7:30AM REGISTRATION OPEN
7:45AM CONTINENTAL BREAKFAST
8:30AM WELCOME AND OPENING REMARKS
8:45AM Astrid Cardona, Ph.D., Department of Biology and STCEID, University of Texas at San Antonio
   Myeloid cells and brain inflammation: Insights into cellular activation, tissue damage and neuroprotection
9:10AM Naomi Sayre, Ph.D., Department of Neurosurgery, University of Texas Health Science Center at San Antonio
   Use of novel monoclonal antibody therapy for spinal cord injury
9:35AM Thomas Forsthuber, M.D., Ph.D., Department of Biology and STCEID, University of Texas at San Antonio
   Pre-clinical models of autoimmune demyelinating CNS disease for translational research
10:00AM Jonathan Savitz, Ph.D., Laureate Institute for Brain Research, University of Tulsa
   Relationship between neurotoxic kynurenine metabolites and hippocampal structure and function in depression
10:30AM KEYNOTE LECTURE
   Katerina Akassoglou, Ph.D., Department of Neurology and Gladstone Institute of Neurological Disease, University of California San Francisco
   Neurovascular Interactions: mechanisms, imaging, therapeutics
11:30AM LUNCH
12:30PM POSTER SESSION
2:00PM COFFEE (GATHER FOR ORAL SESSION 2)
2:15PM Pooja Singhmar, Ph.D., Department of Symptom Research, MD Anderson Cancer Center
   GRK2/EPAC1: central players in regulating chronic pain
2:40PM Erzi Kokovay, Ph.D., Department of Cell and Structural Biology, University of Texas Health Science Center at San Antonio
   Microglia in the adult stem cell niche
3:05PM Katherine Serafine, Ph.D., Department of Psychology, University of Texas at El Paso
   High fat diet-induced dopamine system dysfunction: Implications for obesity and metabolic diseases
3:30PM Jason O’Connor, Ph.D., Department of Pharmacology and Audie L. Murphy VA Hospital, University of Texas Health Science Center at San Antonio
   Brain kynurenine metabolism mediates cognitive and behavioral consequences of inflammation
   High fat diet-induced dopamine system dysfunction: Implications for obesity and metabolic diseases
4:00PM TRAINEE SESSION (ALL UNDERGRADUATE AND GRADUATE STUDENTS AND POSTDOCTORAL FELLOWS)
5:00PM CLOSING REMARKS
Dr. Akassoglou identified blood clotting factors as major mediators of neurologic disease. She made the unanticipated discovery that the blood clotting factor fibrinogen is a major activator of innate immune responses in the CNS. She developed novel imaging tools to study the neurovascular interface and therapeutic strategies to protect from neuroimmune diseases by blocking the damaging effects of blood factors in the brain without affecting their beneficial effects in blood clotting. Dr. Akassoglou takes a multifaceted approach to her research, incorporating animal modeling, in vivo two-photon microscopy, drug discovery, preclinical translational research, and biomarker studies. Her laboratory is a fertile training ground for junior faculty, postdoctoral fellows, graduate and medical students. Dr. Akassoglou has published over 68 papers in peer-reviewed journals and she is active in several national and international organizations, editorial boards, and funding agencies.

Dr. Akassoglou was awarded by the White House the Presidential Early Career Award for Scientists and Engineers (PECASE), “the highest honor bestowed by the U.S. government on outstanding early-career scientists and engineers”, the John J. Abel Award from the American Society of Pharmacology and Experimental Therapeutics (ASPET) for “original and outstanding research contributions in pharmacology”, and The Marilyn Hilton Award for Innovation in MS Research by the Conrad N. Hilton Foundation. She has also received the Dana Foundation Award in Brain and Immunoimaging and a EUREKA (Exceptional Unconventional Research Enabling Knowledge Acceleration) award from NINDS.

Dr. Akassoglou earned a BSc degree in biology and a PhD in neurobiology at the University of Athens, Greece. She was trained in neuropathology at the University of Vienna before performing her postdoctoral work at the Rockefeller University, and New York University. She started her laboratory as an Assistant Professor at the Department of Pharmacology at the University of California, San Diego where she was promoted to Associate Professor with tenure. She is now a Senior Investigator at the Gladstone Institute of Neurological Disease, and a Professor in the Department of Neurology at the University of California, San Francisco. She is also the founder and Director of the Gladstone Center for In Vivo Imaging Research, Associate Adjunct Professor of Pharmacology at the University of California, San Diego, and Secretary/Treasurer of the Molecular Pharmacology Division of ASPET.
Astrid E. Cardona, Ph.D.
Dr. Astrid Cardona is an Associate Professor of immunology at the University of Texas at San Antonio. After receiving her Ph.D in Microbiology and Immunology in 2002 at the University of Texas Health Science Center at San Antonio she continued her post-doctoral training at the Cleveland Clinic in the Department of Neurosciences at the Lerner Research Institute. She is currently a faculty of the Department of Biology and a member of the South Texas Center for Emerging Infectious Diseases. Her research is focused on microglia: neuronal communication during chronic inflammatory diseases including, multiple sclerosis, neurocysticercosis and diabetic retinopathy.

Naomi L. Sayre, Ph.D.
Dr. Naomi L. Sayre is an Assistant Professor of research for the UTHSCSA Department of Neurosurgery. She earned her Ph.D. from Tufts Sackler School of Graduate Biomedical Sciences in Boston, Massachusetts. Her research focus involves investigating the role astrocytes play in the central nervous system's ability to recover after stroke or traumatic injury.

Thomas Forsthuber, M.D., Ph.D.
Dr. Forsthuber is Professor and Endowed Chair of Biotechnology at the University of Texas at San Antonio. He received his M.D. and Ph.D. from the University of Tübingen, Germany and subsequently completed post-doctoral training in immunology at UCLA in Los Angeles and CWRU in Cleveland, where he also completed his Pathology residency at University Hospitals. Dr. Forsthuber's research focuses on translational models for the investigation of human autoimmune diseases, cytokine differentiation of autoimmune T cells using cytokine ELISPOT assay, and biomarker discovery for EAE/MS.

