receptors and shown to be susceptible to stress. METHODS/STUDY POPULATION: This study explored behavioral and neural impacts of early life stress in Long-Evans rats reared with or without limited access to bedding material during postnatal day (PND) 2-9. Corticosterone (CORT) levels were measured at PND8 and 70. During PND50-70, rats were assessed on Novel Object Recognition to test memory, Rotarod to evaluate cerebellar integrity, Elevated Plus Maze to assay anxiety, Social Preference, and Eyeblink Conditioning, a cerebellar-dependent and endocannabinoid-mediated task. Lipid analysis was performed on PND70 tissue samples of cerebellar interpositus (IP) nucleus via high-performance liquid chromatography and tandem mass spectrometry. RESULTS/ANTICIPATED RESULTS: Both male and female rats experiencing early life stress exhibited significantly impaired recognition memory (N = 16-20/group). Female rats having undergone stress exhibited decreased social preference compared to normally reared females (N = 11/group). Stressed males showed facilitated eyblink conditioning compared to normally reared males (N = 7-9/group). There were no group differences in rotarod or elevated plus maze performance or CORT levels at PND8 or 70 across rearing groups. At PND70, male rats experiencing early life stress exhibited a significant decrease in 2-arachidonoyl glycerol (2-AG) and arachidonic acid levels in the IP nucleus compared to normally reared males (N = 8-9/group). Compared to normally reared females, those experiencing early life stress exhibited a significant increase in prostaglandin E2 levels in the IP nucleus (N = 6-7/group). DISCUSSION/SIGNIFICANCE OF IMPACT: Early life stress, induced by limited bedding, resulted in sex-specific behavioral and lipid impairments. Results suggest that stress causes long-term alterations in endocannabinoid dynamics in males in the cerebellar IP nucleus and sex-related lipids in female cerebellum. These changes may contribute to observed long-term behavioral aberrations. Moreover, findings suggest these behavioral changes may be the result of negative-feedback dysfunction (as evidenced by decreased endocannabinoids in males) or increased neural inflammation or proliferation (as evidenced by increased prostaglandins in females). Future analysis will quantify mRNA and protein for cannabinoid receptors to better characterize aberrations to this system. Moreover, other neural regions dense with cannabinoid receptors (i.e., PFC, hippocampus) will be investigated. This work provides a basis for understanding stress impacts on the development of cognitive deficits observed in psychotic and anxiety disorders. Specifically, facilitation of eyblink conditioning complements research in humans with anxiety disorders. Broadly, understanding stress-related endocannabinoid dysregulation may provide insights into risks for, and the development of, psychopathology and uncover novel therapeutic targets with high translational power.

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Effects of Local Interleukin-6 on Mitochondrial Physiology in Skeletal Muscle

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OBJECTIVES/SPECIFIC AIMS: In the context of skeletal muscle, IL-6 plays a major role in muscle quality. The goal of this project was to study the influence of systemic IL-6 on skeletal muscle mitochondrial physiology, most notably mitochondrial function (respiration and ROS production) and mitochondrial content. METHODS/STUDY POPULATION: To determine the influence of interleukin-6 (IL-6) on skeletal muscle mitochondria, high-resolution respirometry was performed to simultaneously measure oxygen consumption (JO2) and ROS production in differentiated myotubes incubated with increasing IL-6 (0, 10, 50, 100 ng/mL) for 18 hours in serum free conditions. To evaluate the impact of IL-6 on mitochondrial content we performed western blots on cell lysates from treated cells, measuring proteins of the mitochondrial electron transport chain (ETC) using a cocktail antibody and PGC-1α/PGC-1ß for mitochondrial biogenesis. To determine the role of mitochondrial ROS production on JO2 and mitochondrial content, we co-treated differentiated myotubes for 18 hours with 50 and 100ng/mL IL-6 and the mitochondrial specific antioxidant, MitoQ and performed respirometry for mitochondrial functional measurements and western blots for mitochondrial content.Statistical significance was evaluated by using a 2-tailed Student's t-test and two-way ANOVA. Post hoc all-group analyses were conducted to determine which groups were different when the model was significant. RESULTS/ANTICIPATED RESULTS: Mitochondrial functional measurements show increased JO2 and increased ROS production in an IL-6 dose-dependent manner. Targeting mitochondrial ROS production with 0.5µm MitoQ attenuated IL-6 induced increases in JO2 and ROS production. Complexes I and II (CI, CII) of the ETC increased significantly in an IL-6 dose-wise fashion, and co-treatment with MitoQ normalized increases at 100ng/mL Il-6. 100ng/mL IL-6 significantly increased protein expression of PGC-1α and PGC-1ß. Co-treatment with MitoQ normalized IL-6 induced increase in PGC-1α. DISCUSSION/SIGNIFICANCE OF IMPACT: Our data suggest that when treated chronically at a high dose, IL-6 increases mitochondrial respiration, ROS production, and content. Targeting mitochondrial ROS production normalizes these mitochondrial adaptations. The present study provides new insights into mitochondrial physiology in the context of inflammation. Therapeutically targeting mitochondrial ROS production may impact skeletal muscle quality in certain populations.

