Anatomy-based estimates indicate that cortical stimulation can only sparsely affect long-range connections

Dora Hermes (hermes.dora@mayo.edu)
Mayo Clinic, Rochester, MN
Maria-Guadelupe Yanez-Ramos (Yanez-Ramos.MariaGuadalupe@mayo.edu)
Mayo Clinic, Rochester, MN
Nicholas M. Gregg (Gregg.Nicholas@mayo.edu)
Mayo Clinic, Rochester, MN
Gregory A. Worrell (Worrell.Gregory@mayo.edu),
Mayo Clinic, Rochester, MN
Cameron McIntyre (cameron.mcintyre@duke.edu)
Duke University, Durham, NC
Hiromasa Takemura (htakemur@nips.ac.jp)
National Institute for Physiological Sciences, Japan
Kai J. Miller (Miller.Kai@mayo.edu)
Mayo Clinic, Rochester, MN

Abstract

Knowledge of how human neuroanatomy influences stimulation induced neural signal propagation is essential for understanding brain network function and advancing neuromodulation technologies. Here, we investigate how neuroanatomical properties of visual white matter pathways guide signal propagation when stimulating ventral temporal cortex. We calculate that the convoluted dorsal and ventral surface areas in the human brain span centimeters of gray matter cortex, while the smallest cross sectional area of the white matter pathway connecting these areas only spans millimeters. Using single pulse electrical stimulation of the ventral temporal cortex, we find that evoked responses measured with intracranial EEG (iEEG) follow this neuroanatomical layout. Ventral temporal gray matter stimulation evokes little responses in dorsal visual electrodes, whereas adjacent white matter stimulation evokes strong responses in many dorsal electrodes. The influence of cortical stimulation on connected areas in the human brain thus seems limited by inherently sparse cortico-cortical connectivity, whereas white matter stimulation may provide more widespread influence.

Keywords: connectivity; brain stimulation; visual pathways

Introduction

Electrical stimulation is used to map human brain function, influence perception and treat neurological and neuropsychiatric diseases. While some studies stimulate cortical gray matter (e.g. visual prosthetics, epilepsy; Beauchamp et al., 2020; Lundstrom et al., 2016), other studies find high therapeutic outcomes from white matter stimulation (e.g. depression, Mayberg et al., 2005). It is therefore important to understand the fundamental anatomical principles that guide how cortical and white matter stimulation affects human brain networks.

The ventral and dorsal visual streams are involved in categorical and spatial information processing (Mishkin et al., 1983). These areas are anatomically connected through the vertical occipital fasciculus (VOF) (Yeatman et al., 2014). These cortical endpoints in the human brain are highly distributed, and the gray matter surface area on a gyrus is much larger than the cross sectional area through the white matter at the base of a gyrus. Estimates of the number of axons that can traverse these cross sectional areas suggest that cortico-cortical connectivity may be extraordinarily sparse (Rosen & Halgren, 2022). To better understand the sparseness of connectivity between the visual pathways, we estimate the dorsal area that can be influenced by stimulating ventrally and evaluate this prediction with iEEG data collected during single pulse electrical stimulation.

Methods

Analysis of the VOF. We visualized the dorsal and ventral endpoints of the VOF in the cortical surface by utilizing previous work (Schurr et al., 2019). Dorsal and ventral surface areas were estimated by summing the area of the triangles from the cortical rendering (Figure 1a-b). The smallest cross-sectional area of the VOF was calculated from a population averaged tractography atlas (Yeh, 2022); Figure 1c).

Single pulse electrical stimulation. One patient with epilepsy who had iEEG electrodes implanted for clinical purposes gave informed consent and participated in the study, which was approved by the Mayo Clinic Institutional Review Board (IRB #15-006530). Single pulses of electrical stimulation were delivered at different ventral temporal electrodes, with 100 μs pulse width, 6mA amplitude and ~0.3Hz with jitter. Brain Stimulation Evoked Potentials (BSEPs) were recorded throughout all other electrodes at 4800 Hz on a g.HIamp (gTec). Data were re-referenced to an adjusted common average (Huang et al., 2024) and reliable evoked responses were identified using canonical response parameterization (Miller et al., 2023). We estimate that such stimulation spreads across ~5-78 mm^2 of cortex, because the surface area of a typical iEEG electrode is ~5 mm^2 and previous heuristics suggest spread across a radius of ~5 mm (Dembek et al., 2017). This range matches previous estimates of the area of visual cortex activated during intracranial stimulation (Winawer & Parvizi, 2016).

