The Implications of Early Life Stress on the Endogenous Dopamine System with a Focus on Sex Differences

Proposal for Undergraduate Research Opportunities Program Summer 2017

University of Utah

Mentor: _____

Department of Psychiatry

Example

Statement of the Topic of Research:

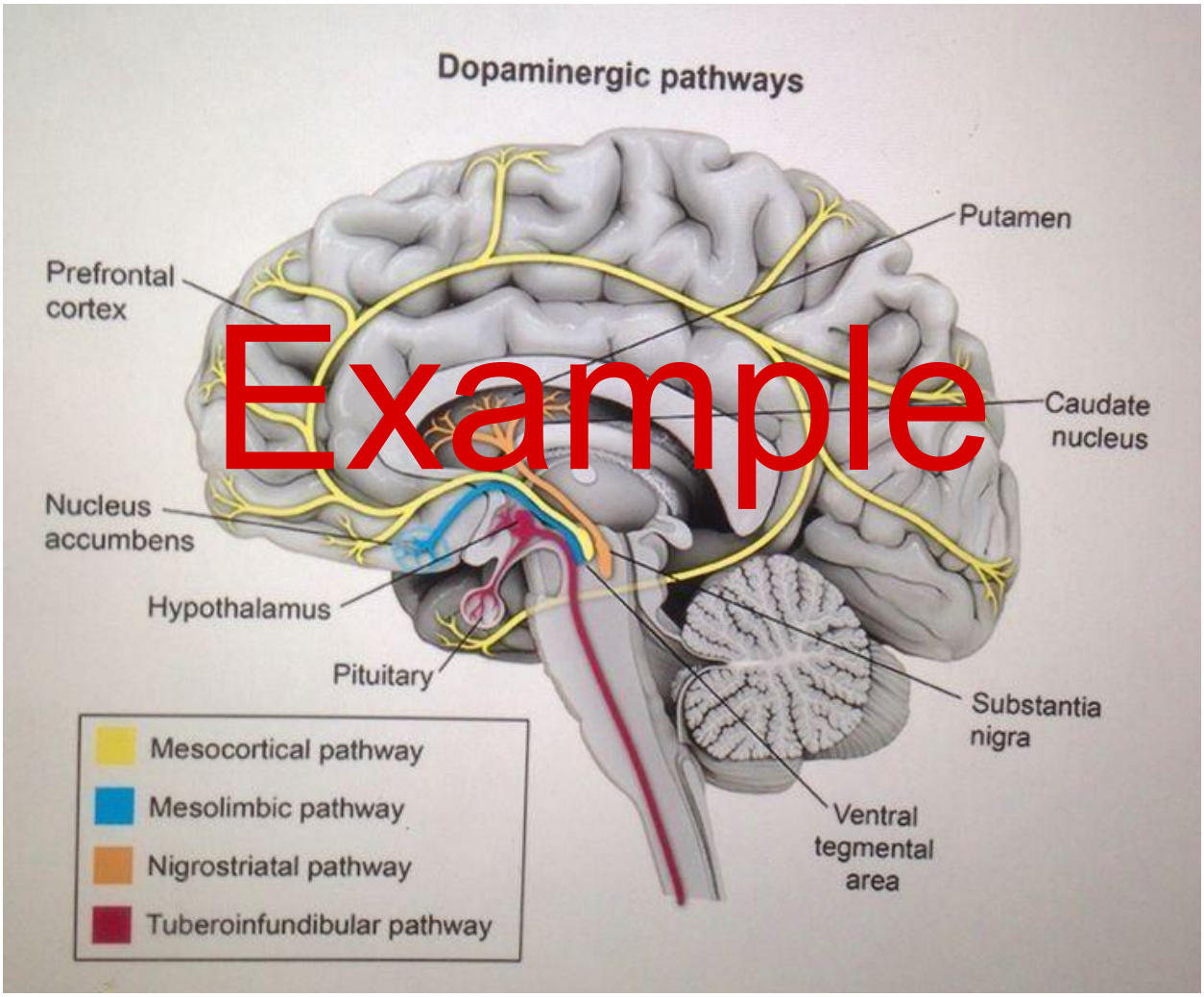
Early life stress (ELS) has been shown as a predictor for locomotor hyperactivity and inattentiveness toward an emotionally meaningful acoustic stimulus (Bock, 2016) as well as anxiety, depression, and schizophrenia in animals (Majicher-Maslanka, 2017) and predictor for anxiety, alcohol, and drug dependence in humans (Enoch, 2010). Early life stress can be measured using a self-report questionnaire like the adverse childhood experiences (ACE) and family experiences questionnaire (FEQ). According to the Center for Disease Control and Prevention, the ACE questionnaire is used as guidance for risk factors ranging from risky health behaviors to early death. This research study intends on better identifying what endogenous dopamine changes may arise with correlating ACE scores.

Much of the research on ELS has been focused on studying rodent populations; few studies have targeted endogenous dopamine changes in human populations and even less have evaluated these dopamine differences in females compared to males using Positron Emission Tomography (PET). This research opportunity is designed to observe how stress in childhood correlates to physiological changes in several brain structures along later in life.

