming at baseline and were excluded from analyses, resulting in usable datasets from 11 participants for these analyses.

4.3. Diffusion-weighted imaging

DTI data were preprocessed using FMRIB's Diffusion Toolbox (FDT fsl.fmrib.ox.ac.uk/fsl/fslwiki/FDT), a part of Functional MRI of the Brain software (FSL; Analysis Group, FMRIB, Oxford, United Kingdom; Smith et al., 2004). We first removed noncortical tissue with the Brain Extraction Tool within FSL. To correct for head movement and eddy current distortions, we used Eddy Correct. Next, we used DTIfit to calculate fractional anisotropy (FA) maps for each participant. The FA maps were input into Tract-based Spatial Statistics in order to create a mean FA skeleton (Smith et al., 2006) by aligning to a common space (FMRIB58_FA; FA > 0.2 threshold). We analyzed individual white matter tracts generated with the Johns Hopkins University white matter atlas included with FSL (Mori et al., 2008; Wakana et al., 2007). As we did not expect significant change in FA in a month, we focused on the pre-tACS baseline DTI scan. This analysis is in line with our previous research demonstrating a correlation between baseline FA and tACS efficacy in healthy older adults (Jones et al., 2022).

We selected 4 specific white matter tracts that serve our functional ROIs (Pars, IPL, Hipp). First, we selected the Fornix (FX) as it serves as the dominant outflow tract of the hippocampus (Senova et al., 2020). In addition, the FX is essential for acquiring and consolidating new episodic memories, weakened FA predicts memory decline and progression to AD (Fletcher et al., 2013; Mielke et al., 2012), and FA predicts resting-state functional connectivity in healthy but not aMCI adults (Kehoe et al., 2015). Given that we employ a recall component of the PAT, it is notable that FA in the FX correlates with memory recall, but not recognition performance (Rudebeck et al., 2009). Second, we selected the Arcuate Fasciculus (AF) as it connects the frontal and temporal lobes by passing through the parietal lobe, therefore acting as an important tract for the IPL and Pars ROIs (Ivanova et al., 2021). Importantly, the AF is critical for language (Ivanova et al., 2021) and in this protocol we include verbal learning of lists in the CVLT and verbal/semantic fluency tasks as outcome measures. Third, we selected the Superior Longitudinal Fasciculus (SLF) as it directly connects the IPL and Pars ROIs (Burks et al., 2017). The SLF also plays a major role in language, attention, and memory (Kamali et al., 2014), all of which are relevant to the tasks in this protocol. Fourth, we selected the Uncinate (UN) as it connects the Pars and Hipp ROIs. The UN does not extend into the hippocampus, but it is positioned to serve as the major path between the Hipp and lateral prefrontal cortex (Von Der Heide et al., 2013), and FA in the UN correlates with memory functioning (Lockhart et al., 2012; Mabbott et al., 2009; Niogi et al., 2008). Furthermore, lower FA in the UN is predictive of early AD symptoms (Kiuchi et al., 2009).

4.4. Electrical field modeling

Current modeling of the tACS was performed using the Realistic vOlumetric Approach to Simulate Transcranial Electric Stimulation (ROAST; Huang et al., 2019) software toolbox for Matlab (The Mathworks Inc., 2016) to map electrical field (EF) changes throughout the cortex. ROAST is an open-source MATLAB-based, automated pipeline that applies SPM segmentation to the head and neck. Following segmentation, typical isotropic electrical conductivities are assigned to the tissues and electrodes, typical boundary conditions are assigned to the surfaces, and simulation of current flow is achieved by solving the Laplace equation $(\nabla\cdot(\sigma\nabla V) = 0)$, where V is potential and σ is conductivity. Current modeling was conducted on the skull-striped cortex of each participant's baseline T1 and T2 scan then fit to the MNI-152 standard head (Grabner et al., 2006).

4.5. Exploratory neural analyses

To measure changes in neural metrics, we assessed changes in RSFC (pairwise connectivity between Pars, Hipp, and IPL ROIs), and MRS-based E/I within in voxels of interest (Pars and Hipp). Changes in neural measures were assessed with nonparametric Wilcoxon signed-rank tests. To link behavioral tACS changes with underlying neural changes, we conducted correlations between the outcome metrics and neural metrics that had significant changes in the prior analyses. All correlation analyses were conducted using nonparametric Spearman's correlations (rho). In addition, we conducted a separate exploratory correlational analysis between change in neural outcome metrics and the change in predictor metrics: E/I ratio (Hipp, Pars), average functional connectivity (IPL-Hipp, Pars-Hipp, Pars-IPL). Finally, we examined whether baseline neural measures could predict tACS effects on the secondary outcome measures (CVLT, fluency). These predictors included metrics at baseline: E/I ratio (Hipp, Pars), modeled EF, and FA in individual white matter tracts. Because correlations between modeled EF and the outcome measures were conducted at the whole-brain level, a cluster threshold was applied based on a Monte Carlo simulation to correct for multiple comparisons. Clusters of significant correlations were corrected to $p < 0.001$ to ensure only the strongest correlations were identified. To minimize the influence of large EF values within the CSF, all EF values greater than 0.25 V/m were set to 0. Additionally, after the cluster thresholding procedure, any clusters of activity that bordered the CSF (i.e. outermost gray matter) were masked out (i.e. considered insignificant).

5. Results

5.1. Primary outcomes: feasibility and tolerability

All 13 aMCI participants who began the initial cognitive testing session successfully completed the entire study (i.e. there were no postbaseline assessment dropouts). There were additionally no adverse events and no side effects reported that would have required tACS to stop for that participant (as indexed by responses of 7 or more out of 10 on the side effect survey collected at the end of each tACS session). Average ratings for this study were as follows: headache 0.08 (SD: 0.28), neck pain 0.16 (0.34), scalp pain 0.30 (0.66), tingling 1.59 (0.85), burning sensation 0.63 (0.91), increased alertness 0.87 (1.01), increased sleepiness 0.30 (0.62), trouble concentrating 0.38 (0.43), acute mood change 0.16 (0.30), and phosphenes 0.78 (1.10).

To test whether side effects were significantly different from an active tACS group (6 Hz, 1 mA, 20 min) in a previous older adult study (Zanto et al., 2021), we conducted Mann-Whitney U tests comparing average side effects between the 2 studies on each category. The only categories that were rated significantly higher in the current study were headache ($W = 82.5$, $p = 0.033$, $r_{rb} = -0.37$), tingling ($W = 204$, $p = 0.006$, $r_{rb} = 0.57$), itching ($W = 193$, $p = 0.02$, $r_{rb} = 0.49$), and phosphenes ($W = 186.5$, $p = 0.004$, $r_{rb} = 0.44$). Despite differences between studies, it is important to note that the averages

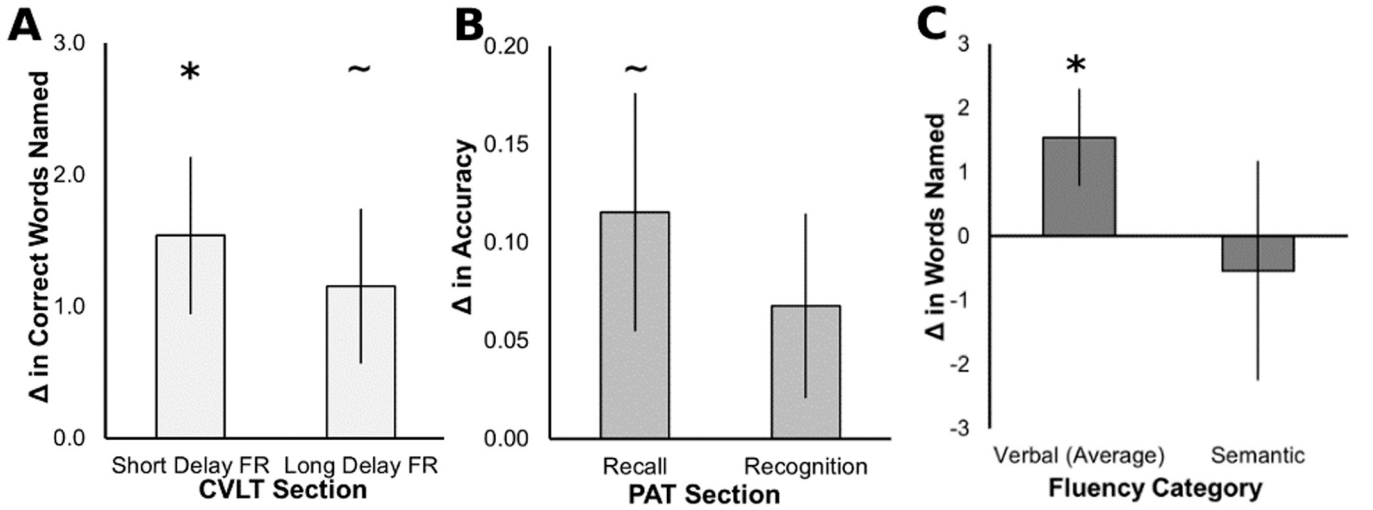

Fig. 3. Behavioral change following 8 sessions of gamma tACS over 4 weeks. (A) Change from baseline on the CVLT SDFR and LDFR. (B) Change from baseline on the PAT recall and recognition portions completed during the 20-minute break in the CVLT. (C) Change from baseline on verbal and semantic fluency tasks. Parentheses represent the standard deviation of the mean. * = $p < 0.05$, ~ = $p < 0.10$.

for each rating were still quite low (1.59 or less out of 10), indicating that these side effects were barely noticeable. The increased phosphenes are to be expected given that phosphenes are less common at 6 Hz than frequencies 10 Hz or higher (Kar and Krekelberg, 2012; Turi et al., 2013). Similarly, the increased perception of headache, tingling, and itching were likely due to the higher stimulation intensity and longer duration applied in this study.

5.2. Secondary outcomes: memory and fluency

To assess our hypothesis that 8 sessions of gamma tACS improves memory performance, we first compared the correct items named during the SDFR and LDFR, respectively, from pre- to post-tACS using Wilcoxon signed-rank tests (see Table 2 for averages and effect sizes). The results revealed a significant improvement in the SDFR ($W = 10$, $p = 0.024$, $r_{rb} = 0.74$; Fig. 3A) and a nonsignificant 'trend' for gain in the LDFR ($W = 15.5$, $p = 0.066$, $r_{rb} = 0.69$). Next, to assess improvements in visual memory on the PAT, we compared the pre- and post-tACS accuracy on the recall and recognition sections. The results revealed a nonsignificant 'trend' for accuracy gains on the PAT recall ($W = 10$, $p = 0.083$, $r_{rb} = 0.64$; Fig. 3B) but not recognition ($W = 7$, $p = 0.148$, $r_{rb} = 0.61$) portions of the task. To measure improvements in verbal fluency, we compared the average correct items named from the FAS task, pre- to post-tACS. The results revealed a significant improvement in words named ($W = 13.5$, $p = 0.049$, $r_{rb} = 0.65$; Fig. 3C), was which driven by a significant gain in only A words ($W = 4.5$, $p = 0.021$, $r_{rb} = 0.86$). Repeating this analysis for semantic fluency (animals) revealed no significant improvement following tACS ($W = 48.5$, $p = 0.861$, $r_{rb} = 0.07$).

Given the single-arm nature of the study, we sought to assess whether the participants' survey results prior to tACS predicted any gains in memory or fluency (i.e. to help rule out potential placebo or expectancy effects from receiving stimulation). Spearman's correlations of the self-reported level of comfort and anxiety of receiving tACS and the expected benefits on both memory and cognition revealed no significant correlation with changes in any of these secondary outcome measures (comfort: all $p > 0.217$, anxiety: all $p > 0.115$, memory: all $p > 0.201$, cognition: all $p > 0.166$). Importantly, this suggests that the participants' reported experience with tACS or their expected benefits were not predictive of the objective benefits observed on the secondary outcome tasks.

