Unveiling the neural mechanism of ASD by brain stimulation

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Autism Spectrum Disorder (ASD) are a group of behaviorally-defined neurodevelopmental disorders. They are usually characterized by impairments in social communication, restricted interests and repetitive behaviours. There exist various theories, but mainly the ASD has found to be rooted from both the cognitive neural network (prefrontal cortex, superior temporal gyrus and anterior cingulate cortex) and the affective network (insula and the sub-cortical areas).

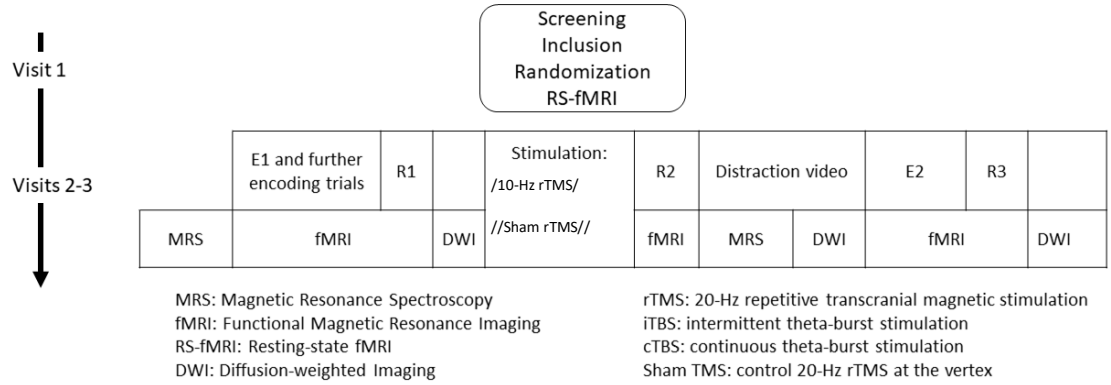
Transcranial magnetic stimulation (TMS) is a promising, tool for the study and potential treatment of ASD [1]. Recent studies suggest that TMS measures provide rapid and noninvasive pathophysiological ASD biomarkers. Furthermore, repetitive TMS (rTMS) may represent a novel treatment strategy for reducing some of the core and associated ASD symptoms [2]. Nevertheless, the exact mechanism of action on ASD effect of rTMS in the cognitive neuroscience aspect remains unknown. Specifically, we would like to revealing how the cognitive ToM and affective ToM network are affected in different interventions of TMS.

Considering the effect of TMS include but are not limited to: (1) the strengthening or weakening of brain regions/networks that are associated with a specific dysfunction using excitatory and inhibitory rTMS, (2) the targeting of brain oscillations in order to entrain natural oscillations or to modulate phase-, amplitude or frequency and thereby rectifying aberrant endogenous frequencies, (3) the remodeling of neural representations by opening a time window of increased neural plasticity. Finding out the explanations can not only discover the mechanisms of TMS intervention, but also help us to understand the neurological cause of ASD at a macroscopic scale.

The on-going study is divided into two parts. **At study 1**, sixty right-handed healthy participants dialogized with ASD will undergo several hours of training to memorize a set of 100 face-word associations (Encoding sessions, E1). After successful memory consolidation and acquisition (99% success rate of recalls at R1), participants undergo a first stimulation session in which they will receive 30 minutes of High Frequency (HF) of rTMS (n=20) of the left lateral parietal cortex (lPC). The lPC target will be individually defined based on the highest functional connectivity with the hippocampus using functional magnetic resonance imaging (fMRI). Recall capacity will be evaluated directly after stimulation (R2). After a pause of several minutes (distraction video) participants will then undergo a new encoding session (E2), consisting of new combinations of associations using a subsample of the same set of stimuli as in E1. This is followed by an evaluation of their recall capacity for the newly acquired combinations (R3). Participants will perform the same procedure again after a wash-out of one week, whereby either active stimulation or sham stimulation (vertex) will be delivered on the first or second visit in a counterbalanced cross-over design.

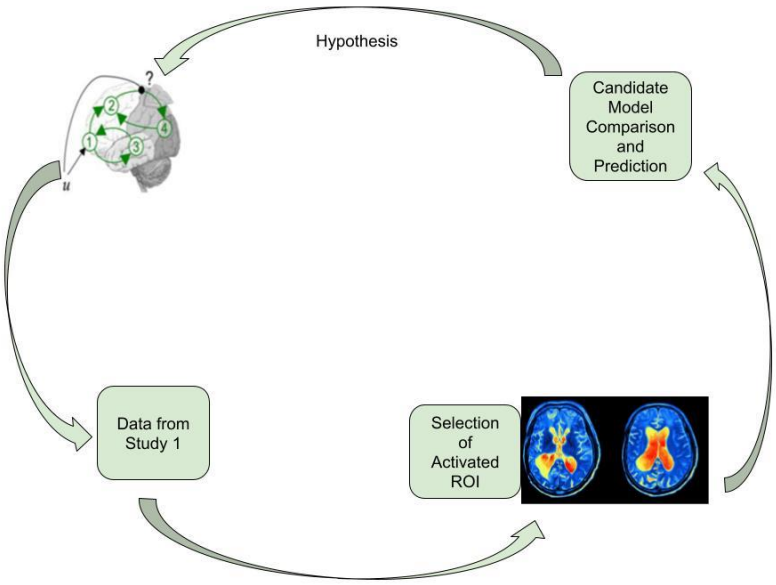
In addition to recall performance, we will evaluate the effects of stimulation on brain structure and function by means of a variety of MRI sequences before, during and after learning

and recall trials, see Figure. Outcome variables include, but are not limited to: classical BOLD contrast changes, functional and structural connectivity changes, neurochemical changes (glutamate, GABA), as well as diffusion-weighted imaging indices.



In study 2, we aim to model the impact of TMS on the inter-regional dynamics of the affective/cognitive network. There has been much focus on the neuromodulatory effect of TMS on the specific region that is being stimulated [3,4]. However, in the brain each region does not function as an isolated entity, but instead each region is connected to other regions and function in a concerted manner. How exactly does the excitation of an individual brain region would also modulate the inter-regional connection in a whole-brain level is poorly understood. This needs to be done by estimating the statistical dependencies between regions using Dynamic Causal Model (DCM) [5]. Using the fMRI data obtained from study 1, this study will identify the functional integration as a macroscale network by constructing a graphical model.

In sum, we hypothesize that HF rTMS compared to sham stimulation will open a time window of increased response variability and loosening of neural associations, accompanied by respective neurofunctional, structural and neurochemical changes. Hence, HF rTMS will increase recall capacity of the newly learned associations due to reduced proactive interference. The resulting DCM model will also shed light in building a robotic model for ASD.



[1] Oberman, Lindsay M., et al. "Transcranial magnetic stimulation in autism spectrum disorder: challenges, promise, and roadmap for future research." Autism Research 9.2 (2016): 184-203.

[2] Casanova, Manuel, et al. "Repetitive transcranial magnetic stimulation (RTMS) modulates event-related potential (ERP) indices of attention in autism." Translational neuroscience 3.2 (2012): 170-180.

[3] Castrillon, Gabriel, et al. "The physiological effects of noninvasive brain stimulation fundamentally differ across the human cortex." Science advances 6.5 (2020): eaay2739.

[4] Seo, Hyeon, et al. "A multi-scale computational model of the effects of TMS on motor cortex." F1000Research 5 (2016).

[5] Friston, Karl J., Lee Harrison, and Will Penny. "Dynamic causal modelling." Neuroimage 19.4 (2003): 1273-1302.