

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

Kunitoki, K, Ankeeta A, Ma Y, Gao S, Adhikari BM, Du X, Kochunov P, Hong LE

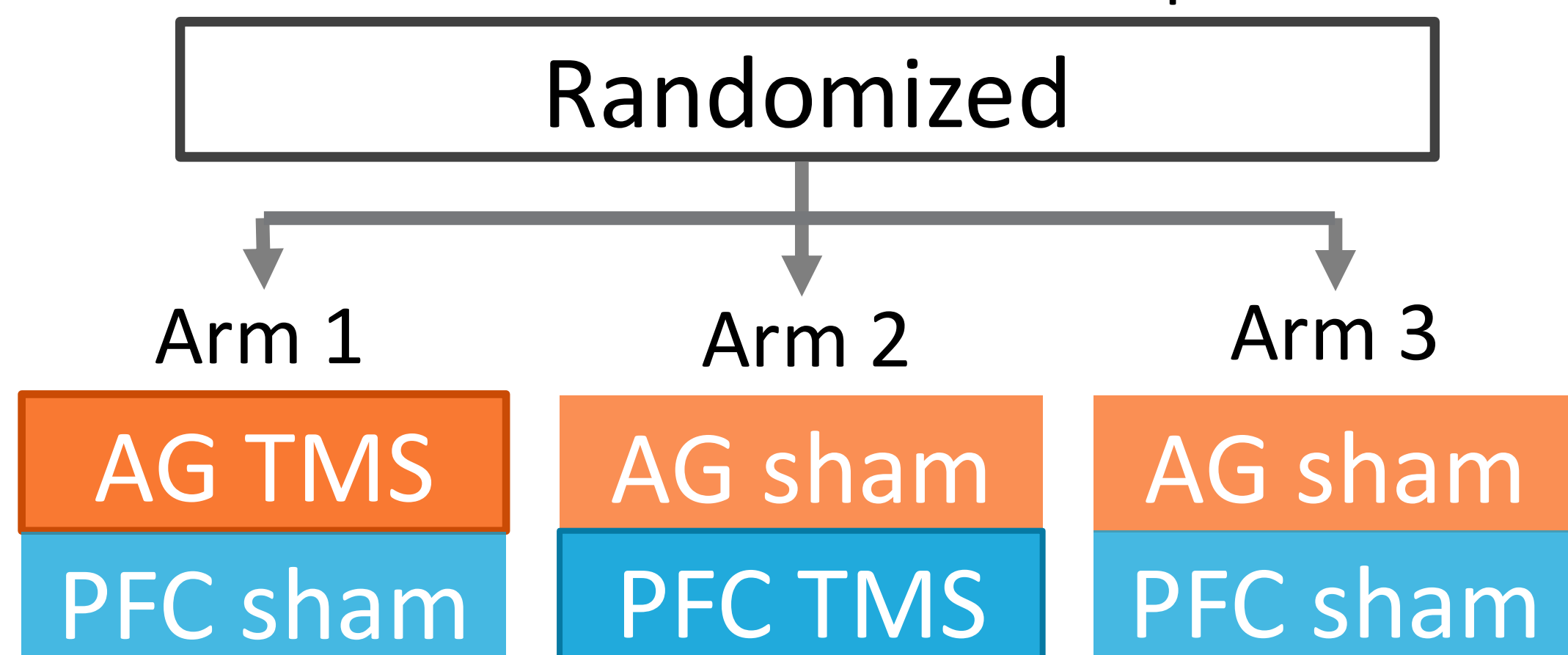
Department of Psychiatry and Behavioral Sciences, University of Texas Health Science Center at Houston

## Introduction

Negative symptoms in schizophrenia spectrum disorders (SSD) are major contributors of long-term disability and treatment-resistance. Limited pharmacological options have proven effective for negative symptoms and transcranial magnetic stimulation (TMS) on the dorsolateral prefrontal cortex (dlPFC) has been commonly tested, however, results are heterogeneous and neurobiological justification is unclear. Previous study showed abnormal water-exchanges at angular gyrus (AG) are significantly associated with negative symptoms in SSD. **AIMS:** Identify brain mechanisms and neurocircuits responsible for negative symptoms of SSD and test the clinical utility of intervention with TMS.