5.3. Secondary outcomes: AD biomarkers

To assess our hypothesis that 8 sessions of gamma tACS affect biomarker load in the plasma of aMCI participants, we first compared the concentration of Aβ40, Aβ42, and the ratio of Aβ42 to Aβ40 (Aβ42/40) from pre- to post-tACS. The results revealed no significant change in Aβ (all $p > 0.34$; see Table 1). Similarly, there were no significant changes in pTau181 ($p = 0.305$) or NfL ($p = 0.675$) following tACS ($p = 0.305$). Of note, the biomarker data are consistent with prior research assessing plasma-based biomarkers in an MCI population. Specifically, Simoa immunoassays previously used to characterize the Aβ42/40 ratio have exhibited higher values in control groups (0.073) compared to an MCI population (0.066; Jiang et al., 2022; Karikari et al., 2020), indicating our observed Aβ42/40 ratios (0.058 pre-tACS, 0.059 post-tACS) were more comparable to an MCI population than a healthy control group. Similarly, the observed pTau181 values (3.38 pg/mL pre-tACS, 3.60 pg/mL post-tACS) were more closely aligned with previous published values for an MCI population (3.7 pg/mL) than a healthy control group (2.4 pg/mL; Thijssen et al., 2021).

5.4. Exploratory cognitive outcomes

We also assessed changes in performance on the MDT task that was completed during each of the 8 tACS sessions over 4 weeks. To do this, we measured change in the LDI from the initial tACS session to the final tACS session and observed a significant gain in performance (for details, see Supplementary Results). Most interestingly, we compared performance to a healthy older adult group that also conducted this task in a separate study (Wais et al., 2021). Results demonstrated lower performance in the MCI group at baseline, but comparable performance between groups post-tACS (see Supplementary Results; Supplementary Fig. 2). This result suggests that multiple sessions of gamma tACS with repeated sessions of MDT rescued performance to that of a healthy aged-matched control group.

We measured change on each IADL metric with a Wilcoxon signed-rank test between pre-tACS and post-tACS time points. All metrics revealed no significant change between time points (all $p > 0.33$). The lack of significance for IADL changes was due to ceiling effects at baseline: most responses were marked '4' (96.2%),

Table 1
Average biomarker load detected in plasma (pg/mL) pre-tACS and post-tACS

Biomarker	Pre-tACS	Post-tACS	W	*p* Value	r_{rb}
Aβ40	132.02 (29.02)	135.05 (34.38)	37.5	0.600	−0.18
Aβ42	7.65 (2.40)	7.93 (2.75)	38.0	0.635	−0.17
Aβ42/40	0.058 (0.02)	0.059 (0.02)	31.0	0.340	−0.32
pTau181	3.38 (0.97)	3.60 (1.24)	30.0	0.305	−0.34
NfL	22.62 (7.48)	22.45 (8.71)	52.0	0.675	0.14
GFAP	232.62 (59.31)	248.54 (56.62)	22	0.108	−0.52

Nonparametric Wilcoxon sign-ranked test statistics (W) for each pre-post tACS biomarker comparison are listed along with significance (*p*) values and rank-biserial correlations (r_{rb}). All parentheses represent standard deviation of the mean.

indicating most participants were able to do daily tasks independently prior to the intervention.

5.5. Exploratory outcomes: neural measures

To measure changes in RSFC across key regions involved in episodic memory, we analyzed the average connectivity between each of the ROI pairs (IPL-Hipp, Pars-Hipp, IPL-Pars, including within- and between-hemispheric connections), using Wilcoxon signed-rank tests between tACS time points. The results revealed a significant increase in IPL-Hipp RSFC (W = 13, $p = 0.042$, $r_{rb} = 0.67$; Fig. 4); however, there were no changes in average RSFC for Par-Hipp or IPL-Pars ROI pairs (Table 2). We confirmed that this pattern of results was similar when excluding the potential 'outlier' participant with high RSFC values at baseline (see Supplementary Table 2). Further, as RSFC estimates can be spuriously affected by in-scanner motion (Power et al., 2012; Satterthwaite et al., 2013, 2012; Van Dijk et al., 2012), we confirmed that these findings were not influenced by participant motion (quantified as the Euclidean norm of motion parameters using AFNI). Motion levels were comparable before and after tACS ($p = 0.81$), and changes in motion before and after tACS were not related to changes IPL-Hipp RSFC ($r = 0.02$ $p = 0.95$).

Next, we assessed the neuronal excitatory/inhibitory (E/I) balance as the ratio of Glx/Water to GABA+/Water from the MRS data. We conducted Wilcoxon signed-rank tests for each of the ROIs (Hipp, Pars) to assess change from the pre-tACS to post-tACS session. The results revealed no significant difference between time points for either of the ROIs (Table 2).

5.6. Exploratory correlations

Given the significant increase in IPL-Hipp RSFC following tACS, we sought to investigate whether changes in this functional connectivity were related to the observed alterations in episodic memory (i.e. CVLT SDFR) or verbal fluency. The results of a Spearman's correlation revealed that the change in IPL-Hipp RSFC correlated positively with behavioral improvements in SDFR (Rho [r] = 0.75, $p = 0.005$; Fig. 5A), such that those who had the greatest gains in IPL-Hipp RSFC improved the most on the SDFR. However, no such relationship was observed for verbal fluency ($r = 0.02$, $p = 0.956$). Next, we sought to investigate whether changes in IPL-Hipp RSFC correlated with change in the E/I balance within the same ROI (Hipp). The results revealed a significant correlation between changes in IPL-Hipp RSFC and changes in E/I in the left Hipp ($r = 0.683$, $p = 0.05$; Fig. 5B), such that participants with greater increases in IPL-Hipp functional connectivity exhibited the largest increase in hippocampal excitability (i.e. higher E/I ratio).

We previously observed that baseline white matter microstructure (FA) predicted tACS-induced strengthening of (EEG) functional connectivity in a group of healthy older adults (Jones et al., 2022). Therefore, we also conducted exploratory correlations

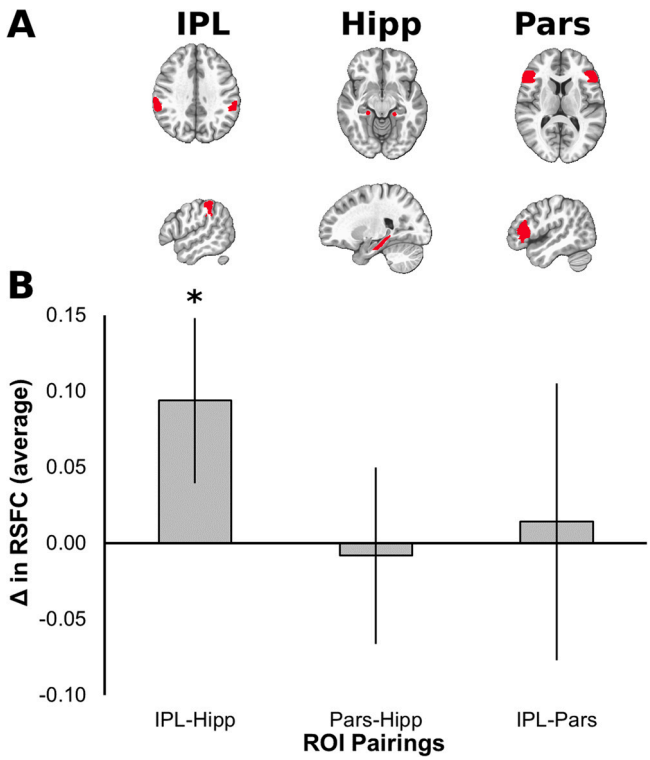

Fig. 4. Change in RSFC between ROI pairings from pre-tACS to post-tACS MRI sessions. (A) Axial (top) and sagittal (bottom) view of ROI masks in MNI space for the inferior parietal lobule (IPL), hippocampi (Hipp), and Pars triangularis (Pars), marked in red. (B) Changes in average RSFC between ROI pairings from pre-tACS to post-tACS MRI sessions. Data presented with 'outlier' data point included. * = $p < .05$. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

between changes in RSFC and FA in individual white matter tracts (FX, AF, SLF, UN). The results revealed a positive correlation between change in IPL-Hipp RSFC and each individual white matter tract (range of $r = 0.52–0.66$; Fig. 5C); however, only the FX ($r = 0.62$, $p = 0.048$), SLF ($r = 0.65$, $p = 0.037$), and UN ($r = 0.62$, $p = 0.048$) reached significance, although the AF numerically approached a trend ($r = 0.52$, $p = 0.107$). We confirmed that these patterns of RSFC results were similar when excluding the potential outlier participant (Supplementary Table 2).

Next, we tested whether baseline measures of the E/I ratio correlated with either of the observed changes in the behavioral outcome measures (i.e. CVLT SDFR and verbal fluency). For this analysis, E/I ratio was calculated from 2 ROIs (Hipp, Pars). Results from Spearman's correlations between baseline E/I and behavioral metrics showed no significant relationships between these baseline measures and performance changes (all $p > 0.182$).

Table 2
Outcome metric statistics from Wilcoxon signed-ranked test between pre-tACS and post-tACS time points

Metric	Pre-tACS Avg	Post-tACS Avg	W	*p* Value	r_{rb}
CVLT: SDFR (words)	6.54 (4.29)	8.08 (4.34)	10	**0.024**	0.74
CVLT: LDFR (words)	6.69 (4.85)	7.85 (4.95)	15.5	*0.066*	0.60
PAT: Recall (%)	0.54 (0.16)	0.69 (0.26)	10	*0.083*	0.64
PAT: Recognition (%)	0.67 (0.11)	0.76 (0.18)	7	0.148	0.61
Fluency: Semantic (words)	16.85 (8.37)	16.31 (5.31)	48.5	0.861	0.07
Fluency: Verbal (avg words)	14.67 (3.78)	16.05 (3.71)	13.5	**0.049**	0.65
Fluency: F (words)	15.23 (4.29)	17.00 (4.16)	15.5	0.129	0.53
Fluency: A (words)	12.31 (3.64)	14.62 (3.91)	4.5	**0.021**	0.84
Fluency: S (words)	15.69 (4.15)	16.23 (3.56)	23.5	0.421	0.29
MRS: E/I (Hipp)	2.17 (1.68)	1.62 (3.55)	24	0.91	0.07
MRS: E/I (Pars)	2.56 (2.34)	1.89 (0.78)	22	0.641	0.22
RSFC: IPL-Hipp (Avg)	0.06 (0.17)	0.15 (0.13)	13	**0.042**	0.67
RSFC: Pars-Hipp (Avg)	0.12 (0.15)	0.11 (0.14)	34	0.733	0.13
RSFC: IPL-Pars (Avg)	0.39 (0.30)	0.39 (0.25)	27	0.38	0.31

All parentheses represent standard deviation of the mean. The *p-values in bold represent p < 0.05, and italicized values represent a trend of p < 0.10.*
Key: CVLT, California Verbal Learning Test; SDFR, short-delay free recall; LDFR, long-delay free recall; PAT, Paired-Associates Task; MRS, magnetic resonance spectroscopy; E/I, excitatory/inhibitory balance; RSFC, resting-state functional connectivity; IPL, inferior parietal lobe; Pars, pars triangularis; Hipp, hippocampus; tACS, transcranial alternating current stimulation.

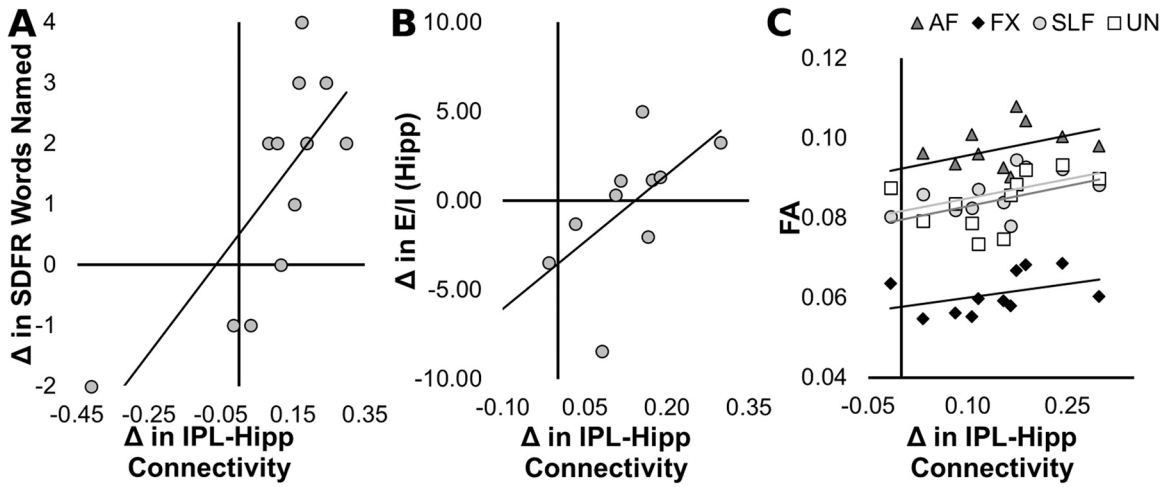

Fig. 5. Spearman's correlations between the change in IPL-Hipp RSFC and (A) the change in SDFR on the CVLT, (B) change in E/I ratio within the Hipp and (C) baseline FA in the Fornix (black diamonds), Arcuate Fasciculus (dark gray diamonds), SLF (light gray circles), and Uncinate (white squares) white matter tracts.