Jonathan Savitz, Ph.D.
Jonathan Savitz is a principal investigator at the Laureate Institute for Brain Research and an Assistant Professor in the Faculty of Community Medicine at The University of Tulsa. He graduated with a Ph.D in human genetics from the University of Cape Town in 2006 and subsequently completed post-doctoral training in neuroimaging at the NIMH. Jonathan's research is focused on understanding the role of the immune system in mood disorders by combining traditional immunological techniques with morphometric and functional MRI.
Pooja Singhmar, Ph.D.

Pooja Singhmar, Ph.D., is a postdoctoral research fellow in the Laboratory of Neuroimmunology, Department of Symptom Research, MD Anderson Cancer Center, Houston. She earned her Bachelor’s in Biochemistry from Delhi University, India followed by Masters in Biotechnology from IIT Bombay. She received Ph.D. in molecular and cell biology in 2012 from Indian Institute of Science where she worked on studying the molecular and genetic basis of neurological disorder microcephaly. She then joined Prof. Annemieke Kavelaars and Prof. Cobi Heijnen for postdoctoral training. Her present scientific research area includes the understanding the pathophysiology of different chronic pain disorders. Her main focus is understanding how GRK2 and Epac signaling regulate transition to chronic pain.

Erzi Kokovay, Ph.D.

Dr. Kokovay received a PhD in Biomedical Sciences from the University of New Mexico, School of Medicine in Albuquerque, NM where she studied the contribution of peripheral immune cells to degeneration and repair in animal models of Parkinson’s disease and stroke. She then went on to do Post-doctoral training at the Neural Stem Cell Institute in Rensselaer, NY. She is currently an Assistant Professor in the department of Cellular and Structural Biology at UT Health Science Center at San Antonio. Her research focuses on adult neural stem cells which are stem cells that persist throughout life in the mammalian brain and continuously produce neurons, astrocytes and oligodendrocytes. Neural stem cells are important in learning and memory as well as brain repair, thus understanding how they are regulated is key to understanding plasticity associated with memory and strategies to increase brain repair following injury. Her lab focuses on the influence of the neurogenic niche in regulating neural stem cell migration, activation and quiescence. Specifically, she is interested in how niche microglia and vasculature regulate neural stem cell function in the context of brain homeostasis, aging and brain injury.
Katherine Serafine, Ph.D.

Dr. Serafine received her B.A. in psychology from Norwich University in Northfield, VT. She received her M.A. in psychology as well as her Ph.D. in Behavior, Cognition, and Neuroscience from American University in Washington, DC. Her dissertation research focused on the neurochemical mediation of the aversive effects of cocaine, using classical conditioning procedures. Dr. Serafine then completed a postdoctoral fellowship in behavioral pharmacology at the University of Texas Health Science Center in San Antonio, TX. It was there that she developed a strong interest in the impact of diet on vulnerability to drug abuse. While in San Antonio, Dr. Serafine also worked with more complex procedures including operant conditioning assays like drug discrimination and self-administration. Her research interests include the impact of diet and drug history on abuse vulnerability. Recently, Dr. Serafine's research has also focused on the robust sex differences observed in diet-induced changes in drug sensitivity. Dr. Serafine joined the faculty in the Department of Psychology at the University of Texas at El Paso in 2015.

Jason O’Connor, Ph.D.

Dr. O’Connor received his Ph.D. at the University of Illinois at Urbana-Champaign in the Department of Animal Sciences. He then continued his postdoctoral training as a T32 postdoctoral fellow in the Division of Nutritional Sciences at Illinois where his research to understand the mechanisms by which inflammation impair brain function and contribute to depression began. In 2010, he moved to the University of Texas Health Science Center at San Antonio to begin his independent research career, and in 2014 he accepted an appointment as Research Health Specialist at the Audie L. Murphy VA Hospital.
Development of Potential Biomarkers to Forecast Treatment Response and Clinical Relapses of Multiple Sclerosis by Investigating the CNS-Specific Proteome Fingerprint of EAE.

Itay Raphael and Thomas G. Forsthuber

University of Texas at San Antonio

Despite extensive research, MS remains a disease that lacks a definitive prognostic test to predict imminent disease relapses. Thus, patients may undergo years of unnecessary treatments. Additionally, current treatments for MS vary significantly in efficacy between individual patients, and thus there is a critical need to develop biomarkers for treatment efficacy and resistance. To address these issues, we recently developed a high-throughput quantitative proteomics method to measure changes in proteome expression over the course of the preclinical experimental autoimmune encephalomyelitis (EAE) model. Interestingly, using the EAE model we revealed characteristic CNS-specific protein expression waves prior to the onset of clinical symptoms. Moreover, we have identified key proteins with altered expression that correlated with the therapeutic efficacy of glucocorticoid treatment. Bioinformatics analysis revealed candidate protein biomarkers to predict treatment efficacy and clinical disease course. Importantly, these proteins could be detected in serum and expression trajectories analysis identified a strong correlation of the CNS proteome to their levels in serum. Prospective studies in the EAE model using these candidate protein biomarkers showed their effectiveness in predicting clinical disease and treatment responses. Our studies suggest the utility for establishing homologous protein biomarkers in human MS patients. Finally, our work investigating the CNS proteome over the course of EAE may provide novel insights and molecular targets for disease mechanisms and treatments of MS.
The Effect of IFN-γ on T cell Epitope Spreading to Myelin Antigens in Experimental Autoimmune Encephalomyelitis.

