Remediating depressive cognition using a novel brain stimulation device

Summary

Depression is a leading cause of disability worldwide, with a third of patients not responding to traditional treatments, i.e., medication/psychotherapy. Transcranial magnetic stimulation (TMS) has shown great potential for treating those with treatment resistant depression (TRD). In particular, Intermittent theta burst stimulation (iTBS) is a clinically used form that can be delivered in ~3 minutes (compared to a conventional 37-minute session), with intensive multi-session approaches showing high levels of effectiveness. However, response to TMS varies markedly between individuals, and conventional clinical devices constrain stimulation pulse shape, limiting optimisation of how stimulation engages prefrontal circuits.

This project tested whether pulse shape can further optimise stimulation effectiveness of iTBS, thus developing a more effective treatment. Using a novel prototype programmable TMS device, we compared monophasic versus biphasic iTBS targeted to an individually localised left dorsolateral prefrontal cortex (dlPFC) site defined by resting-state connectivity. Participants completed cognitive tasks while ECG was recorded during stimulation to quantify heart–brain coupling (HBC)**.** Preliminary results suggest waveform-dependent differences in cognitive markers, HBC, and tolerability.

Aims

- Test whether iTBS to left dlPFC (vs sham) alters markers of cognitive function**.**
- Test whether monophasic iTBS produces stronger cognitive effects than biphasic iTBS**.**
- Test whether iTBS to left dlPFC (vs sham) induces heart–brain coupling (HBC)**.**
- Test whether monophasic iTBS induces stronger HBC than biphasic iTBS**.**

Methods overview

N = 40 participants with low mood were recruited. The study used a single-blind, sham-controlled, within-subject 2×2 design**:** pulse shape (monophasic vs biphasic) × stimulation type (real vs sham). Each participant completed two sessions (≥1 week apart): one session with monophasic iTBS and one with biphasic iTBS (order counterbalanced). Within each session, participants received real and sham iTBS in counterbalanced order, separated by a **~**1-hour washout.

Targets were individualised using structural + resting-state MRI**,** defining the left dlPFC site most anti-correlated with the sgACC. Motor thresholding was completed in a separate familiarisation/thresholding visit, including waveform-specific RMTs. iTBS was delivered at 70% RMT (600 pulses, ~3 minutes). Immediately after stimulation, participants completed preregistered cognitive tasks: facial emotional recognition task (FERT), Oxford memory task (OMT), and a digit symbol substitution task (DSST). ECG was recorded during stimulation to quantify HBC. At the end of each session, an intensity sweep (stepped bursts up to ~120% RMT) was conducted to quantify HBC at different intensities.

Results

Across preregistered outcomes, both waveforms show patterns consistent with improved performance on DSST and OMT markers relative to sham. With no clear overall effect on primary FERT measures. Against our predictions in some more sensitive measures (i.e., Imprecision) the effects appear more pronounced for biphasic than monophasic (figure) 1.

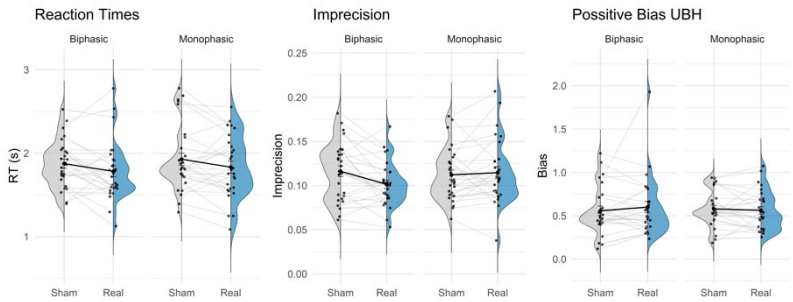

Figure 1: Paired Raincloud plots for performance on cognitive tasks.

The HBC data show clear coupling in the biphasic condition (evidenced by entrainment at .1Hz), but this was weaker in the monophasic condition (figure 2), suggesting that at the same relative intensity monophasic iTBS is having a smaller effect on physiological measures. However, intensity sweep data indicate that HBC becomes more detectable at higher monophasic stimulation intensities, suggesting waveform-dependent differences in effective dosing at dlPFC. Additionally, participants generally reported monophasic iTBS as more tolerable than biphasic stimulation and tolerated higher intensities during monophasic sweeps.

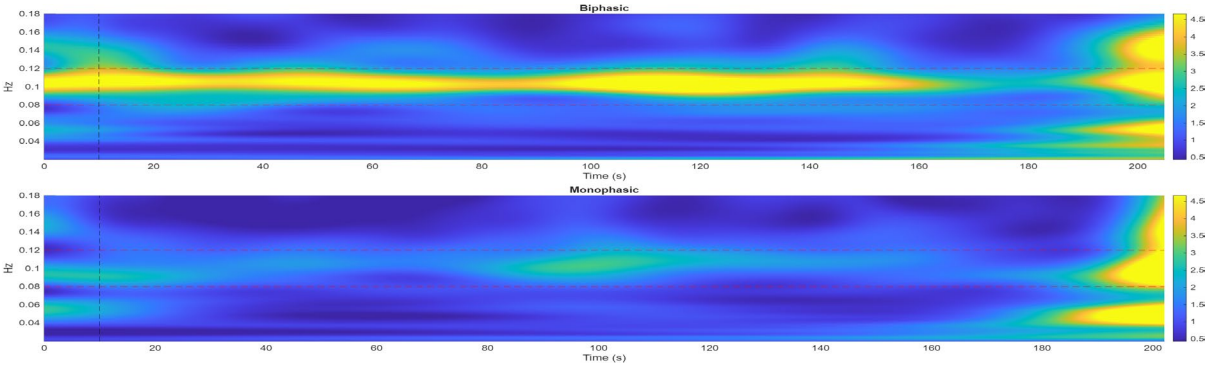

Figure 2: Time-frequency plot showing HBC (increased power at .1hz) during iTBS stimulation

Interpretation

Both monophasic and biphasic iTBS modulated cognitive and physiological markers, with larger effects for conventional biphasic iTBS compared to our newer experimental monophasic form of iTBS. However, HBC and tolerability data indicate that monophasic iTBS (if delivered at a higher intensity) is likely to yield comparable cognitive and physiological effects while also expanding access to iTBS, owing to lower pain and discomfort ratings. This has practical significance as low tolerability of conventional biphasic iTBS limits its clinical viability for depressed patients.

Impact and outcomes

This is the first study to compare the relative efficacy of novel monophasic iTBS versus conventional biphasic iTBS on cognitive and physiological markers. The overall picture suggests that monophasic iTBS was under-dosed and hence less effective – a clear study outcome. However, the data further suggest that increasing stimulation intensity should yield improved efficacy and tolerability. We are currently investigating this prediction in a follow-up experiment.

The study has contributed to furthering the Neuromod+ network aims of: **collaboration** (our team: cognitive neuroscientists, engineers, industry); **involvement** (lived experience experts with depression advised on our recruitment processes); **translation** (testing the potential of monophasic iTBS – higher intensities needed for prefrontal than motor cortex) and **mechanism** (testing the cognitive and physiological mechanisms of action of prefrontal iTBS).