Finally, we assessed whether the amount of tACS current that reached the brain was related to the observed changes in the behavioral outcome measures (i.e. CVLT SDFR and verbal fluency). Therefore, the tACS-induced EF was modeled within the gray and white matter for each individual and correlated across individuals with the change (post-pre) in outcome measures via Spearman's method. Results of the correlation between the modeled EF and change in SDFR exhibited a positive correlation with multiple brain regions, including the precentral gyrus, superior frontal gyrus, superior parietal lobule, frontal pole, lateral occipital cortex, and lingual gyrus. Most notably, a positive correlation was observed between the change in SDFR and the modeled EF within right IPL (MNI coordinates: [41, −61, 47]) and right Pars (MNI coordinates: [50, 27, 4]), such that those participants who received the largest amount of stimulation in these regions also exhibited the greatest increase in episodic memory performance (Fig. 6A). No negative correlations were observed. Results of the correlation between the modeled EF and change in verbal fluency exhibited a positive correlation with multiple brain regions, including the precentral gyrus, middle frontal gyrus, cuneus, insula, frontal pole, supramarginal gyrus, lateral occipital cortex, temporal pole, cerebellum, and parahippocampal gyrus. Notably, a positive correlation was observed between the change in verbal fluency and the modeled EF within right IPL (MNI coordinates: [60, −26, 37]) and right Pars (MNI coordinates: [36, 28, 7]), such that those participants who received the largest amount of stimulation in these regions also exhibited the greatest increase in verbal fluency (Fig. 6B). Again, no negative correlations were observed.

6. Discussion

We conducted a single-arm 8-week clinical trial to assess the feasibility and tolerability of tACS targeting key regions involved in AD to improve cognitive function and biofluid and neuroimaging variables in aMCI. The results of this study demonstrate that gamma tACS is a tolerable and feasible intervention for individuals with aMCI. Additionally, we showed that eight 60-minute sessions of gamma tACS across 4 weeks improves performance on the untrained CVLT, as well as verbal fluency measures. Even despite the single-arm nature of the study, we nonetheless observed that the gains in the untrained episodic memory task (i.e. CVLT SDFR) were most pronounced in those with higher modeled EF and changes in functional connectivity between the IPL and hippocampi. This supports the interpretation that these effects are likely due to the stimulation

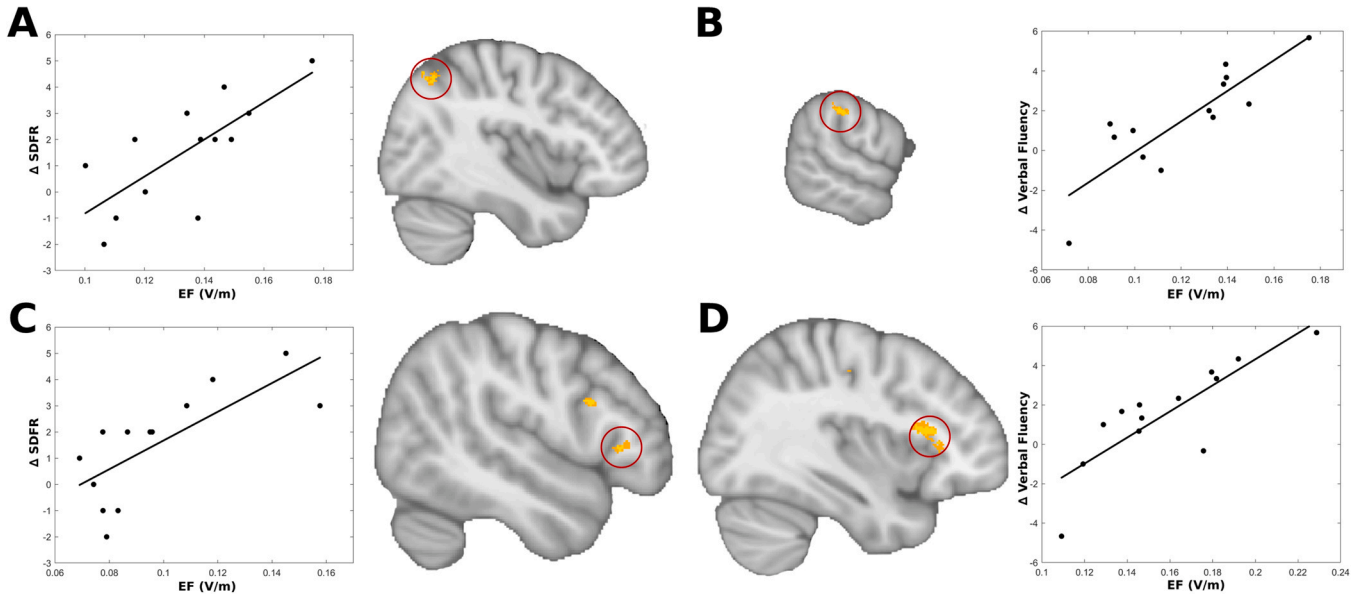

Fig. 6. Spearman's correlations between the modeled EF and (A) the change in SDFR on the CVLT and (B) the change in verbal fluency. Color represents significant correlation. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

rather than a placebo effect and warrants additional investigation with a randomized controlled trial. These results suggest that gamma tACS applied broadly throughout the cortex may improve episodic memory by facilitating functional connectivity between regions known to support episodic memory.

We also observed novel evidence that changes in IPL-HIPP functional connectivity were related to increased excitability (Glx/GABA ratio) within the hippocampus. This finding supports prior research indicating a relationship between functional connectivity and regional excitability (Levar et al., 2019; Maximo et al., 2021). Moreover, this provides additional support for the potential efficacy of this intervention as MCI and AD populations are known to exhibit deficits in these metabolites (Huang et al., 2017; Oeltzschner et al., 2019). However, it should be noted that group changes were not observed in the E/I (Glx/GABA) ratio within our ROIs. It is possible that our small sample size in the current study may be underpowered to detect such a group effect. Nonetheless, the results of this research certainly warrant additional investigation.

The extent of increased IPL-Hipp functional connectivity was also correlated with changes in baseline white matter integrity, such that people with the highest FA at baseline showed the greatest neuroplastic changes within a portion of an episodic memory network. This pattern of results supports our previous tACS research in healthy older adults where preserved structural integrity allowed for greater tACS-induced alterations in functional connectivity between distant cortical regions as well as greater tACS effects on cognitive performance (Jones et al., 2022). Given that FA is known to decline in aging and MCI (Mayo et al., 2019, 2017), these results suggest that tACS effects may be more pronounced prior to the degradation of white matter. This notion is further supported by a recent study in early AD individuals where gamma tACS improved episodic memory the most in individuals with the highest baseline MMSE scores (Benussi et al., 2022). Thus, tACS and related interventions would be best suited at the earliest stages of (or prior to) AD progression.

The question remains as to why such a relationship exists between tACS effects on functional connectivity and white matter integrity. One possibility is that higher FA enables the stimulating current to reach distant cortical regions, thereby affecting more network nodes. In support of this, computational models have converged to show that increased white matter anisotropy increases the current density along cortical gyri under the electrodes, between the electrodes, and in regions distant from the electrodes following white matter tracts (Bhalerao et al., 2019; Lee et al., 2012; Shahid et al., 2013). An alternative explanation is that tACS affects local cortical processing, and that increased FA simply improves network-level communication (van den Heuvel et al., 2008). In either case, this would explain our current results as well as recent experimental research demonstrating greater white matter integrity in stimulated regions yields the greatest effects of transcranial electrical stimulation on behavioral performance (Zhao et al., 2021; Zheng and Schlaug, 2015). These results highlight white matter as an important mediator of tACS effects, and additional research will be required to understand the mechanism by which tACS is affected by white matter integrity.

Interestingly, our protocol also improved episodic memory performance on the trained MDT task to levels comparable to that of healthy age-matched controls from a prior study. Importantly, the MCI patients in the current study had repeated practice on different versions of the MDT task over the 8 tACS sessions and had a qualitatively different experience than participants in the previous study. Therefore, we cannot make strong claims regarding the source of their improved performance. However, it is encouraging that their final performance is equal to that of healthy controls.

While this was a single-arm study of only 13 individuals without a control group, we believe our results are likely due to gamma tACS rather than practice or placebo effects, as previous research finds that CVLT scores do not improve with repeated tests following placebo neurostimulation in AD populations (Bystad et al., 2016). Other cognitive training studies in older adult populations have also failed to find transfer to improvements in CVLT recall metrics (Chapman et al., 2016; Richmond et al., 2011; Stamenova et al., 2014); therefore, the current results support the potential for gamma tACS to rescue cognition in cognitively declining adults. In addition, we probed participants expectations for how tACS would affect them, and the results further ruled out a link between participants' expectancy and their observed cognitive gains. It is also worth noting that improvements in CVLT (SDFR) and verbal fluency were greatest in those participants who had the highest modeled EF within the brain – particularly in regions known to be involved in episodic memory.

This suggests that tACS indeed helped facilitate cognitive function and implies that tACS is increasingly effective with higher stimulation intensities, replicating our recent results in older adults (Zanto et al., 2021). Finally, it is worth noting that we counterbalanced the order of distinct versions of the outcome measures (CVLT, PAT) and training tasks (MDT) to minimize practice effects. Together with other promising results employing gamma tACS in early AD individuals (Benussi et al., 2022), we believe the combined nature of repeated tACS paired with engaging cognitive tasks likely resulted in improved episodic memory performance in our aMCI participants. As such, these results warrant further investigation and need to be confirmed in larger sample sizes and in a double-blind manner with a proper control group.

In a similar vein, there are several reasons why we consider the observed increases in RSFC to be meaningful without a control group, and not a practice or placebo effect. First, we have previously demonstrated that fMRI data exhibit high test-retest reliability in MCI patients over a 3-month period (Zanto et al., 2014), suggesting that changes in such a small timeframe would be minimal in the absence of an intervention. Similarly, an MCI control group for a 7-week intervention did not exhibit significant RSFC changes (Liu et al., 2021), and numerically, the (nonsignificant) changes were a decline in RSFC. Indeed, over the course of 2 years, the probability of conversion from MCI to AD increases, and this occurs with a concomitant decrease in RSFC (Li et al., 2016). As such, it is unlikely that RSFC would significantly increase in an MCI population without some form of meaningful intervention. Second, we demonstrated that the observed changes are likely not due to nonneural sources that can affect RSFC, such as in-scanner motion. Specifically, we showed that (1) motion levels were comparable before and after tACS and that (2) changes in motion were not related to changes in our main RSFC finding. This adds confidence that the observed RSFC changes are indeed neural and not related to in-scanner artifacts.

In aging, patterns of neural activity similar to younger adults are linked with preserved cognition (Chen et al., 2022; Park et al., 2013; Vidal-Piñeiro et al., 2019), highlighting the importance of preserved functional connectivity. Importantly, functional connectivity between IPL and hippocampus has been associated with episodic memory performance (Hermiller et al., 2019; Warren et al., 2019) and the strength of connectivity between these regions decline in healthy aging (Oren et al., 2019) and AD (Wang et al., 2015). Our results suggest that gamma tACS increased functional connectivity between the IPL and hippocampi, and this was correlated with improvements in episodic memory. Thus, the effects of gamma tACS on episodic memory performance were likely subserved by connectivity alterations in the IPL-Hipp portion of a larger episodic memory network. These results support research demonstrating that tACS can alter long-range connectivity as measured by EEG (Jones et al., 2022, 2020) and fMRI (Gundlach et al., 2020; Mondino et al., 2020), which occur in networks that support changes in behavior.