Rachel R Robinson, Itay Raphael and Thomas G Forsthuber

University of Texas at San Antonio

Multiple sclerosis (MS) is the most common demyelinating autoimmune disease of the central nervous system affecting over 2.3 million people worldwide. Although initially the majority of patients are diagnosed with relapsing-remitting MS, the vast majority of those will eventually develop progressive MS. Importantly, the mechanisms which contribute to the progression of the disease are largely unknown. IFN-γ, a well-studied pro-inflammatory cytokine, has been long implicated in the pathogenesis of MS and its preclinical model, experimental autoimmune encephalomyelitis (EAE). Both a disease-promoting as well as a protective function have been shown for this cytokine. Previous studies in our lab revealed that mice lacking IFN-γ signaling developed severe and progressive EAE due to increased presence of myelin debris and lipid peroxidation in the CNS. We hypothesized that persistence of oxidized-lipids may lead to disease progression by promoting demyelination and axonal/neuronal damage via the release of hitherto hidden/cryptic neuroantigens, a mechanism known as epitope spreading. Our preliminary studies suggest increased epitope spreading in IFNγR-/- mice compared with wild type mice. Additionally, we found increased numbers of neutrophils in the CNS of mice with impaired IFNγ-signaling, suggesting that neutrophils could contribute to lipid peroxidation and epitope spreading. Taken together our data suggest a novel mechanism for T cell epitope spreading mediated via lipid peroxidation and neutrophils. A better understanding of the underlying mechanisms may lead to new treatments to prevent progression of MS.
Identifying Biomarkers for Monitoring Progression of Multiple Sclerosis

Carol Chase Huizar, Itay Raphael and Thomas G. Forsthuber

University of Texas at San Antonio

There are currently no reliable methods for assessing the progression of multiple sclerosis (MS) from the relapsing-remitting to the secondary progressive form. This gap in knowledge hinders the ability for therapeutic intervention and ultimately results in continued relapses and physiological deterioration. To begin to address the urgent need for biomarkers of progressive MS we investigated proteome changes over the disease course of progressive experimental autoimmune encephalomyelitis (EAE) in NOD mice as a preclinical model of the disease. Our lab has pioneered a novel high-throughput quantitative proteomic technique which we used to quantify expression levels of central nervous system (CNS) proteins over the course of monophasic EAE in C57BL/6 mice. We utilized bioinformatics tools to prioritize key proteins whose expression level correlated specifically with the progressive phase of disease in the NOD EAE model. Importantly, we were able to detect corollary changes in these CNS-specific proteins in the serum, pointing to a minimally invasive means of monitoring disease progress and measuring drug efficacy. Our studies will provide a proof-of-concept for identifying homologous human biomarkers to guide treatment in individual patients. Furthermore, our results may provide insights into mechanisms that contribute to disease pathology and offer additional therapeutic targets for slowing the progression of MS.
Dissecting the Role of Fractalkine Receptor During EAE: New Approach Utilizing a Humanized Animal Model

Sandra M. Cardona, Kaira Church, Eric Christensen, Qun Li, Jose Vela and Astrid E. Cardona
University of Texas at San Antonio

Fractalkine is a transmembrane chemokine expressed by neurons and peripheral endothelial cells, which acts both as an adhesion molecule and as a soluble chemoattractant upon proteolytic cleavage. In the CNS, fractalkine functions by signaling through its unique receptor, CX3CR1 expressed by microglia. Fractalkine/CX3CR1 signaling regulates microglia neurotoxicity in models of neurodegeneration. During experimental autoimmune encephalomyelitis (EAE), CX3CR1 deficiency confers exacerbated disease characterized by severe inflammation and neuropathology. Among the CX3CR1 human polymorphisms, the CX3CR1\[^{I249/M280}\] variant is present in ~20% of the population and exhibits reduced adhesion for fractalkine conferring defective signaling. However, the role of CX3CR1, microglia function and its effect on neuronal damage during multiple sclerosis remains unsolved. The aim of this study is to assess the effect of weaker signaling through the human CX3CR1\[^{I249/M280}\] receptor on EAE disease, axonal damage and expression of ciliary neurotrophic factor (CNTF). We hypothesize that dysregulated microglial responses in absence of CX3CR1 signaling enhance neuronal/axonal damage via downregulation of CNTF, a key survival factor for neurons and oligodendrocytes. We have generated an animal model by inserting the CX3CR1\[^{I249/M280}\] human variant into the mouse CX3CR1 locus. Active EAE was induced in humanized mice via MOG\[^{35-55}\] peptide immunization. Our results show an exacerbated EAE phenotype in mice expressing the human CX3CR1\[^{I249/M280}\] receptor, characterized by accelerated disease onset and higher maximum EAE score in comparison to WT mice. These results correlated with severe CNS inflammation, microglia activation and increased demyelination in the cerebellum, a similar phenotype observed in mice lacking the mouse Cx3cr1 gene. Interestingly, flow cytometry data showed slight down-regulation of MHC-II and CD68 activation markers in humanized mice, suggesting an alteration in microglia function induced by defective CX3CR1 signaling. Our results provide instrumental validation of defective function of the CX3CR1\[^{I249/M280}\] human variant and the foundation to broaden the understanding of microglia dysfunction during neuroinflammation.
Inhibition of MIF as a novel treatment for autoimmune myocarditis and dilated cardiomyopathy.

