UROP Application Summer 2018

Statement of the problem or topic of the research or creative work:

Over the last few decades, there has been a great deal of research done in neuromodulation treatments for a variety of neurological and psychiatric disorders, such as chronic pain, depression, and movement disorders such as Parkinson's disease. There are popular non-invasive electrical methods of neuromodulation like electroconvulsive therapy (ECT) and non-invasive magnetic methods like transcranial magnetic stimulation (TMS), but effectiveness has been highly variability. Recent research suggests that invasive electrical methods may help to reduce this variability by increasing the accuracy and potency of stimulus delivery. Invasive methods such as deep brain stimulation (DBS), occipital nerve stimulation (ONS) to ar en ronic headache, or chronic epidural stimulation (EpCS) to treat major en positive ts, that continue to depression disorder rave rargely th outcome es hO variability due to a need for patient-specific electrode location and stimulation settings. In this research, we propose to attempt to reduce this unpredictability by performing a statistical shape analysis of the heads across an adult patient sample to determine regions of variability to design a better fitting and more effective stimulator.

Relevant background/literature review:

We can examine the current efficacy and limitations of two widely researched invasive neuromodulation treatments that may be aided by a statistical shape analysis of the skull: Occipital nerve stimulation (ONS) and chronic epidural stimulation (EpCS). With regard to indications for this type of therapy, chronic daily headache (CDH) refers to patients that suffer from headache 15 or more days per month for more than three months. The World Health Organization (WHO) considers those with CDH to be as disabled as those with dementia, active psychosis, or quadriplegia. CDH affects 3-5% of the population, a significant minority of which do not respond to conventional treatments. Disorder of the greater occipital nerve is one of the causes of cervicogenic headache, and stimulation of this nerve has shown great success for these refractory cases. Precision Brain, Spine & Pain Centre claims ONS helps up to 70% of the patients selected for treatment, and that on average, pain scores are reduced by around 50%.

Several studies have been done to further examine the efficacy and best approach for ONS, with varied results depending on the patient's specific condition. A 2003 study by Popeney and Alo administered ONS for 25 migraine patients who didn't respond to conventional treatments. There was an average follow up time of 18 months, in which 88% of patients reported at least 50% reduction in headache frequency or severity after the ONS was implanted. The average 3-month headache frequency decreased from 76 days to 38 days, and average severity (reported on the Visual Rating Score, scaled from 0-10) decrease from 9.3 to 5 gues with 10 er migraine patients re ing more than 90 ter one month, and all ulted in 9 repo pain patients stating they would have the operation again. Similar results were reported at the 6-month follow up as well. Studies in other forms of CDH have shown more mixed results. In 2007, Magis and colleagues studied eight patients with chronic cluster headache (CCH). After an average follow up of 15 months, two were pain free, three reported a 90% reduction in attack frequency, and two had improvement around 40%. However, when stimulators were turned off, attacks often worsened within days. Similar studies have been done for cases of hemicrania continua, SUNCT, and SUNA, all of which showed a majority of patients showing substantial improvement, but again a wide variety of results. In some cases, there were adverse effects such as lead migration or muscle recruitment, but these were easily treated. Most of these studies concluded that it would be helpful to have better predictors of success with ONS, as the mode of action is currently poorly understood.

Major depressive disorder (MDD) affects nearly 16% of the American population, and is the leading cause of disability according to WHO. Historically, ECT and TMS have been used to treat depression, but there are concerns with amnesia, tolerability, high relapse rates, and a need for daily treatment for over a month. Thus, for severe refractors forms of depression, EpCS in the dorsolateral prefrontal cortex (DLPFC) may be a more effective and feasible treatment.

One EpCS study for eleven patients with MDD resulted in eight subjects reporting at least 40% reduction in the Hamilton Depression Rating Scale 28 (HDRS-28) (Pathak et al, 2012). At certain stimulated nodes in each patient's region of interest, they found large HDRS improvements, ranging from 52% to 93%. However, it was unclear where electrodes should be placed during EpCS in order to maximize the efficacy of the treatment. Another EpCS study showed a linear relationship between improvement in HDRS and distance from the precentral sulcus, but neuronavigational surgical suites are 11). Similarly, in an not designed to measure distan (Yopel es a lo urfa rTMS study for depr ween coil placement and ssion with line r r latio und HDRS improvement.