Given the single-arm design of this study, we are unable to determine whether our tACS protocol affected biomarker load in the aMCI participants. It is possible that while we did not observe a statistical change in biomarker load, the values may have been different in these participants had they not received the intervention such that we may have slowed decline (or maintained current state). A second possibility is that a greater dose (higher intensity or longer duration) of tACS may be necessary to reduce biomarker load, as the EF applied to the cortex in our protocol was slightly less than what animal models of AD received with intracranial stimulation (Liu et al., 2020). Given the high tolerability reported, future research may consider higher tACS current intensities. A third possibility is that plasma biomarkers may not be sensitive to change in such a small sample. Finally, it is possible that gamma tACS may have enhanced memory functioning on the tasks without affecting biomarker load. Rather, observed improvements on the behavioral tasks may simply be related to functional changes. While we did not observe significant changes in any of the plasma-based biomarkers, future studies with a larger number of participants and/or higher stimulation intensity may be able to detect such changes and identify optimal protocols for replicating animal studies in humans (Iaccarino et al., 2016; Jeong et al., 2014; Liu et al., 2020; Martorell et al., 2019; Singer et al., 2018; Zhen et al., 2017).

Although the results of this pilot study strongly support feasibility of gamma tACS and initial evidence for efficacy of remediating AD-related decline, there are some limitations that could be addressed in future work. First, the key limitation to the current study is the lack of a sham or no-stimulation control group. Future research should be expanded to include multiple groups in a randomized controlled trial with placebo or mechanistic controls and a larger sample size. Second, while we show gains in cognition and underlying neural function over 4 weeks, the extent that these benefits persist following the end of treatment is unknown. Although additional research will be needed to address persistence of these effects, prior research has shown that behavioral gains and changes in hippocampal volume following memory training are maintained in the weeks following training (Bråthen et al., 2022), and we have previously demonstrated that tACS effects can last for at least 1-month post intervention (Zanto et al., 2021). Third, the cause of MCI was not determined in our small population. Finally, future research should also assess the correct timing and/or necessity of 'booster' tACS sessions to maintain benefits that result from the tACS intervention.

Beyond assessing whether tACS may recover lost cognitive abilities, it is equally important to understand whether this interventional approach may prevent or delay additional decline, effectively altering the course of disease progression. Following individuals with aMCI over the course of years after or with concurrent tACS would elucidate the prophylaxis potential of gamma stimulation to act as a protective treatment against cognitive decline. Finally, additional research should attempt to identify whether a critical period exists in which individuals would most benefit from such a treatment. The current results tentatively suggest that applying the stimulation early in disease course (or prior to decline) may yield the best outcomes, but this needs to be directly tested.

Given the limited treatment options for those with MCI, these results show promise as a clinical therapeutic for rescuing lost cognitive capabilities in those who are progressing towards AD. The results replicate previous attempts to use oscillatory gamma stimulation to improve cognition (but not reduce biomarkers) associated with AD progression as evidenced in both animal (Iaccarino et al., 2016; Jeong et al., 2014; Liu et al., 2020; Zhen et al., 2017) and human research (Benussi et al., 2022, 2021; Kehler et al., 2020; Sprugnoli et al., 2021). Our results extend this work to show that changes in episodic memory occur in an intensity-dependent manner and coincide with increased functional connectivity in a portion of an episodic memory network. Interestingly, those with the greatest gains in functional connectivity were the ones who exhibited high baseline FA in tracts serving the episodic memory network and exhibited the greatest gains in excitability within the hippocampus. These observed connections between RSFC, neuronal excitability, and behavioral improvements should be future targets for interventions in MCI that employ neurostimulation methods such as tACS. These promising results warrant future clinical trials research to expand upon the potential of tACS to remediate MCI deficiencies and alter disease progression.

CRediT authorship contribution statement

Kevin T. Jones: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Data Curation, Writing – Original Draft, Writing – Review & Editing, Visualization, Project administration. **Courtney L. Gallen:** Software, Validation, Formal analysis, Investigation, Data Curation, Writing – Original Draft, Writing – Review & Editing, Visualization, Project administration. **Avery E. Ostrand**: Investigation. **Julio C. Rojas**: Resources, Supervision, Funding acquisition. **Peter Wais**: Conceptualization, Resources, Supervision. **James Rini**: Resources. **Brandon Chan**: Formal analysis. **Argentina Lario Lago**: Formal analysis. **Adam Boxer**: Supervision, Resources, Funding acquisition. **Min Zhao**: Conceptualization, Methodology. **Adam Gazzaley**: Conceptualization, Resources, Supervision, Writing – Original Draft, Writing – Review & Editing, Funding acquisition. **Theodore P. Zanto**: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Data Curation, Writing – Original Draft, Writing – Review & Editing, Visualization, Project administration, Funding acquisition.

Data availability statement

We commit to sharing all raw and analyzed data files collected in this study. These include deidentified behavioral, structural and rs-MRI, MRS, and participant survey data.

Disclosure statement

A.G. is a scientific advisor for Neuroelectrics, which is the company that makes the neurostimulation device used in the current study.

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We verify that these data are not under review or published in any other location.

Author contributions

T.Z., K.J., P.W., M.Z., J.K., and A.G. designed the protocol. T.Z., M.Z., A.G., J.K., and A.B. secured funding. J.R., J.R-M., and A.O. recruited participants. A.O. and K.J. collected the behavioral and neuroimaging data. C.L.G. processed and analyzed the resting-state fMRI data. J.R-M., B.C., and A.L.L. processed the biomarker data. K.J. and T.Z. conducted EF modeling and analyzed biomarkers. K.J. analyzed behavioral and MRS data. C.L.G., T.Z., and K.J. drafted the manuscript.

Code availability statement

Deidentified data will be stored at the Neuroscape Center at UCSF and will be made available upon reasonable request to one of the corresponding authors.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neurobiolaging.2023.04.005.

References

Alexopoulos, P., Grimmer, T., Perneczky, R., Domes, G., Kurz, A., 2006. Progression to dementia in clinical subtypes of mild cognitive impairment. Dement. Geriatr. Cogn. Disord. 22 (1), 27–34. https://doi.org/10.1159/000093101

Ambrus, G.G., Pisoni, A., Primaßin, A., Turi, Z., Paulus, W., Antal, A., 2015. Bi-frontal transcranial alternating current stimulation in the ripple range reduced overnight forgetting. Front. Cell. Neurosci. 9 (374). https://doi.org/10.3389/fncel.2015.00374. PMID: 26441544; PMCID: PMC4585169. http://journal.frontiersin.org/Article/10.3389/fncel.2015.00374/abstract.

Anstey, K.J., Ee, N., Eramudugolla, R., Jagger, C., Peters, R., 2019. A systematic review of meta-analyses that evaluate risk factors for dementia to evaluate the quantity, quality, and global representativeness of evidence. J. Alzheimers Dis. https://doi.org/10.3233/JAD-190181

Aslaksen, P.M., Bystad, M.K., Ørbo, M.C., Vangberg, T.R., 2018. The relation of hippocampal subfield volumes to verbal episodic memory measured by the California Verbal Learning Test II in healthy adults. Behav. Brain Res. 351, 131–137. https://doi.org/10.1016/j.bbr.2018.06.008. https://www.sciencedirect.com/science/article/pii/S0166432818300597.

Badhwar, A.P., Tam, A., Dansereau, C., Orban, P., Hoffstaedter, F., Bellec, P., 2017. Resting-state network dysfunction in Alzheimer's disease: a systematic review and meta-analysis. Alzheimers Dement. https://doi.org/10.1016/j.dadm.2017.03.007

Bai, X., Harris, D., Gong, A., A. J. Puts, N, T., Wang, G., Schär, M., Barker, B., P., A. E, Edden, R., 2017. Voxel placement precision for GABA-edited magnetic resonance spectroscopy. Open J. Radiol. https://doi.org/10.4236/ojrad.2017.71004

Bakker, A., Kirwan, C.B., Miller, M., Stark, C.E.L., 2008. Pattern separation in the human hippocampal CA3 and dentate gyrus. Science. https://doi.org/10.1126/science.1152882

Becker, R.E., Greig, N.H., Giacobini, E., 2008. Why do so many drugs for Alzheimer's disease fail in development? Time for new methods and new practices? J. Alzheimers Dis. 15 (2), 303–325. https://doi.org/10.3233/jad-2008-15213. https://pubmed.ncbi.nlm.nih.gov/18953116.

Benussi, A., Cantoni, V., Cotelli, M.S., Cotelli, M., Brattini, C., Datta, A., Thomas, C., Santarnecchi, E., Pascual-Leone, A., Borroni, B., 2021. Exposure to gamma tACS in Alzheimer's disease: a randomized, double-blind, sham-controlled, crossover, pilot study. Brain Stimul. 14 (3), 531–540. https://doi.org/10.1016/j.brs.2021.03.007

Benussi, A., Cantoni, V., Grassi, M., Brechet, L., Michel, C.M., Datta, A., Thomas, C., Gazzina, S., Cotelli, M.S., Bianchi, M., Premi, E., Gadola, Y., Cotelli, M., Pengo, M., Perrone, F., Scolaro, M., Archetti, S., Solje, E., Padovani, A., Pascual-Leone, A., Borroni, B., 2022. Increasing brain gamma activity improves episodic memory and restores cholinergic dysfunction in Alzheimer's disease. Ann. Neurol. 92 (2), 322–334. https://doi.org/10.1002/ana.26411

Bhalerao, G., Selvaraj, S., Parlikar, R., Sreeraj, V., Shivakumar, V., Damodharan, D., Chhabra, H., Bose, A., Narayanaswamy, J., Rao, N., Venkatasubramanian, G., 2019. White matter correlates of electric field activity in HD-tDCS for schizophrenia: a computational neuromodeling study. Brain Stimul. 12 (2), 503. https://doi.org/10.1016/j.brs.2018.12.649

Brady, T.F., Konkle, T., Alvarez, G.A., Oliva, A., 2013. Real-world objects are not represented as bound units: independent forgetting of different object details from visual memory. J. Exp. Psychol. Gen. https://doi.org/10.1037/a0029649

Bråthen, A.C.S., Sørensen, Ø., de Lange, A.-M.G., Mowinckel, A.M., Fjell, A.M., Walhovd, K.B., 2022. Cognitive and hippocampal changes weeks and years after memory training. Sci. Rep. 12 (1), 7877. https://doi.org/10.1038/s41598-022-11636-4

Bréchet, L., Michel, C.M., Schacter, D.L., Pascual-Leone, A., 2021. Improving autobiographical memory in Alzheimer's disease by transcranial alternating current stimulation. Curr. Opin. Behav. Sci. 40, 64–71. https://doi.org/10.1016/j.cobeha.2021.01.003. https://www.sciencedirect.com/science/article/pii/S2352154621000048.

Briggs, R., Kennelly, S.P., O'Neill, D., 2016. Drug treatments in Alzheimer's disease. Clin. Med. 16 (3), 247–253. https://doi.org/10.7861/clinmedicine.16-3-247. https://pubmed.ncbi.nlm.nih.gov/27251914.

Brookmeyer, R., Johnson, E., Ziegler-Graham, K., Arrighi, H.M., 2007. Forecasting the global burden of Alzheimer's disease. Alzheimers Dement. 3 (3), 186–191. https://doi.org/10.1016/j.jalz.2007.04.381

Brookmeyer, R., Kawas, C.H., Abdallah, N., Paganini-Hill, A., Kim, R.C., Corrada, M.M., 2016. Impact of interventions to reduce Alzheimer's disease pathology on the prevalence of dementia in the oldest-old. Alzheimers Dement. https://doi.org/10.1016/j.jalz.2016.01.004

Burks, J.D., Boettcher, L.B., Conner, A.K., Glenn, C.A., Bonney, P.A., Baker, C.M., Briggs, R.G., Pittman, N.A., O'Donoghue, D.L., Wu, D.H., Sughrue, M.E., 2017. White matter connections of the inferior parietal lobule: a study of surgical anatomy. Brain Behav. 7 (4), e00640. https://doi.org/10.1002/brb3.640

Bystad, M., Grønli, O., Rasmussen, I.D., Gundersen, N., Nordvang, L., Wang-Iversen, H., Aslaksen, P.M., 2016. Transcranial direct current stimulation as a memory enhancer in patients with Alzheimer's disease: a randomized, placebo-controlled trial. Alzheimers Res. Ther. 8 (1), 13. https://doi.org/10.1186/s13195-016-0180-3. https://pubmed.ncbi.nlm.nih.gov/27005937.

