Identifying multidimensional neural correlates of pain perception and efficacy of brain stimulation therapy

Summary

My goal is to create a non-pharmacological treatment for chronic pain that is personalized and receptive to an individual’s subjective experience of pain, including pain intensity and its disruption to quality of life. **My proposed solution is a brain-computer interface (BCI) that uses neural biomarkers to decode when pain reaches an undesirable threshold, and then subsequently delivers electrical stimulation to alter neural activity to reduce pain**. Here, I propose the initial groundwork for this BCI by identifying patient-specific biomarkers for pain and evaluating multi-site stimulation to reduce pain.

Background

Pain is a complex, subjective experience that acts as a biological alert system for injury. While acute pain is temporary and manageable by treating pain symptoms, chronic pain continues to persist as a public health issue with few options for treatment1. An estimated 37% of individuals living in developed countries suffer from chronic pain, and in the US alone, the annual cost of the medical care and loss of productivity is estimated to be $625 billion dollars1. As prevalent and economically costly this issue is, there are limited treatments that exist for chronic pain. Many people are prescribed opioids for pain management, which are highly addictive and a major contributor to the current opioid crisis in the United States, resulting in over 30 thousand unintentional deaths in 20152. Opioid addiction disproportionately affects our military population due to their increased risk of injury, and a recent survey reported past-month opioid use in 15% of military soldiers3. Chronic pain persists as a public health problem, and with stark recognition that opioid misuse is abundant, there is an urgent need for non-pharmacological alternatives for pain management.

Recent evidence shows that neuromodulation, or stimulating the brain to change its activity, can be an effective management strategy for chronic pain4–8. Chronic pain is described as having a multidimensional representation in the brain, with different regions responsible for the somatosensory (where is the pain), cognitive (what is the interpretation of the pain), and affective (how unpleasant is the pain) aspects of pain9. These regions are ideal targets for neuromodulation to disrupt the neural activity responsible for pain perception. Targeting these pain-associated regions using deep-brain stimulation (DBS) has had preliminary success, with significant decreases of reported pain after 1 year based on a 1-10 visual analog scale (VAS) for pain4–6. However, these studies involved patients undergoing constant single-site electrical stimulation with fixed stimulation parameters, which create anatomical and practical limitations. Single-site stimulation is effective in only specific patients and is unable to provide therapeutic effects over a heterogeneous variety of pain7,8. Single-site stimulation does not account for the multi-regional effects of pain, where both internal (attention, mood) and external factors (context) can change the way pain is perceived and subjectively felt10. Open-loop stimulation with fixed parameters creates practical limitations for long-term treatment. Neural adaptation has been demonstrated with long-term stimulation, which decreases stimulation efficacy11. Stimulation parameters need to be adjusted periodically for long-term stimulation efficacy.

To address the anatomical limitations of single-site stimulation and the practical limitations of ongoing long-term stimulation, **my proposed solution is a closed-loop system that can (1) sense when an individual is in pain using patient-specific biomarkers and (2) deliver self-adjusting neural stimulation to return brain activity to a minimal pain state.** With growing interest in building systems for precision medicine, the work proposed here will serve as initial groundwork for developing such a system for individual pain management. This developed system can be applied to new feasibility studies leveraging human-ready implantable devices for personalized pain management.

Approach

Current work in developing closed-loop DBS seeks to maximize treatment efficacy by activating stimulation based on neural biomarkers and minimize side-effects by delivering stimulation only when needed12,13. With similar motivations, I plan to quantitatively characterize patient-specific neural biomarkers of pain in patients implanted with stereo-electroencephalography (sEEG) electrodes for clinical monitoring of epilepsy. These patients are implanted with multiple sEEG electrodes, which allows the unique opportunity to record from several brain regions simultaneously and capture inter-regional interactions that arise from pain. Most neuro-based pain studies implant only one or two DBS electrodes4–7, so the unprecedented electrode coverage with these sEEG patients will provide more spatial information that can aid in understanding mechanisms of pain processing. Using computational methods including power spectrum analysis, phase-coupling analysis, and network connectivity measures, which provide information about local activity and information flow across brain regions, I can determine both local and network differences that occur at different pain states and identify common and patient-specific biomarkers of pain. With these biomarkers, I can predict when pain levels reach an undesirable level. I can then apply direct electrical stimulation to regions found to have altered activity in an elevated pain state to disrupt the abnormal activity. With sensing multidimensional biomarkers of pain and evaluating targeted stimulation to reduce pain, **my proposal aims to spearhead the application of modern computational methods for developing a neuromodulation treatment for pain.**

