Official title: Estimating the Sensitivity of a Mobile Neuro-cognitive Platform ("BrainE") to Detect Neural Plasticity and Cognitive Enhancements Following Theta-burst Stimulation to Superior Frontal/dACC TMS Stimulation.

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Study Protocol: Participants provided written informed consent for the TMS study protocol approved by the UCSD IRB (#190059). Participants were screened for this study prior to enrollment. Any individuals with a history of seizure disorder; vascular, traumatic, tumoral, infectious or metabolic lesion of the brain; administration of drugs that lower the seizure threshold; implanted or non-removable metallic objects above the neck; implanted devices with electrical circuits (pace-makers, cochlear implants) were excluded from enrollment. In addition, subjects were excluded if they had chronic sleep deprivation or confirmed heavy alcohol use (defined as greater than 5 episodes of binge drinking in the past month with >5 alcohol drink-equivalents per sitting for men (or >4 drink-equivalents per sitting for women). Subjects were also excluded if they reported the use of stimulant drugs in the past month (cocaine, methamphetamines), or if they were pregnant, or had any history of severe cardiovascular disease (i.e. history of transient ischemic attack, heart attack or stroke).

Repetitive Transcranial Magnetic Stimulation (rTMS). We used the FDA-approved Magventure stimulator (MagPro R30) for rTMS delivery. Each participant made two visits for this study, separated by a one-week interval, and each visit lasted up to 2 hours. Participants were provided either the continuous theta burst stimulation (cTBS) or intermittent TBS (iTBS) TMS protocol at each visit. Participants were blinded to the stimulation type, and stimulation order in week 1 or 2 was counterbalanced across subjects. The research staff who performed stimulation were blind to the effects of the cTBS or iTBS protocol, and the data analytics lead and study principal investigator were blind to the identity of the protocol i.e. all data were analyzed with cTBS blinded as stim A and iTBS as stim B. TBS stimulation was delivered to the midline at FCz target location, consistent with the pre-supplementary motor area site for rTMS in superior frontal cortex, which was active in most of our cognitive tasks (Verbruggen et al., 2010). A train of 3 pulses, spaced 20 msec apart (50 Hz stimulation), followed by an inter-train interval of at least 200 msec (5 Hz) was applied either continuously (cTBS), or intermittently (iTBS) with a jitter between trains as has been tested in prior research (Rossi, Hallett, Rossini, Pascual-Leone, et al., 2009; Oberman et al., 2011). In cTBS, bursts of 3 pulses at 50 Hz were applied at a frequency of 5 Hz for 20 sec, total 100 bursts. In iTBS, ten 2 sec periods (10 bursts) of TBS were applied at a rate of 0.1 Hz for a total 100 bursts. Stimulation amplitude was set at 80% of motor threshold individually determined in each participant.

At each rTMS study visit, participants first performed a set of neuro-cognitive assessments (pre-stim), then immediately received either cTBS or iTBS TMS stimulation, then performed the neuro-cognitive assessments again (post-stim). We investigated the sensitivity of the neuro-cognitive assessments to measure brain plasticity in pre-stim versus post-stim comparisons, as a function of the rTMS protocols. Details of the neuro-cognitive assessments are provided in Balasubramani, et al., Mapping Cognitive Brain Functions at Scale. Neuroimage 2021 *in Press* https://doi.org/10.1016/j.neuroimage.2020.117641

Statistical Analysis Plan:
For neural analyses for the primary outcome, we applied a uniform processing pipeline to all EEG data acquired simultaneous to the cognitive tasks. This included: 1) data pre-processing, and 2) cortical source localization of the EEG data filtered within the relevant theta frequency bands.

For the secondary outcome, behavioral data for cognitive assessments were analyzed for signal detection sensitivity, d', computed as z(Hits)-z(False Alarms) (Heeger and Landy, 2009). Task speeds were calculated as log(1/RT); RT is response time acquired in milliseconds then converted to RT in seconds to be used in the log speed calculation. Then, task efficiency was calculated as a product of d' and speed (Barlow et al., 1980; Vandierendonck, 2017), and global task efficiency was the average efficiency across all cognitive tasks.

Both for the primary (neural) and secondary (behavioral) outcome, data were compared across stimulation type (iTBS vs cTBS) using repeated measures analyses of variance (rm-ANOVA) with a within-subject factor of task-type; the Tukey-Kramer method was used for post-hoc testing.