

ACCELERATED THETA-BURST STIMULATION TARGETING THE DORSOLATERAL PREFRONTAL CORTEX IN HUNTINGTON'S DISEASE: A PLACEBO-CONTROLLED EEG STUDY

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BACKGROUND: Huntington's disease (HD) is a neurodegenerative disorder leading to motor, cognitive and behavioral impairments (1). Managing neurocognitive symptoms in HD remains challenging, and transcranial magnetic stimulation (TMS) is a promising non-invasive approach (2). Current models suggest that the dorsolateral prefrontal cortex (DLPFC) plays a key role in executive cognitive processes (3), and the EEG-based Stroop task offers a reliable marker of cognitive control. This sham-controlled trial evaluates the effects of accelerated theta-burst repetitive TMS (TB-rTMS) targeting the DLPFC on clinical and EEG-based Stroop measures in HD.

METHODS: Eleven 11 HD patients (stage 1-2, mean age: 49.5±15.9) underwent clinical and neurocognitive assessments, including executive and social control functions evaluation. High-density EEG was recorded during the administration of the cognitive Stroop task, allowing extraction of event-related potentials. Sham and real accelerated TB-rTMS (4 sessions/day for 4 consecutive days) was applied over the left DLPFC. Clinical and neurophysiological assessments were performed at baseline (T0), after sham (T1) and real stimulation (T2), and at 60-day follow (T3).

RESULTS: At T0, patients had a Total Functional Capacity score of 10±2.56 and an Independence Scale score of 81.25±13.56. The Mini-Mental State Examination score was 26.37±2.32. While no changes were observed after sham stimulation, real TB-rTMS induced significant improvements in mood, executive functions, processing speed, and social cognition, with some effects partially persisting at T3 (**Figure 1**). Baseline cognitive status influenced response patterns, while improvements appeared independent of the main demographic or clinical factors. P300 and N400 amplitudes showed slight modulation after real stimulation (T2), persisting at T3, without reaching statistical significance (**Figure. 2**).

MAJOR REFERENCES: 1. Novak MJ, Tabrizi SJ. Huntington's disease: clinical presentation and treatment. *Int Rev Neurobiol.* 2011;98:297-323. doi: 10.1016/B978-0-12-381328-2.00013-4. PMID: 21907093. 2. Sharbafshahr M, Cirillo G, Esposito F, Tedeschi G, Trajst F. Harnessing Brain Plasticity: The Therapeutic Power of Repetitive Transcranial Magnetic Stimulation (rTMS) and Theta Burst Stimulation (TBS) in Neurotransmitter Modulation, Receptor Dynamics, and Neuroimaging for Neurological Innovations. *Biomedicines.* 2024 Nov 1;12(11):2506. doi: 10.3390/biomedicines12112506. PMID: 39595072; PMCID: PMC11592033. 3. Weissman DH, Perkins AS, Woldorff MG. Cognitive control in social situations: a role for the dorsolateral prefrontal cortex. *Neuroimage.* 2008 Apr 1;40(2):955-962. doi: 10.1016/j.neuroimage.2007.12.021. *Epub* 2007 Dec 23. PMID: 18234518; PMCID: PMC252237.

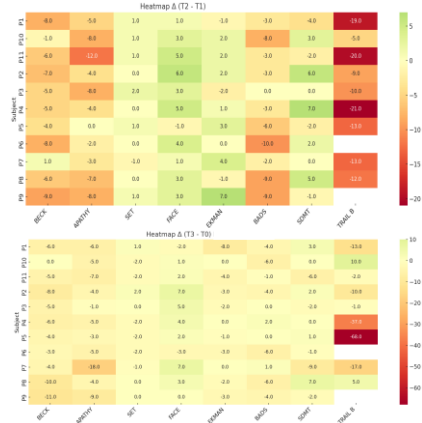


FIGURE 1: Neurocognitive results after TB-rTMS (T2-T1, upper part) and at 60-day follow (T3-T0, lower part) in patients with Huntington's disease (HD). Note that at T2, BECK, APATHY, BADS, SDMT and EKMAN scores significantly improved, with some effects partially persisting at follow-up (T3).

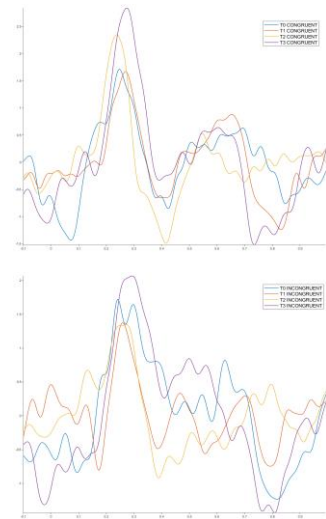


FIGURE 2: Upper panel: Grand average of event-related responses in the frontal regions during congruent (upper part) and incongruent (lower part) Stroop stimuli in Huntington's disease (HD) patients at T0, T1 (after sham aTB-rTMS), T2 (after real aTB-rTMS), and T3 (60-day follow).

DISCUSSION AND CONCLUSIONS: Accelerated TB-rTMS over the left DLPFC appears feasible and well-tolerated in HD. Preliminary findings suggest potential effects on mood, executive, and social cognitive functions, possibly reflecting neuromodulatory influences on fronto-striatal circuits involved in neurocognitive processes.