Relevant background/literature review:

Positron Emission Tomography utilizes radiotracers which bind to receptors and emit photons as they decay. The PET machine detects these photons as they are emitted into space and generates a three-dimensional image of a brain. There is a plethora of radiotracers available to be used by scientists; selection depends on exactly what the intention of study is. Radiotracers are created by either proton bombardment or neutron irradiation, either method operates by changing the atomic weight of an atom, which ultimately outturns a highly unstable compound that will emit a detectable photon as it decays. Some radiotracers and their function include Xenon-133 which is used to image the lungs and has a half-life of 5.27 days (Jones, 1978) or Fluorine-18 which has a half-life of 109 minutes and is used

to image cancer (Rodriguez, 2016). The data set which will be analyzed in this research project included the 11C-raclopride radiotracer which has a half-life to 20 minutes and was chosen due to its selectivity toward cerebral dopamine receptors along with its ability to monitor dopamine receptor activity along the mesolimbic pathway (see fig. 1) in the brain (Kohler, 1985). Mesolimbic structures include the nucleus accumbens, ventral tegmental area, ventral striatum, amygdala, hippocampus, and hypothalamus. Raclopride's binding to D2 receptors is inversely correlated with dopamine release.



(Figure 1)

Research on the mesolimbic pathway has led to an understanding that it plays a significant role in both reward and stress. Colleagues to the lab investigated this pathway during a study by inducing participants in a pain/stress state and found the dopamine release in the basal ganglia to be higher than that at baseline. This observation suggests that there is a mesolimbic dopamine response to aversive stimuli in addition to reward (Scott, 2006). Alongside that, an earlier PET study showed that upon acute stress, individuals with low maternal care had a significant release of dopamine into the ventral striatum (Prussner, 2004). Prussner's findings showed that humans release dopamine in the ventral striatum in response to stress. This work will be extended by further investigation of early life trauma on biological sex differences because there is a possibility that men and women are affected differently by these mechanisms.

It is important to research endogenous dopamine activity for countless reasons especially for both clinical and educational reasons. Clinically, it is important to develop drugs to aid people with brain diseases or as preventative supplements. It is also important to study these mechanisms so that the scientific community has a better understanding of how the brain operates. Using baseline PET data and questionnaires like the ACE, the intention of this research is to further infer what endogenous dopamine changes happen at the receptor level of the brain and how these changes correlate with ACE scores.

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

Activity 1: Compile data and compute trauma scores

Compile data from the family experience questionnaire (FEQ) and work alongside a trauma researcher in the lab to analyze this data to compute scores. This will extend my understanding of how scoring of questionnaires is facilitated as well as the neurobiological effects of early life trauma. This will also increase my understanding of neurobiological changes that may place persons at risk of certain psychiatric conditions such as addiction. People with ACE scores above 4 are considered at risk of

chronic health conditions such as heart disease or lung cancer as well as psychological conditions such as depression and violent behavior.

Timeline: May-June 2018

Activity 2: Analyze the data through Matrix Laboratory, Statistical Package for the Social Sciences, and Statistical Parametric Mapping.

This data to be worked with is currently available and ready to be preprocessed and analyzed. Once I have preprocessed the data, I will then perform a thorough data analyses on the differences between people who reported experiencing early life trauma and on people who did not report experiencing early life trauma, I will analyze sex differences between people with reported early life trauma, and I will analyze differences in the age of onset of traumas. To do this, I will be using the software mentioned above to perform statistical analyses of the participant's data. Matrix Laboratory (MATLAB) and Statistical Package for the Social Sciences (SPSS) are used by a multitude of industries; I will gain valuable knowledge from both computing programs by running an in-depth analysis of my data. Statistical Parametric Mapping (SPM) is software limited to analyzing brain imaging data; by utilizing this software, I will procure apprehension of testing hypothesis of PET data. Alongside processing, I will become accustomed to organizing a standardized template space for storage of the data. By volunteering at the lab, I have become accustomed to using the Linux command line and I will further contribute to this skill by translating it to the MATLAB and SPM command lines. Using the data analysis software will be the most intensive because I hope to acquire profuse comprehension of the data-analysis step in scientific research. I believe accomplishing a thorough analysis of data will institute a better researcher out of me.

Timeline: June-July 2018

Activity 3: Preparation for presentation

After meticulously analyzing my trauma data, I will I will prepare it for presentation for the upcoming UROP research symposium. To do this, I will prepare and submit an abstract as well as prepare a poster for presentation.

Timeline: July-August 2018

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

_____ is faculty in the Psychiatry Department of the University of Utah and has been mentoring me in the lab since May of 2017 in which I assisted her in the lab's current clinical trials on Oxytocin & Motivation. _____ work focuses on oxytocin, reward, and motivation. Her current clinical trial is investigating how oxytocin influences social rewards. She is a member of the Society for Neuroscience and has over three dozen publications. In the past she has emphasized my independence as important for gaining adequate experience but also insists that I come to her for questions whenever I am confused. She has another student doing UROP this spring 2018 semester and already has the experience necessary to help me in my research.

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

By volunteering in the lab, I have gained valuable knowledge to how participants have been run in a clinical trial, how data is processed and stored, and how a research lab operates. Because of this I aim to focus on gaining skills in data analysis through common software used in this field such as MATLAB, SPSS, and SPM. Because these software systems are so versatile, I will be able to apply knowledge to many different fields. I will also gain experience analyzing data using multiple forms of statistics, which will give me further knowledge in how data analysis is conducted.

The proposed research will aid me in acquiring the skills necessary for me to continue my education toward achieving a master's degree in the field of neuroscience. I hope to attend graduate

school soon after I graduate with my bachelor's degree in psychology and to eventually begin doing my own research and start contributing as a member of the scientific community. This research project is heavily focused on the data analysis aspect of research because I have minimal experience in this area. I believe that It is important for me to have proper comprehension in this aspect of research. Having already assisted in clinical trials and entering data, moving forward toward performing statistical analysis will prompt me into being a well-rounded researcher, therefore better able to achieve in the field of academia.

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