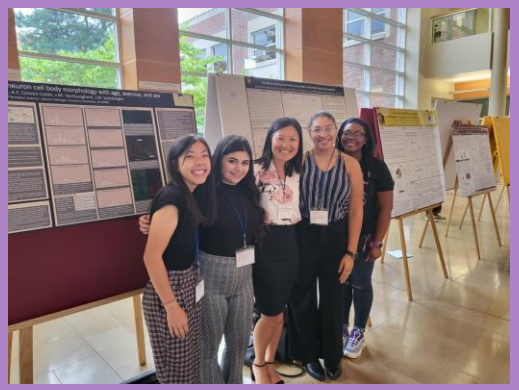
Society for Neuroscience Michigan Chapter

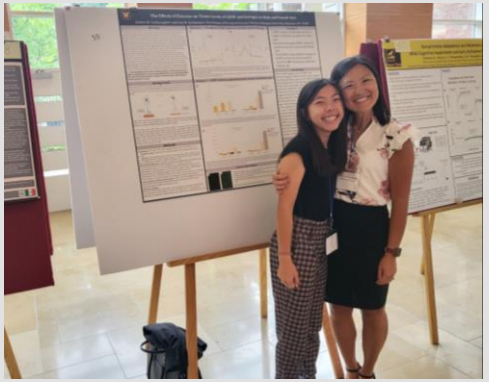
Western Michigan University

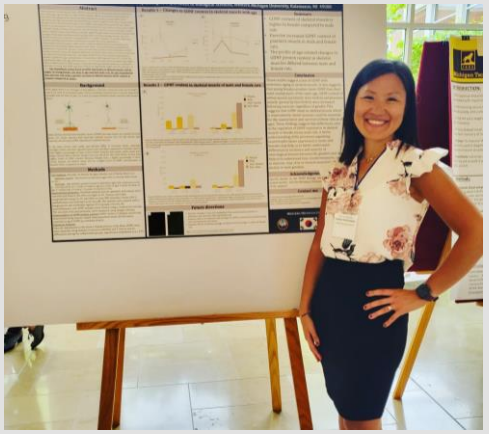
Hosted by CMU Central Michigan University

MISFN Annual Meeting

In August, graduate students from Spitsbergen and Byrd-Jacobs labs attended the 52nd annual meeting for the Michigan Chapter Society for Neuroscience, hosted at Central Michigan University.







The Effects of Exercise on GDNF and Estrogen Concentration in Male and Female Rats

Juliana M VanGyseghem (*presentor*), John M Spitsbergen

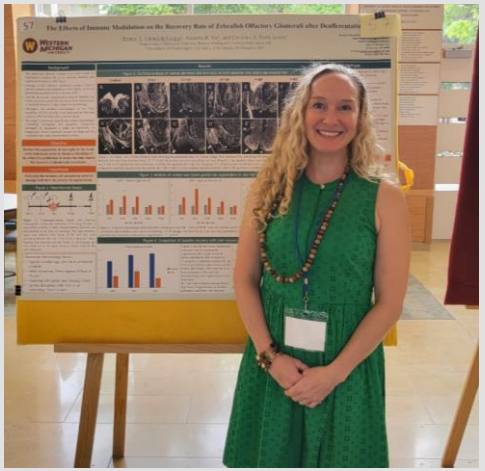
Males and females differ hormonally and neurologically as they age yet are given the same treatment for many neurological diseases. As aging occurs there is a loss of motor neurons, which could be explained by the reduced neurotrophic factor concentration. A possible way to maintain neuroprotection would be the production and release of a target-derived neurotrophic factor, such as glial cell line-derived neurotrophic factor (GDNF). Previous studies have shown that GDNF concentration has increased in skeletal muscle after exercise. However, this study has only been done in male rats. While exercise has been shown to mitigate the rate of development of degenerative loss of skeletal muscle mass, quality and strength called sarcopenia it has additionally been shown to increase estrogen receptors on skeletal muscle and increase levels of GDNF in skeletal muscle. Furthermore, it has been shown that GDNF and estrogen signal through similar intracellular pathway,

