

## **Interventional Study Protocol**

### **Official Title:**

Probing homeostatic plasticity with priming theta-burst stimulation of the dorsolateral prefrontal cortex

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## **2) Brief Summary:**

Priming stimulation is a highly promising tool to boost the beneficial effects of therapeutic repetitive transcranial magnetic stimulation (rTMS) in psychiatry. The potentiating effects of priming stimulation, however, depend on the time interval between the priming and the test stimulation. Although it is known that too short and too long intervals have no effects, systematic studies that identify the time needed to maximize efficacy have not yet been done. Thus, there is a need for studies to investigate the effects of priming stimulation in order to fully utilize the potential benefits and advantages of this promising new rTMS protocol. Here we propose a research program that will systematically investigate the neuromodulatory process underlying priming stimulation to enhance metaplasticity in the left dorsolateral prefrontal cortex (DLPFC) – one of the main targets for therapeutic rTMS – in individuals with subclinical depression.

The brain is a highly plastic organ and its activity can be influenced using rTMS. At the same time, the brain also has a mechanism – called homeostatic metaplasticity – which counteracts extreme plastic changes. Homeostatic metaplasticity therefore can limit the beneficial effects of brain stimulation interventions. However, priming stimulation protocols that include both a priming and a test stimulation session may utilize homeostatic metaplasticity to increase the beneficial effects of brain stimulation, although the optimal treatment parameters for priming are not known. Moreover, little is known about homeostatic metaplasticity in the DLPFC, an area that is particularly relevant for psychiatric conditions given its role in the top-down control of emotions. Here, we will systematically study metaplasticity using priming theta-burst stimulation (TBS), a potent form of rTMS in the left DLPFC. The optimized stimulation intensity will be investigated by a pilot study. Changes in blood oxygenation that signal brain activity changes will be assessed using functional near-infrared spectroscopy (fNIRS) at rest and during engagement in several cognitive tasks. The findings from this study will (1) elucidate the optimal time interval between priming and test stimulation; (2) elucidate the influence of priming TBS on emotion discrimination as well as executive function and its underlying brain activity in subclinical depression; and (3) validate homeostatic metaplasticity in the left DLPFC.

Subclinical depression has serious consequences for the quality of life and is associated with considerable economic costs but adequate treatments are poorly explored. Therefore, by systematically testing priming stimulation and investigating its underlying neural processes, this study will pave the way towards developing adequate antidepressant treatments that will reduce personal suffering, reduce costs and occupational disability.

**3) Detailed Description:** Please refer to the ECS proposal

**4) Primary Disease or Condition being studied in the trial, or the focus of the study:**  
Subclinical Depression

**5) Keywords:** Priming Stimulation, Theta-Burst Stimulation, Functional NIRS, Emotion Discrimination, Subclinical depression

**6) Primary Purpose:** Optimization of stimulation parameters for a priming stimulation protocol

**7) Study Phase:** N/A

**8) Intervention Study Model:** Parallel, sham-control

**9) Model Description:** (Objectives)

The proposed research has two primary objectives.

The first objective is to understand the effects of priming stimulation timing of the left DLPFC using fNIRS at rest. The time window between priming cTBS and test iTBS will be either 0, 10, or 20 minutes. We hypothesize that 0 minutes will eliminate the effect of the test iTBS, whereas 10 minutes will potentiate it; 20 minutes will have no effect (i.e., result in no difference, relative to sham priming).

The second objective is to evaluate the effects of priming stimulation in the context of facial emotion processing and executive function in subclinical depression. Previous evidence indicates that DLPFC stimulation modulates affective processing on the neural and behavioral level. We hypothesize that optimal priming stimulation will affect reaction times in an emotion-specific way and will reduce the negative bias observed in subclinical depression.

**10) Interventions:**

Number of Arms: 4

Allocation: Randomized

Enrollment Type: Anticipated

Number of Subjects: 80 participants with subclinical depression

Arm 1: Control

Arm Title: Priming sham TBS – followed by iTBS after an ISI of 0 minutes

Arm Description: self-explanatory, see Arm Title

Arm 2: Experimental

Arm Title: Priming cTBS – followed by iTBS after an ISI of 0 minutes

Arm Description: self-explanatory, see Arm Title

Arm 3: Experimental

Arm Title: Priming cTBS – followed by iTBS after an ISI of 10 minutes

Arm Description: self-explanatory, see Arm Title

Arm 4: Experimental

Arm Title: Priming cTBS – followed by iTBS after an ISI of 20 minutes

Arm Description: self-explanatory, see Arm Title

## **11) Outcome Measures:**

### **Outcome 1: Primary Outcome Measure**

Title: HbO during rest before and after stimulation (raw values and change scores)

Description: Prefrontal neural activity will be measured using fNIRS before (baseline) and about 10-15 minutes after the stimulation (delay will be recorded). TBS-induced blood oxygen changes (HbO) at rest will be evaluated in the frontal cortex