Saisha Nalawade, Braxton Jamison, Julian Casabar, Daniel Maldonado and Thomas G. Forsthuber
University of Texas at San Antonio

Myocarditis is an inflammatory disease of the myocardium and a major cause of sudden death in young adults. It is characterized by the presence of immune infiltrates and necrotic myocytes in the myocardium. Importantly, patients often progress to a more severe form of the disease termed dilated cardiomyopathy (DCM), which leads to ventricular dilation and impaired cardiac function. Despite the inflammatory and autoimmune nature of disease condition, immunosuppressive treatments such as corticosteroids (CSs) have not been very effective in preventing myocarditis and its progression to DCM. We hypothesized that macrophage migration inhibitory factor (MIF) may play a role in resistance to CSs, as it is the only known pro-inflammatory cytokine to be induced by CSs. Importantly, MIF counter-regulates CS-mediated immunosuppression. Using the experimental autoimmune myocarditis (EAM) animal model, we observed that MIF−/− mice treated with Dexamethasone (Dex) were highly resistant to EAM and progression to DCM. Furthermore, using small molecule inhibitors of MIF combined with Dex treatment recapitulated this phenotype in wild type mice. Investigating the mechanism, we found that treatment with MIF inhibitors and Dex decreased the expression of key chemokines and adhesion molecules and implicated these molecules in the progression of EAM to DCM. Our results suggest that MIF promotes the recruitment of inflammatory cells to the myocardium to promote DCM. Moreover, the results suggest therapeutic inhibition of MIF in combination with CSs as a novel treatment approach to prevent DCM. Last, our studies may provide new insights into the mechanisms driving DCM.
Oligodendrocyte Progenitor Cells control CNS remyelination during chronic neuroinflammation in a TNF dependent manner

Francisco Gomez-Rivera, Itay Raphael and Thomas G. Forsthuber
University of Texas at San Antonio

Tumor necrosis factor alpha (TNF) is a pleiotropic inflammatory cytokine that has been associated with the pathogenesis of several autoimmune diseases, including multiple sclerosis (MS). Consequently, TNF-blocking drugs have been widely used to treat many autoimmune and/or inflammatory conditions and have proven highly efficacious; however, treatment of MS patients with anti-TNF drugs leads to severe exacerbation of disease and triggers demyelination. This effect has been specifically associated with lack of TNF signaling through its receptor, TNFR2. However, the underlying mechanisms are not fully understood. Experimental autoimmune encephalomyelitis (EAE) is the most common animal model to study MS. Our lab has recently generated TNFR2−/− DR2b+/− mice, which lack TNFR2 signaling and are transgenic for HLA-DR2b (DRB1*1501), a haplotype strongly associated with MS. Importantly, we found that TNFR2−/− DR2b+/+ mice developed chronic-progressive EAE unlike TNFR2+/+ DR2b+/+ littermates which remit. Furthermore, TNFR2−/− DR2b+/+ mice had an increase of demyelinating lesions, consistent with the phenotype of patients treated with the anti-TNF drugs. Notably, we identified several novel mechanisms which contribute to progressive disease in these mice. Specifically, we found that lack of TNFR2 signaling resulted in decreased numbers of oligodendrocyte progenitor cells (OPC) in the CNS during the progressive phase of the disease, suggesting that TNFR2 signaling is pivotal for remyelination via OPC recruitment and maturation following an inflammatory demyelinating event. Our studies provide key insights into the repair and regulatory mechanisms controlled by TNF and its receptor TNFR2 and this information may lead to the development of novel therapeutic strategies.
Fractalkine signaling mitigates microglial activation and fibrinogen leakage after systemic inflammation in mouse models of diabetic retinopathy

Andrew S. Mendiola¹, Rolando Garza¹, Sandra M. Cardona¹, Sergio A. Lira², Katerina Akassoglou³,⁴, and Astrid E. Cardona¹

¹University of Texas at San Antonio
²Immunology Institute Icahn School of Medicine at Mount Sinai
³University of California
⁴University of California

Diabetic retinopathy (DR) is the most common cause of vision loss among diabetic patients. Besides clinical complications, diabetes increases the susceptibility to infectious diseases. An association between diabetes and chronic inflammation has been established, but the impact of systemic inflammation to the pathology of retinopathy is unknown. Our group has shown that signaling between the chemokine fractalkine (FKN) and CX3CR1 on microglia is important to maintain neuroprotection and that CX3CR1-deficiency directs microglial-mediated inflammation and neurotoxicity in the diabetic retina. To extend these studies, we tested the hypothesis that acute endotoxemia perpetuates microglial activation and that CX3CR1-deficient mice will be more susceptible to retinal pathology due to dysregulated microglial responses. Systemic inflammation was induced in nondiabetic and diabetic CX3CR1-HET and CX3CR1-KO mice by administration of four intraperitoneal injections of LPS (1 mg/kg; n=20) over four-consecutive days. Our results show that systemic inflammation triggers leakage of the blood-protein fibrinogen in the retina, and the absence of fractalkine signaling negatively influences microglial responses by increasing cellular activation, proliferation, and perivascular microglial lesion formation. This effect was associated with leukostasis and areas of disrupted vascular networks that resolved with evidence of increased angiogenesis. Additionally, fibrinogen leakage correlates with activated microglia evident by expression of IL-1β and iNOS. Lastly, intraocular treatment with soluble recombinant FKN (30 ng) into FKN-KO mice attenuated microglial activation, perivascular clustering and astrogliosis in the diabetic retina after systemic inflammation. These data suggest that systemic inflammation influences breakdown of the blood-retinal barrier, and may provide therapeutic advances by fractalkine treatment to mitigate DR pathogenesis.
Autonomic Function in Sjogren’s Patients with and without Positive Serologies

Pearl K Jones1, Istvan Bonyhay2, Rebecca Romero1 and Ratna Bhavaraju-Sanka1

1University of Texas Health Science Center at San Antonio
2Center for Autonomic and Peripheral Nerve Disorders, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston MA

OBJECTIVE
Characterize the autonomic dysfunction in patients with primary Sjogren’s syndrome, with and without positive serologies (SSA/SSB). Background: Sjogren’s syndrome is an autoimmune disorder with diffuse systemic manifestations. We have observed clinical symptoms which correlated to autonomic dysfunction in Sjogren’s patients. However, the clinical phenotype and autonomic function abnormalities in patients with and without positive serologies have not been evaluated. We report the demographics and autonomic function testing characteristics of Sjogren’s patients with and without positive blood markers.

DESIGN/METHODS
We performed a retrospective analysis of 25 patients referred to the UT Neurology Autonomic lab with sicca complex and clinical diagnosis of Sjogren’s syndrome. Autonomic testing with quantitative sudomotor axon reflex test (QSART), heart rate variability, Valsalva and tilt table test was performed using standard techniques. Autonomic function parameters were evaluated in relation to positive or negative blood serologies.

