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Extensive, non-uniform neural activation from intracortical electrical stimulation drives weak sensory perception in mice

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Introduction: Electrical brain stimulation (EBS) is a powerful tool for modulating neural activity and influencing behavior, with growing potential for use in cortical prostheses to evoke perceptible sensations and provide sensory feedback. While biophysical models and clinical psychophysics offer insights into EBS effectiveness, *in vivo* validation is limited. This project aims to directly measure neural responses to single pulses of EBS in mouse V1 with high spatial precision, exploring the volume of evoked potentials, direct and circuit-wide responses of single neurons, and what EBS-evoked neural activity drives detectable sensations.

Material, methods, and results: We simultaneously implanted three Neuropixels orthogonal to a stimulating electrode in mouse primary visual cortex, allowing three-dimensional sampling of neural tissue around a source of stimulation. First, the volume of the evoked potential increases sub-linearly with stimulation amplitude. Further, the shape of the evoked potential was non-uniform, extending asymmetrically through cortex and less likely to penetrate subcortically beyond the corpus callosum (figure 1a). Next, we explored the direct single unit spiking response within the volume of activated tissue. Increasing amplitude recruits more directly responsive cells (example unit in figure 1b), but overall activation remains sparse, peaking at ~10%. Fast-spiking units (putative inhibitory cells) were more likely to be directly activated and clustered closer to the electrode than regular-spiking units. Despite sparse direct activation of single units, we observed large, synchronous circuit responses spreading asymmetrically through the cortex but not subcortically (figure 1c). Lastly, we tested the behavioral availability of single pulses and trains of V1 EBS compared to visual stimuli of varying contrasts**.** The same single pulses that generated large, evoked potentials and synchronous circuit responses were weakly detected, comparable to 2-4% contrast visual stimuli, while high frequency trains were more detectable, comparable to 8% contrast visual stimuli (figure1d).

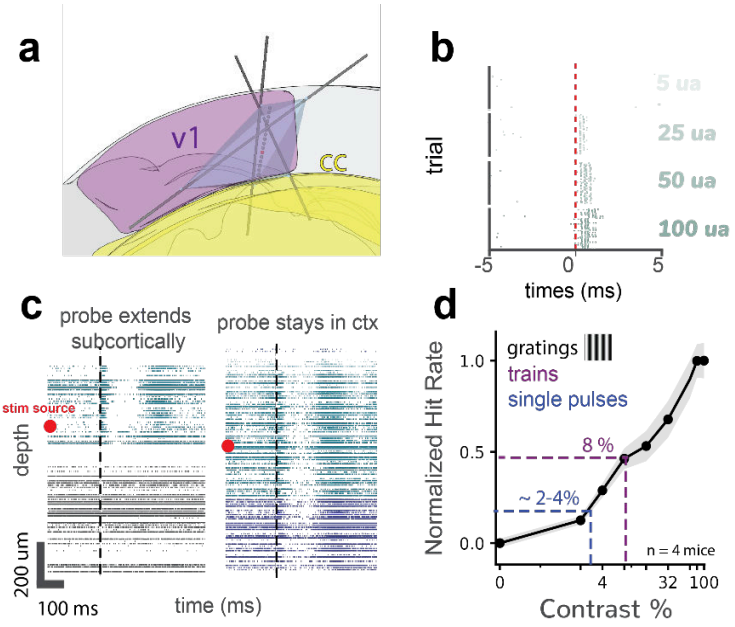

Figure 1 a) asymmetric evoked potential (blue) with anatomical borders. b) example raster of direct responding unit. c) stacked raster of single units extending subcortically (left) and through cortex (right). d) behavioral detection of visual and EBS stimuli (single pulses: blue, trains: purple)

Conclusion: Overall, we show that the volume of evoked potentials is non-uniform, direct single-unit activation is sparse, and circuit responses are large and asymmetric yet weakly behaviorally available. Together, this suggests that EBS nonuniformly propagates through neural tissues, influenced by anatomical heterogeneity such as white matter boundaries and functional connectivity. Further, these results provide critical insights into the importance of neural specificity over activation strength when applying EBS to write information into the brain and call for spatiotemporal stimulation patterns that may better recapitulate sensory stimuli.

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