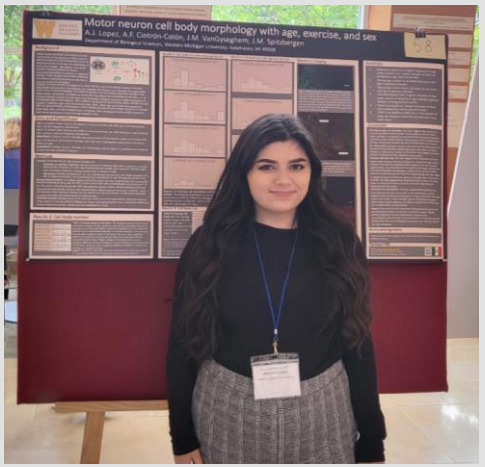
and through such pathways, estrogen can enhance intracellular GDNF signaling. Our hypothesis is that GDNF concentration will be lower in sedentary rats when compared to exercised. In order to gain a more complete picture of what is happening neurologically as we age, I will be looking at female rats and comparing them to male rats of the same age. Hindlimb skeletal muscle was taken from Sprague-Dawley rats, from both sedentary and voluntarily exercised males and females. Their ages ranged from 4 weeks to 18 months. Sedentary muscle was taken at 4 weeks, 6 weeks, 8 weeks, 12 weeks, 12 months and 18 months. Exercised muscle was harvested from 4 week old rats that had access to running wheels for 2 weeks, from, 8 week old rats exercised for 4 weeks, and from 12 month old rats who voluntarily exercised for 6 months. Western blot and ELISAs were used to measure GDNF concentration, while immunohistochemistry was used to visualize the motor neuron, end plates, and GDNF. There were differences in GDNF concentration between male and females as they aged and if they were sedentary vs. exercised. Motor end plates showed more complexity and larger surface area from skeletal muscle in exercised rats as compared to sedentary. Future studies will investigate if estrogen concentration changes in the same trend in these groups as GDNF concentrations. Understanding the role that neurotrophic factors play in neuroprotection as we age and exercise between different sexes, may help develop novel pharmacological treatments and could impact our healthcare system, as we can think about it in a more nuanced way.

Motor neuron cell body morphology with age, exercise, and sex

Lopez, A.J. (*presenter*); Cintron-Colon, A.F.; VanGyseghem, J.M.; Spitsbergen, J.M.

The number of individuals of old age has continued to increase within the last few years, accompanied by an increase in senescence - an increased risk for diseases and ailments, one of the most common being sarcopenia, or loss of muscle mass. In aged rat models, the neuromuscular junction shows morphological changes such as decreased end plate areas, pointing to possible changes in the muscle's associated motor neuron and proposes an interest in the motor neuron cell bodies in the ventral horn of the spinal cord. Exercise has been shown to exhibit neuroprotective effects on motor systems with age. Prior studies in our laboratory have shown a 13% decrease in the number of motor neurons in old male rats compared to younger male rats (Cintron-Colon, 2022). Males only make up 50% of the population and have distinctive features from females regarding certain health risks and effects of aging. The focus of this study is to examine the motor neuron cell bodies in sedentary vs exercised aged male and female rats, including the number, area, and area distribution of cell bodies. Time points of 8, 12, 52, and 78 weeks were analyzed to correlate to major developmental markers of the Sprague-Dawley rat model. The lumbar region (L4-5) of the spinal cord was cryoprotected and sectioned at 20 µm, followed by immunohistochemical staining with anti-choline acetyltransferase, a neuronal marker, and DAPI. Sections were viewed under a confocal microscope to identify, count, and measure motor neurons in lamina 9 of the ventral horn. A comparison of average cell body sizes showed no significant ($p<0.05$) difference between 8-week male vs female (667.61 ± 0.08 µm2 and 463.068 ± 0.11 µm2, respectively), between 52-week vs 78-week females (423.26 ± 0.12 µm2 and 326.76 ± 0.09 µm2, respectively). However, there was a significant difference between 12-week (531.91 ± 0.08 µm2) vs 52-week females, and between 12-week vs 78-week females. Exercised females showed a significantly larger average cell body size compared to their sedentary counterpart. Following histogram analysis, 12-week females showed a higher frequency of cell bodies >1000 µm2 in size, while 52-week and 78-week females showed a higher frequency of cell bodies between 100 and 500 µm2 in size. The average number of cell bodies showed a decreasing trend with age, and there was no significant difference in the average number of cell bodies per section between 52-week (19.56 ± 0.19) vs 78-week (17 ± 0.17) females. The decrease in frequency distribution of cell bodies >1000 µm2 in size may be attributed to an overall decrease in size of all cell bodies with age or may suggest a loss of fast-type motor neurons with age since larger cell body sizes are observed in lower numbers in aged rats.





