Probing Cortical Excitability and Cognitive Function With TMS

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Participants:

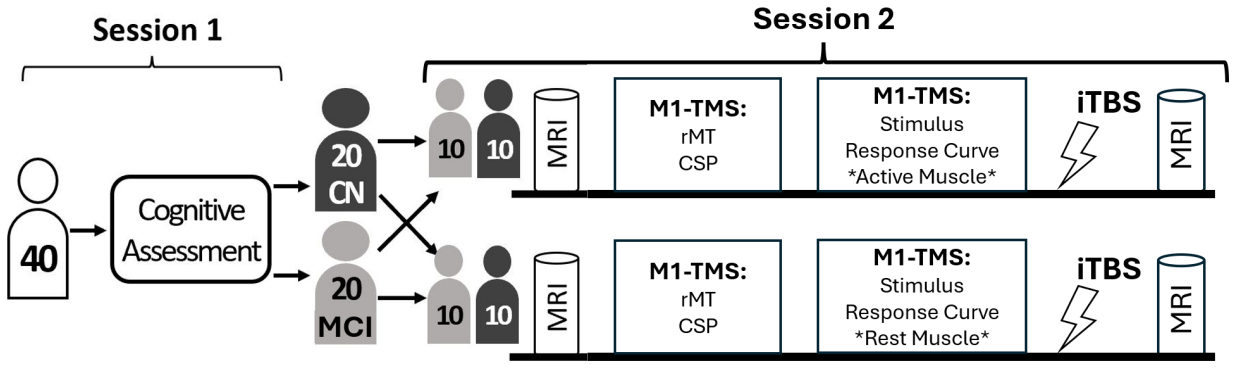
Forty community-dwelling older adults were enrolled in this study. All participants completed comprehensive neuropsychological assessments to determine cognitive status based on the revised Mayo Clinic criteria for mild cognitive impairment (MCI), which include: (a) a self- or informant-reported cognitive complaint; (b) objective evidence of cognitive impairment; (c) preserved independence in functional abilities; and (d) absence of dementia(Petersen et al., 2014).

Classification of MCI was further supported using the Jak/Bondi actuarial neuropsychological method and the National Alzheimer's Coordinating Center (NACC) Uniform Data Set Version 3.0 Neuropsychological Battery(Weintraub et al., 2018). Participants were classified as cognitively impaired if they scored more than 1 standard deviation below age- and education-adjusted normative data on either: (i) two tasks within the same cognitive domain, or (ii) one task in each of three different domains, consistent with the Jak/Bondi criteria(Jak et al., 2009; Jak et al., 2016).

Based on these criteria, 20 participants were classified as having MCI, while the remaining 20 were demographically matched and served as cognitively normal controls.

Trial Design:

Each participant attended two study visits (Fig. 1). During session 1, participants completed a comprehensive neuropsychological battery. The groups were counterbalanced to include 20 classified as cognitively normal (CN) and 20 classified as MCI.



Session 2 comprised both Magnetic Resonance Imaging (MRI) and Transcranial Magnetic Stimulation (TMS). We acquired functional MRI (fMRI) data both before and immediately upon completion of the TMS protocols. We evaluated resting-state functional connectivity between the stimulation site (M1) and neighboring regions (e.g., somatosensory cortex; S1).

TMS was applied to the primary motor cortex using an infrared-based frameless stereotactic neuronavigation system (Polaris System, Localite *Version 3.0.41*). Single-pulse protocols were

used to assess the features of cortical excitability, as described in the outcome measures below(Chou et al., 2022). To identify the stimulation target corresponding with the APB muscle, the motor 'hand knob' area was visually identified on the left pre-central gyrus for each participant's anatomical MRI. The stimulation target was subsequently refined based on observed motor responses from the APB. The optimal motor hotspot was recorded within the neuronavigation system, which enabled precise coil positioning throughout the TMS session.

