

# TMS targets for multiple sclerosis related depression derived using a precomputed functional connectome

William Drew<sup>1,2</sup>, Isaiah Kletenik<sup>1,2,3,4</sup>, Rohit Bakshi<sup>2,5,6</sup>, Michele Cavallari<sup>6,7</sup>, Tanuja Chitnis<sup>2,5</sup>, Bonnie I. Glanz<sup>2,5</sup>, Charles R.G. Guttmann<sup>6,7</sup>, Miklos Palotai<sup>6,7</sup>, Michael D. Fox<sup>1,2,3,4</sup>, Shan H. Siddiqi<sup>1,3,4,8</sup>

<sup>1</sup>Center for Brain Circuit Therapeutics, Brigham and Women's Hospital, Boston, MA, USA. <sup>2</sup>Department of Neurology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA. <sup>3</sup>Center for Brain/Mind Medicine, Brigham and Women's Hospital, Boston, MA, USA. <sup>4</sup>Department of Cognitive and Behavioral Neurology, Brigham and Women's Hospital, Boston, MA, USA. <sup>5</sup>Partners Multiple Sclerosis Center, Brigham and Women's Hospital, Boston, MA, USA. <sup>6</sup>Department of Radiology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA. <sup>7</sup>Center for Neurological Imaging, Brigham and Women's Hospital, Boston, MA, USA. <sup>8</sup>Department of Psychiatry, Brigham and Women's Hospital, Boston, MA, USA.

## Introduction

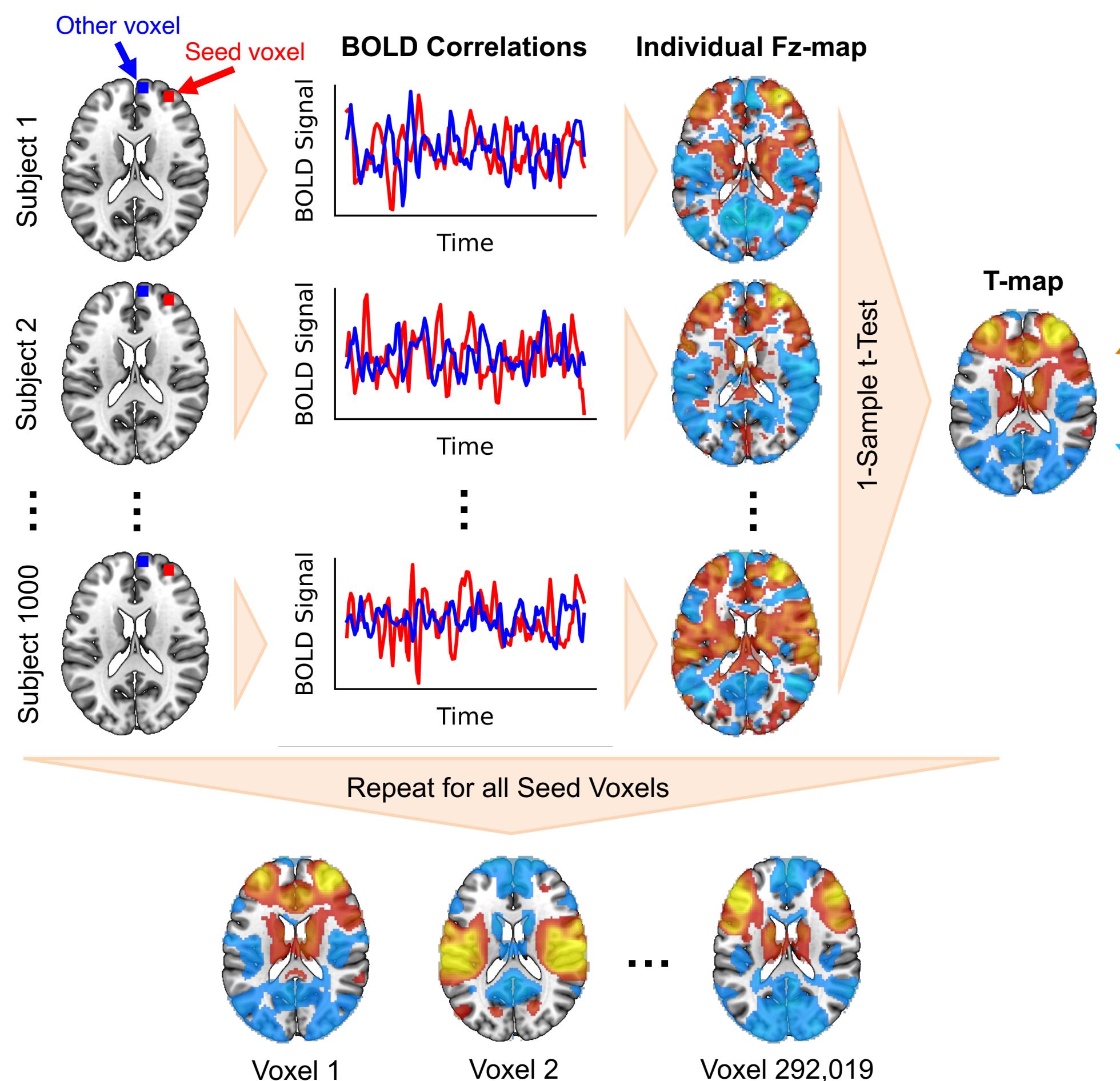
- There are no clinical TMS trials for **depression in multiple sclerosis (MS)**, which is poorly responsive to conventional pharmacotherapy.
- We developed a method to identify treatment targets based on distributed brain circuit maps derived from depression-causing MS lesions (Siddiqi et al. 2023, *Nature Mental Health*).
- We then tested this method using published maps that define circuits connected to stroke lesions and penetrating head trauma associated with depression, which have been shown to predict TMS outcomes (Siddiqi et al. 2021, *Nature Human Behaviour*).