Specific Aims

***Aim 1: Classify pain intensity using intracranial depth electrodes***

**Hypothesis:** Distinct neural features change with the perception of pain, and such dynamic neural features can quantify and predict subjective pain experience (Figure 1).

**Rationale**: There are many known brain regions that are associated with pain. A meta-analysis of studies compiled a list of regions with increased activity during pain, including: primary and secondary somatosensory (S1, S2), insula, anterior cingulate, and prefrontal cortices, and thalamus (Th)14. I plan to use frequency analysis to quantify how these regions change with pain. A range of studies have reported pain-related changes across all frequency bands under different contexts, and an overarching consensus has yet to be reached15. More recently, two studies showed converging evidence that increased gamma oscillations in S1 correlated with pain behavior and perception16,17. With this aim, I expect to have similar findings and additionally characterize how these regions are changing in response to pain using spectral analysis. After determining neural correlates of pain, I will train a multivariate regression model to use neural features to classify pain levels and identify which biomarkers are most predictive of pain rating. Success of Aim 1 will result in identification of target biomarkers for pain across patients and a system that can predict patient pain levels given neural data.

A close up of a map

Description automatically generated

**Figure 1:** Procedure of obtaining neural recordings and pain metrics, extracting both local (frequency band power) and network-level (phase-locking, coherence) neural features, and performing multivariate linear regression to predict pain perception.

**Aim 1.1: Collect neural electrophysiology data and pain-ratings**. Continuous week-long neural recordings are collected from patients undergoing seizure monitoring for intractable epilepsy at Harborview Medical Center. Patients are implanted with multiple sEEG electrodes, which range from 12-16 individual recording channels per electrode. Electrode placement is based on the hypothesized epileptogenic zone, with common targets in the medial-temporal lobe, medial-frontal lobe, basal-frontal lobe, the insular cortex, and cingulate gyrus18,19. These patients experience mostly head pain after implant surgery and continue to take pain medication during the week. I will ask patients who consent to research to fill out a short survey several times a day on a provided device (iPad or similar), with hourly reminders prompted by the device. The survey includes the 1-10 visual analog scale, Wong-Baker Faces Scale for pain rating, and how bothersome their pain is on a 1-10 scale to have a complete measure of pain perception. Completed surveys will be time-stamped and stored locally on the device.

**Aim 1.2: Analyze neural electrophysiology data based on different pain-ratings.** Epochs of invasive neural recordings will be will identified, extracted and stratified into distinct categories ranging from: (1) pain free, (2) mild (ratings 1-3), (3) moderate (ratings 4-7) and (4) severe (ratings 8-10). I will examine the neural data ~30 seconds before they completed the questionnaire. This time span assumes that their pain level did not significantly change during the time they were taking the survey. I will process neural electrophysiology data to remove line noise (60 Hz + harmonics) and artifacts and then down-sample to 500 Hz. I will extract frequency band power over standard frequency bands as neural features (delta 0.1-4 Hz, theta 4-8 Hz, alpha 8-12 Hz, beta 12-30 Hz, gamma 30-60 Hz, high-gamma 60-120 Hz). I will also determine network connectivity features using methods such as coherence analysis, phase-amplitude coupling, and phase-locking analysis. Initial analysis will allow us to compare the relationship between these neural features and the pain reported. I will perform significance testing to determine potential neural features to be used as biomarkers of pain.