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European Ancestry as a Risk Factor for Atrial Fibrillation in Puerto Rican Hispanics

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OBJECTIVES/SPECIFIC AIMS: Consequently, we have decided to evaluate the presence of single nucleotide polymorphism (SNP) previously associated with AF on a European-descent population in an attempt to first identify the most common loci present in the PRH population and then search for specific PRH SNP associated with AF. METHODS/STUDY POPULATION: A secondary analysis of a Puerto Rican population sample (n = 120) from The Pharmacogenetics of Warfarin in Puerto Ricans Study will be performed. We will implement data from the 1000 genome project to establish a control group of healthy PRH population. Will evaluate the presence of 111 known single nucleotide polymorphisms associated with AF in Europeans and determine the frequency in PRH population sample, and validate predictability of such SNPs. Using admixture informatic markers (AIM) analysis will determine the percentage of admixture by Yoruba, Native American and Iberic-European. Statistical analysis will include the use of the Pearson Product-Moment Coefficient correlation analysis and multivariate linear regression. For admixture will use Maximum Likelihood Estimation and Markov Chain Monte Carlo models. RESULTS/ANTICIPATED RESULTS: A higher frequency of AF associated European single nucleotide polymorphisms, and an overall higher percentage of European admixture will be associated with atrial fibrillation in Puerto Rican Hispanic patients.

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DISCUSSION/SIGNIFICANCE OF IMPACT: Our contributions here are expected to be the elucidation of European ancestry as a risk factor for AF. These contributions will be significant because it can provide a robust scientific basis for larger GWAS studies in the Puerto Rican community and further narrow down the mechanism specific to this population. Research in this subject could lead to early identification of patients with high risk of developing atrial fibrillation and further decrease incidence and disease burden in the PRH population. Puerto Rican Hispanics have an exclusive genetic admixture that makes for an appealing research subject that could deliver unique results.

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Expression profile of the ribbon synapse protein Ribeye in the zebrafish

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OBJECTIVES/SPECIFIC AIMS: Although two Ribeye protein isoforms have been identified in zebrafish, information about the identities of their variants is incomplete. This study aims to identify and characterize both of the Ribeye isoforms and their splice variants. METHODS/STUDY POPULATION: Immunohistochemistry was performed on the retina and neuromasts of zebrafish larva and adults.Ribeye expression was analyzed by western blot. Ribeye proteins will be separated, isolated and identified by mass spectrophotometry. RESULTS/ANTICIPATED RESULTS: Immunohistochemistry performed on larval and adult zebrafish retinas revealed the expression of Ribeye A in the inner and outer plexiform layers. Ribeye B was likewise expressed in both plexiform layers in larval zebrafish, but more pronounced expression in the outer plexiform layer in the adult zebrafish retina. Immunohistochemical experiments also demonstrated the co-expression of both Ribeye isoforms in the hair cells of both larval and adult neuromasts. Analysis of Ribeye expression by western blot showed the presence of more than the three previously identified variants. Current experiments are being conducted to characterize the additional Ribeye variants. We expect to identify the residual Ribeye protein as a result of this analysis. DISCUSSION/SIGNIFICANCE OF IMPACT: This study is necessary in order to gain a clear understanding of Ribeye expression in zebrafish tissues. Doing so will enable us to target this protein for gene editing to address outstanding questions about the mechanisms that govern ribbon synapse function. Synapse and synapse-associated proteins are involved in a wide-array of diseases that arise as a result of their dysfunction (e.g. blindness, deafness, bradycardia, autism spectrum disorders, and schizophrenia). Thus, it is important for us to identify the shared and distinct mechanisms that give rise to diseases associated with synaptic dysregulation. Such information could provide the basis for novel therapeutic interventions for synaptic disorders.

