Interleaved TMS-fMRI for Hippocampal Stimulation: Modeling Dose-Response Relationship in Amnestic Mild Cognitive Impairment

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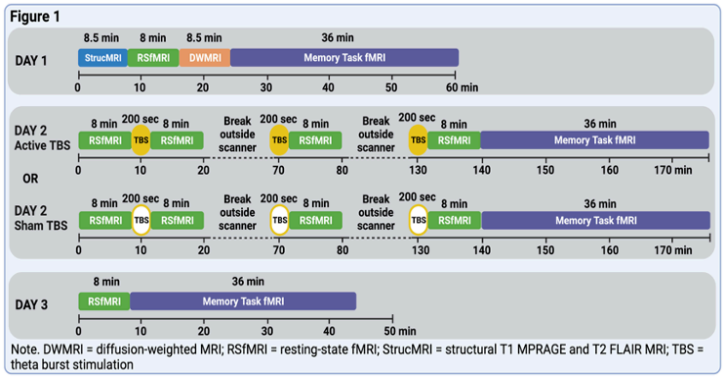
Approach

Participants

Thirty-eight right-handed individuals with aMCI (50-80 years old) will be enrolled in this study. The following revised Mayo clinic criteria for MCI[1] will be used for the inclusion of individuals with MCI: (a) self- or informant-reported cognitive complaint; (b) objective cognitive impairment; (c) preserved independence in functional abilities; and (d) absence of dementia. The MCI diagnosis will be supported by the measures of general cognitive function using Mini-Mental State Exam (MMSE) 24-27 (inclusive); (2) Montreal Cognitive Assessment (MoCA) 18-26 (inclusive); and (3) Clinical Dementia Rating Scale score of 0.5. Only individuals with aMCI (i.e., memory is significantly impaired) will be included in the study. The Jak/Bondi actuarial neuropsychological test method[2] and NACC UDS 3.0 Neuropsychological battery[3] will be used to identify aMCI (i.e., 1 standard deviation below the mean for their age and education matched peers on normative data in at least 2 tasks of the memory domain[2]). A web-based normative calculator will be used to estimate the level of performance (i.e., Z score and percentile) on each NACC UDS measure[4]. We will not include individuals with unstable medical condition, contraindications to MRI and TMS, clinical evidence of stroke, psychiatric disorder, and other neurological disorders or head injury.

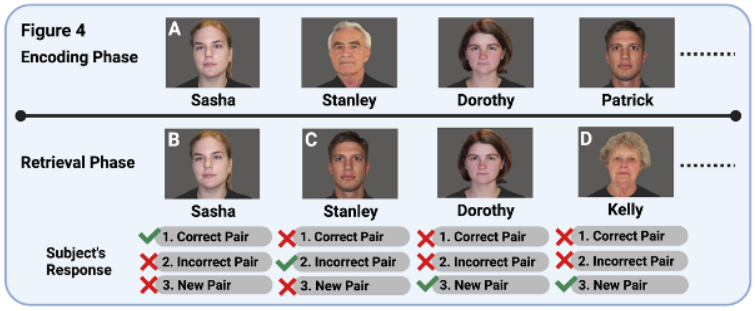
Trial design

Thirty-eight individuals with aMCI will be enrolled in the 3-day interleaved TBS-fMRI study. Participants will be randomly assigned into one of the two TBS groups: active TBS or sham TBS (Figure 1). Participants will receive 3 TBS sessions on day 2 with each TBS session separated by 60 minutes to maximize the TBS effect[5,6]. Participants in the active TBS group will receive 3 excitatory TBS sessions (the 3 yellow ovals in Figure 1). Participants in the sham TBS group will undergo a procedure identical to the active TBS except that no TBS will be provided (the 3 white ovals in Figure 1). Research participants and outcome assessors will be blinded for participants' allocated group. Outcome measures assessing memory function, hippocampal functional connectivity, and hippocampal activation during a memory task will be acquired on day 1 (baseline), day 2 (immediate effect), and day 3 (lasting effect). We hypothesize that active spaced TBS will enhance memory function, strengthen hippocampal functional connectivity, and increase hippocampal activation compared to the sham TBS immediately and 24 hours after the last TBS session.