**Aim 1.3:** **Classifying pain perception.** I will use multivariate linear regression to determine which neural features correlate with pain perception (intensity and bothersome-ness). Multivariate regression allows me to leverage the use of multiple neural features and more closely represent the multidimensionality of pain. Using the regression model, I will determine which neural features are the strongest predictors of each component of pain perception. I will compare results between patients to identify which features are common predictors of pain and which are unique to individual patients. I will perform cross-validation to assess prediction accuracy.

***Aim 2: Perform targeted direct electrical stimulation to change neural activity related to pain***

**Hypothesis:** Direct electrical stimulation to regions correlated with pain disrupts neural activity responsible for pain and changes pain perception.

**Rationale:** Direct electrical stimulation (DES) is used to modulate neural activity for functional mapping and for DBS20. Successful target regions for DBS are related to neural pathophysiology, where the activity of these regions is altered to produce therapeutic effects. Similarly, I will use DES to target regions correlated with pain perception in order to alter their activity. These target regions include known regions from imaging studies that increase in activity with pain and patient-specific regions identified in Aim 1. The success of Aim 2 will identify target regions for effective stimulation in addition to ideal stimulation parameters.

**Aim 2.1: Evaluate target stimulation regions and stimulation parameters for decreasing pain perception.** I will perform single-site and multi-site stimulation on epilepsy patients experiencing mild head pain related to implant surgery. I plan to modulate activity of known regions associated with pain, including primary and secondary somatosensory (S1, S2), insula, anterior cingulate, and prefrontal cortices, and thalamus (Th)14, depending on available electrode coverage and maintaining a respectable distance from known seizure foci. I will start with stimulation parameters similar to DBS and iterate on those parameters to determine effective parameters for neuromodulation, adhering to strict charge density safety limits21 and monitoring for epileptic discharge. To evaluate stimulation efficacy, I will conduct a randomized trial-based task where each stimulation paradigm (parameters, target region) will be on for short (< 1 min) blocks of time and ask patients to indicate their pain perception after each block. Multiple sessions will be performed to account for natural fluctuations of pain. I will determine ideal stimulation regions and parameters based on patient response. I will perform post-hoc analysis on the neural activity immediately following stimulation to quantify how effective stimulation paradigms alter neural activity.

**References**

1. Institute of Medicine (US) Committee on Advancing Pain Research. RELIEVING PAIN IN AMERICA: A BLUEPRINT FOR TRANSFORMING PREVENTION, CARE, EDUCATION, AND RESEARCH RELIEVING PAIN IN AMERICA: A BLUEPRINT FOR TRANSFORMING PREVENTION, CARE, EDUCATION, AND RESEARCH Committee on Advancing Pain Research, Care, and Education o. *J Pain Palliat Care Pharmacother*. 2012;26(2):197-198. doi:10.3109/15360288.2012.678473

2. Rudd RA, Aleshire N, Zibbell JE, Matthew Gladden R. *Increases in Drug and Opioid Overdose Deaths - United States, 2000-2014*. Vol 64.; 2016. https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6450a3.htm. Accessed December 5, 2019.

3. Toblin RL, Quartana PJ, Riviere LA, Walper KC, Hoge CW. Chronic pain and opioid use in us soldiers after combat deployment. *JAMA Intern Med*. 2014;174(8):1400-1401. doi:10.1001/jamainternmed.2014.2726

4. Coffey RJ. Deep Brain Stimulation for Chronic Pain: Results of Two Multicenter Trials and a Structured Review. *Pain Med*. 2001;2(3):183-192. doi:10.1046/j.1526-4637.2001.01029.x

5. Boccard SGJ, Prangnell SJ, Pycroft L, et al. Long-Term Results of Deep Brain Stimulation of the Anterior Cingulate Cortex for Neuropathic Pain. *World Neurosurg*. 2017;106:625-637. doi:10.1016/j.wneu.2017.06.173