Chaieb, L., Antal, A., Pisoni, A., Saiote, C., Opitz, A., Ambrus, G.G., Focke, N., Paulus, W., 2014. Safety of 5 kHz tACS. Brain Stimul. 7 (1), 92–96. https://doi.org/10.1016/j.brs.2013.08.004

Chapman, S.B., Aslan, S., Spence, J., Keebler, M.W., DeFina, L.F., Didehbani, N., Perez, A., Lu, H., D'Esposito, M., 2016. Distinct brain and behavioral benefits from cognitive versus physical training: a randomized trial in aging adults. Front. Hum. Neurosci. 10 (338), 1–15. https://doi.org/10.3389/FNHUM.2016.00338

Chatterjee, P., Pedrini, S., Stoops, E., Goozee, K., Villemagne, V.L., Asih, P.R., Verberk, I.M.W., Dave, P., Taddei, K., Sohrabi, H.R., Zetterberg, H., Blennow, K., Teunissen,

C.E., Vanderstichele, H.M., Martins, R.N., 2021. Plasma glial fibrillary acidic protein is elevated in cognitively normal older adults at risk of Alzheimer's disease. Transl. Psychiatry 11 (1), 27. https://doi.org/10.1038/s41398-020-01137-1

Chen, X., Rundle, M.M., Kennedy, K.M., Moore, W., Park, D.C., 2022. Functional activation features of memory in successful agers across the adult lifespan. Neuroimage, 119276. https://doi.org/10.1016/j.neuroimage.2022.119276. https://www.sciencedirect.com/science/article/pii/S1053811922003974.

Christa Maree Stephan, B., Minett, T., Pagett, E., Siervo, M., Brayne, C., McKeith, I.G., 2013. Diagnosing mild cognitive impairment (MCI) in clinical trials: a systematic review. BMJ Open 3 (2), 1–8. https://doi.org/10.1136/bmjopen-2012-001909. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3586181&tool=pmcentrez&rendertype=abstract.

Cox, R.W., 1996. AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. Comput. Biomed. Res.

Cullen, N.C., Leuzy, A., Palmqvist, S., Janelidze, S., Stomrud, E., Pesini, P., Sarasa, L., Allué, J.A., Proctor, N.K., Zetterberg, H., Dage, J.L., Blennow, K., Mattsson-Carlgren, N., Hansson, O., 2021. Individualized prognosis of cognitive decline and dementia in mild cognitive impairment based on plasma biomarker combinations. Nat. Aging. https://doi.org/10.1038/s43587-020-00003-5

Delis, D.C., Kramer, J.H., Kaplan, E., Ober, B.A., 2000. California Verbal Learning Test, Second ed. The Psychological Corporation, San Antonio, TX.

Dhaynaut, M., Pascual-Leone, A., Santarnecchi, E., El Fakhri, G., 2020. Effects of modulating gamma oscillations via 40 Hz transcranial alternating current stimulation (tACS) on Tau PET imaging in mild to moderate Alzheimer's disease. J. Nucl. Med.

Edden, R.A.E., Puts, N.A.J., Harris, A.D., Barker, P.B., Evans, C.J., 2014. Gannet: a batch-processing tool for the quantitative analysis of gamma-aminobutyric acid-edited MR spectroscopy spectra. J. Magn. Reson. Imaging. https://doi.org/10.1002/jmri.24478

Fink, F., Eling, P., Rischkau, E., Beyer, N., Tomandl, B., Klein, J., Hildebrandt, H., 2010. The association between California Verbal Learning Test performance and fibre impairment in multiple sclerosis: evidence from diffusion tensor imaging. Mult. Scler. 16 (3), 332–341. https://doi.org/10.1177/1352458509356367

Fischl, B., 2012. FreeSurfer. Neuroimage. https://doi.org/10.1016/j.neuroimage.2012.01.021

Fletcher, E., Raman, M., Huebner, P., Liu, A., Mungas, D., Carmichael, O., DeCarli, C., 2013. Loss of fornix white matter volume as a predictor of cognitive impairment in cognitively normal elderly individuals. JAMA Neurol. 70 (11), 1389–1395. https://doi.org/10.1001/jamaneurol.2013.3263

Forlenza, O.V., Diniz, B.S., Nunes, P.V., Memória, C.M., Yassuda, M.S., Gattaz, W.F., 2009. Diagnostic transitions in mild cognitive impairment subtypes. Int. Psychogeriatrics 21 (6), 1088. https://doi.org/10.1017/S1041610209990792. http://www.journals.cambridge.org/abstract_S1041610209990792.

Gaetani, L., Blennow, K., Calabresi, P., Di Filippo, M., Parnetti, L., Zetterberg, H., 2019. Neurofilament light chain as a biomarker in neurological disorders. J. Neurol. Neurosurg. Psychiatry. https://doi.org/10.1136/jnnp-2018-320106

Garside, P., Arizpe, J., Lau, C.-I., Goh, C., Walsh, V., 2014. Cross-hemispheric alternating current stimulation during a nap disrupts slow wave activity and associated memory consolidation. Brain Stimul. 8 (3), 520–527. https://doi.org/10.1016/j.brs.2014.12.010. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4464303&tool=pmcentrez&rendertype=abstract.

Goodglass, H., Kaplan, E., 1983. The assessment of aphasia and related disorders. Boston Diagnostic Aphasia Examination Booklet, second ed.

Goukasian, N., Porat, S., Blanken, A., Avila, D., Zlatev, D., Hurtz, S., Hwang, K.S., Pierce, J., Joshi, S.H., Woo, E., Apostolova, L.G., 2019. Cognitive correlates of hippocampal atrophy and ventricular enlargement in adults with or without mild cognitive impairment. Dement. Geriatr. Cogn. Dis. Extra 9 (2), 281–293. https://doi.org/10.1159/000490044

Grabner, G., Janke, A.L., Budge, M.M., Smith, D., Pruessner, J., Collins, D.L., 2006. Symmetric atlasing and model based segmentation: an application to the hippocampus in older adults. Lecture Notes in Computer Science (Including Subseries Lecture Notes in Artificial Intelligence and Lecture Notes in Bioinformatics). https://doi.org/10.1007/11866763_8

Greene, S.J., Killiany, R.J., Initiative, A.D.N., 2010. Subregions of the inferior parietal lobule are affected in the progression to Alzheimer's disease. Neurobiol. Aging 31 (8), 1304–1311. https://doi.org/10.1016/j.neurobiolaging.2010.04.026. https://pubmed.ncbi.nlm.nih.gov/20570398.

Gujar, S.K., Maheshwari, S., Björkman-Burtscher, I., Sundgren, P.C., 2005. Magnetic resonance spectroscopy. J. Neuro-Ophthalmol. Off. J. North Am. Neuro-Ophthalmol. Soc. 25 (3), 217–226. https://doi.org/10.1097/01.wno.0000177307.21081.81

Gundlach, C., Müller, M.M., Hoff, M., Ragert, P., Nierhaus, T., Villringer, A., Sehm, B., 2020. Reduction of somatosensory functional connectivity by transcranial alternating current stimulation at endogenous mu-frequency. Neuroimage 221, 117175. https://doi.org/10.1016/j.neuroimage.2020.117175. https://www.sciencedirect.com/science/article/pii/S1053811920306613.

Hashimoto, M., Araki, Y., Takashima, Y., Nogami, K., Uchino, A., Yuzuriha, T., Yao, H., 2016. Hippocampal atrophy and memory dysfunction associated with physical inactivity in community-dwelling elderly subjects: the Sefuri study. Brain Behav. 7 (2). https://doi.org/10.1002/brb3.620. e00620–e00620. https://pubmed.ncbi.nlm.nih.gov/28239530.

Hermiller, M.S., Karp, E., Nilakantan, A.S., Voss, J.L., 2019. Episodic memory improvements due to noninvasive stimulation targeting the cortical-hippocampal network: a replication and extension experiment. Brain Behav. 9 (12), e01393. https://doi.org/10.1002/brb3.1393

Herrmann, C.S., Rach, S., Neuling, T., Strüber, D., 2013. Transcranial alternating current stimulation: a review of the underlying mechanisms and modulation of cognitive processes. Front. Hum. Neurosci. 7 (279), 1–13. https://doi.org/10.3389/fnhum.2013.00279

Huang, D., Liu, D., Yin, J., Qian, T., Shrestha, S., Ni, H., 2017. Glutamate-glutamine and GABA in brain of normal aged and patients with cognitive impairment. Eur. Radiol. 27 (7), 2698–2705. https://doi.org/10.1007/s00330-016-4669-8

Huang, Y., Datta, A., Bikson, M., Parra, L., 2019. ROAST: a fully-automated, open-source, Realistic vOlumetric-Approach-based Simulator for TES. Brain Stimul. https://doi.org/10.1016/j.brs.2018.12.253

Iaccarino, H.F., Singer, A.C., Martorell, A.J., Rudenko, A., Gao, F., Gillingham, T.Z., Mathys, H., Seo, J., Kritskiy, O., Abdurrob, F., Adaikkan, C., Canter, R.G., Rueda, R., Brown, E.N., Boyden, E.S., Tsai, L.-H., 2016. Gamma frequency entrainment attenuates amyloid load and modifies microglia. Nature 540 (7632), 230–235. https://doi.org/10.1038/nature20587. http://www.nature.com/doifinder/10.1038/nature20587.

Ivanova, M.V., Zhong, A., Turken, A., Baldo, J.V., Dronkers, N.F., 2021. Functional contributions of the arcuate fasciculus to language processing. Front. Hum. Neurosci. 15. https://www.frontiersin.org/article/10.3389/fnhum.2021.672665.

Janelidze, S., Zetterberg, H., Mattsson, N., Palmqvist, S., Vanderstichele, H., Lindberg, O., van Westen, D., Stomrud, E., Minthon, L., Blennow, K., Hansson, O., 2016. CSF Aβ42/Aβ40 and Aβ42/Aβ38 ratios: better diagnostic markers of Alzheimer disease. Ann. Clin. Transl. Neurol. 3 (3), 154–165. https://doi.org/10.1002/acn3.274

Jaušovec, N., Jaušovec, K., 2014. Increasing working memory capacity with theta transcranial alternating current stimulation (tACS). Biol. Psychol. 96 (1), 42–47. https://doi.org/10.1016/j.biopsycho.2013.11.006

Jaušovec, N., Jaušovec, K., Pahor, A., 2014. The influence of theta transcranial alternating current stimulation (tACS) on working memory storage and processing functions. Acta Psychol. (Amst.) 146 (1), 1–6. https://doi.org/10.1016/j.actpsy.2013.11.011

Jenkinson, M., Beckmann, C.F., Behrens, T.E.J., Woolrich, M.W., Smith, S.M., 2012. FSL. Neuroimage 62 (2), 782–790.

Jeong, D.U., Lee, J.E., Lee, S.E., Chang, W.S., Kim, S.J., Chang, J.W., 2014. Improvements in memory after medial septum stimulation are associated with changes in hippocampal cholinergic activity and neurogenesis. Biomed. Res. Int. 2014, 568587. https://doi.org/10.1155/2014/568587. Epub 2014 Jul 2. PMID: 25101288; PMCID: PMC4101966.

Jiang, L., Ding, X., Wang, W., Yang, X., Li, T., Lei, P., 2022. Head-to-head comparison of different blood collecting tubes for quantification of Alzheimer's disease biomarkers in plasma. Biomolecules 12 (9). https://doi.org/10.3390/biom12091194

Jones, K.T., Arciniega, H., Berryhill, M.E., 2019. Replacing tDCS with theta tACS provides selective, but not general WM benefits. Brain Res. https://doi.org/10.1016/j.brainres.2019.146324

Jones, K.T., Johnson, E.L., Gazzaley, A., Zanto, T.P., 2022. Structural and functional network mechanisms of rescuing cognitive control in aging. Neuroimage, 119547. https://doi.org/10.1016/j.neuroimage.2022.119547. https://www.sciencedirect.com/science/article/pii/S1053811922006620.

Jones, K.T., Johnson, E.L., Tauxe, Z.S., Rojas, D.C., 2020. Modulation of auditory gamma-band responses using transcranial electrical stimulation. J. Neurophysiol. 123 (6), 2504–2514. https://doi.org/10.1152/jn.00003.2020

Joundi, R.A., Jenkinson, N., Brittain, J.S., Aziz, T.Z., Brown, P., 2012. Driving oscillatory activity in the human cortex enhances motor performance. Curr. Biol. 22 (5), 403–407. https://doi.org/10.1016/j.cub.2012.01.024. http://www.ncbi.nlm.nih.gov/pubmed/22305755%5Cnhttp://pdn.sciencedirect.com/science?_ob=MiamiImageURL&_cid=272099&_user=2160112&_pii=S0960982212000255&_check=y&_origin=article&_zone=toolbar&_coverDate=06-Mar-2012&view=c&originContentFamily=serial&wchp=dGLbV.

