Opioid Abuse Risk in Chronic Pain Patients: An fMRI Analysis of Anticipation Pathway Activity using Monetary Incentive Delay (MID) Tasks

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Abstract

As it has been estimated that approximately 10% of chronic pain patients misuse opioid analgesics, current research is being performed to analyze why this population may be more at risk than other patient populations (Garland, Froeliger, Zeidan, Partin, & Howard, 2013). Using the fMRI data of over 70 subjects, collected at the University of Michigan, this study will analyze whether there is significantly different brain activity in the dopamine pathways of chronic pain patients versus their control counterparts. If a physiological difference can be found, it would increase the ability of healthcare providers to identify and prevent opioid abuse by opening up another method to screen patients for risk.

Background

The American Pain Society outlined a series of criteria in 2009 that helped healthcare providers assess which chronic pain patients would do best on an opioid analgesic plan as part of a campaign to decrease opioid abuse in the United States (Chou, et al., 2009). Despite this outline of recommendations to healthcare providers, certain studies have found that approximately 10% of chronic pain patients on opioid pain management plans struggle with opioid misuse (Garland, Froeliger, Zeidan, Partin, & Howard, 2013). Little research has been done to see how chronic pain can affect likeliness of abuse, though other factors such as "baseline pain intensity, psychological distress, and status as a cigarette smoker" have been found to be good indicators of a high potential for abuse (Garland, Froeliger, Zeidan, Partin, & Howard, 2013). Currently, there is a lack of research on how chronic pain can affect neuropathways, and it is for the purpose of filling that gap that the current research project was proposed.

One understudied aspect of chronic pain is how experiencing chronic pain can affect the anticipation and reward pathways of the brain—pathways that are connected with addiction formation. Much of the psychological studies today that deal with those pathways rely on a task called Monetary Incentive Delay (MID) developed by Brian Knutson in the late 1990s. The MID task functions as follow: a

task incentive is presented, in the form of some monetary consequence, followed by a fixation phase (usually a blank screen with a plus sign) for a set amount of time. After the fixation state, the subject is required to complete a specific, pre-practiced task, following which their performance is announced to them. This incentive, fixation, task, and feedback loop is then repeated several times, with varying incentive conditions and difficulty levels. The benefit of using this task, as opposed to others, lies in the fact that a researcher can induce an anticipatory phase in a subject regularly and reliably. The amount of the reward or punishment can be varied, generally establishing itself as a seven-condition task: three reward possibilities (high, medium, and low), three punishment possibilities (high, medium, and low), and one neutral condition, where no money is at stake. These feedback options are shuffled and presented to the subject in a random order, allowing the researcher to analyze the anticipation of the subject under several conditions of magnitude and association (positive or negative) in one experiment. The feedback stage of the MID task also allows for the analysis of positive and negative consequences in the brain, whereas the fixation phase is critical for looking at anticipation (Knutson & Heinz, 2015). This task has been applied in many different studies in a variety of ways, and its multiplicity of analyzable data recommended it to be the method of choice when the University of Michigan experiment was designed.

The progress of the MID task can be imaged using functional magnetic resonance imaging (fMRI). An MRI machine utilizes magnetic field pulses to alter the alignment of the hydrogen molecules in the body, and can give precise imaging of the body without the use of radiation. An fMRI relies on blood oxygen level dependent (BOLD) imaging to track areas of activity, as blood flow will increase to active parts of the brain in response to an increased need for glucose in the area; the reason this shows up on an fMRI has to do with the difference in how oxygenated and deoxygenated hemoglobin react to magnetic fields (Gaillard & Goel). In 2001, Knutson performed an experiment with the MID task and fMRI images that showed that the nucleus accumbens codes for the expectation of a positive consequence, whereas the medial caudate performs to relate to the brain the magnitude of an incentive, good or bad (Knutson, Adams, Fong, Walker, & Hommer, 2001). The current study has built off of that discovery, and wishes to analyze

the differences in the nucleus accumbens and the medial caudate specifically within chronic pain patients, at low and high risk of opioid misuse, in comparison with a control group in order to see if the way the brain reacts to anticipation and magnitude of the consequence changes in this population. A difference in their response to either could indicate that the brain is more likely to form addictive habits.

Methods and Timeline

The study on this topic was designed and performed at the University of Michigan. My project, since beginning at this lab in October of 2017, has been to organize, identify, and sort the data so that analyses could be performed. This work will continue until the end of the spring semester, as there is still much to be done before the actual project can commence. In the months of March and April, I will finish identifying the behavioral data obtained during the fMRI scans, and then I will write up algorithms that will allow us to calculate the start times of each phase of interest (anticipation and feedback especially). With that knowledge, we can commence the process of modeling and reconstruction.

Over the course of the summer, three main phases will need occur within the 120 hours allotted for the project. The first phase (the first 30 hours) will be creating models for the computational analysis of brain activity. These models will tell our programs when to look for certain brain activity, with the principle focus of the project being periods of anticipation. Additionally, these models will have to take into account the effects of the delay of hemodynamic responses. In building these models, I will work closely with my mentor and other University of Utah faculty within the bioengineering department to understand the mathematical functions behind this process, specifically the convolution of a hemodynamic response functions.

The second phase, and next 30 hours, will be to reconstruct the fMRI files. Thanks to the information we collected this fall and winter—year of scan, model of the MRI, etc—we are currently contacting our colleagues at the University of Michigan in order to figure out how each group's images need to get reconstructed. Our goal is to reconstruct in two different ways: once by the conventional method,

which is quick and standardly used, and once using an iterative method that has been shown to give better image quality. Based on the results of both methods of reconstruction, we will be able to decide which method gives the better image for each subject and produces the least amount of artifacts. My interest in this portion of the project is to understand more about the inverse Fourier Transforms that are applied to take the image out of the frequency domain, in preparation for an Image Modeling course I hope to take in Fall 2018.

