Single Neuron Recruitment during Direct Electrical Stimulation in the Human Cortex

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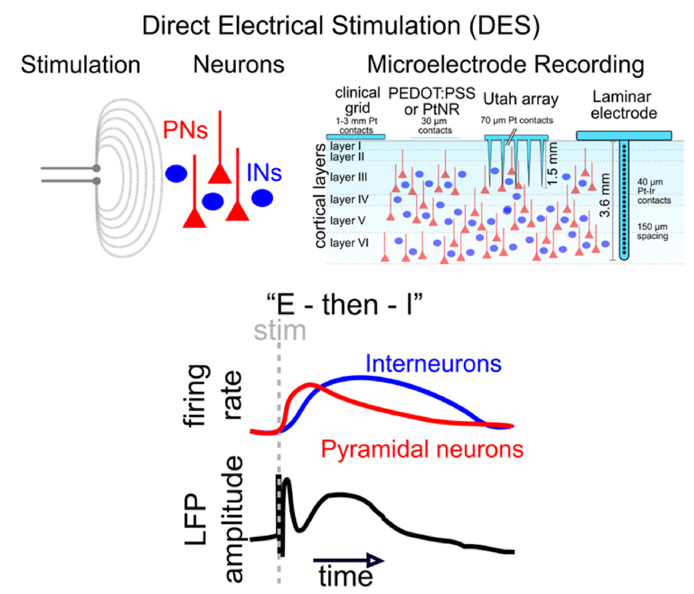
INTRODUCTION

- Direct electrical stimulation (DES) has become a standard treatment for a multitude of neurological diseases including Parkinson's disease and epilepsy.
- Yet, we only have a rudimentary understanding of the mechanistic effects of DES on single cortical neurons in the human brain. It has been postulated that DES activates excitatory (E) cells followed by engagement of inhibitory (I) neurons. This is supported by *in vitro* and *ex vivo* research in different animal models but has not been verified through in vivo investigations in humans.



HYPOTHESIS

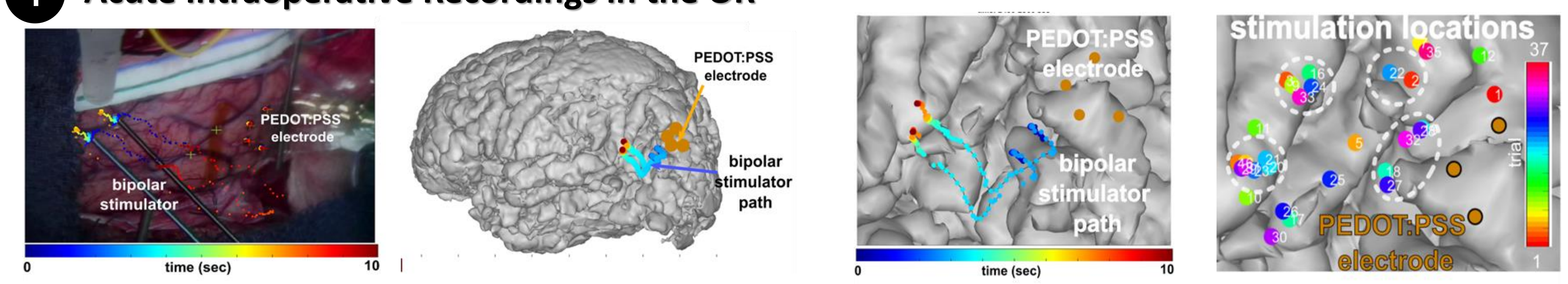
- We hypothesize that direct electrical stimulation of brain regions will induce the activity of single cells to split into early (excitatory activation) and late (inhibitory activation) phases.

MATERIALS & METHODS

- Using microelectrodes during intraoperative neurosurgical resection and mapping (1-3), we applied DES to examine single unit activity and local circuit responses in human lateral prefrontal and temporal cortices (N=11).
- Separately, in the Epilepsy Monitoring Unit (EMU), we examined neural responses from microelectrodes implanted semi-chronically (defined as < 29 days) in patients (N=4).
- We examined excitatory or inhibitory cell-type dynamics from extracellular recordings and the relationship between stimulation intensity, distance, and the E-then-I sequence response.