Kaeser, S.A., Lehallier, B., Thinggaard, M., Häsler, L.M., Apel, A., Bergmann, C., Berdnik, D., Jeune, B., Christensen, K., Grönke, S., Partridge, L., Wyss-Coray, T., Mengel-From, J., Jucker, M., 2021. A neuronal blood marker is associated with mortality in old age. Nat. Aging 1 (2), 218–225. https://doi.org/10.1038/s43587-021-00028-4

Kallel, L., Mondino, M., Brunelin, J., 2016. Effects of theta-rhythm transcranial alternating current stimulation (4.5 Hz-tACS) in patients with clozapine-resistant negative symptoms of schizophrenia: a case series. J. Neural Transm. 123 (10), 1213–1217. https://doi.org/10.1007/s00702-016-1574-x

Kamali, A., Flanders, A.E., Brody, J., Hunter, J.V., Hasan, K.M., 2014. Tracing superior longitudinal fasciculus connectivity in the human brain using high resolution diffusion tensor tractography. Brain Struct. Funct. 219 (1), 269–281. https://doi.org/10.1007/s00429-012-0498-y

Kar, K., Krekelberg, B., 2012. Transcranial electrical stimulation over visual cortex evokes phosphenes with a retinal origin. J. Neurophysiol. 108 (8), 2173–2178. https://doi.org/10.1152/jn.00505.2012

Karikari, T.K., Pascoal, T.A., Ashton, N.J., Janelidze, S., Benedet, A.L., Rodriguez, J.L., Chamoun, M., Savard, M., Kang, M.S., Therriault, J., Schöll, M., Massarweh, G., Soucy, J.P., Höglund, K., Brinkmalm, G., Mattsson, N., Palmqvist, S., Gauthier, S., Stomrud, E., Zetterberg, H., Hansson, O., Rosa-Neto, P., Blennow, K., 2020. Blood phosphorylated tau 181 as a biomarker for Alzheimer's disease: a diagnostic performance and prediction modelling study using data from four prospective cohorts. Lancet Neurol. https://doi.org/10.1016/S1474-4422(20)30071-5

Kehler, L., Francisco, C.O., Uehara, M.A., Moussavi, Z., 2020. The effect of transcranial alternating current stimulation (tACS) on cognitive function in older adults with dementia. Annu. Int. 2020, 3649–3653. https://doi.org/10.1109/EMBC44109.2020.9175903

Kehoe, E.G., Farrell, D., Metzler-Baddeley, C., Lawlor, B.A., Kenny, R.A., Lyons, D., McNulty, J.P., Mullins, P.G., Coyle, D., Bokde, A.L., 2015. Fornix white matter is correlated with resting-state functional connectivity of the thalamus and hippocampus in healthy aging but not in mild cognitive impairment – a preliminary study. Front. Aging Neurosci. 7. https://doi.org/10.3389/fnagi.2015.00010

Khalil, M., Pirpamer, L., Hofer, E., Voortman, M.M., Barro, C., Leppert, D., Benkert, P., Ropele, S., Enzinger, C., Fazekas, F., Schmidt, R., Kuhle, J., 2020. Serum neurofilament light levels in normal aging and their association with morphologic brain changes. Nat. Commun. https://doi.org/10.1038/s41467-020-14612-6

Khalil, M., Teunissen, C.E., Otto, M., Piehl, F., Sormani, M.P., Gattringer, T., Barro, C., Kappos, L., Comabella, M., Fazekas, F., Petzold, A., Blennow, K., Zetterberg, H., Kuhle, J., 2018. Neurofilaments as biomarkers in neurological disorders. Nat. Rev. Neurol. https://doi.org/10.1038/s41582-018-0058-z

Kiuchi, K., Morikawa, M., Taoka, T., Nagashima, T., Yamauchi, T., Makinodan, M., Norimoto, K., Hashimoto, K., Kosaka, J., Inoue, Y., Inoue, M., Kichikawa, K., Kishimoto, T., 2009. Abnormalities of the uncinate fasciculus and posterior cingulate fasciculus in mild cognitive impairment and early Alzheimer's disease: a diffusion tensor tractography study. Brain Res. 1287, 184–191. https://doi.org/10.1016/j.brainres.2009.06.052

Knopman, D.S., Jones, D.T., Greicius, M.D., 2021. Failure to demonstrate efficacy of aducanumab: an analysis of the EMERGE and ENGAGE trials as reported by Biogen, December 2019. Alzheimers Dement. 17 (4), 696–701. https://doi.org/10.1002/alz.12213

Lawton, M.P., Brody, E.M., 1969. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist 9 (3), 179–186. https://doi.org/10.1093/geront/9.3_Part_1.179. http://gerontologist.oxfordjournals.org/cgi/doi/10.1093/geront/9.3_Part_1.179.

Lee, W.H., Deng, Z., De, Kim, T.S., Laine, A.F., Lisanby, S.H., Peterchev, A.V., 2012. Regional electric field induced by electroconvulsive therapy in a realistic finite element head model: influence of white matter anisotropic conductivity. Neuroimage 59 (3), 2110–2123. https://doi.org/10.1016/j.neuroimage.2011.10.029

Lehmann, S., Delaby, C., Boursier, G., Catteau, C., Ginestet, N., Tiers, L., Maceski, A., Navucet, S., Paquet, C., Dumurgier, J., Vanmechelen, E., Vanderstichele, H., Gabelle, A., 2018. Relevance of Aβ42/40 ratio for detection of Alzheimer disease pathology in clinical routine: the PLM(R) scale. Front. Aging Neurosci. 10, 138. https://doi.org/10.3389/fnagi.2018.00138

Levar, N., Van Doesum, T.J., Denys, D., Van Wingen, G.A., 2019. Anterior cingulate GABA and glutamate concentrations are associated with resting-state network connectivity. Sci. Rep. 9 (1), 2116. https://doi.org/10.1038/s41598-018-38078-1

Li, Yuxia, Wang, X., Li, Yongqiu, Sun, Y., Sheng, C., Li, H., Li, X., Yu, Y., Chen, G., Hu, X., Jing, B., Wang, D., Li, K., Jessen, F., Xia, M., Han, Y., 2016. Abnormal resting-state functional connectivity strength in mild cognitive impairment and its conversion to Alzheimer's disease. Neural Plast. 2016, 4680972. https://doi.org/10.1155/2016/4680972

Liu, Q., Contreras, A., Afaq, M.S., Yang, W., Hsu, D.K., Russell, M., Lyeth, B., Zanto, T.P., Zhao, M., 2022. Intensity-dependent gamma electrical stimulation regulates microglial activation, reduces beta-amyloid load, and facilitates memory in a mouse model of Alzheimer's disease. SSRN Electron. J. https://doi.org/10.2139/ssrn.4168479

Liu, Q., Jiao, Y., Yang, W., Gao, B., Hsu, D.K., Nolta, J., Russell, M., Lyeth, B., Zanto, T.P., Zhao, M., 2020. Intracranial alternating current stimulation facilitates neurogenesis in a mouse model of Alzheimer's disease. Alzheimers Res. Ther. 12 (89), 1–12. https://doi.org/10.1186/s13195-020-00656-9

Liu, T., Spector, A., Mograbi, D.C., Cheung, G., Wong, G.H.Y., 2021. Changes in default mode network connectivity in resting-state fMRI in people with mild dementia receiving cognitive stimulation therapy. Brain Sci. 11 (9). https://doi.org/10.3390/brainsci11091137

Lockhart, S.N., Mayda, A.B.V., Roach, A.E., Fletcher, E., Carmichael, O., Maillard, P., Schwarz, C.G., Yonelinas, A.P., Ranganath, C., Decarli, C., 2012. Episodic memory function is associated with multiple measures of white matter integrity in cognitive aging. Front. Hum. Neurosci. 6, 56. https://doi.org/10.3389/fnhum.2012.00056

Lopez, A.D., Mathers, C.D., Ezzati, M., Jamison, D.T., Murray, C.J., 2006. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. Lancet. https://doi.org/10.1016/S0140-6736(06)68770-9

Mabbott, D.J., Rovet, J., Noseworthy, M.D., Smith, M., Lou, Rockel, C., 2009. The relations between white matter and declarative memory in older children and adolescents. Brain Res. 1294, 80–90. https://doi.org/10.1016/j.brainres.2009.07.046. https://www.sciencedirect.com/science/article/pii/S0006899309014802.

Martorell, A.J., Paulson, A.L., Suk, H.J., Abdurrob, F., Drummond, G.T., Guan, W., Young, J.Z., Kim, D.N.W., Kritskiy, O., Barker, S.J., Mangena, V., Prince, S.M., Brown, E.N., Chung, K., Boyden, E.S., Singer, A.C., Tsai, L.H., 2019. Multi-sensory gamma stimulation ameliorates Alzheimer's-associated pathology and improves cognition. Cell. https://doi.org/10.1016/j.cell.2019.02.014

Mascali, D., DiNuzzo, M., Serra, L., Mangia, S., Maraviglia, B., Bozzali, M., Giove, F., 2018. Disruption of semantic network in mild Alzheimer's disease revealed by resting-state fMRI. Neuroscience 371, 38–48. https://doi.org/10.1016/j.neuroscience.2017.11.030. https://www.sciencedirect.com/science/article/pii/S0306452217308242.

Maximo, J.O., Briend, F., Armstrong, W.P., Kraguljac, N.V., Lahti, A.C., 2021. Salience network glutamate and brain connectivity in medication-naïve first episode patients – a multimodal magnetic resonance spectroscopy and resting state functional connectivity MRI study. NeuroImage Clin. 32, 102845. https://doi.org/10.1016/j.nicl.2021.102845. https://www.sciencedirect.com/science/article/pii/S2213158221002898.

Mayo, C.D., Garcia-Barrera, M.A., Mazerolle, E.L., Ritchie, L.J., Fisk, J.D., Gawryluk, J.R., 2019. Relationship between DTI metrics and cognitive function in Alzheimer's disease. Front. Aging Neurosci. https://doi.org/10.3389/fnagi.2018.00436

Mayo, C.D., Mazerolle, E.L., Ritchie, L., Fisk, J.D., Gawryluk, J.R., 2017. Longitudinal changes in microstructural white matter metrics in Alzheimer's disease. NeuroImage Clin. https://doi.org/10.1016/j.nicl.2016.12.012

Meiron, O., Lavidor, M., 2014. Prefrontal oscillatory stimulation modulates access to cognitive control references in retrospective metacognitive commentary. Clin. Neurophysiol. 125 (1), 77–82. https://doi.org/10.1016/j.clinph.2013.06.013

Mescher, M., Merkle, H., Kirsch, J., Garwood, M., Gruetter, R., 1998. Simultaneous in vivo spectral editing and water suppression. NMR Biomed. https://doi.org/10.1002/(SICI)1099-1492(199810)11:6<266::AID-NBM530>3.0.CO;2-J

Mielke, M.M., Okonkwo, O.C., Oishi, K., Mori, S., Tighe, S., Miller, M.I., Ceritoglu, C., Brown, T., Albert, M., Lyketsos, C.G., 2012. Fornix integrity and hippocampal volume predict memory decline and progression to Alzheimer's disease. Alzheimers Dement. 8 (2), 105–113. https://doi.org/10.1016/j.jalz.2011.05.2416

Mondino, M., Ghumman, S., Gane, C., Renauld, E., Whittingstall, K., Fecteau, S., 2020. Effects of transcranial stimulation with direct and alternating current on resting-state functional connectivity: an exploratory study simultaneously combining stimulation and multiband functional magnetic resonance imaging. Front. Hum. Neurosci. 13. https://doi.org/10.3389/fnhum.2019.00474

Mori, S., Oishi, K., Jiang, H., Jiang, L., Li, X., Akhter, K., Hua, K., Faria, A.V., Mahmood, A., Woods, R., Toga, A.W., Pike, G.B., Neto, P.R., Evans, A., Zhang, J., Huang, H., Miller, M.I., van Zijl, P., Mazziotta, J., 2008. Stereotaxic white matter atlas based on diffusion tensor imaging in an ICBM template. Neuroimage. https://doi.org/10.1016/j.neuroimage.2007.12.035

Nakamura, A., Kaneko, N., Villemagne, V.L., Kato, T., Doecke, J., Doré, V., Fowler, C., Li, Q.X., Martins, R., Rowe, C., Tomita, T., Matsuzaki, K., Ishii, Kenji, Ishii, Kazunari, Arahata, Y., Iwamoto, S., Ito, K., Tanaka, K., Masters, C.L., Yanagisawa, K., 2018. High performance plasma amyloid-β biomarkers for Alzheimer's disease. Nature. https://doi.org/10.1038/nature25456

Naros, G., Gharabaghi, A., 2017. Physiological and behavioral effects of beta-tACS on brain self-regulation in chronic stroke. Brain Stimul. 10 (2), 251–259. https://doi.org/10.1016/j.brs.2016.11.003

Nasreddine, Z.S., Phillips, N.A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., Cummings, J.L., Chertkow, H., 2005. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J. Am. Geriatr. Soc.

