

A naturalistic trial comparing the efficacy of uni- and bi-lateral theta burst stimulation in treating major depression, a study protocol



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BACKGROUND

- Repetitive transcranial magnetic stimulation (rTMS) is recognized as a first-line treatment for major depressive disorder (MDD)^[1].
- Technological advancements have led to theta burst stimulation (TBS), which reduces treatment time 15 fold, whilst maintaining clinical efficacy^[2,3].
- It remains to be determined if TBS is more efficient when applied to one or both prefrontal hemispheres, i.e. unilateral, left dorsolateral prefrontal cortex (DLPFC) and bilateral, left and right DLPFC.
- Very few studies have investigated rTMS maintenance protocols.
- TMS and electroencephalography (TMS-EEG) can be used to track excitability changes following TBS^[4,5].

OBJECTIVES

- Compare efficacy of bilateral and unilateral TBS.
- Investigate if baseline capacity for plasticity, assessed with TMS-EEG, is predictive of the clinical response to TBS.
- Compare efficacy of a fixed versus a flexible schedule of maintenance over 6 months.



Figure 1. TBS Treatment

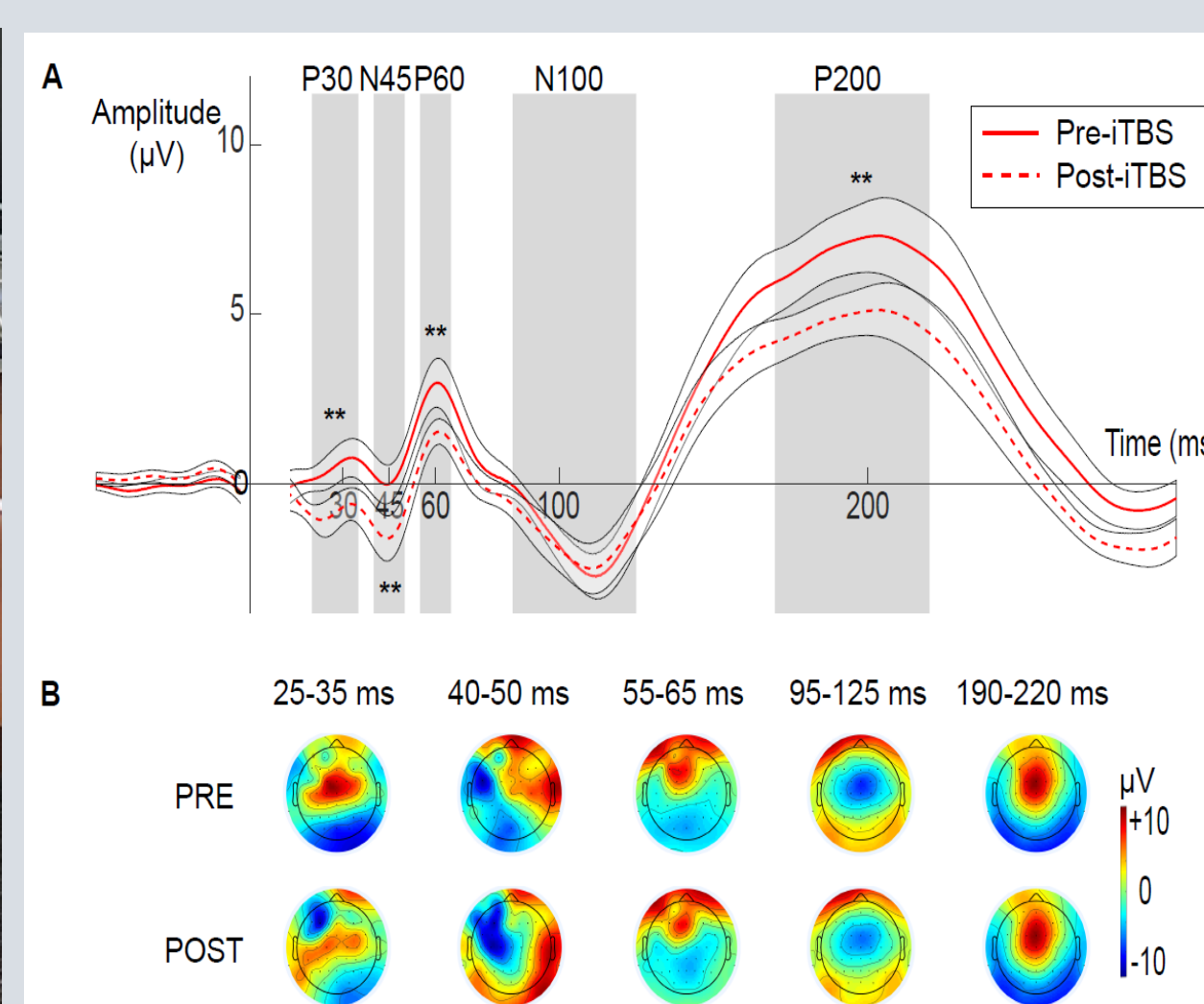


Figure 2. Example of TEPs

REFERENCES

1. Lefaucheur et al. (2020) Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): An update (2014-2018). Clinical neurophysiology.
2. Huang YZ, Rothwell JC. (2005) The effect of short-duration bursts of high-frequency, low-intensity transcranial magnetic stimulation on the human motor cortex. Clinical neurophysiology.
3. Blumberger et al. (2018). Effectiveness of theta burst stimulation versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a randomized non-inferiority trial. Lancet
4. Tremblay et al. (2019) Clinical utility and prospective of TMS-EEG. Clinical Neurophysiology.
5. Ilmoniemi, R. J., & Kicić, D. (2010). Methodology for combined TMS and EEG. Brain Topography.

METHOD

- Participants : 256, male and female, 18+ with primary MDD diagnosis.
- Main inclusion criteria: No symptom improvement after ≥ 1 but ≤ 7 adequate antidepressant trials in current depressive episode.
- Treatment: 5 days per week over 4 to 6 weeks with a Magpro X100 and active/sham B65 cooled-coil.
- Left DLPFC: standard intermittent TBS (iTBS), 80% AMT, 190 sec
- Right DLPFC: standard continuous TBS (cTBS), 80% AMT, 40 sec
- Double-blinded study design:
 - Unilateral = active iTBS followed by sham cTBS
 - Bilateral = active iTBS followed by active cTBS
- Main outcome measures: HRSD-17, MADRS
- Neuronavigation (Brainsight, Rogue Research inc.): Coordinates (x, y, z: +/-38, 44, 26)
- If response or remission is achieved, participants are randomized into either a fixed or flexible 6-month maintenance phase.