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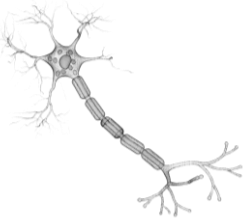

Potential Sex Differences in Mitral Cell Dendritic Morphology Following Injury and Recovery

John P. Rozofsky (*presenter*), Joanna M. Pozzuto, Bonnie E. Ebendick, Tara L. Maser, Abdulaziz S. Shebrain, Brittany A. Richards and Christine A. Byrd-Jacobs

Recovery after neuronal injury remains an enigmatic dilemma to the scientific community. The zebrafish(ZF) olfactory system provides an excellent model to address this issue due to its inherent plasticity. Mitral cells (MC) of the olfactory bulb (OB) serve as the primary relay neurons for transmitting odorant information from the olfactory epithelium to output targets. Our lab has developed a novel methodology to quantify the extent of injury and recovery of MC dendritic arborization as a result of chronic deafferentation, which was achieved through the repeated application of the detergent Triton-X 100 to the right olfactory epithelium. The left side remained untreated to serve as an internal control. ZF were then allowed to recover for 3 or 8 weeks, and morphological measures were quantified based on number of tips, total length of dendritic branches, size of dendritic field, and distribution of fine processes.

Consideration of sex as a biological variable has become increasingly important in scientific research. Previous work has shown that female animals of some species have a propensity to recover more quickly than males following neuronal injury. We hypothesize that sex differences may extend to ZF, which could lead to further understanding of the differences between male and female neuronal recovery. Current work aims to decipher potential differences that may exist within OB structures during growth as well as following injury and recovery between males and females. Control measurements of MC dendritic arbor features show potential differences in male and female ZF with males possessing fewer number of tips and a decreased optical density at the 8-week timepoint. However, this significant difference appears to attenuate at 16 weeks within control animals. Combined data of males and females shows that following 8 weeks of repeated damage, MC dendritic morphology within the deafferented OB significantly decreased in number of tips, total length of dendritic branches, size of dendritic field, and distribution of fine processes. When ZF are allowed to recover for 3 or 8 weeks these significant differences are alleviated as shown by a return of the analyzed morphological structures to near internal control levels. Interestingly, preliminary results appear to show quicker recovery of branch length in males while the number of tips appears to recover more quickly in females at the 8-week recovery time point. Although skepticism is warranted due to small sample sizes, this research furthers our understanding of the neurogenic processes in the ZF olfactory system, as well potential neurogenic differences between males and females. Understanding the morphological changes that take place within neuronal structures following injury and recovery is essential to demystifying the processes underlying neural regeneration and may lead to potential avenues for therapeutics in human populations.

The effects of immune modulation on the recovery rate of Zebrafish olfactory glomeruli after deafferentation

Bonnie Ebendick-Corpus (*presenter*), Susanna Var, Christine Byrd-Jacobs

Full recovery after neuronal damage is elusive for many organisms due, in part, to limited neurogenesis in adulthood. Zebrafish, however, are renowned for their persistent neurogenesis and regenerative ability. Although the brain's primary defense cells, microglia, play a vital role in both pro- and anti-inflammatory stages of recovery, the role of the immune system in Zebrafish injury response is not known. In under a week, Zebrafish are able to recover completely from olfactory epithelium chemical lesions. Since recovery depends on immune cell activity, we explored how modulating the microglial population would affect recovery rate of neuronal structures in the olfactory bulb. We hypothesized that reducing the immune cell population prior to damage will slow the process of regeneration. Our lab previously established a baseline recovery rate following chemical lesioning via detergent application to the right olfactory epithelium, with the left side acting as an internal control. This baseline characterization allows for time-matched comparisons with fish lesioned after exposure to the apoptotic drug L-clodronate which specifically targets and reduces the population of phagocytic cells. Locally injecting clodronate greatly diminishes the microglial population prior to lesioning. Using confocal microscopy to identify three glomerular structures labeled with anti-KLH after 4hr, 12hr, 24hr, 4 days, and 7 days post-lesioning, we compared the clodronate-treated recovery rate to baseline recovery rate based on changes in glomerular morphology. Previous work demonstrated that most fish fully recover in 7 days, with partial recovery evident at 4 days. We expected a delayed recovery after reducing microglial populations; however, clodronate-treated fish appeared to recover glomerular structure at the same rate or faster than baseline. Glomeruli were fully recovered in 7 days and many recovered by 4 days, several days sooner than untreated fish. While it is unclear if drug mechanism or pre-stimulating the immune system affected the rate, future projects will address this with three additional treatment groups: saline pretreatment, zymosan pretreatment, and clodronate treatment concurrent with damage.

In addition to structural analysis, behavioral experiments will address functional recovery. This work-in-progress will use perception of an odorant that maps to one of the assessed glomerular regions, as a marker for recovery. Detergent damages sensory neurons, thereby reducing sensitivity to some odorants, and recovered behavioral responses indicate restoration of neuronal function. Using both morphological and functional approaches in Zebrafish can better inform us of how conserved immune system features promote complete recovery in the nervous system of adult mammals.