RESULTS
Twenty-five patients (age 50±15 years, 80% female) were included in the analysis. Forty-four percent of patients had positive blood marker (SSA/SSB), and 12% of patients had positive early marker (SP I IgG). In the positive serology group, significantly more patients had abnormal sudomotor function compared to the negative serology group (92% vs. 54%, P<0.05). Also, significantly more patients had abnormal sympathetic adrenergic function in the positive group than in the negative group (69% vs. 20%, P<0.05). Although blood pressure tended to be lower in the positive group, measures of parasympathetic function and hemodynamic response to tilt test were not different between the groups.

CONCLUSIONS
Sjogren’s syndrome is a chronic inflammatory disorder with widespread neurologic effects. Our results indicate a higher prevalence of sudomotor and sympathetic adrenergic abnormalities in patients with positive serologies compared to patients with negative serologies. The underlying mechanism behind the abnormal sudomotor and sympathetic adrenergic function in relation with positive blood markers in Sjogren’s syndrome needs further investigation.
Early and Sustained Microglia Activation Contributes to Age-Associated Reductions in Neurogenesis.

**Rene Solano Fonseca**¹, **Swetha Mahesula**¹, **Deana M Apple**¹, **Allison Dugan**¹, **Astrid Cardona**², **Jason O’Connor**¹ and **Erzsebet Kokovay**³

¹University of Texas Health Science Center at San Antonio
²University of Texas at San Antonio

The ventricular-subventricular zone (V-SVZ) is the largest neural stem cell (NSC) reservoir of the mammalian forebrain. However, NSC proliferation and neurogenesis is sharply reduced at mid-age through unknown mechanisms. Our studies establish microglia, the resident immune cells in the brain, as integral V-SVZ niche cells closely associated with NSCs, germinal pinwheels and the microvasculature. During aging, microglia undergo substantial positional changes within the niche, losing their close association to the vasculature while becoming increasingly associated with the ependyma and germinal pinwheels. We observed an early and chronic activation of V-SVZ microglia not seen in microglia outside of the niche during aging. This activation was accompanied by increased inflammatory mediators within the NSC compartment. A substantial increase of monocyte infiltration was observed within the aged V-SVZ niche, suggesting the peripheral immune system may also mediate V-SVZ inflammation during aging.

Induction of sustained inflammation in young mice results in increased microglia activation accompanied by reduced proliferation in the V-SVZ and in vitro studies revealed secreted factors from activated microglia reduced proliferation and neuron production compared to secreted factors from resting microglia. Furthermore, minocycline treatment in aged mice reduces microglia activation, niche inflammation and partially restores proliferation in the aged niche. Interestingly, microglia depletion in the young V-SVZ results in a reduction of proliferation that is restored after microglia numbers are allowed to normalize. Our results suggest that age-associated chronic inflammation contributes to decline in NSC function within the aging neurogenic niche and microglia may sustain or negatively affect neurogenesis depending on age.
Region-Specific Stereotaxic Injection of Recombinant Cre Protein into Adult Murine Brain

Christopher Rhodes, Douglas A. Grow, Shu-Wei Angela Huang, Mitchel S. Berger and Chin-Hsing Annie Lin
University of Texas at San Antonio

Substantial evidence suggests that epigenetic modification plays a critical role in neurogenesis and neuroimmunology, yet the question remains whether loss of epigenetic modifiers alter cell fate in region-specific manner. As vast majority of histone methyltransferases (HMTs) and resulting histone methylation are present in wide ranges of heterogeneous populations within the adult neurogenic niches, we utilized site-specific knock-down of HMTs by stereotaxic injection of Cre protein into the subventricular zone (SVZ) of lateral ventricle and the subgranular zone (SGZ) of dentate gyrus (DG). In this report, we focus on using Cre recombination to the mice harboring floxed HMTs including enhancer of zeste homolog 2 (EZH2) or Suppressor of variegation homolog (Suv4-20h). We confirmed that Cre proteins were enzymatically active in vivo, and recombination events were restricted to the vicinity of injection areas. As a technical intervention, we demonstrate a system to administer Cre protein into spatially targeted areas without excessive spreading to distant tissue. While our Cre delivery system targeted adult neural stem cell niches, this novel delivery system offers a framework for protein-based modulation of immune system components within the brain, as well as region-specific manipulation of pro-inflammatory genes.
The Oxidative Regulating Effects of Thiazolidinedione Intervention on the CISD1 Protein, mitoNEET, in Late Onset Alzheimer’s Disease

Charles D. Hammack, Clyde F. Phelix and George Perry
University of Texas at San Antonio

Oxidative stress is considered to be a central component to the pathophysiological progression of late-onset Alzheimer's disease (LOAD). Using 8-hydroxyguanosine (8-OHG) as a biomarker for oxidized ribonucleic acid (RNA), Perry and colleagues have hypothesized that oxidative damage is the earliest event in LOAD far preceding neuronal degradation and localized cellular insults such as neurofibrillary tangles (NFTs). In our current study, an in silico biosimulation of the deterministic kinetic model, Transcriptome-To-Reactome: Oxidative Pathways to Apoptosis (TTR:OPA), was used to test this hypothesis. Gene expression levels were used to derive kinetic parameters for 375 reactions, utilizing 561 species, within 18 compartments. Gene expression microarrays from hippocampal Cornu Ammonis-1 (CA1) region of 30 human subjects identified as having incipient, moderate, or severe stages of LOAD, as well as an age-matched control group were accessed from the NCBI-GEO website (GSE28146). Simulations were performed utilizing the COPASI software. Our results showed a significant increase in the production of 8-OHG in the incipient population when compared to their age-matched counterparts (p = 0.0392; α<.05), supporting the hypothesis. A significant regression equation to predict 8-OHG concentrations (mmol/L) based on Mini-Mental-State Examination (MMSE) scores was also found [F (1, 27) = 6.11, p <.05], with an R² of 0.4296. These results parallel the work done by Perry et al who not only indicated a positive correlation between 8-OHG concentrations and MMSE scores with disease progression, but also demonstrated that RNA oxidation of 8-OHG was statistically most significant during the initial stages of LOAD prior to cognitive decline. As a follow up study, our research team tested the efficacy of pioglitazone, a thiazolidinedione class drug currently in phase 3 clinical trials to delay onset of LOAD, acting on mitoNEET to reduce localized oxidative stress. Our results indicated a significant reduction in the oxidized variant of mitoNEET within the incipient population of LOAD patients when a 0.8mg dose of pioglitazone was simulated in silico (p = 0.0242; α<.05). This is extremely critical as recent studies have reported that pioglitazone may inhibit 2Fe-2S cluster transfer from mitoNEET to apo-acceptor proteins subsequently attenuating the cell's stress response.
Neurotoxic kynurenine metabolism modulates microglial activity following lipopolysaccharide challenge