6. Boccard SGJ, Pereira EAC, Aziz TZ. Deep brain stimulation for chronic pain. *J Clin Neurosci*. 2015;22(10):1537-1543. doi:10.1016/j.jocn.2015.04.005

7. Bittar RG, Kar-Purkayastha I, Owen SL, et al. Deep brain stimulation for pain relief: A meta-analysis. *J Clin Neurosci*. 2005;12(5):515-519. doi:10.1016/j.jocn.2004.10.005

8. Rasche D, Rinaldi PC, Young RF, Tronnier VM. Deep brain stimulation for the treatment of various chronic pain syndromes. *Neurosurg Focus*. 2006;21(6). doi:10.3171/foc.2006.21.6.10

9. Shirvalkar P, Veuthey TL, Dawes HE, Chang EF. Closed-loop deep brain stimulation for refractory chronic pain. *Front Comput Neurosci*. 2018;12. doi:10.3389/fncom.2018.00018

10. Tracey I, Mantyh PW. The Cerebral Signature for Pain Perception and Its Modulation. *Neuron*. 2007;55(3):377-391. doi:10.1016/j.neuron.2007.07.012

11. Romanelli P, Heit G. Patient-controlled deep brain stimulation can overcome analgesic tolerance. *Stereotact Funct Neurosurg*. 2004;82(2-3):77-79. doi:10.1159/000077404

12. Rosin B, Slovik M, Mitelman R, et al. Closed-loop deep brain stimulation is superior in ameliorating parkinsonism. *Neuron*. 2011;72(2):370-384. doi:10.1016/j.neuron.2011.08.023

13. Herron JA, Thompson MC, Brown T, Chizeck HJ, Ojemann JG, Ko AL. Cortical Brain–Computer Interface for Closed-Loop Deep Brain Stimulation. *IEEE Trans Neural Syst Rehabil Eng*. 2017;25(11):2180-2187. doi:10.1109/TNSRE.2017.2705661

14. Apkarian AV, Bushnell MC, Treede RD, Zubieta JK. Human brain mechanisms of pain perception and regulation in health and disease. *Eur J Pain*. 2005;9(4):463-484. doi:10.1016/j.ejpain.2004.11.001

15. Ploner M, Sorg C, Gross J. Brain Rhythms of Pain. *Trends Cogn Sci*. 2017;21(2):100-110. doi:10.1016/j.tics.2016.12.001

16. Tan LL, Oswald MJ, Heinl C, et al. Gamma oscillations in somatosensory cortex recruit prefrontal and descending serotonergic pathways in aversion and nociception. *Nat Commun*. 2019;10(1). doi:10.1038/s41467-019-08873-z

17. Hu L, Iannetti GD. Neural indicators of perceptual variability of pain across species. *Proc Natl Acad Sci U S A*. 2019;116(5):1782-1791. doi:10.1073/pnas.1812499116

18. Youngerman BE, Khan FA, McKhann GM. Stereoelectroencephalography in epilepsy, cognitive neurophysiology, and psychiatric disease: Safety, efficacy, and place in therapy. *Neuropsychiatr Dis Treat*. 2019;15:1701-1716. doi:10.2147/NDT.S177804

19. Iida K, Otsubo H. Stereoelectroencephalography: Indication and efficacy. *Neurol Med Chir (Tokyo)*. 2017;57(8):375-385. doi:10.2176/nmc.ra.2017-0008

20. Caldwell DJ, Ojemann JG, Rao RPN. Direct Electrical Stimulation in Electrocorticographic Brain–Computer Interfaces: Enabling Technologies for Input to Cortex. *Front Neurosci*. 2019;13. doi:10.3389/fnins.2019.00804

21. Guler S, Dannhauer M, Roig-Solvas B, et al. Computationally optimized ECoG stimulation with local safety constraints. *Neuroimage*. 2018;173:35-48. doi:10.1016/j.neuroimage.2018.01.088

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