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Functional brain mechanisms of sensorimotor deficits in individuals with autism spectrum disorder

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OBJECTIVES/SPECIFIC AIMS: Abnormalities in sensorimotor behavior are present in the majority of individuals with ASD and associated with core symptoms. Cortico-cerebellar networks that control sensorimotor behavior have been implicated in ASD, but little is known about their function during sensorimotor actions. The purpose of this functional magnetic resonance imaging (fMRI) study was to examine cortical-cerebellar function during feedback-guided motor behavior in ASD. METHODS/STUDY POPULATION: Individuals with ASD (11-30 years; N = 18) and age-matched controls (N = 15) completed a visuomotor task of feedback-guided precision gripping during fMRI. Participants pressed with their right thumb and forefinger on a force transducer while viewing a green FORCE bar on a screen that moved upwards with increased force toward a fixed white TARGET bar. Individuals were instructed to maintain the FORCE bar at the level of the TARGET bar for 24 seconds. Target force levels were set at 20% and 60% of each participant's maximum voluntary contraction (MVC). Force variability was characterized as the coefficient of variation (i.e., standard deviation of the force time series / mean force output; CoV). RESULTS/ANTICIPATED RESULTS: Mean force did not differ between groups indicating participants were able to follow task demands. Participants with ASD showed increased force variability ($F(1,30) = 5.214$, $p = 0.03$) at both 20% ($d = .45$) and 60% ($d = .77$) MVC compared to controls. Compared to controls, individuals with ASD showed decreased activation in left angular gyrus during the visuomotor task compared to rest (AG; maximum $t = 4.31$). Individuals with ASD also showed greater visuomotor activation compared to controls in ipsilateral ventral M1, extending anteriorly into posterior ventral pre-motor cortex (PMv; maximum $t = -4.06$, cluster size = 38 voxels). This difference reflected the finding that control participants showed a selective deactivation of ipsilateral M1/PMv during visuomotor behavior, whereas individuals with ASD did not show this pattern. A significant group x force interaction was observed for contralateral Crus I activation (maximum $t = -2.42$) that was driven by an increase in activity during 60% compared to 20% MVC in control participants, while individuals with ASD showed no change in Crus I activation between force levels. DISCUSSION/SIGNIFICANCE OF IMPACT: Increased force variability in individuals with ASD suggests impaired processing of sensory feedback to guide precision motor behaviors. Individuals with ASD did not show deactivation of right motor cortex during visuomotor behavior relative to rest, suggesting reduced ability to selectively modulate motor cortical output. Reduced activation in left AG may reflect an inability to integrate visual, haptic, and proprioceptive inputs to reactively adjust ongoing motor output. Failure to show force-dependent scaling of Crus I in ASD suggests lateral cerebellar circuits do not adapt sensory prediction and error processes to maintain precision motor output during more demanding conditions. Together, our results demonstrate multiple cortical-cerebellar mechanisms associated with sensorimotor imprecision in ASD.

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Genomic Analysis of Primary Plasma Cell Leukemia reveals Complex Cytogenetic Alterations and High Risk Mutational Patterns

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OBJECTIVES/SPECIFIC AIMS: 1) Determine the mutational landscape, including translocation, mutations and mutational signatures as well as copy number variations of pPCL and identify significant

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