Allison M. Dugan, Jennifer M. Parrott, Jennifer N. Delgado and Jason C. O’Connor

University of Texas Health Science Center at San Antonio

The kynurenine pathway (KP) of tryptophan metabolism is the major tryptophan degradation pathway in the body, and disruption of KP metabolic balance within the brain has been implicated in both neurodegenerative and neuropsychiatric disease. Inflammation in the brain skews KP metabolism toward increased production of oxidative and excitatory metabolites, but the role of microglia in this process remains poorly understood. To investigate this further, BV-2 murine microglia were challenged in vitro with lipopolysaccharide (LPS), a component of gram-negative bacteria cell wall. LPS treatment up-regulated pro-inflammatory cytokine and inducible nitric oxide synthase mRNA expression. Extracellular accumulation of nitrite, an indirect index of nitric oxide production, was significantly increased 24 hours following LPS challenge. Additionally, mRNA expression of the rate limiting enzymes for the formation of oxidative/excitatory KP metabolites, indoleamine-2,3-dioxygenase (IDO)-1 and kynurenine monooxygenase (KMO), was significantly increased 6 hours after LPS. Accumulation of kynurenine and the excitotoxic metabolite quinolinic acid was also increased in the media of microglia 24 hours after LPS. To determine whether synthesis of oxidative/excitatory KP metabolites contributes to microglial activation, BV-2 cells were treated with the KMO inhibitor Ro 61-8048 at the same time as LPS challenge. Ro 61-8048 attenuated the production of extracellular nitrite and up-regulation of KMO and tumor necrosis factor-α, but not other pro-inflammatory gene targets following LPS challenge. Further, this experiment was repeated in primary microglia isolated from neonatal C57BL6/J wild type (WT) and KMO knockout (KMO−/−) mice. The KMO−/− genotype was sufficient to reduce nitrite accumulation with or without LPS treatment. There was also a main effect of LPS in both WT and KMO−/− microglia. These data indicate that microglia are likely playing an important role in skewing KP metabolism in the brain during inflammatory conditions, and oxidative/excitatory KP metabolites modulate microglial activity during immune challenge.
Ketamine Corrects Stress-Induced Cognitive Dysfunction Through JAK/STAT3 Signaling In The Orbitofrontal Cortex

Michael Patton, David Morilak and Milena Girotti
University of Texas Health Science Center at San Antonio

Deficits in cognitive flexibility are prominent in stress-related psychiatric disorders, including depression. Ketamine has rapid antidepressant efficacy, but it is unknown if ketamine also improves cognitive symptoms. In rats, chronic cold stress impairs reversal learning, a form of cognitive flexibility mediated by the orbitofrontal cortex (OFC) that we have used to model cognitive dysfunction in depression. We have previously shown that activating JAK/STAT3 signaling in the OFC rescued the chronic stress-induced reversal learning deficit. Thus, in the present study we determined if ketamine also corrects the stress-induced reversal learning deficit, and if JAK/STAT3 signaling is involved in this effect. We then tested the role of JAK/STAT3 in ketamine-induced plasticity in the OFC, and the downstream molecular effects of ketamine-mediated JAK/STAT3 phosphorylation. We found that a single injection of ketamine (10mg/kg) 24h prior to testing rescued the deficit in reversal learning induced by two weeks of chronic intermittent cold stress. Co-administration of the JAK inhibitor, AG490, with ketamine prevented the therapeutic effect on reversal learning. In addition, we found that ketamine depressed field potentials evoked in the OFC by excitatory thalamic afferent activation, and this effect was also prevented by JAK2 inhibition. Finally, we found that activity of the JAK/STAT pathway regulates expression of the neural plasticity-related protein, Arc. In summary, these results suggest that the JAK/STAT3 pathway is a novel mechanism by which ketamine may exert therapeutic effects on cognition in the orbitofrontal cortex.
A Role for JAK2 Signaling in Ketamine-Induced mTOR Activation in the Orbitofrontal Cortex

