Targeting Angular Gyrus with TMS to Improve Negative Symptoms in Schizophrenia Spectrum Disorders

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Methodological Issue Being Addressed This study explores a novel transcranial magnetic stimulation (TMS) target, the right angular gyrus (AG), to address negative symptoms in schizophrenia spectrum disorders (SSD). Unlike conventional TMS approaches targeting the prefrontal cortex (PFC), our method is informed by recent neuroimaging evidence linking AG dysfunction to blood-brain barrier (BBB) water exchange abnormalities and negative symptom severity. We aim to test whether AG-targeted TMS can modulate BBB physiology and improve clinical outcomes. In addition, we will objective behavioral assessments for negative symptoms through digital actigraphy and video recording of speech, as negative symptoms are sometimes difficult to assess and differentiate from depression.

Introduction Negative symptoms in SSD are a major contributor to long-term disability and treatment resistance. While the PFC has been the most tested TMS target for negative symptoms, its efficacy remains limited. Our recent findings using diffusion-prepared arterial spin labeling (dp-ASL) reveal significant associations between AG water exchange dysfunction and negative symptoms. This study proposes a novel design comparing AG-targeted TMS with standard PFC stimulation to evaluate therapeutic potential and mechanistic effects on BBB function.

Methods We propose a proof-of-concept randomized controlled trial with 90 participants across three arms: (1) AG TMS + PFC sham, (2) AG sham + PFC TMS, and (3) AG sham + PFC sham. Outcomes will include dp-ASL imaging of BBB water exchange, resting-state fMRI, the Brief Negative Symptom Scale (BNSS), and digital objective monitoring of negative symptoms. Statistical analysis will employ mixed-effects models to assess group differences and treatment effects.

Results We hypothesize that AG-targeted TMS will modulate BBB water exchange and lead to greater improvement in negative symptoms compared to PFC stimulation. Additionally, we will monitor changes in facial expression, speech patterns, and activity levels, including the number of unique locations visited.

Conclusion This study introduces a novel TMS target and mechanistic rationale for treating negative symptoms in SSD, utilizing digital behavioral measurements as objective means to assess these symptoms. If successful, AG-targeted TMS could represent a novel neuromodulation strategies, offering improved outcomes through BBB modulation and objective symptom tracking.

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Keywords

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