Nilakantan, A.S., Mesulam, M.-M., Weintraub, S., Karp, E.L., VanHaerents, S., Voss, J.L., 2019. Network-targeted stimulation engages neurobehavioral hallmarks of age-related memory decline. Neurology 92 (20), e2349–e2354. https://doi.org/10.1212/WNL.0000000000007502. e2349 LP-e2354. http://n.neurology.org/content/92/20/e2349.abstract.

Niogi, S.N., Mukherjee, P., Ghajar, J., Johnson, C.E., Kolster, R., Lee, H., Suh, M., Zimmerman, R.D., Manley, G.T., McCandliss, B.D., 2008. Structural dissociation of attentional control and memory in adults with and without mild traumatic brain injury. Brain 131 (Pt 12), 3209–3221. https://doi.org/10.1093/brain/awn247

O'Shea, A., Cohen, R., Porges, E., Nissim, N., Woods, A., 2016. Cognitive aging and the hippocampus in older adults. Front. Aging Neurosci. 8. https://doi.org/10.3389/fnagi.2016.00298

Oeltzschner, G., Wijtenburg, S.A., Mikkelsen, M., Edden, R.A.E., Barker, P.B., Joo, J.H., Leoutsakos, J.-M.S., Rowland, L.M., Workman, C.I., Smith, G.S., 2019. Neurometabolites and associations with cognitive deficits in mild cognitive impairment: a magnetic resonance spectroscopy study at 7 Tesla. Neurobiol. Aging 73, 211–218. https://doi.org/10.1016/j.neurobiolaging.2018.09.027

Oren, N., Ash, E.L., Shapira-Lichter, I., Elkana, O., Reichman-Eisikovits, O., Chomsky, L., Lerner, Y., 2019. Changes in resting-state functional connectivity of the hippocampus following cognitive effort predict memory decline at older age—a longitudinal fMRI study. Front. Aging Neurosci. 11. https://doi.org/10.3389/fnagi.2019.00163

Park, H., Kennedy, K.M., Rodrigue, K.M., Hebrank, A., Park, D.C., 2013. An fMRI study of episodic encoding across the lifespan: changes in subsequent memory effects are evident by middle-age. Neuropsychologia 51 (3), 448–456. https://doi.org/10.1016/j.neuropsychologia.2012.11.025. https://www.sciencedirect.com/science/article/pii/S0028393212004927.

Peirce, J., Gray, J.R., Simpson, S., MacAskill, M., Höchenberger, R., Sogo, H., Kastman, E., Lindeløv, J.K., 2019. PsychoPy2: experiments in behavior made easy. Behav. Res. Methods. https://doi.org/10.3758/s13428-018-01193-y

Petersen, R.C., 1995. Normal aging, mild cognitive impairment, and early Alzheimer's disease. Neurologist 1 (6), 326–344.

Petersen, R.C., 2003. Mild cognitive impairment clinical trials. Nat. Rev. Drug Discov. 2 (8), 646–653.http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12904814.

Petersen, R.C., 2004. Mild cognitive impairment as a diagnostic entity. J. Intern. Med. 256 (3), 183–194.http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15324362.

Petersen, R.C., Smith, G.E., Waring, S.C., Ivnik, R.J., Tangalos, E.G., Kokmen, E., 1999. Mild cognitive impairment: clinical characterization and outcome. Arch. Neurol. 56 (3), 303–308.http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10190820.

Pohlack, S.T., Meyer, P., Cacciaglia, R., Liebscher, C., Ridder, S., Flor, H., 2014. Bigger is better! Hippocampal volume and declarative memory performance in healthy young men. Brain Struct. Funct. 219 (1), 255–267. https://doi.org/10.1007/s00429-012-0497-z

Polanía, R., Nitsche, M. a, Korman, C., Batsikadze, G., Paulus, W., 2012. The importance of timing in segregated theta phase-coupling for cognitive performance. Curr. Biol. 22 (14), 1314–1318. https://doi.org/10.1016/j.cub.2012.05.021

Power, J.D., Barnes, K.A., Snyder, A.Z., Schlaggar, B.L., Petersen, S.E., 2012. Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. Neuroimage 59 (3), 2142–2154. https://doi.org/10.1016/j.neuroimage.2011.10.018

Pozueta, A., Rodríguez-Rodríguez, E., Vazquez-Higuera, J.L., Mateo, I., Sánchez-Juan, P., González-Perez, S., Berciano, J., Combarros, O., 2011. Detection of early Alzheimer's disease in MCI patients by the combination of MMSE and an episodic memory test. BMC Neurol. 11, 78. https://doi.org/10.1186/1471-2377-11-78. https://pubmed.ncbi.nlm.nih.gov/21702929.

Prehn-Kristensen, A., Munz, M., Göder, R., Wilhelm, I., Korr, K., Vahl, W., Wiesner, C.D., Baving, L., 2014. Transcranial oscillatory direct current stimulation during sleep improves declarative memory consolidation in children with attention-deficit/hyperactivity disorder to a level comparable to healthy controls. Brain Stimul. 7 (6), 793–799. https://doi.org/10.1016/j.brs.2014.07.036

Preische, O., Schultz, S.A., Apel, A., Kuhle, J., Kaeser, S.A., Barro, C., Gräber, S., Kuder-Buletta, E., LaFougere, C., Laske, C., Vöglein, J., Levin, J., Masters, C., Martins, R., Schofield, P., Rossor, M.N., Graff-Radford, N., Salloway, S., Ghetti, B., Ringman, J., Noble, J., Chhatwal, J., Goate, A., Benzinger, T., Morris, J., Bateman, R., Wang, G., Fagan, A., McDade, E., Gordon, B., Jucker, M., Allegri, R., Amtashar, F., Berman, S., Bodge, C., Brandon, S., Brooks, W., Buck, J., Buckles, V., Chea, S., Chrem, P., Chui, H., Cinco, J., Clifford, J., Cruchaga, C., D'Mello, M., Donahue, T., Douglas, J., Edigo, N., Erekin-Taner, N., Farlow, M., Farrar, A., Feldman, H., Flynn, G., Fox, N., Franklin, E., Fujii, H., Gant, C., Gardener, S., Goldman, J., Gray, J., Gurney, J., Hassenstab, J., Hirohara, M., Holtzman, D., Hornbeck, R., DiBari, S.H., Ikeuchi, T., Ikonomovic, S., Jerome, G., Karch, C., Kasuga, K., Kawarabayashi, T., Klunk, W., Koeppe, R., Lee, J.H., Marcus, D., Mason, N.S., Maue-Dreyfus, D., Montoya, L., Mori, H., Nagamatsu, A., Neimeyer, K., Norton, J., Perrin, R., Raichle, M., Roh, J.H., Shimada, H., Shiroto, T., Shoji, M., Sigurdson, W., Sohrabi, H., Sparks, P., Suzuki, K., Swisher, L., Taddei, K., Wang, J., Wang, P., Weiner, M., Wolfsberger, M., Xiong, C., Xu, X., 2019. Serum neurofilament dynamics predicts neurodegeneration and clinical progression in presymptomatic Alzheimer's disease. Nat. Med. https://doi.org/10.1038/s41591-018-0304-3

Rajkumar, R., Régio Brambilla, C., Veselinović, T., Bierbrier, J., Wyss, C., Ramkiran, S., Orth, L., Lang, M., Rota Kops, E., Mauler, J., Scheins, J., Neumaier, B., Ermert, J., Herzog, H., Langen, K.-J., Binkofski, F.C., Lerche, C., Shah, N.J., Neuner, I., 2021. Excitatory–inhibitory balance within EEG microstates and resting-state fMRI networks: assessed via simultaneous trimodal PET–MR–EEG imaging. Transl. Psychiatry 11 (1), 60. https://doi.org/10.1038/s41398-020-01160-2

Reinhart, R.M.G., Nguyen, J.A., 2019. Working memory revived in older adults by synchronizing rhythmic brain circuits. Nat. Neurosci. 22, 820–827. https://doi.org/10.1038/s41593-019-0371-x

Richmond, L.L., Morrison, A.B., Chein, J.M., Olson, I.R., 2011. Working memory training and transfer in older adults. Psychol. Aging. https://doi.org/10.1037/a0023631

Risacher, S.L., Fandos, N., Romero, J., Sherriff, I., Pesini, P., Saykin, A.J., Apostolova, L.G., 2019. Plasma amyloid beta levels are associated with cerebral amyloid and tau deposition. Alzheimers Dement. (Amst.) 11, 510–519. https://doi.org/10.1016/j.dadm.2019.05.007

Rothman, D.L., Petroff, O.A.C., Behar, K.L., Mattson, R.H., 1993. Localized ^{1}H NMR measurements of γ-aminobutyric acid in human brain in vivo. Proc. Natl. Acad. Sci. U. S. A.

Rudebeck, S.R., Scholz, J., Millington, R., Rohenkohl, G., Johansen-Berg, H., Lee, A.C.H., 2009. Fornix microstructure correlates with recollection but not familiarity memory. J. Neurosci. 29 (47), 14987–14992. https://doi.org/10.1523/JNEUROSCI.4707-09.2009. http://www.jneurosci.org/content/29/47/14987.abstract.

Thurstone, L.L., 1938. Primary mental abilities. Math. Gaz. https://doi.org/10.2307/3607923

Satterthwaite, T.D., Elliott, M.A., Gerraty, R.T., Ruparel, K., Loughead, J., Calkins, M.E., Eickhoff, S.B., Hakonarson, H., Gur, R.C., Gur, R.E., Wolf, D.H., 2013. An improved framework for confound regression and filtering for control of motion artifact in the preprocessing of resting-state functional connectivity data. Neuroimage 64, 240–256. https://doi.org/10.1016/j.neuroimage.2012.08.052

Satterthwaite, T.D., Wolf, D.H., Loughead, J., Ruparel, K., Elliott, M.A., Hakonarson, H., Gur, R.C., Gur, R.E., 2012. Impact of in-scanner head motion on multiple measures of functional connectivity: relevance for studies of neurodevelopment in youth. Neuroimage 60 (1), 623–632. https://doi.org/10.1016/j.neuroimage.2011.12.063

Schaapsmeerders, P., van Uden, I.W.M., Tuladhar, A.M., Maaijwee, N.A.M., van Dijk, E.J., Rutten-Jacobs, L.C.A., Arntz, R.M., Schoonderwaldt, H.C., Dorresteijn, L.D.A., de Leeuw, F.-E., Kessels, R.P.C., 2015. Ipsilateral hippocampal atrophy is associated with long-term memory dysfunction after ischemic stroke in young adults. Hum. Brain Mapp. 36 (7), 2432–2442. https://doi.org/10.1002/hbm.22782

Schindler, S.E., Bollinger, J.G., Ovod, V., Mawuenyega, K.G., Li, Y., Gordon, B.A., Holtzman, D.M., Morris, J.C., Benzinger, T.L.S., Xiong, C., Fagan, A.M., Bateman, R.J., 2019. High-precision plasma β-amyloid 42/40 predicts current and future brain amyloidosis. Neurology 93 (17), e1647–e1659. https://doi.org/10.1212/WNL.0000000000008081

Scott, A.J., Ellison, M., Sinclair, D.A., 2021. The economic value of targeting aging. Nat. Aging 1 (7), 616–623. https://doi.org/10.1038/s43587-021-00080-0