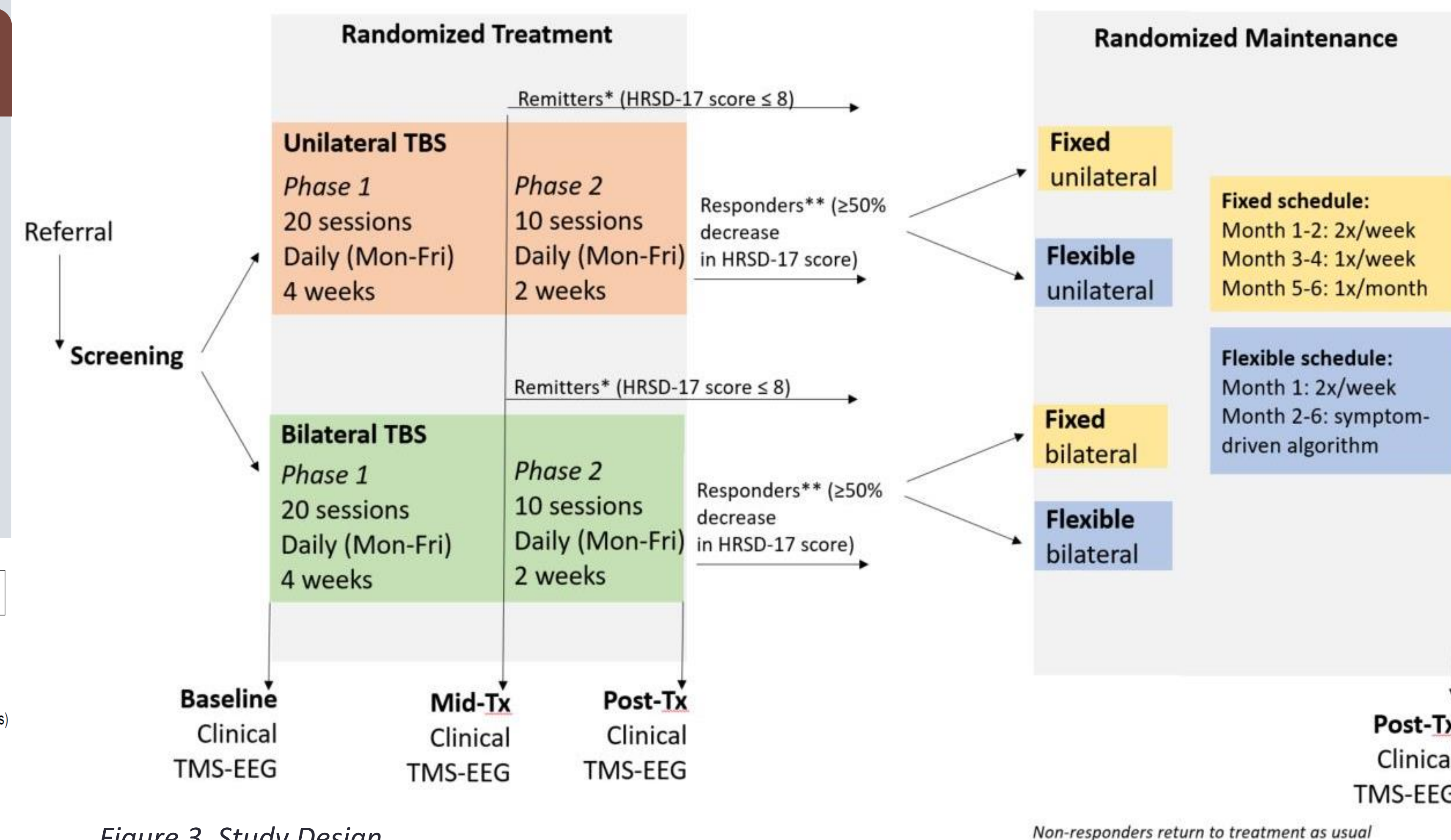


Figure 3. Study Design

DATA ANALYSIS

- EEG data is analyzed using EEGLAB and Matlab (Mathworks Inc)
- Clinical scores and neurophysiological measures will be analyzed using two-way ANOVAs for repeated measures.
- Prediction of response is assessed using correlational analyses and logistic regression models.
- Categorical outcomes (response/remission rates) are examined using Chi-Squared tests.