Samantha Adler, Michael Patton, David Morilak and Milena Girotti

University of Texas Health Science Center at San Antonio

Because depression treatment is often ineffective and slow, ketamine's rapid antidepressant effects provide an exciting alternative. In the past, our lab has shown that acute injection of a low dose of ketamine reverses chronic-stressed induced deficits in cognitive flexibility mediated in the prefrontal cortex that model cognitive symptoms of depression. One such form of cognitive flexibility is reversal learning, mediated in the orbitofrontal cortex (OFC), which is compromised by chronic cold stress. We have further demonstrated that acute ketamine administration rapidly induces Janus Kinase 2 (JAK2) signaling in the OFC, and that this signaling is important for the therapeutic effect on reversal learning in chronically stressed rats. We are now investigating the mechanism by which JAK2 signaling in the OFC may mediate ketamine's therapeutic effects on reversal learning. Because ketamine is known to activate mammalian target of rapamycin (mTOR) in the pre-frontal cortex, we tested if this signaling molecule is also activated by ketamine in the OFC. We then tested a potential role of JAK2 in this activation. In the OFC, we observed a clear effect of ketamine on phosphorylated S6 levels, a protein that is activated downstream of mTOR. In order to determine whether JAK2 participates in the activation of the mTOR pathway by ketamine, we examined OFC lysates from animals that that received both ketamine and a JAK2 inhibitor, AG490. We examined phosphorylation levels of S6 as well as Akt, a protein that phosphorylates and activates mTOR. We see a trend for AG490 to block ketamine's increase of phosphorylated S6. In addition, blockade of JAK2 significantly reduced ketamine-induced Akt phosphorylation. These results show that ketamine activates the mTOR pathway in the OFC, and JAK2 participates in the ketamine-induced activation of mTOR.
Intranasal Delivery of Stem Cells to the Brain

Carlos Galeano, Zhifang Qiu, Anuja Mishra, Nicholas Edenhoffer, Jacob Hemmi, Steven Farnsworth, Peter Edenhoffer, Alvaro Moreira and Peter Hornsby

University of Texas Health Science Center San Antonio

Stem cell therapy is believed to have great potential for the treatment of neurological diseases. Delivery of stem cells to the central nervous system in experimental cell therapy has usually been accomplished via stereotactic injection. However, over the last few years it has also been shown that a noninvasive form of cell delivery via introduction of cells into the nasal cavity is feasible. The route by which cells can enter the CNS from the nasal cavity has not been determined. In these experiments, this question was addressed using human mesenchymal stem cells in immunodeficient mice. Cells were derived from Wharton’s jelly of newborn umbilical cord and were labeled with fluorescent quantum dot beads. In each experiment, 300,000 cells were introduced into the mouse nasal cavity in 10 μl PBS with 100 units hyaluronidase, previously shown to increase cell delivery. After 2 hours mice were sacrificed. Cells were found within the nasal cavity, beneath the olfactory epithelium, passing through the cribriform plate, and around the olfactory bulbs in the subarachnoid space. Immunohistochemistry indicated that cells are within lymphatic vessels. The route taken by the cells appears to be the reverse of that reported in the literature for India ink particles injected into the cerebral ventricles. In that case the particles are observed in the subarachnoid space, crossing the cribriform plate, in nasal lymphatic vessels, and in cervical lymph nodes. It is not clear how and why cells introduced into the nasal cavity appear to follow the reverse route. Understanding how cells can penetrate from the nose to the brain will help improve this mode of stem cell delivery, with practical therapeutic implications.
Gene X Environment Interactions in the Development of an Autistic-Phenotype in Mice

Danielle Santana Coelho¹, Karen Jimenez¹, Laney Redus¹, Leslie Myatt¹ and Jason C. O’Connor¹²

¹University of Texas Health Science Center at San Antonio
²Audie L. Murphy VA Hospital

The etiology of autism spectrum disorder (ASD) is not well understood. Prenatal exposure to certain environmental factors or genetic mutations increase the risk for developing ASD. However, whether exposure to environmental risk factors by genetically susceptible individuals increases the severity of the disorder remains unknown. Therefore, we tested the hypothesis that mice with a targeted deletion of the contactin associated protein-like 2 (CNTNAP2) gene would exhibit a more severe ASD-like behavioral phenotype following maternal immune activation during gestation. CNTNAP2 mutation has been associated with the development of autism in humans and a mild ASD-like phenotype, characterized by deficits in communication, sociability and stereotypic behavior, in mice. Additionally, maternal immune challenge with the viral mimic polynucleotide polypyridylic acid (poly I:C) during gestation results in a neurodevelopmental and behavioral phenotype resembling ASD (i.e. impaired communication, disrupted social behavior and repetitive, stereotypic behaviors). Pregnant dams were administered poly I:C (20mg/kg) or saline intraperitoneally on gestational day 12.5. At various ages, the behavior of offspring was measured in the following tests; ultrasonic vocalization, juvenile play behavior, grooming, marble burying, Y-maze, 3-chamber social interaction and pre-pulse inhibition. Consistent with previous reports, CNTNAP2 gene deletion independently caused an increase in ASD-like behaviors, but in contrast with much of the literature, maternal immune challenge with poly I:C failed to induce a robust ASD-like phenotype in WT mice. In CNTNAP2 deficient mice, maternal immune challenge with poly I:C did precipitate several ASD-like behaviors in affected offspring, including increased marbles buried and decreased social interaction in the juvenile play test. Additionally, social interaction was significantly more impaired in male mice versus female mice born from poly I:C challenged dams. Consistent with previous reports, our data indicate that deletion of the CNTNAP2 gene in mice results in an ASD-like phenotype, and males appear more vulnerable to some, but not all, of the behavioral consequences of maternal immune challenge with poly I:C. In our hands, poly I:C had little behavioral impact on WT mice as they developed, and the severity of the CNTNAP2 phenotype was more profound than previous reports. The latter could have obscured our ability to measure gene x environment interactions in the development of an autistic-like phenotype in mice.
Modeling exposure therapy in rats: fear extinction-induced infralimbic activity underlies reversal of chronic stress-induced shift towards passive coping

Elizabeth Fucich, Madeleine Saunders and David Morilak
University of Texas Health Science Center at San Antonio