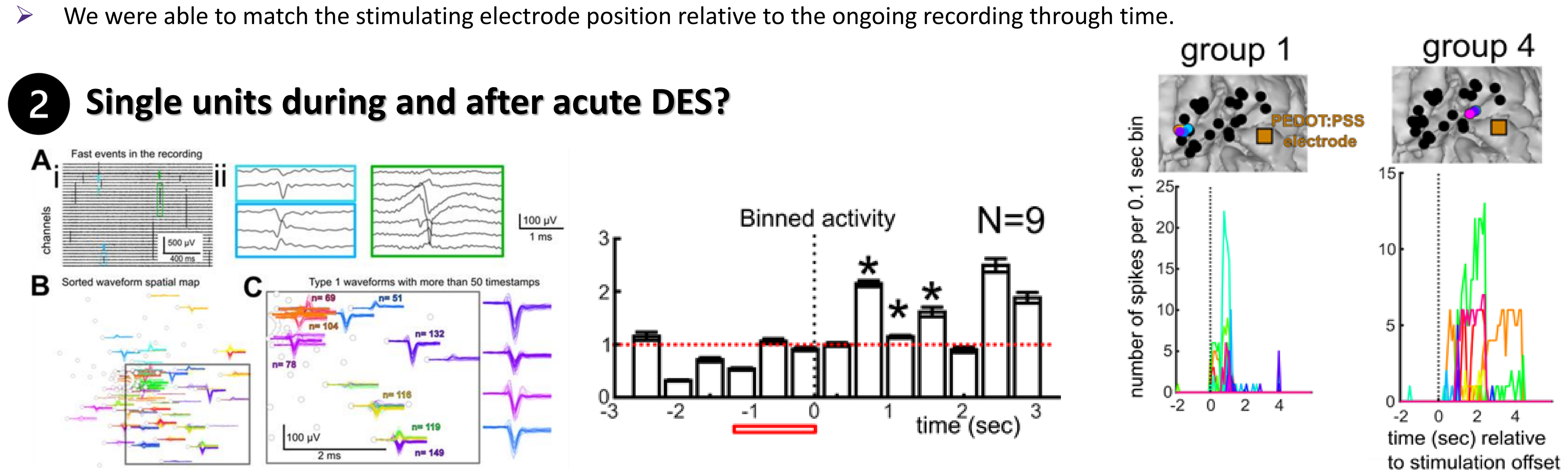
RESULTS

1 Acute Intraoperative Recordings in the OR



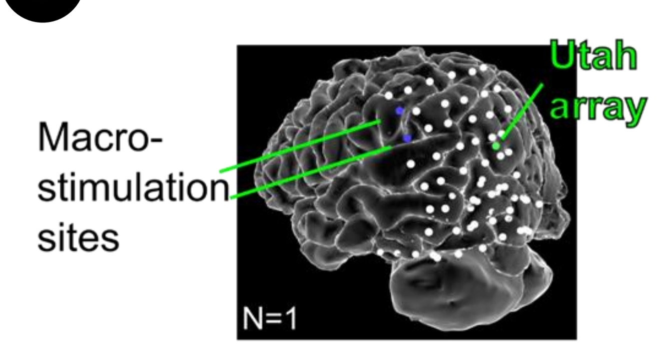
- DeepLabCut (4, 5), computer vision software which uses deep learning for tracking, was used to track the stimulation location relative to the PEDOT:PSS electrode.
- We were able to match the stimulating electrode position relative to the ongoing recording through time.