Results

To better understand how white matter anatomy guides the influence of electrical stimulation, we estimated the surface area of ventral and dorsal areas connected by the VOF. Each area spans about 1800-2500 mm^2 (Figure 1d). If electrical stimulation influences 5-78 mm^2 of ventral temporal gray matter, only ~0.25-4% of the dorsal area would be expected to respond (assuming unidirectional connections in this direction) (Figure 1e, left). However, given that the estimated cross sectional area in the middle of the VOF only spanned ~55 mm^2, electrical stimulation applied to VOF white matter is expected to result in an increased number of responses in dorsal areas (Figure 1e, right).

The iEEG data follow this prediction and show that ventral gray matter stimulation induced sparse responses in lateral visual areas and no significant responses were observed in dorsal visual areas (Figure 1f, left). However, when stimulation involved white matter, significant responses were observed in all 3 dorsal electrodes (Figure 1f, middle and right).

Discussion

Our results indicate that cortical stimulation of ventral temporal gray matter only sparsely influences connections in the dorsal stream. These results align with previous studies estimating that long-range connections in the arcuate and superior longitudinal fasciculi are extremely sparse (Rosen & Halgren, 2022). In contrast, white matter stimulation closer to the smallest cross-sectional area of a fiber bundle can likely increase the influence of stimulation on connected areas. These results suggest that the anatomical layout of the white matter tracts has a major impact on understanding the effects of electrical stimulation in the human brain.

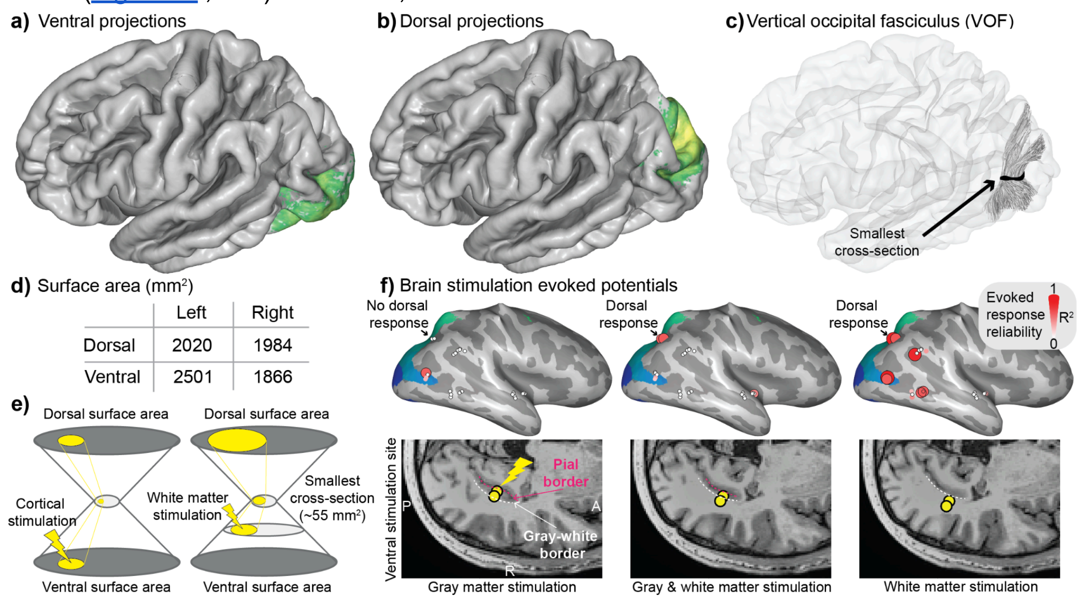

Figure 1: Ventral-dorsal connectivity. a-b) VOF endpoint density from (Schurr et al., 2019). c) VOF rendering with the estimated smallest cross-section. d) Estimates of ventral and dorsal surface areas. e) Schematic showing how the anatomical layout of the VOF guides the effects of stimulation. f) Electrodes with significant stimulation evoked responses shown as red dots on the cortical surface. Significant dorsal responses were observed when white matter electrodes, below the gray/white matter border, were stimulated (Middle and Right panels) (Blue/green on the rendering indicate visual pathways (Wang et al., 2015))