## Methods

**Design:** SSD patients N=90, Double-blind, Randomized Controlled Trial with 3 parallel arms.

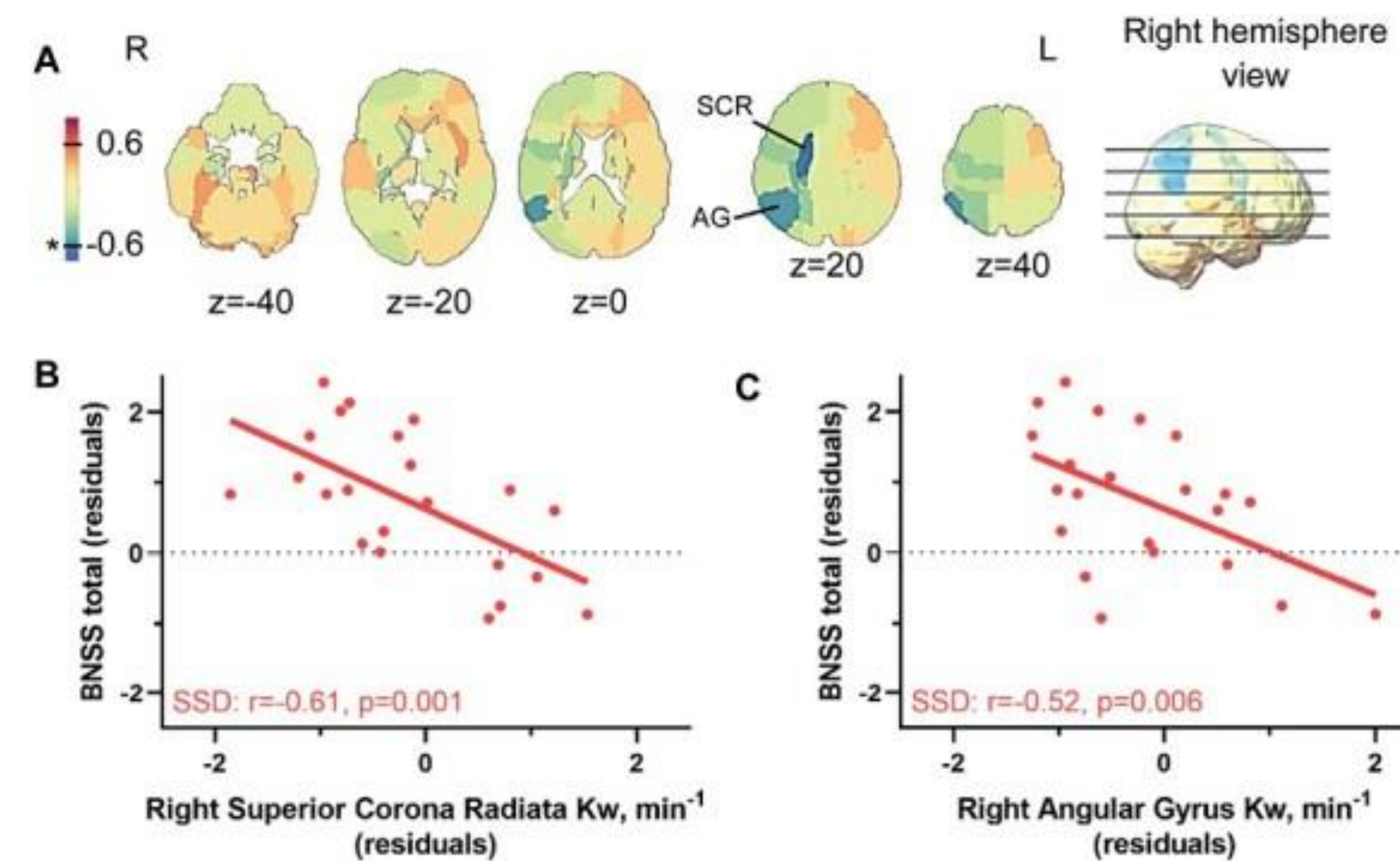


• **Intervention:** Daily repetitive TMS (rTMS) vs sham control for 4 weeks.  
 • **Primary Outcomes:** Change in blood brain barrier (BBB) water exchange rate via diffusion-prepared Arterial Spin Labeling (dp-ASL).  
 • **Secondary Outcomes:** resting-state fMRI connectivity, clinical assessments (positive, negative, cognitive symptoms), EEG, Digital Objective Monitoring.

## Methodological Issues Addressed

### Unclear Brain Mechanism of Negative Symptoms

**Methodological Solution: BBB imaging.** dp-ASL is a novel, non-contrast sequence, which allows estimation of the water exchange rate (kw) across the BBB. By combining TMS and this imaging modality, we aim to test the potential role of TMS on enhancing active water exchange across the BBB, thought to be through the glymphatic system, as well as improvement in clinical outcomes.





Negative symptoms associated with regional Kw measurements. (Goldwaser et al. 2023)

### Heterogeneous Results from TMS on PFC

**Methodological Solution: The 3-arm active-comparator and sham controlled design.** We use PFC as an active comparator site, having demonstrated potentially beneficial but heterogeneous results across many studies. By comparing AG TMS to PFC plus a double-sham condition, we will assess clinical benefit as well as biological markers for non-neuronal effect of TMS.

### The "Subjectivity" Challenge: Measuring Negative Symptoms

**Methodological Solution:** While the brief negative symptom scale (BNSS) and clinical assessment interview for negatives symptoms (CAINS) rely on retrospective self-report (subject to recall bias), digital phenotyping provides continuous measures of actual behavior (GPS/Actigraphy) and observable expression (Video/Audio analysis).

Domain	Negative Symptoms	Suggested Solution: Objective Digital Proxy