We utilized electromyography to record M1-TMS measures of cortical excitability, described below. Electromyography data were collected from the abductor pollicis brevis (APB) muscle, which was identified via manual palpation. Three electrodes were placed in a belly–tendon montage, with the grounding electrode placed on the ulnar tuberosity. The EMG data captured motor evoked potentials (MEPs), from the APB muscle activity induced by single pulses of TMS. There were two different experimental conditions for the M1-TMS stimulus-response curve, with half of the participants in each cohort assigned to each condition.

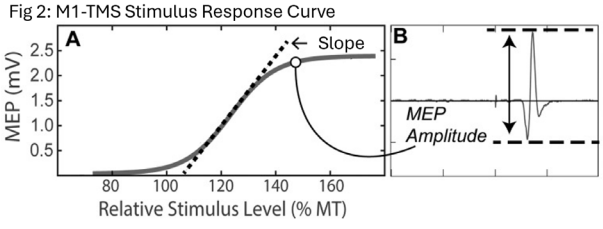
In addition to single-pulse measures of cortical excitability, intermittent theta-burst stimulation (iTBS) was applied to the same stimulation target. The iTBS protocol comprised 600 pulses at 80% of the active MT. The stimuli were patterned in three-pulse bursts at 50 Hz, which repeated at a frequency of 5 Hz, and were delivered in intermittent trains, each lasting 2s with a 6.9-s inter-train interval for a total duration of 178s.

Outcome Measures:

This study comprised several M1-TMS measures of cortical excitability; these included resting motor threshold (rMT), the stimulus-response curve, and the cortical silent period.

rMT is the minimum TMS intensity necessary to elicit a twitch in a targeted muscle at rest, which is operationally defined as an MEP ≥ 50μV in at least 50% of trials. A decrease in resting motor threshold (rMT) indicates that less energy is required to transsynaptically depolarize pyramidal tract neurons, signifying heightened cortical excitability(Ziemann et al., 2015).

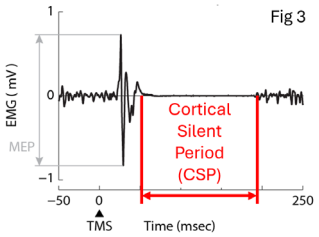
Fig 2: M1-TMS Stimulus Response Curve



The **stimulus-response curve** is evaluated by examining how MEP amplitude—typically measured as peak-to-peak response—varies across different stimulus intensities(Devanne et al., 1997). This relationship follows a sigmoidal trajectory, often called the stimulus-response, recruitment, or input-output curve. The curve is typically modeled using a sigmoidal function, such as Boltzmann's

equation, by plotting stimulus intensity against corresponding MEP amplitudes. Among the various parameters that can be derived from this function, our analysis focused on the slope of the curve's linear region, which reflects corticospinal excitability (Fig. 2). This outcome measure was collected under two experimental conditions: with a tonic voluntary muscle contraction (20% of max voluntary contraction) or with the corresponding muscle at rest. Half of the participants from each cohort were assigned to each experimental condition.

The **CSP** is the temporary disruption of background voluntary muscle activity immediately following the MEP, resembling electrical silence in the EMG signal (Fig 3). Quantified as the duration of EMG absence following an MEP, CSP is a measure of GABA-mediated intracortical inhibition(Paulus et al., 2008).



Lastly, we assessed the resting-state functional connectivity of the stimulation site (M1). We assessed group differences at baseline as well as group differences in the iTBS-induced change in functional connectivity.

Statistical Design and Analysis

This cross-sectional study examined group differences across the outcome measures described above. Two-sample t-tests compared the MCI and cognitively normal control groups on resting motor threshold (rMT), cortical silent period (CSP), and resting-state functional connectivity. We conducted a two-way factorial ANOVA with Group (MCI vs. control) and Condition (active vs. rest) as between-subject factors for the stimulus-response curve, which included an additional experimental condition. Our primary parameter of interest was the slope of the sigmoidal input-output curve, which reflects corticospinal excitability. We applied a Bonferroni-adjusted significance threshold to account for multiple comparisons across the stimulus-response parameters.

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