Acknowledgements

We are grateful for the patients and staff at Saint Mary Hospital, Mayo Clinic, Rochester, MN. Research reported in this abstract was supported by the National Institute of Mental Health under Award Number R01MH122258 and the National Eye Institute under Award Number R01EY035533.

References

Beauchamp, M. S., Oswalt, D., Sun, P., Foster, B. L., Magnotti, J. F., Niketeghad, S., Pouratian, N., Bosking, W. H., & Yoshor, D. (2020). Dynamic stimulation of visual cortex produces form vision in sighted and blind humans. *Cell*, *181*(4), 774–783.e5.

Dembek, T. A., Barbe, M. T., Åström, M., Hoevels, M., Visser-Vandewalle, V., Fink, G. R., & Timmermann, L. (2017). Probabilistic mapping of deep brain stimulation effects in essential tremor. *NeuroImage. Clinical*, *13*, 164–173.

Huang, H., Ojeda Valencia, G., Gregg, N. M., Osman, G. M., Montoya, M. N., Worrell, G. A., Miller, K. J., & Hermes, D. (2024). CARLA: Adjusted common average referencing for cortico-cortical evoked potential data. *Journal of Neuroscience Methods*, *407*(110153), 110153.

Lundstrom, B. N., Van Gompel, J., Britton, J., Nickels, K., Wetjen, N., Worrell, G., & Stead, M. (2016). Chronic subthreshold cortical stimulation to treat focal epilepsy. *JAMA Neurology*, *73*(11), 1370–1372.

Mayberg, H. S., Lozano, A. M., Voon, V., McNeely, H. E., Seminowicz, D., Hamani, C., Schwalb, J. M., & Kennedy, S. H. (2005). Deep brain stimulation for treatment-resistant depression. *Neuron*, *45*(5), 651–660.

Miller, K. J., Müller, K.-R., Valencia, G. O., Huang, H., Gregg, N. M., Worrell, G. A., & Hermes, D. (2023). Canonical Response Parameterization: Quantifying the structure of responses to single-pulse intracranial electrical brain stimulation. *PLoS Computational Biology*, *19*(5), e1011105.

Mishkin, M., Ungerleider, L. G., & Macko, K. A. (1983). Object vision and spatial vision: two cortical pathways. *Trends in Neurosciences*, *6*, 414–417.

Rosen, B. Q., & Halgren, E. (2022). An estimation of the absolute number of axons indicates that human cortical areas are sparsely connected. *PLoS Biology*, *20*(3), e3001575.

Schurr, R., Filo, S., & Mezer, A. A. (2019). Tractography delineation of the vertical occipital fasciculus using quantitative T1 mapping. *NeuroImage*, *202*(116121), 116121.

Wang, L., Mruczek, R. E. B., Arcaro, M. J., & Kastner, S. (2015). Probabilistic Maps of Visual Topography in Human Cortex. *Cerebral Cortex* , *25*(10), 3911–3931.

Winawer, J., & Parvizi, J. (2016). Linking Electrical Stimulation of Human Primary Visual Cortex, Size of Affected Cortical Area, Neuronal Responses, and Subjective Experience. *Neuron*, *92*(6), 1213–1219.

Yeatman, J. D., Weiner, K. S., Pestilli, F., Rokem, A., Mezer, A., & Wandell, B. A. (2014). The vertical occipital fasciculus: a century of controversy resolved by in vivo measurements. *Proceedings of the National Academy of Sciences of the United States of America*, *111*(48), E5214–E5223.

Yeh, F.-C. (2022). Population-based tract-to-region connectome of the human brain and its hierarchical topology. *Nature Communications*, *13*(1), 4933.