TMS-EEG

TMS-EEG: a biomarker approach to clinical trials

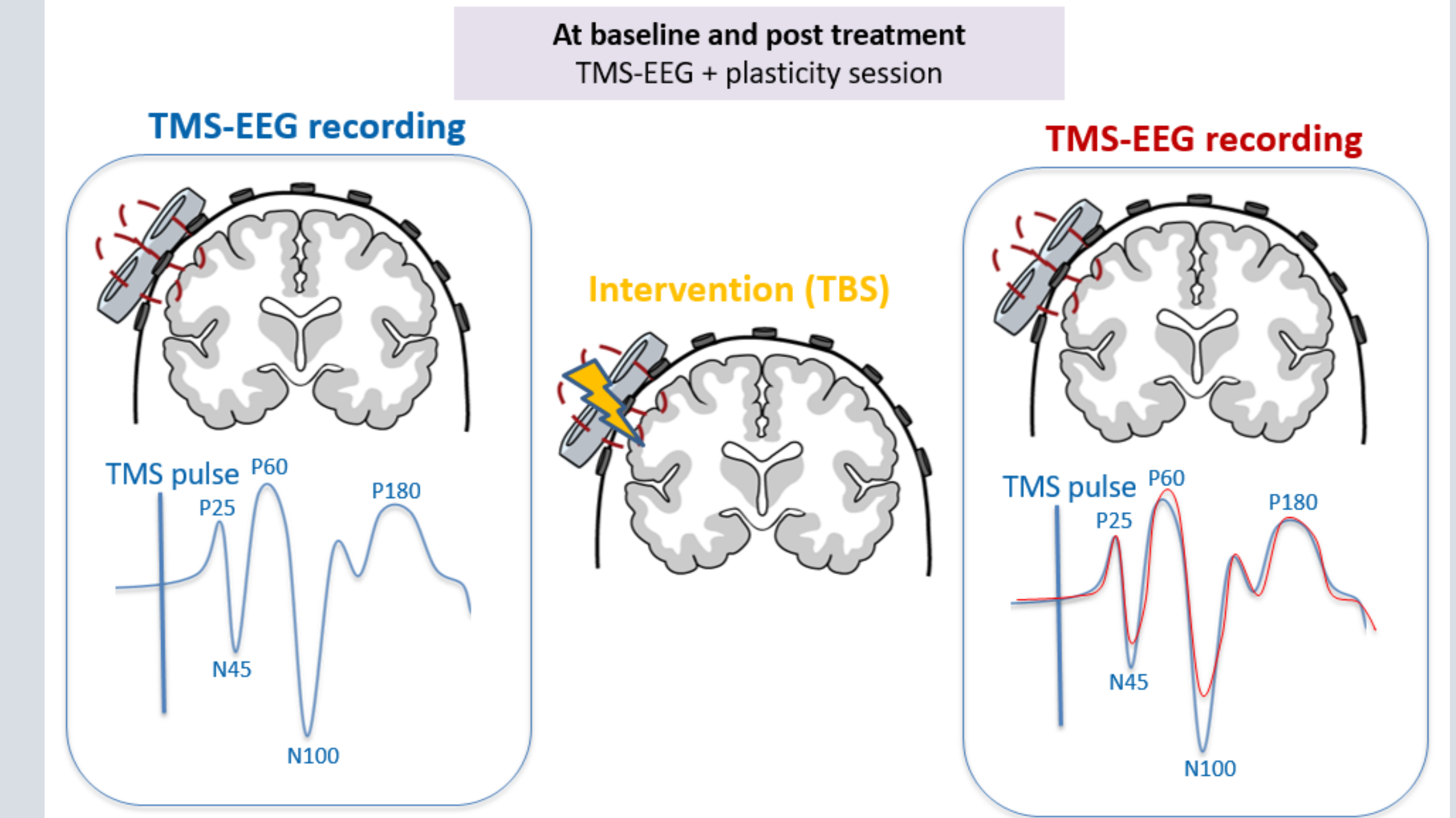


Figure 4. TMS-EEG biomarker approach

- TMS-EEG recordings during the first and last TBS sessions of the treatment phase
- 64 channels BrainCap with BrainAmp DC amplifier (BrainProducts, Gmb)
- Recordings pre and post iTBS: 80 single pulse at 120% of RMT, to the left and right DLPFC

Figure 7. TMS-EEG

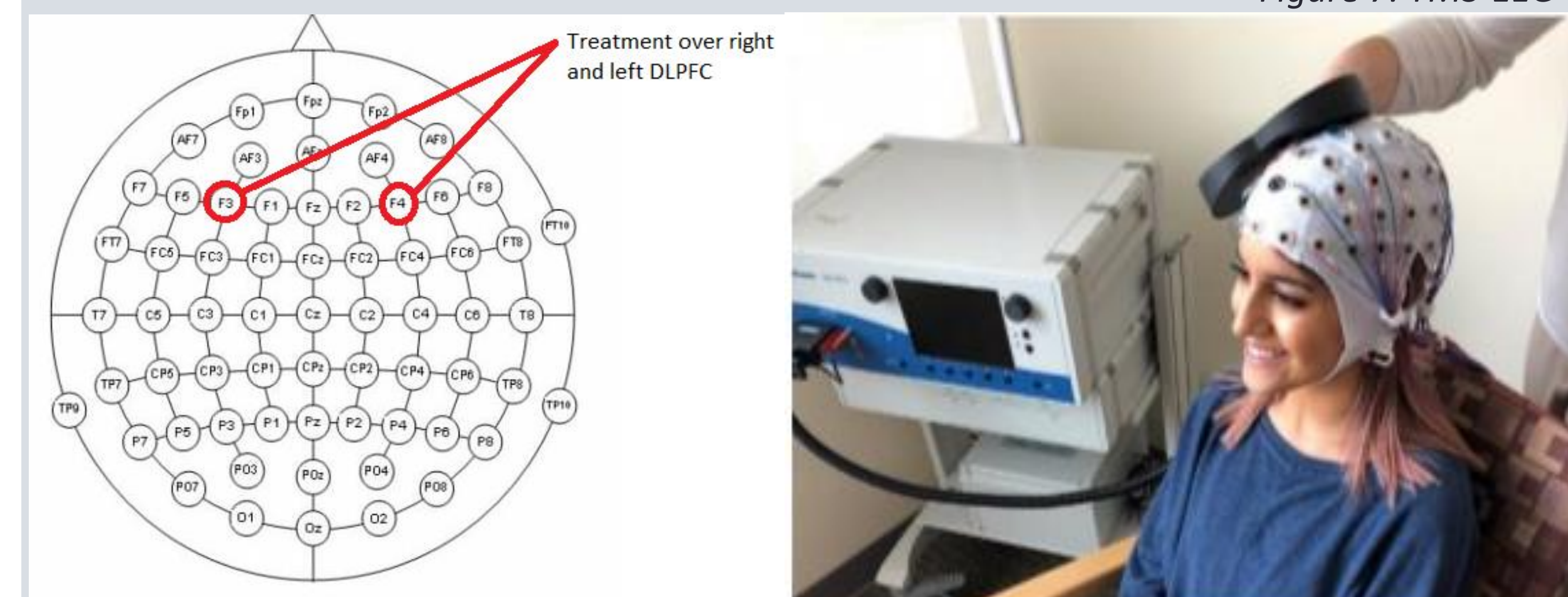


Figure 6. Areas of stimulation during TMS-EEG at Coordinates (x, y, z: +/-38, 44, 26)

RELEVANCE AND IMPACT

- First study comparing unilateral and bilateral TBS in a largescale naturalistic setting.
- Could help elucidate the mechanisms of action of TBS in the DLPFC
- Researching predictors of response could be beneficial in establishing bespoke protocols for individual brain response, increase efficacy rates and save time and money.
- Establish optimal TMS maintenance schedules.