## Methods

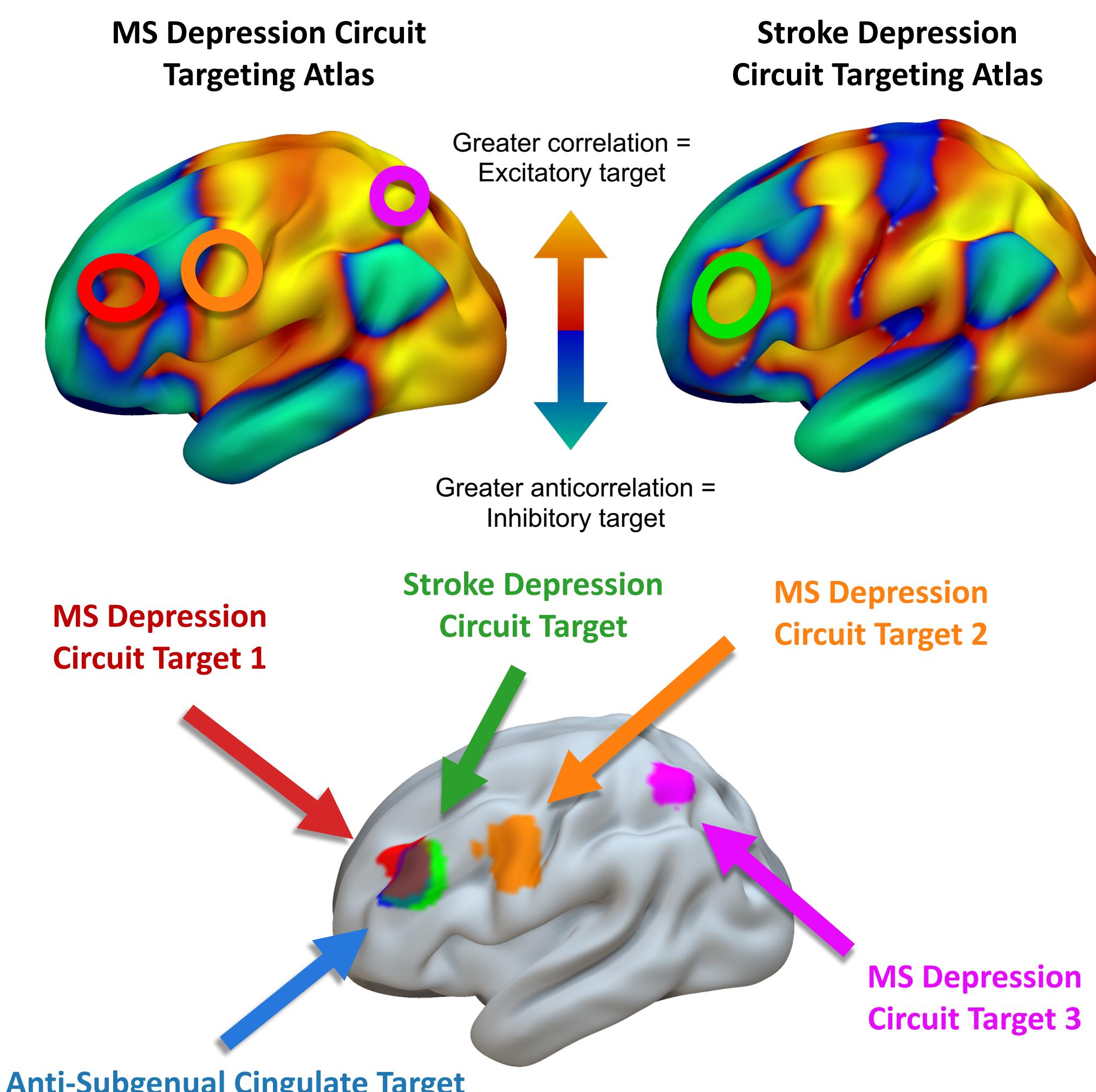
- We analyzed a recently-published “**MS depression circuit map**” based on the normative connectivity of MS lesions (N=281) that increase risk of depression in MS.
- We created a **precomputed functional connectome** using mean whole-brain functional connectivity of 292,019 8mm<sup>3</sup> brain voxels across 1,000 healthy participants. The precomputed functional connectome is a high-resolution atlas of voxel-wise functional connectivity.
- We generated a “**targeting atlas**” that compares each voxel’s connectivity map to the MS depression circuit map using spatial correlations. Voxels whose connectivity profile most strongly correlates with the MS depression circuit map are identified as potential TMS targets.

- For comparison purposes, we conducted the same “targeting” analysis to identify potential TMS targets using a previously published depression circuit map derived from stroke lesions and penetrating head trauma (N=461), which has previously been shown to reveal better TMS targets.