Senova, S., Fomenko, A., Gondard, E., Lozano, A.M., 2020. Anatomy and function of the fornix in the context of its potential as a therapeutic target. J. Neurol. Neurosurg. Psychiatry 91 (5), 547–559. https://doi.org/10.1136/jnnp-2019-322375

Shahid, S., Wen, P., Ahfock, T., 2013. Numerical investigation of white matter anisotropic conductivity in defining current distribution under tDCS. Comput. Methods Programs Biomed. 109 (1), 48–64. https://doi.org/10.1016/j.cmpb.2012.09.001

Sheline, Y.I., Raichle, M.E., 2013. Resting state functional connectivity in preclinical Alzheimer's disease. Biol. Psychiatry. https://doi.org/10.1016/j.biopsych.2012.11.028

Singer, A.C., Martorell, A.J., Douglas, J.M., Abdurrob, F., Attokaren, M.K., Tipton, J., Mathys, H., Adaikkan, C., Tsai, L.H., 2018. Noninvasive 40-Hz light flicker to recruit microglia and reduce amyloid beta load. Nat. Protoc. https://doi.org/10.1038/s41596-018-0021-x

Smith, S.M., Jenkinson, M., Johansen-Berg, H., Rueckert, D., Nichols, T.E., Mackay, C.E., Watkins, K.E., Ciccarelli, O., Cader, M.Z., Matthews, P.M., Behrens, T.E.J., 2006. Tract-based spatial statistics: Voxelwise analysis of multi-subject diffusion data. Neuroimage. https://doi.org/10.1016/j.neuroimage.2006.02.024

Smith, S.M., Jenkinson, M., Woolrich, M.W., Beckmann, C.F., Behrens, T.E.J., Johansen-Berg, H., Bannister, P.R., De Luca, M., Drobnjak, I., Flitney, D.E., Niazy, R.K., Saunders, J., Vickers, J., Zhang, Y.Y., De Stefano, N., Brady, J.M., Matthews, P.M., 2004. Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage 23, S208–S219. https://doi.org/10.1016/J.Neuroimage.2004.07.051

Song, J., Qin, W., Liu, Y., Duan, Y., Liu, J., He, X., Li, K., Zhang, X., Jiang, T., Yu, C., 2013. Aberrant Functional Organization within and between Resting-State Networks in AD. PLoS One. https://doi.org/10.1371/journal.pone.0063727

Sprugnoli, G., Munsch, F., Cappon, D., Paciorek, R., Macone, J., Connor, A., El Fakhri, G., Salvador, R., Ruffini, G., Donohoe, K., Shafi, M.M., Press, D., Alsop, D.C., Pascual Leone, A., Santarnecchi, E., 2021. Impact of multisession 40Hz tACS on hippocampal perfusion in patients with Alzheimer's disease. Alzheimers Res. Ther. 13 (1), 203. https://doi.org/10.1186/s13195-021-00922-4

Stamenova, V., Jennings, J.M., Cook, S.P., Walker, L.A.S., Smith, A.M., Davidson, P.S.R., 2014. Training recollection in healthy older adults: clear improvements on the training task, but little evidence of transfer. Front. Hum. Neurosci. 8. https://www.frontiersin.org/article/10.3389/fnhum.2014.00898.

Stark, S.M., Yassa, M.A., Lacy, J.W., Stark, C.E.L., 2013. A task to assess behavioral pattern separation (BPS) in humans: data from healthy aging and mild cognitive impairment. Neuropsychologia. https://doi.org/10.1016/j.neuropsychologia.2012.12.014

Tabert, M.H., Manly, J.J., Liu, X., Pelton, G.H., Rosenblum, S., Jacobs, M., Zamora, D., Goodkind, M., Bell, K., Stern, Y., Devanand, D.P., 2006. Neuropsychological prediction of conversion to Alzheimer disease in patients with mild cognitive impairment. Arch. Gen. Psychiatry 63 (8), 916. https://doi.org/10.1001/archpsyc.63.8.916

The Mathworks Inc, 2016. MATLAB – MathWorks [WWW Document]. Available at: www.mathworks.com/products/matlab.

Thijssen, E.H., La Joie, R., Strom, A., Fonseca, C., Iaccarino, L., Wolf, A., Spina, S., Allen, I.E., Cobigo, Y., Heuer, H., VandeVrede, L., Proctor, N.K., Lago, A.L., Baker, S., Sivasankaran, R., Kieloch, A., Kinhikar, A., Yu, L., Valentin, M.A., Jeromin, A., Zetterberg, H., Hansson, O., Mattsson-Carlgren, N., Graham, D., Blennow, K., Kramer, J.H., Grinberg, L.T., Seeley, W.W., Rosen, H., Boeve, B.F., Miller, B.L., Teunissen, C.E., Rabinovici, G.D., Rojas, J.C., Dage, J.L., Boxer, A.L., 2021. Plasma phosphorylated tau 217 and phosphorylated tau 181 as biomarkers in Alzheimer's disease and frontotemporal lobar degeneration: a retrospective diagnostic performance study. Lancet. Neurol. 20 (9), 739–752. https://doi.org/10.1016/S1474-4422(21)00214-3. https://pubmed.ncbi.nlm.nih.gov/34418401/ (November 18, 2022).

Turi, Z., Ambrus, G.G., Janacsek, K., Emmert, K., Hahn, L., Paulus, W., Antal, A., 2013. Both the cutaneous sensation and phosphene perception are modulated in a frequency-specific manner during transcranial alternating current stimulation. Restor. Neurol. Neurosci. 31 (3), 275–285. https://doi.org/10.3233/RNN-120297

van den Heuvel, M., Mandl, R., Luigjes, J., Hulshoff Pol, H., 2008. Microstructural organization of the cingulum tract and the level of default mode functional connectivity. J. Neurosci. Off. J. Soc. Neurosci. 28 (43), 10844–10851. https://doi.org/10.1523/JNEUROSCI.2964-08.2008

Van Dijk, K.R.A., Sabuncu, M.R., Buckner, R.L., 2012. The influence of head motion on intrinsic functional connectivity MRI. Neuroimage 59 (1), 431–438. https://doi.org/10.1016/j.neuroimage.2011.07.044

Van Schouwenburg, M., Zanto, T.P., Gazzaley, A., 2017. Spaital attention and the effects of frontoparietal alpha band stimulation. Front. Hum. Neurosci. 10 (658). https://doi.org/10.3389/fnhum.2016.00658. PMID: 28174529; PMCID: PMC5259681.

Vidal-Piñeiro, D., Sneve, M.H., Nyberg, L.H., Mowinckel, A.M., Sederevicius, D., Walhovd, K.B., Fjell, A.M., 2019. Maintained frontal activity underlies high memory function over 8 years in aging. Cereb. Cortex 29 (7), 3111–3123. https://doi.org/10.1093/cercor/bhy177

Viskontas, I.V., Knowlton, B.J., Fried, I., 2016. Responses of neurons in the medial temporal lobe during encoding and recognition of face-scene pairs. Neuropsychologia. https://doi.org/10.1016/j.neuropsychologia.2016.07.014

Von Der Heide, R.J., Skipper, L.M., Klobusicky, E., Olson, I.R., 2013. Dissecting the uncinate fasciculus: disorders, controversies and a hypothesis. Brain : a J. Neurol. 136 (Pt6), 1692–1707. https://doi.org/10.1093/brain/awt094

Vossen, A., Gross, J., Thut, G., 2015. Alpha power increase after transcranial alternating current stimulation at alpha frequency reflects plastic changes rather than entrainment. Brain Stimul. 8 (3), 499–508.

Vosskuhl, J., Huster, R.J., Herrmann, C.S., 2015. Increase in short-term memory capacity induced by down-regulating individual theta frequency via transcranial alternating current stimulation. Front. Hum. Neurosci. 9 (257), 1–10. https://doi.org/10.3389/fnhum.2015.00257

Wais, P., Arioli, M., Angera, R., Gazzaley, A., 2021. Virtual reality video game improves high-delity memory in older adults. Sci. Rep. 11 (2552).

Wais, P.E., Arioli, M., Anguera-Singla, R., Gazzaley, A., 2021. Virtual reality video game improves high-fidelity memory in older adults. Sci. Rep. 11 (1), 2552. https://doi.org/10.1038/s41598-021-82109-3

Wais, P.E., Jahanikia, S., Steiner, D., Stark, C.E.L., Gazzaley, A., 2017. Retrieval of high-fidelity memory arises from distributed cortical networks. Neuroimage. https://doi.org/10.1016/j.neuroimage.2017.01.062

Wais, P.E., Montgomery, O., Stark, C.E.L., Gazzaley, A., 2018. Evidence of a causal role for mid-ventrolateral prefrontal cortex based functional networks in retrieving high-fidelity memory. Sci. Rep. 8 (1), 14877. https://doi.org/10.1038/s41598-018-33164-w

Wakana, S., Caprihan, A., Panzenboeck, M.M., Fallon, J.H., Perry, M., Gollub, R.L., Hua, K., Zhang, J., Jiang, H., Dubey, P., Blitz, A., van Zijl, P., Mori, S., 2007. Reproducibility of quantitative tractography methods applied to cerebral white matter. Neuroimage. https://doi.org/10.1016/j.neuroimage.2007.02.049

Wang, Z., Xia, M., Dai, Z., Liang, X., Song, H., He, Y., Li, K., 2015. Differentially disrupted functional connectivity of the subregions of the inferior parietal lobule in Alzheimer's disease. Brain Struct. Funct. 220 (2), 745–762. https://doi.org/10.1007/s00429-013-0681-9

Warren, K.N., Hermiller, M.S., Nilakantan, A.S., Voss, J.L., 2019. Stimulating the hippocampal posterior-medial network enhances task-dependent connectivity and memory. Elife 8. https://doi.org/10.7554/eLife.49458

Wassermann, E.M., Cohen, L.G., Flitman, S.S., Chen, R., Hallett, M., 1996. Seizures in healthy people with repeated "safe" trains of transcranial magnetic stimuli. Lancet 347 (9004), 825–826.http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8622349.

Yang, Z., Wang, K.K.W., 2015. Glial fibrillary acidic protein: from intermediate filament assembly and gliosis to neurobiomarker. Trends Neurosci. 38 (6), 364–374. https://doi.org/10.1016/j.tins.2015.04.003

Yassa, M.A., Mattfeld, A.T., Stark, S.M., Stark, C.E.L., 2011. Age-related memory deficits linked to circuit-specific disruptions in the hippocampus. Proc. Natl. Acad. Sci. U. S. A. https://doi.org/10.1073/pnas.1101567108

Yiannopoulou, K.G., Papageorgiou, S.G., 2020. Current and future treatments in Alzheimer disease: an update. J. Cent. Nerv. Syst. Dis. 12https://doi.org/10.1177/1179573520907397. 1179573520907397.

Zanto, T.P., Jones, K.T., Ostrand, A.E., Hsu, W.-Y., Campusano, R., Gazzaley, A., 2021. Individual differences in neuroanatomy and neurophysiology predict effects of transcranial alternating current stimulation. Brain Stimul. 14 (5), 1317–1329. https://doi.org/10.1016/j.brs.2021.08.017

Zanto, T.P., Pa, J., Gazzaley, A., 2014. Reliability measures of functional magnetic resonance imaging in a longitudinal evaluation of mild cognitive impairment. Neuroimage 84, 443–452. https://doi.org/10.1016/J.Neuroimage.2013.08.063

Zhao, Y., Ficek, B., Webster, K., Frangakis, C., Caffo, B., Hillis, A.E., Faria, A., Tsapkini, K., 2021. White matter integrity predicts electrical stimulation (tDCS) and language therapy effects in primary progressive aphasia. Neurorehabil. Neural Repair 35 (1), 44–57. https://doi.org/10.1177/1545968320971741

Zhen, J., Qian, Y., Fu, J., Su, R., An, H., Wang, W., Zheng, Y., Wang, X., 2017. Deep brain magnetic stimulation promotes neurogenesis and restores cholinergic activity in a transgenic mouse model of Alzheimer's disease. Front. Neural Circuits 11 (48). https://doi.org/10.3389/fncir.2017.00048. PMID: 28713248; PMCID: PMC5492391.

Zheng, X., Schlaug, G., 2015. Structural white matter changes in descending motor tracts correlate with improvements in motor impairment after undergoing a treatment course of tDCS and physical therapy. Front. Hum. Neurosci. 9 (229). https://doi.org/10.3389/fnhum.2015.00229. PMID: 25983684; PMCID: PMC 4415397.