It is remarkable how simplistic our knowledge of the human head is. Specifically, while surgical atlases exist based on a very small number of patients (usually 1 or 2 per atlas), we still have little quantitative information on the range of shapes of the human skull and nerves. A few studies have attempted to characterize individual features (Loukas et al, 2006), but even these have provided very simplistic and descriptive statistics. Hence, there is a need for better quantification of the shape of the human skull and nerves as a basis for the design of medical devices.

Specific activities to be undertaken and a timeline allotted for each activity:

Using CT scans of roughly 15-20 patients representative of the population (adult men and women), I will segment the skull and occipital nerve of each subject using Seg3D

(http://sci.utah.edu/software/seg3d.html), an open source program developed at the Scientific Computing & Imaging (SCI) Institute. Next I will perform a statistical shape analysis of the head using ShapeWorks, another open source program developed at SCI

(http://sci.utah.edu/software/shapeworks.html). I will translate the image from scans into a modifiable Shapeworks model. Shapeworks also allows us to define correspondence points on the head so that we can find group shape variation. Using these different degrees of variations at different points in the head, we can create a shape map that reflects the statistically significant group difference and easily visualize skull variability. In the future, this will give us the ability to also segment the occipital nerve from the patient scans and map this segmentation onto our shape map of the head. This will give us a better idea of how to design patient-specific occipital nerve stimulators. All images will be provided from the International Neuromodulation Registry (University of Utah IRB #79586). is the PI for the registry, and will be added to this protocol as soon as he completes his CITI certification and Good Clinical Plactice (GCP) ining subects rch. na ese 1. May 4-14: complete CITI and GCP certification; upon con-pletion will add

to the IRB protocol.

 May 14-June 11: perform segmentation of skull from CT images using Seg3D; perform segmentation of occipital nerve from MRI; both activities will be performed under supervision of



- 3. June 11-July 9: perform shape analysis of segmentations under supervision of **and and**
- July 9-August 3: document results and work with provide the second second
- Throughout summer semester: attend weekly Lab meetings; attend weekly mentorship meetings with Dr.

Relationship of the proposed work to the expertise of the faculty mentor:

Dr. is an expert at clinical and computational analysis of invasive and non-invasive experience performing patient-specific computational analysis of neuromodulation therapies based on medical imaging (MRI and CT). On this subject he currently teaches the Introduction to Image Based Modeling (IIBM) course (BIOEN 4702/6702). His office and lab are at the SCI Institute, which has unparalleled resources for conducting the work proposed in this UROP application. A full listing of resources is beyond the scope of this application, but through the Lab, the SCI Institute and the IIBM course laboratory we will have all of the hardware and software resources necessary to conduct the activities proposed in this application. Dr. has previously mentored two UROP awardees and is very familiar with the process and expectations of the program. In addition, two add lav agre d t ıst, E idance on skull oar **Ipa** segmentation will b or of Spine Imaging tis fron in the Department of Radiology at the University of Utah. Dr. will provide expertise on bone segmentation from computed tomography (CT) images as well as identification of the occipital nerve from structural MRI. Second, guidance on ShapeWorks will be supplemented with expertise from

Dr. PhD, Director of the School of Computing at the University of Utah. Dr. was the originator of ShapeWorks who developed the statistical models that are the basis of the software, and since then he has overseen its development. Dr. will provide expertise on identifying correspondence points on each medical image.

Relationship of the proposed work to the student's future goals:

I am currently working towards an honors degree in Computer Science with a minor in Mathematics, and while the proposed research is far from pure computer science or mathematics, there is a great deal of overlap with both my degree and my personal interests. I joined the Lab during the Fall 2017 semester with the hope of applying computer science skills outside the world of computers, and was immediately offered the opportunity to do so. With some of my research, such as programming imaging software in Python, I've been able to apply my education directly, but with other work in the lab, the most valuable skill has been being able to quickly familiarize myself with new software and design processes to work efficiently. With the proposed work, I intend to continue to work on this skill as I use the Shapeworks software to discover a process that others can use to do statistical shape analysis of the head. This research experience will also give me a strong foundation to work from as I continue into graduate school in the next few years, where I intend to continue to research emerging technologes, nopefully in neuroscience. While my current backgound in neuroscience is limited, I intend to ange that w 1 this xperence as continue b unfamiliar ch to territory as I have over the last semester. Although I do plan to have a career in computer science, the proposed work would give me the necessary background to continue to work and research in these highly interesting fields of neuroimaging and biomedical engineering and apply my computer science skills in a unique way that my classes alone could not teach me.