Oxytocin Genotypes and Social Affiliation: A Model of the Genetic Underpinnings behind Social Bonding

*Project Purpose:

The proposed project will investigate the role of oxytocin receptor genetic variation on social affiliation using a rhesus monkey (*Macaca mulatta*) model. Specifically, this project aims to study the association of genetic variation within the oxytocin receptor (OXTR) gene and social affiliation and aggression. This project will make use of an existing data set collected in 2016 and 2017. I played a primary role managing and coordinating student intern data collection and entry over the summer of 2017. To accomplish this goal, I will use behavioral data that interns and I collected using an established ethogram and DNA that I extracted from blood samples.

*Project Importance:

It is widely-accepted that the neuropeptide oxytocin plays a role in mediating social behavior and bonding between humans. Oxytocin is a phylogenetically old biochemical believed to modulate bonding across many mammalian species, including primates (McCall, Singer, 2012). Deficits in the oxytocin system are suspected to play a role in the development of many disorders associated with severe social deficits, such as autism spectrum disorder (ASD), a disorder typically characterized by poor social skills, including deficits in understanding social cues, and in social bonding (Campbell et al., 2011). On the other end of social spectrum, other studies suggest that a shortage of oxytocin availability may increase the risk for aggression and violence (De Jong & Neumann, 2017).

As oxytocin does not cross the blood brain barrier, to investigate this neuropeptide, some researchers have opted to administer oxytocin intranasally, which studies demonstrate that it increases oxytocin levels in the brain, resulting in increased sociality and positive feelings towards a social partner (Lukas et al., 2011). Some studies suggest that some of the social deficits exhibited by children with ASD can be ameliorated via intranasal oxytocin administration (Andari et al., 2009).

However, there is some suggestion that this experimental administration is more effective for some individuals than it is for other (Bartz, Saki, Bolger, & Ochsner, 2011), and there is evidence that this variation may be genetically mediated (Skuse et al., 2014). The proposed project investigates the contributions of a single-nucleotide-polymorphism (SNP) G-to-A mutation of the oxytocin receptor gene (OXTR), a gene that others have suggested may contribute to oxytocin-mediated deficits in social behaviors related to social bonding and affiliation in humans (Skuse et al., 2014), and aggression using a rhesus monkey model.

In humans, one variant, a G-to-A mutation of in the OXTR gene is believed to reduce central nervous system OXTR functioning (Jacob, Brunea, Carter, Leventhal, Lord, & Cook, 2007), with one study suggesting that individuals with the OXTR G-to-A mutation exhibit a variety of social deficits (Baribeau et. al, 2017). Because genetic expression is environmentally- and situationally-dependent, the discovery that individuals an A allele SNP variant exhibit social deficits indicates that the oxytocin receptor gene shows promise as an area of future research. The proposed project will measure behaviors indicative of social affiliation or deficits, with the hypothesis that subjects possessing an A allele will exhibit reductions in bonding and sociality, leading to reductions in positive sociality and increases in aggressive behaviors. Rhesus monkeys are ideally-suited for these kinds of studies due to their similarity to humans at the genetic level, with a nonsynonymous SNP in the OXTR gene (rs53576) recently characterized in rhesus monkeys by our NIH collaborators (Baker et al., 2017). Rhesus monkeys exhibit human-like similarities in development and social behavior. Most importantly, the rhesus monkey environment can be closely-controlled in the laboratory setting, assuring homogenous experiences, and environments across subjects, something that is not possible in studies involving human subjects.

Studying the link between OXTR genotype and phenotypic expression may lead to early identification of risk for social deficits and psychopathology, and more importantly, to early interventions and potential treatments. Moreover, in a clinical setting, OXTR gene variation could be used as a potential diagnostic tool or as a window to potential treatments (e.g. gene therapy) for individuals with ASD and/or other disorders involving social deficits.

***Project Overview:**

To perform this research, I will use behavioral data collected on adult rhesus monkeys housed in semi-naturalistic conditions (i.e. outdoors in large social groups) at the California National Primate Research Center (CNPRC). Using an existing ethogram developed and used extensively by my research mentor and his laboratory, subjects' behaviors were recorded over the summer of 2017. The ethogram includes measuring subjects' time in social contact, time in close proximity, frequency of grooming, frequency of aggressive interactions, and the number of individuals within arm's reach at the end of each coding session. Blood samples were obtained for all subjects, from which I am in the process of extracting DNA. Samples will be genotyped for the OXTR gene by our NIH collaborators. Once genotypes and behavioral data are collected, I will use multiple regressions to assess the stability of interindividual differences in social affiliation and aggression. Then, genotype will be used as a second variable to assess the relationship of OXTR genotype and social behavior and aggression.

***Qualifications of Thesis Committee:**

Dr. Higley is internationally-recognized as an expert on primate social behavior, social development, and psychopathology. His work centers on gene-by-environment interactions and their influence on primate social development. He has over 150 publications, with over half investigating social development and development outcomes. Many of his publications, showing the effects of GxE interactions on social behavior, have been cited over 100 times. Dr. Higley has been a professor at BYU since 2006 and has mentored over 100 BYU students as they study nonhuman primates during a summer internship.

Dr. Lundwall is an expert in the field of cognitive neuroscience and has extensive experience researching ASD. She conducts research with infants, children, and adults, focusing on visual cognitive development. She has numerous publications and poster presentations, many of which are student projects that she has supervised. Each year she trains new research assistants totaling 88 students over the last 4 years.

***Project Timeline:**

- June-August 2018—Behavioral data were collected and DNA extraction began during a summer internship at the CNPRC.
- September—Genotyping of DNA samples.
- October 2018—Analyses will be run.
- November-December 2018—Manuscript will be prepared for submission.
- March 2019—Presentation of findings at the 2019 Mary Lou Fulton Conference
- April 2019—Thesis defense

* March 8 - last day to defend thesis!

***IRB or IACUC Approvals (Optional):**

All protocols were approved by the Institutional Animal Care and Use Committee of the University of California-Davis prior to beginning this work.

***Funding:**

For DNA extraction, a DNeasy Blood & Tissue Kit (250) was needed. The manufacturer is QIAGEN and amounted to $700.00. DNA shipping and the supplies are estimated to be about $200.00 and an additional $750.00 is requested to pay for genotyping and oxytocin assays. Thus, total amount of expenses equals $1650.00.

***Culminating Experience:**

I will present these data via poster session at the Utah Conference of Undergraduate Research in February, 2019 and at the Mary Lou Fulton Conference in April, 2019. Upon completion of this project, we aim to use our preliminary findings to guide the collection of additional data during June-July 2019. Once these additional data are collected, we will submit a manuscript for publication in a peer-reviewed scientific journal by Fall 2019.