2 Single units during and after acute DES?

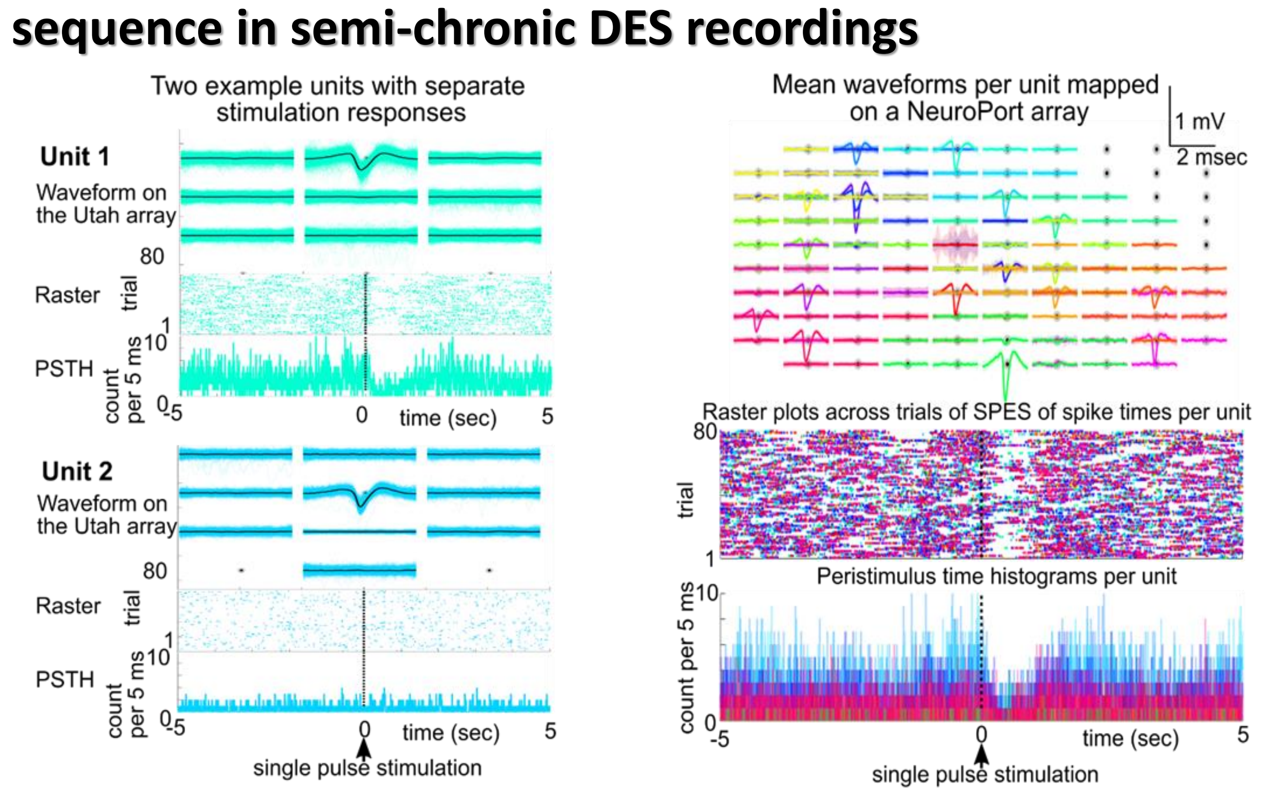


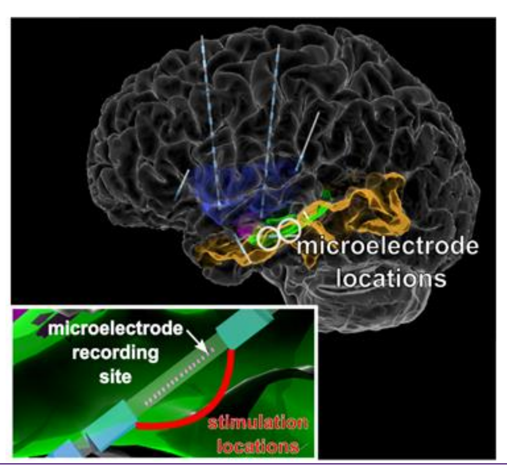
- Single units as represented by different colors is a different single cell with the overlaid waveforms indicating these waveforms repeat through time at the same locations during stable microelectrode recordings.
- We found, across patients, stimulation (as indicated by the red bar below the graph) induced increased single unit activity in these recordings. Asterisks indicate significant change relative to baseline, Wilcoxon rank sum test, p<0.001.
- We also found that moving the stimulating site induced different subsets of units to respond after stimulation. Each color in the rightmost figure indicates a different unit.

3 Evidence of E vs. I stimulation sequence in semi-chronic DES recordings

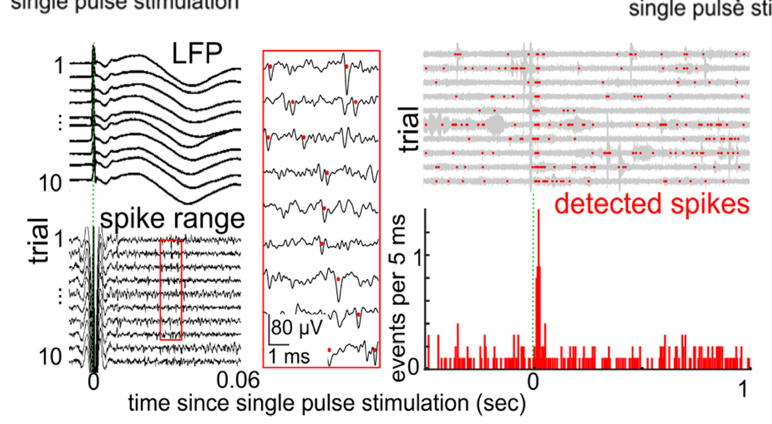


- Individual cells (units) have different response profiles in response to stimulation.
- Though, on the level of the population (18 cells) the stimulation induced longer lasting (2 second) inhibition.