Outcome measures

Accuracy of the face-name associative memory (FNAME) task, *resting-state hippocampal functional connectivity,* and *hippocampal activation pattern* will be the primary outcome measures. Participants will perform the FNAME task, which was adapted from previous paradigm[7,8], inside the MRI scanner. The FNAME task consists of both encoding and retrieval phases (Figure 4). During the encoding phase, participants will be instructed to remember the name that goes with each face and make a subjective decision as to how well each name fits the corresponding face (a strategy designed to augment associative encoding)[9]. Encoding phase will be divided across 4 functional runs, each consisting of 16 face-name pairs (display duration = 5.5 sec for each pair), interspersed with fixation trials (duration = 0.5-12.5 sec), yielding a total of 64 face-name pairs. Following encoding with a 5-min break, participants will be presented with 3 types of face-name pairs (correct face-name pairs, incorrect face-name pairs, or new face-name pairs) inside the MRI scanner during the retrieval phase. There are 4 functional runs, each consisting of 10 correct, 6 incorrect, and 6 new face-name pairs interspersed with fixation trials, yielding a total of 88 face-name pairs. *Accuracy* will be measured as the number of right responses (e.g., Figure 4 face-name pairs B-D) relative to the total number of face-name pairs shown during the retrieval phase. We created 8 versions of the face-name tasks. Our pilot data from 20 healthy adults indicated excellent parallel-forms reliability across the 8 test versions (ICC = 0.93, 95%CI = [0.88, 0.97]). The administration order of different versions will be randomized across the participants. The score of the FNAME task has been found to be correlated with beta amyloid burden[7], reduced hippocampal volume, and APOE4 carrier status in cognitively normal older adults[10]. The FNAME task is sensitive to longitudinal clinical decline in MCI[11] and in those at genetic risk for AD[12-14].



Statistical design and analysis

This study employs a parallel group design with 2 groups (active TBS and sham TBS) and 3 primary data collection time points (day1, day 2, and day 3). Participants will be randomized to one of the 2 groups using a randomization scheme stratified on age (50-65 vs. 66-80) and sex. For the *accuracy of the FNAME task,* a linear mixed effects model will be fit to the accuracy scores from the FNAME task to look at the change in accuracy over time for both the active and sham TBS groups. The model will include fixed predictors for time (3 levels: day 1, day 2, and day 3), group (2 levels: active TBS and sham TBS), their interaction, age, sex, and education. A

random intercept per participant will be included to account for the potential correlation among data from the same participant.

1. Petersen, R. C. *et al.* Mild cognitive impairment: a concept in evolution. *J Intern Med* **275**, 214-228 (2014). https://doi.org/10.1111/joim.12190
2 . Jak, A. J. *et al.* Neuropsychological Criteria for Mild Cognitive Impairment and Dementia Risk in the Framingham Heart Study. *J Int Neuropsychol Soc* **22**, 937-943 (2016). https://doi.org/10.1017/S1355617716000199
3. Weintraub, S. *et al.* Version 3 of the Alzheimer Disease Centers' Neuropsychological Test Battery in the Uniform Data Set (UDS). *Alzheimer Dis Assoc Disord* (2017). https://doi.org/10.1097/WAD.0000000000000223
4. Shirk, S. D. *et al.* A web-based normative calculator for the uniform data set (UDS) neuropsychological test battery. *Alzheimer's research & therapy* **3**, 32 (2011). https://doi.org/10.1186/alzrt94
5. Kramar, E. A. *et al.* Synaptic evidence for the efficacy of spaced learning. *Proc Natl Acad Sci U S A* **109**, 5121-5126 (2012). https://doi.org/10.1073/pnas.1120700109
6. Lynch, G., Kramar, E. A., Babayan, A. H., Rumbaugh, G. & Gall, C. M. Differences between synaptic plasticity thresholds result in new timing rules for maximizing long-term potentiation. *Neuropharmacology* **64**, 27-36 (2013). https://doi.org/10.1016/j.neuropharm.2012.07.006
7. Rentz, D. M. *et al.* Face-name associative memory performance is related to amyloid burden in normal elderly. *Neuropsychologia* **49**, 2776-2783 (2011). https://doi.org/10.1016/j.neuropsychologia.2011.06.006
8. Carr, V. A. *et al.* Individual differences in associative memory among older adults explained by hippocampal subfield structure and function. *Proc Natl Acad Sci U S A* **114**, 12075-12080 (2017). https://doi.org/10.1073/pnas.1713308114
9. Sperling, R. A. *et al.* fMRI studies of associative encoding in young and elderly controls and mild Alzheimer's disease. *J Neurol Neurosurg Psychiatry* **74**, 44-50 (2003). https://doi.org/10.1136/jnnp.74.1.44
10. Sperling, R. A. *et al.* Amyloid deposition is associated with impaired default network function in older persons without dementia. *Neuron* **63**, 178-188 (2009). https://doi.org/10.1016/j.neuron.2009.07.003
11. O'Brien, J. L. *et al.* Longitudinal fMRI in elderly reveals loss of hippocampal activation with clinical decline. *Neurology* **74**, 1969-1976 (2010). https://doi.org/10.1212/WNL.0b013e3181e3966e
12. Miller, S. L. *et al.* Age-related memory impairment associated with loss of parietal deactivation but preserved hippocampal activation. *Proc Natl Acad Sci U S A* **105**, 2181-2186 (2008). https://doi.org/10.1073/pnas.0706818105
13. Celone, K. A. *et al.* Alterations in memory networks in mild cognitive impairment and Alzheimer's disease: an independent component analysis. *J Neurosci* **26**, 10222-10231 (2006). https://doi.org/10.1523/JNEUROSCI.2250-06.2006
14. Sperling, R. *et al.* Putting names to faces: successful encoding of associative memories activates the anterior hippocampal formation. *Neuroimage* **20**, 1400-1410 (2003). https://doi.org/10.1016/S1053-8119(03)00391-4