Towards Causal Connectomics in Epilepsy; A Chronometric TMS-fMRI Approach

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1 Introduction

TMS administered concurrently with fMRI has been increasingly implemented to explore causal interactions across large-scale brain networks. In epilepsy, a network disorder where pharmacological treatments often prove inadequate, mapping these causal pathways is critical for personalized neuromodulation and presurgical planning.

This exploratory, proof-of-concept pilot study uses interleaved chronometric TMS-fMRI targeting the left dorsolateral prefrontal cortex (dlPFC), a central hub with known downstream projections to epileptic networks, to probe how stimulation-evoked activity propagates under different cognitive states in healthy participants (N=2). The aim is to establish a mechanistic "network stress test" framework to map normal network dynamics, serving as a future clinical reference point for identifying biomarkers of epileptic network instability.

2 Methods

The study design involved individualized 10 Hz TMS to the left dlPFC during rest and an n-back task, interleaved with fMRI, across two sessions separated by four days. Session 1 utilized resting-state fMRI (rs-fMRI) for individualized target definition. Session 2 involved determining the resting motor threshold followed by concurrent TMS-fMRI during low cognitive load (0-back task) and high cognitive load (2-back task) to induce controlled variation of the brain state (Fig. 1).

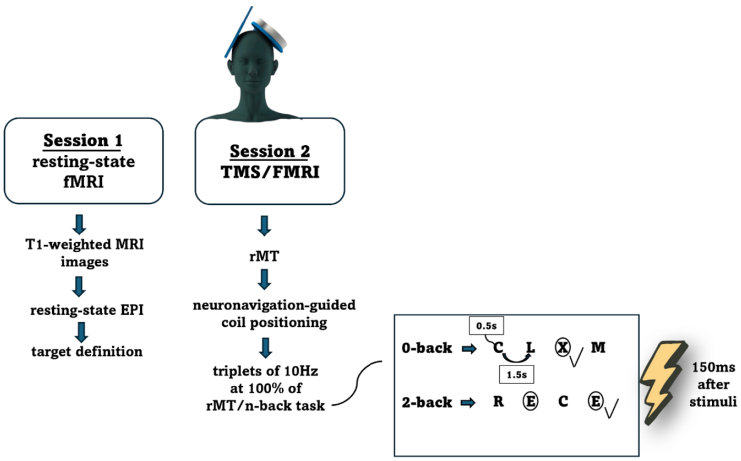

Fig. 1: Experimental Design and Procedural Pipeline.

3 Results

Stimulation produced distinct, condition-dependent BOLD response patterns (t≥3). Stimulation during the 0-back task produced a widespread signal distribution with significant activation in the superior and middle frontal gyri and limited deactivation in the pregenual anterior cingulate cortex (pgACC). During the 2-back task, a more localized network propagated among cortical and subcortical structures, accompanied by significant deactivation in midline and limbic areas, including the mid-cingulate cortex (MCC), posterior cingulate cortex (PCC), and subgenual anterior cingulate cortex (sgACC). Notably, Participant 2 displayed consistent sgACC engagement across both conditions, whereas Participant 1 did not, highlighting notable inter-subject variability in network susceptibility (Fig. 2).

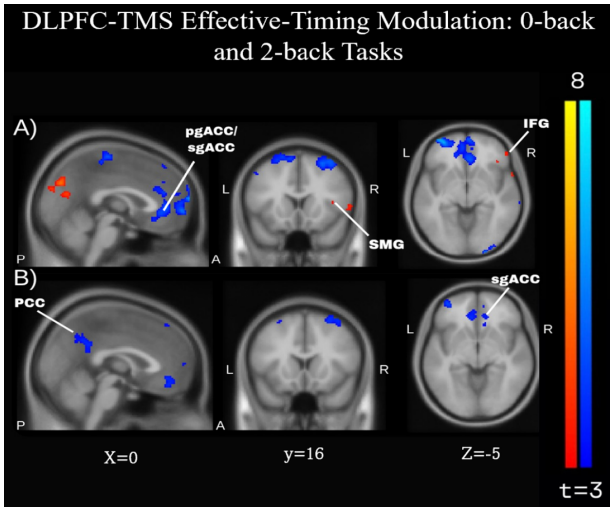

Fig. 2: Comparative Brain Activation under DLPFC-TMS (0-back vs. 2-back) in participant 2.

4 Discussion

While firm conclusions are limited, the preliminary results demonstrate that dlPFC stimulation engages key limbic centers (sgACC, PCC) implicated in seizure propagation (Pana and Nguyen, 2023). The observed stronger deactivation of the Default Mode Network (DMN) during high cognitive load highlights the antagonistic fronto-parietal relationship, frequently disrupted in epileptic disorders and linked to cognitive impairments (Caciagli et al., 2022). Ultimately, this protocol demonstrates the feasibility of a non-invasive "network stress test" to probe limbic connectivity, offering a promising baseline for future patient-specific clinical mapping.

References

Caciagli, L. et al. (2022). Disorganization of language and working memory systems in frontal versus temporal lobe epilepsy. *Brain*, 146(3), 935.

Pana, R. M. and Nguyen, D. K. (2023). Anterior cingulate epilepsy: A review. *Journal of Clinical Neurophysiology: Official Publication of the American Electroencephalographic Society*, pp. 501–506.