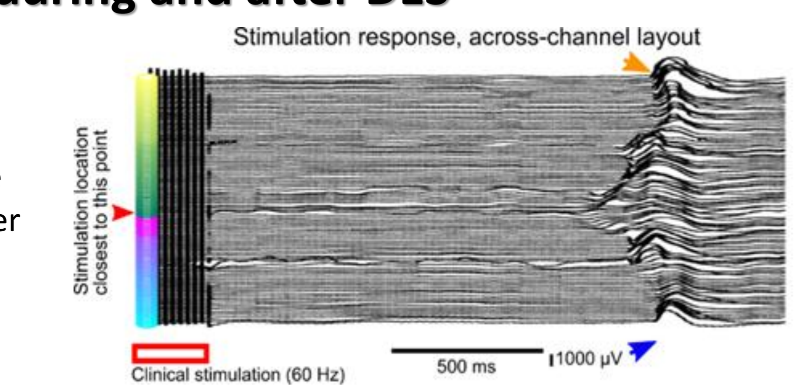
- Using another semi-chronic recording (micromacro electrodes), stimulation induced a short burst of excitation (spiking) along with local field potential (LFP) changes.

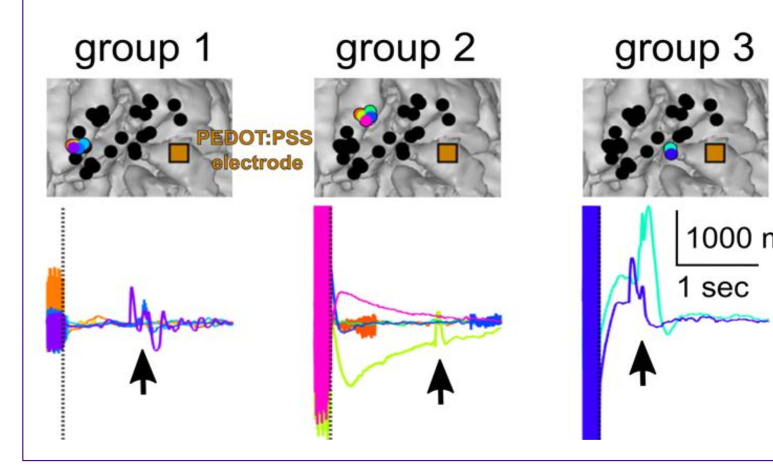


- Spiking only occurred at 4 mA current, but not at 1 or 2 mA, indicating a threshold needed to be reached.

4 Neural Oscillation during and after DES

- In the LFP, we observed propagated waves across the microelectrodes seconds after stimulation.





- Mapping the stimulation location to these recordings, we found that these waves (indicated by the arrow heads) would arrive sooner when the stimulation sites were closer to the recording electrode.
- These waves could represent inhibitory waves across the electrode.

DISCUSSION

- The observed neuronal dynamics supports the hypothesis that DES induces both early (excitatory activation) and late (inhibitory activation) changes in SUA. Through this deeper understanding, we can design more focal, targeted, and informed stimulation approaches targeting specific neuronal cell types.
- This strategy may lead to more precise and tailored therapeutic applications of electrical stimulation for an array of neurological disorders.

REFERENCES

1. A. C. Paulk, et al., Microscale Physiological Events on the Human Cortical Surface. Cereb. Cortex 31, 3678–3700 (2021).
2. S. Sarubbo, et al., Mapping critical cortical hubs and white matter pathways by direct electrical stimulation : an original functional atlas of the human brain. Neuroimage 205, 116237 (2020).
3. S. Borchers, M. Himmelbach, N. Logothetis, H. Karnath, Direct electrical stimulation of human cortex — the gold standard for mapping brain functions? Nat. Rev. Neurosci. 13, 63–70 (2012).
4. A. Mathis, et al., DeepLabCut: markerless pose estimation of user-defined body parts with deep learning. Nat. Neurosci. 21, 1281–1289 (2018).
5. T. Nath, et al., Using DeepLabCut for 3D markerless pose estimation across species and behaviors. Nat. Protoc. 14, 2152–2176 (2019).

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