Time Frame: baseline, post intervention

### **Outcome 2: Secondary Outcome Measure**

Title: HbO during which participants perform cognitive tasks (e.g., emotional stroop task, verbal fluency task, emotion discrimination task )

Description: Prefrontal neural activity will be measured using fNIRS before (baseline) and about 10-15 minutes after the stimulation (delay will be recorded). TBS-induced blood oxygen changes (HbO) during participants perform the cognitive tasks will be evaluated in the frontal cortex

### **Outcome 3: Secondary Outcome Measure**

Title: Behavioral measures including reaction times and recognition accuracy

Description: Reaction times and accuracy during the cognitive tasks will be evaluated before and after stimulation

## **12) Eligibility:**

Sex (all)

Eligibility Criteria:

Inclusion: : (1) age 18-35, (2) education level of primary six or above, (3) right-handedness, (4) normal or corrected-to-normal vision, (5) being able to understand the verbal instructions, (6) willingness to sign the informed consent form.

Exclusion: (1) a history of seizures, (2) current or past psychiatric disorders, (3) current or past severe internal or neurological illness, (4) ferromagnetic implants <20cm from the head, cardiac pacemaker, deep brain stimulation and other common TMS exclusion criteria, (5) history of substance dependence or abuse within the last 3 months, (6) intake of any medication known to affect the excitation threshold (i.e., benzodiazepines, anticonvulsants).

## **13) Statistical Analysis Plan:**

fNIRS data analysis will follow the standard processing steps. This includes spatial registration (recording of standard cranial landmarks nasion, inion, left and right ear, and the 3D locations of the fNIRS probes); transformation to MNI space [39]; band-pass

filtering for motion artifact removal; and estimation of the hemodynamic response function using GLM, as implemented in the NIRS Toolbox for MATLAB. Comparisons between baseline and task HbO will reveal task-related de/activations, corrected for multiple comparisons (52 channels). Average HbO changes will then be determined for each channel and each measurement and entered into second-level analysis. Similarly, means of HbO for pre and post-stimulation will be entered into second-level analysis.

A t-test between pre- and post-stimulation in condition 1 will be performed to test hypothesis 1. Hypothesis 1 will be supported if there is a significant increase in prefrontal HbO after stimulation.

A t-test between condition 2 and 1 using change scores will be performed to test hypothesis 2. Hypothesis 2 will be supported if there is a significant stronger change in HbO in condition 1 compared to condition 2

A t-test between condition 3 and 1 using change scores will be performed to test hypothesis 3. Hypothesis 3 will be supported if there is a significant stronger change in HbO in condition 3 compared to condition 1.

A t-test between pre- and post-stimulation in condition 4 and between change scores of condition 1 and 4 will be performed to test hypothesis 4. Hypothesis 4 will be supported if there is a significant increase in prefrontal HbO after stimulation, but no significant difference in change scores between condition 1 and 4.

Regarding the three exploratory hypotheses about participants' behavior (reaction times, hits and misses) and HbO changes during cognitive tasks, linear mixed models will be conducted to determine differences between conditions, followed by post-hoc pairwise comparisons. Here, a three-way interaction between time, condition and emotion will be evaluated and followed by post-hoc two-way interactions and pairwise comparisons.

Hypothesis E1 will be supported if there is a significant change in HbO and/or behavioral measures in condition 1 in some (e.g. sad) but not other emotions (e.g. happy) after stimulation (following a post-hoc 2-way interaction between time and emotion).

Hypothesis E2 will be supported if there is a significant interaction between time, emotion and conditions 2 and 1.

Hypothesis E3 will be supported if there is a significant interaction between time, emotion and conditions 3 and 1.

Hypothesis E4 will be supported if there is a significant change in condition 4 in some (e.g. sad) but not other emotions (e.g. happy) after stimulation (following a post-hoc 2-way interaction between time and emotion).

Finally, two t-tests comparing ERA- recognition accuracies between subclinically depressed and control participants and between pre and post stimulation in the sample of subclinically depressed participants will be performed in order to test hypotheses E5 and E6, respectively.

Hypothesis E5 will be supported if recognition accuracy is reduced in participants with subclinical depression compared to the control sample.

Hypothesis E6 will be supported if recognition accuracy will be increased after stimulation compared to baseline in participants with subclinical depression.

Behavioral data will be analyzed using the IBM SPSS software (<http://www-01.ibm.com/software/analytics/spss/>). The alpha level will be set at 0.05, adjusted for multiple comparisons using the Bonferroni-Holm procedure. For GLM, post-hoc pairwise comparisons will be corrected using Fisher least significant difference procedure in accordance with the closed test principle, i.e., post hoc comparisons will be declared nonsignificant if the global p value of the main- or interaction effect is nonsignificant, but carried out without further correction in case of a significant global effect.