<b>Motivation &amp; Pleasure</b>	<ul style="list-style-type: none"> <li>• Avolition</li> <li>• Asociality</li> <li>• Anhedonia</li> </ul>	<b>GPS &amp; Actigraphy (Watch)</b> <ul style="list-style-type: none"> <li>• Location: diversity of places visited vs time home</li> <li>• Activity Tracking: total daily movement</li> </ul> 
<b>Expression</b>	<ul style="list-style-type: none"> <li>• Blunted Affect</li> <li>• Alogia</li> </ul>	<b>Video &amp; Audio Analysis</b> <ul style="list-style-type: none"> <li>• Visual: quantify facial expression, gesture</li> <li>• Vocal: acoustic and speech metrics</li> </ul> 

## Expected Results

We are currently preparing a pilot study for this project. If the pilot study is promising and we secure funding, we will proceed with this full study. 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 negative symptoms using not only clinical assessments, but also wristwatches and video recordings to assess facial expression, speech patterns, and activity levels.

## Conclusions

• **Summary:** This trial aims to link a novel TMS target (AG) with a physiological measurement (BBB permeability) to explore mechanisms and potential treatment options for negative symptoms in SSD. Furthermore, we utilize digital phenotyping to capture objective symptom data.

• **Impact:**

1. Validates dp-ASL as a non-invasive biomarker of BBB for interventional trials.
2. Establishes alternative target for TMS for negative symptoms.
3. Provides proof-of-concept for AG modulation as a therapeutic pathway for treatment-resistant negative symptoms.
4. Introduce objective digital measurements in addition to clinical assessment to obtain further detailed symptom assessment.