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Abstract Title: TMS-EEG as a measure of cortical hyperexcitability in motor and parietal cortex in Alzheimer's disease: a pilot study

Buss S.S., Passera B., Ross J., Hagan B., Press D., Shafi M.M.

Background: Patients with Alzheimer's disease (AD) have abnormally high cortical excitability, with an increased risk of seizures and epileptiform discharges. Transcranial magnetic stimulation with electroencephalography (TMS-EEG) can noninvasively measure cortical excitability in local brain regions, and has shown increased excitability in motor cortex in AD. However, practical applications of TMS-EEG measures are currently limited by a dearth of data from brain regions involved early-on in AD, such as the parietal cortex. This pilot study investigated the feasibility of using TMS-EEG to compare "Excitability Gain" across multiple brain regions in AD.

Method: Four biomarker-confirmed AD participants (mean age 72, 1 female) and 7 healthy control participants (HC, mean age 68, 3 female) enrolled in this pilot study. Single-pulse TMS stimulation was applied to left primary motor cortex (M1) and inferior parietal cortex (IPL), with 120 pulses given at both 120% and 135% resting motor threshold (RMT). We assessed tolerability of this protocol. TMS-evoked potentials (TEPs) were measured as the average EEG response after a TMS pulse. The percent change in the area under the curve (AUC) of the TEP between the two stimulation intensities was calculated (TEP Gain, %change). To determine a duration of the TEP response at 120% stimulation, a ratio of late (20-225 msec) to early (225-400 msec) AUC was calculated (TEP Ratio). A power calculation for two sample means was performed to determine the number of subjects needed to demonstrate a between-group difference in IPL excitability. As an exploratory aim, the Benton judgement of line orientation, a task involving the parietal lobe, was related to IPL TEP Gain and IPL TEP Ratio using a t-test.

Result: The procedure was well-tolerated; one HC participant complained of a mild positional neck discomfort. In HCs, TEP Gain was 17 (±26) percent in M1, and -4 (±16 SD) percent in IPL. In HC, TEP Ratio was 0.38 (±0.13) in M1 and 0.47 (±0.19) in IPL. In AD participants, TEP Gain was 12 (±33) percent in M1, and 6 (±24) percent in IPL. In AD, TEP Ratio was 0.50 (±0.27) in M1 and 0.53 (±0.21) in IPL. Assuming a SD of 16 for the IPL stimulation, a sample size of 38 in each group would have a >80% power to detect a between-group difference of 15% in TEP Gain with an alpha of 0.05. Exploratory analysis showed a significant relationship between IPL TEP Ratio and Benton judgement of line orientation (p=0.034).

Conclusion: TMS-EEG measures of excitability are feasible in AD participants. A sample size of 38 in each group will be required to test for a between-group difference of cortical excitability in the parietal lobe. TMS-EEG may be a useful tool to measure cortical excitability across multiple brain regions in AD.