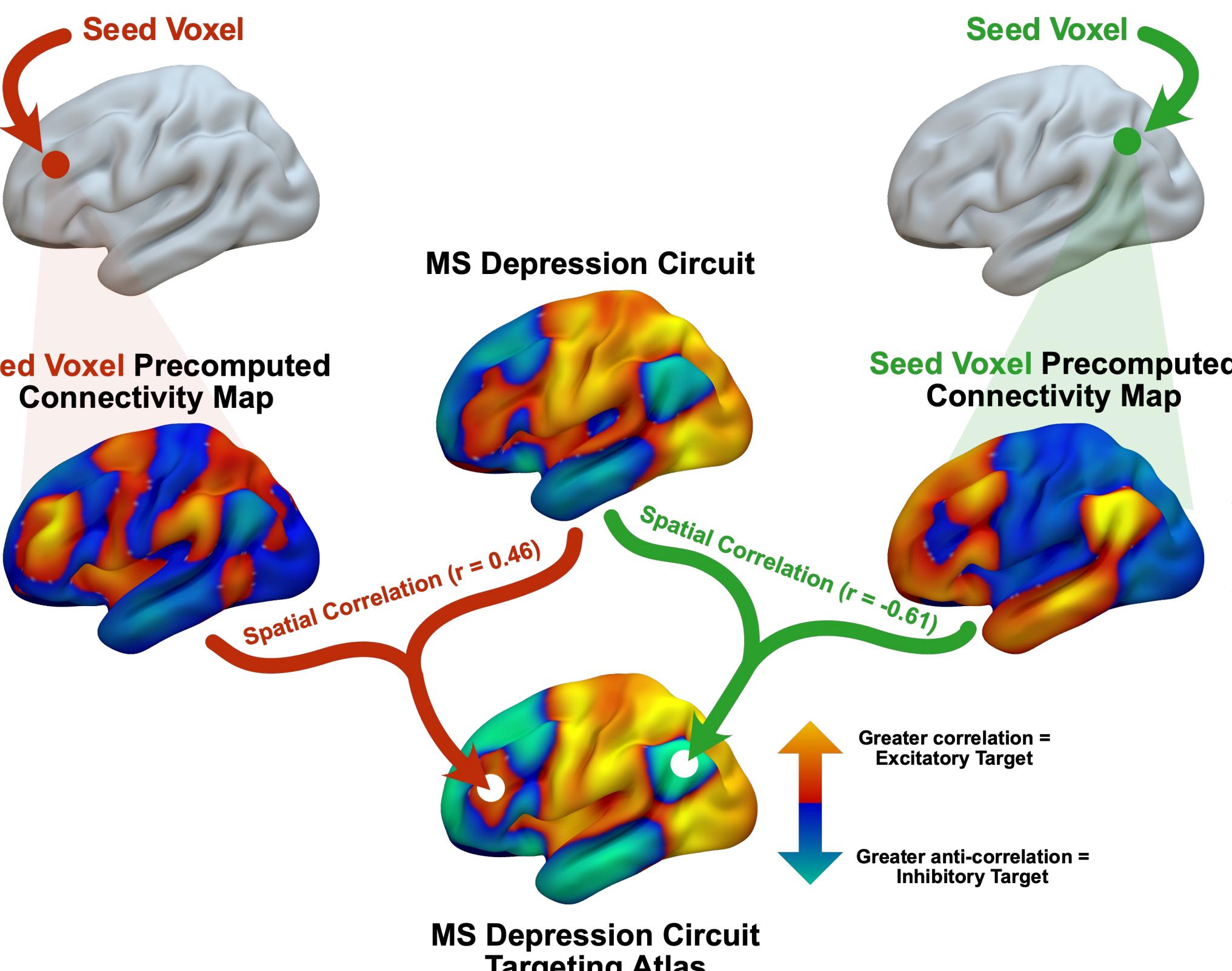
**Figure 1 – Generating the Precomputed Functional Connectome**



**Figure 3 – TMS Targets for MS Depression**



**Figure 2 – Deriving the MS Depression Circuit Targeting Atlas**



## Results

- We identified three potential TMS targets from the MS depression circuit targeting atlas derived from the precomputed functional connectome. The proposed lesion-derived TMS targets for MS depression are at MNI coordinates (-38, 44, 34), (-56, 4, 42) and (-36, -54, 66).
- The proposed MS depression TMS left dorsolateral prefrontal target is **within 1cm** of the TMS target derived from stroke lesions and penetrating head trauma, which is at (-44, 38, 30), and a TMS target derived from subgenual cingulate anti-correlations at (-42, 44, 30), the most common neuro-navigated TMS target.

## Conclusions

- We developed the **precomputed functional connectome**, a high-resolution atlas of voxel-wise functional connectivity. The precomputed functional connectome can reveal potential therapeutic neuromodulation targets by assessing the affinity of their connectivity profiles to a template brain circuit.
- We identified a potential TMS target for MS depression. The proposed target is **near the current clinical TMS targets** for depression, suggesting that **MS depression may be amenable to TMS**.



wdrew@bwh.harvard.edu  
@WilliamDrew\_1  
thewilliamdrew

## References

- Siddiqi, S. H. et al. Lesion network localization of depression in multiple sclerosis. *Nat. Mental Health* 1, 36–44 (2023).
- Siddiqi, S. H. et al. Brain stimulation and brain lesions converge on common causal circuits in neuropsychiatric disease. *Nat. Human Behaviour* 5, 1707–1716 (2021).