Effects of Connectivity-based rTMS and State-Dependency on Amygdala Activation

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Study Protocol

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This blinded, sham-controlled trial will feature a between-subject design with active or sham rTMS applied over the medial prefrontal cortex, while subjects will be viewing fearful video-clips to engage the stimulated network. Study experimental design is illustrated in **Figure 1A**. Twenty five healthy subjects (18 - 35 years old) will participate. In the initial session, which will last about 2 hours, participants will be consented and screened for eligibility. Resting motor threshold (rMT), defined as the TMS pulse intensity producing on average a 50µV peak-to-peak amplitude motor evoked potential, will be assessed using a maximum likelihood method. A 1-hour MRI session that includes a T1-weighted anatomical image and BOLD signal acquisition during passive viewing of fearful and neutral faces in an event-related design, will be performed. Psychophysiological interaction (PPI) or diffusions weighted analyses will be conducted by selecting a seed in the amygdala and defining the spot within the mPFC with the strongest task-related correlation with amygdala activation, or the strongest structural connection with amygdala (**Figure 1B**).

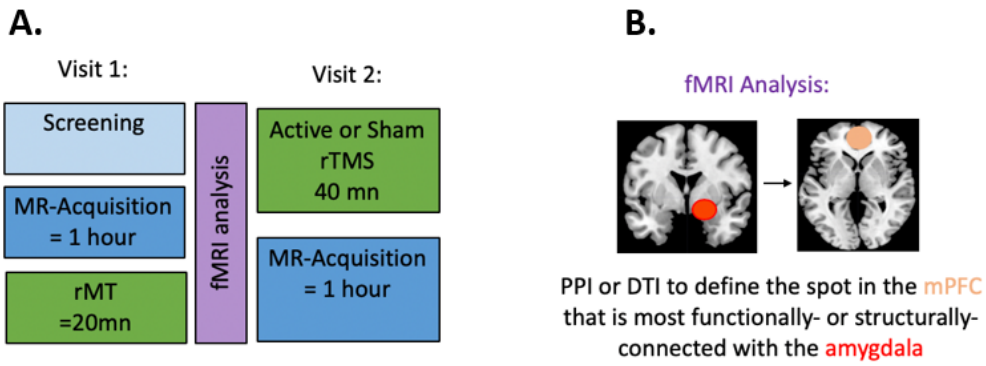

Figure 1*: A) Illustration of the experiment design. B) Illustration of the psychophysiological interaction (PPI) analysis using the right amygdala as the seed to define a TMS target in the medial prefrontal cortex.*

During the second visit, participants will receive active or sham rTMS, counterbalanced across sessions between subjects. 5Hz rTMS will be applied over the mPFC at an intensity up to 120% rMT, replicating parameters used in a promising recent PTSD study. The optimal coil placement during stimulation will be controlled by a neuronavigation system. An electrical sham coil that produces the same auditory and somatosensory stimulations, without a significant magnetic field, will be used as an active control. Participants will view fearful video-clips during rTMS to engage amygdala activation, which we hypothesize will lead to a stronger rTMS effect. Heart rate variability and skin galvanic response will be acquired with the BioPack system during rTMS and will be analyzed as moderators of rTMS efficacy.

To evaluate rTMS-induced changes, MRI will be acquired before and after rTMS, with the acquisition of anatomical scans, resting-state, and task-related functional connectivity, as well as diffusion tensor imaging. These acquisitions will be used to evaluate target engagement within the amygdala and its connectivity with the prefrontal cortex.

Subject Screening:

Twenty-five healthy subjects (18 - 35 years old) will be recruited from the community (to get 19 completers). At the beginning of their first visit to BIAC, they will be screened for the study with a physical examination, the MINI, a handedness questionnaire, and a urine test. If they pass the screening procedure, they will have a short session of TMS (about 0.5 hour), in order to acclimate them to TMS and to obtain right or left hand resting motor thresholds for future dosing of rTMS.

Resting Motor Threshold Determination:

All procedures will occur in Duke Brain Imaging and Analysis Center (BIAC). Resting motor threshold (rMT) is defined as the TMS pulse intensity producing on average a 50μV peak-to-peak amplitude motor evoked potential, will be assessed using a maximum likelihood method. rMT is the standard in the field for determining the intensity of rTMS for each individual to reduce seizure risk. The motor evoked potentials (MEP) for the contralateral first dorsal interosseus (FDI) will be measured with EMG. The scalp region producing the largest amplitude MEP will be identified. At that scalp location, the lowest TMS intensity able to elicit 5 MEP's of ≥50μV in peak-to-peak amplitude will be determined, using a using a maximum likelihood estimator (TMS Motor Threshold Assessment Tool, MTAT 2.0, http://www.clinicalresearcher.org/software.html). rMT will be determined for one or both hemispheres with the muscle at rest (verified by baseline EMG). Individual MT will be used to determine the intensity of stimulation for each individual, as recommended by safety guidelines.

MRI/fMRI Procedure: Localizer:

At BIAC, after obtaining a T1-weighted anatomical image, fMRI data will be acquired during passive viewing of fearful and neutral faces in an event-related design. Stimuli will be back-projected onto a screen located at the head of the MRI bed using an LCD projector. Subjects will view the screen via a mirror system located in the head coil. Task onset will be electronically synchronized with the MRI acquisition computer. Task administration will be computer controlled. The scanning session will take about 1 hr.

Application of rTMS During Fearful video-clips viewing

rTMS will be applied out of the scanner. Subjects will be seated comfortably in a chair, facing a computer screen positioned in front of the subject for visual stimulus presentation. Earplugs will be worn to protect hearing. The participant's head will be held steady by a frame with a chin rest and the rTMS coil holder frame. A figure-of-eight magnetic coil will be placed on the scalp and held in place with a coil fixing system supplied by MagVenture. This will be paired with a neuronavigation system (BrainSight) which provides precise fMRI-guided rTMS coil placement for basic, translational, and clinical applications of rTMS. The neuronavigation system enables to the coil to be placed at precise cortical targets (the spot within the mPFC showing the strongest task-related correlation with amygdala activation, obtained from the first visit) on the individual’s 3-dimensionally rendered brain MRI with less than one millimeter error, and enables to dynamically move the coil to account for slight head movements.

5Hz rTMS will be applied at an intensity up to 120% rMT, stimulation will be applied during 4 seconds separated by 12 seconds of inter-train interval. Sham rTMS will be administered with a sham coil equipped with shielding to block magnetic field output but retain the auditory and some of the tactile aspects of active stimulation. rTMS administration will be controlled by an external computer and will be

time-locked relative to the presentation of fearful video-clips. Heart rate variability and skin galvanic response acquisition will be acquired with a BioPack system during rTMS application and will be analyzed as moderators of rTMS efficacy.

MRI/fMRI Procedure: Evaluation of rTMS-induced changes:

To evaluate rTMS-induced changes, MRI will be acquired before and after rTMS, with the acquisition of anatomical scans, resting-state, and task-related functional connectivity, as well as diffusion tensor imaging. These acquisitions will be used to evaluate target engagement within the amygdala and its connectivity with the prefrontal cortex.

Side effects monitoring:

Subjects' side-effects will be monitored closely. An rTMS side effect rating scale will be administered at the end of each session. Subjects are instructed during the consent process and during the rTMS sessions about all known side effects. They are further instructed during consenting and additionally at the conclusion of the rTMS session to contact the principal investigator or study physician with any questions or concerns (including those that may arise after the experimental session has ended).