The last phase will be an overall analysis of the results, accounting for an additional 40 hours. Our experiment was designed with 7 conditions: 3 degrees of reward (high, medium, and low), 3 degrees of punishment (high, medium, and low), and a neutral condition, where there was neither a reward nor punishment for the subject's performance. Our hypothesis is that there will be physiological changes in the brains of chronic pain patients, particularly in the nucleus accumbens and medial caudate—areas that have been previously shown to react to anticipatory input. The change we are looking for could present itself in one of two forms: or the above mentioned parts of the brain showing an over-abundance of activity during anticipation phases, or two, those same parts of the brain reacting significantly less strongly to anticipatory input than the control group. We will then statistically analyze the differences to see if they are significant or not. Another layer of analysis that can be performed relates to the Pain Medication Questionnaire—a questionnaire that can measure misuse risk. The patients that participated in this study filled out this questionnaire, so further analysis can be completed to compare the results of the fMRI with the results of the questionnaire.

The last 20 hours of the project will be allotted towards collecting the analysis data and writing up a report on the findings that will later to be translated into a poster presentation for the next Undergraduate Research Symposium. The expected completion time for the entire project is the beginning of August.

Mentorship

____ is the Principle Investigator of the Social Motivation Imaging Lab (SMILe), and is also an assistant professor in the Department of Psychiatry at the University of Utah. She obtained her undergraduate degree at the University of New Mexico in Biology and Psychology, with a minor in Chemistry, and later went on to get her PhD at the University of Michigan in Neuroscience. Beyond her traditional courses of study, she has also become proficient in several computer languages, and encourages all of her students to do the same. Much of her research has been focused on the effects of social motivation, especially in cases of substance abuse. ___ has proven to be a great mentor who really encourages her students to work out solutions for themselves. Since joining the lab in October of 2017, she has allowed me to explore my own ways of accomplishing tasks, which has helped to make me a more independent worker and critical thinker. In allowing me to participate in the cleanup and reorganization of the fMRI data from the University of Michigan, she helped me to become intimately familiar with the data, so that this summer I can perform the analysis with a firm understanding of the context of the data. Her foresight, as well as her trust in her undergraduate students, makes her an excellent mentor.

Future Goals

As a Biomedical Engineering major, my position at SMILe has helped me to explore the intersection of engineering and its medical applications. I have been able to work to further develop my coding skills, as wells as apply myself in learning more about the mathematics behind medical imaging through the exploration of fMRI reconstruction. The environment of SMILe has encouraged me to reach out to my professors to deepen my knowledge about the topics we learn in our classes so that I can be a better researcher, and as a consequence, a better student. Working in this lab has also allowed me to become Collaborative IRB Training Initiative (CITI) certified in Good Clinical Practice and Human Research, as well as HIPAA certified, which has allowed me to access a broader spectrum of research and experience. My post-undergraduate aspiration is to apply to medical school in Summer 2019, with the eventual goal of co-owning my own practice. All of the exposure I can get to reading fMRI's and becoming familiar with neuroanatomy can only assist me in preparing for medical school. Additionally, early exposure to medical

research will increase my capacity to seek out and understand the current research in my eventual field of study and ensure that my patients are getting the best care available. This topic of opioid abuse is especially relevant to my future work, and all the research that can be done now will help myself, as well as other healthcare providers, to prepare better courses of treatment for patients who suffer from chronic pain.

Bibliography

Chou, R., Fanciullo, G. J., Fine, P. G., Adler, J. A., Ballantyne, J. C., Davies, P., . . . Miaskowski, C. (2009). Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain. The Journal of Pain, 10(2), 113-130.e22. doi:10.1097/01.tpm.0000348660.36800.e9

Gaillard, F., & Goel, A. (n.d.). BOLD imaging | Radiology Reference Article. Retrieved March 13, 2018, from https://radiopaedia.org/articles/bold-imaging

Garland, E. L., Froeliger, B., Zeidan, F., Partin, K., & Howard, M. O. (2013). The downward spiral of chronic pain, prescription opioid misuse, and addiction: Cognitive, affective, and neuropsychopharmacologic pathways. Neuroscience & Biobehavioral Reviews, 37(10), 2597-2607. doi:10.10

Knutson, B., Adams, C., Fong, G., Walker, J., & Hommer, D. (2001). Anticipation of Increasing Monetary Reward Selectively Recruits Nucleus Accumbens. JNeurosci, 21, rc159, 1-5. doi:10.1016/s1053-8119(01)91773-216/j.neubiorev.2013.08.006

Knutson, B., & Heinz, A. (2015). Probing Psychiatric Symptoms with the Monetary Incentive Delay Task. Biological Psychiatry, 77(5), 418-420. doi:10.1016/j.biopsych.2014.12.022

Knutson, B., Westdorp, A., Kaiser, E., & Hommer, D. (2000). FMRI Visualization of Brain Activity during a Monetary Incentive Delay Task. NeuroImage, 12(1), 20-27. doi:10.1006/nimg.2000.0593

Lindquist, M. A., Loh, J. M., Atlas, L. Y., & Wager, T. D. (2009). Modeling the hemodynamic response function in fMRI: Efficiency, bias and mis-modeling. NeuroImage, 45(1). doi:10.1016/j.neuroimage.2008.10.065