Stress-related psychiatric disorders, like depression or PTSD, are prevalent yet poorly treated. These disorders share many dimensions, including avoidant coping strategies, thought to be modulated by medial prefrontal cortex (mPFC). Psychotherapies invoking mPFC activity can be efficacious even in pharmacotherapy-resistant patients, although, as with pharmacotherapies, patient response and relapse remain issues. Identifying the neurobiological mechanisms underlying psychotherapy’s efficacy could lead to more rapid, efficacious, or long-lasting treatments. Pre-clinically, chronic unpredictable stress (CUS) induces a shift towards passive coping behavior in rats, similar to avoidant coping behaviors seen in patients with stress-related psychiatric illness. We have shown that fear extinction, which engages mPFC and closely resembles exposure therapy for PTSD, can model psychotherapy in rats by restoring active coping in the shock probe defensive burying (SPDB) test after chronic stress (SfN Abstract 468.07, 2014). In this study, we tested the hypothesis that mPFC activity during extinction is necessary for its beneficial reversal of CUS-compromised coping behavior. Rats received AAV microinjections into ventral mPFC (infralimbic cortex, IL) to express Gi-coupled designer receptors exclusively activated by designer drug (hM4Di) or control GFP protein, driven by a CaMKII promoter. After four weeks of viral expression, including 2 weeks of CUS or control treatment, rats received an IP injection of the designer drug clozapine-n-oxide (CNO, 1mg/kg) followed by extinction or control treatment. Coping behavior was measured in SPDB 24h later. Immunohistochemical analyses of IL showed that >60% of extinction-induced cFos was colocalized with CaMKII, and CNO reduced Fos expression by >60% and blocked extinction’s reversal of stress-compromised coping in the SPDB test in rats expressing CaMKII-hM4Di. These results suggest that mPFC activity underlies the effect of extinction on coping behavior. This study further shows that fear extinction is a useful model of exposure therapy, allowing us to investigate neural mechanisms responsible for its therapeutic effects.
CX3CR1 and DAP12-TREM1&2 Signaling in MS-vs-AD: Biosimulations of proteomics differences and effects of a novel orally active CX3CR1 blocker (AZD8797)

Clyde F. Phelix\(^1,2\) Gregory Villareal\(^2\) and George Perry\(^1\)
\(^1\)University of Texas at San Antonio
\(^2\)AL Phahelix Biometrics, Inc.

TYROBP differential gene expression is a causal regulator for immune and microglia response in late-onset Alzheimer’s disease (LOAD). TREM2 and CX3CR1, in this response pathway, were minor nodes in the signaling network. Reactome.org includes TYROBP and TREM1&2 in the DAP12 signaling pathway, and CX3CR1 in the chemokine (fractalkine) and G-protein coupled receptor pathways, associated with G-alpha ‘i’, ‘q’, and ‘z’. Microglia are considered CNS ‘sweepers’ and tissue homeostasis ‘gatekeepers’ in LOAD and multiple sclerosis (MS); implicating IL-34 and Csf1 receptor mechanism for DAP12 activation (cell survival), TREM2 and DAP12 signaling (phagocytosis), CD200 (resting), and both the CX3CR1-dependent ERK signaling (CNS chemotaxis recruitment) and cAMP inhibitory pathways. Our study utilized Transcriptome-To-Reactome™ (TTR™) technology for neuron-microglia interaction biosimulations to examine differences between LOAD and MS using COPASI software and determining kinetic parameters from NCBI GEO transcriptome sets GSE28146 & GSE38010. The TTR™ also tested an [IC50] (350nM; Cederblad et al., 2016) effect of AZD8797 (CID11956767 - AstraZeneca’s developmental non-competitive allosteric CX3CR1 inhibitor to treat MS) to normalize ERK and cAMP biomarkers in both MS and LOAD subjects, in silico. Autodock-Vina was used for ligand-protein docking and proteomic heatmap results were generated with Cluster and Treeview. Principle component analysis was performed with R using the FactoMineR library. LOAD as mild, moderate, and severe were clustered with age-matched control, but separated from control, acute and chronic MS, CNS-white-matter, plaques, which were separated from each other. Heatmaps revealed distinctions among the groups and showed signs of normalization by AZD8797. Fractalkine sequentially binds two sets of residues in the extracellular pocket of CX3CR1, activating G-proteins; AZD8797 binds the secondary residues. AZD8797 increases cAMP levels and lowers ERK markers by approximately 72% and 42%, respectively. Microglial activation pathways are not identically altered.
A Top-Down Method for the Identification of α-Synuclein by Matrix Assisted Laser Desorption Ionization Mass Spectrometry

Madeline E. Colley, Andrea R. Kelley, Stephan B.H. Bach and George Perry
University of Texas at San Antonio

α-Synuclein is a presynaptic neuronal protein linked to Parkinson’s disease (PD) and it is thought to play a considerable role in PD pathogenesis by disrupting cellular homeostasis and causing neuronal death. The extent of its role is not clear and since it is abundantly expressed in the nervous system, determining which post translation modifications (PTMs) and the locations of these become very important. Mass Spectrometry is a powerful tool in the field of proteomics and can be used to reliably determined both the presence and location of (PTMs) in the sequence by fragmentation. Different methods of fragmentation produce distinct and unique ions for identification but only a handful can be applied directly to tissue. This study focuses on the fragmentation methods for matrix assisted laser desorption ionization (MALDI) Mass Spectrometry (MS) for the identification of α-synuclein by in-source decay and post-source decay. MALDI-MS can be performed directly on tissue without complex homogenization methods which can alter the structure of the protein. Since α-synuclein does not hold a native structure in aqueous solutions, the information gained from homogenates is limited. The experiment is performed on synthetic α-synuclein to determine a reliable and specific fragmentation pattern by in-source decay and post-source decay to identify the intact protein with MALDI-MS.
A build-up of senile plaque deposits in the brain is the tell-tale sign of Alzheimer’s disease (AD). The analysis of these samples from AD patients by MALDI MS (matrix-assisted laser desorption/ionization mass spectrometry) presents many obstacles due to the nature of the solvents that they are isolated in and the ways in which they must be kept. Many salts, buffers, and detergents cause adducts and ion suppression that easily convolute the spectra obtained. We previously developed a reproducible fragmentation pattern of synthetic amyloid-beta by laser-induced in-source decay by MALDI MS and determined that amyloid-beta from isolated senile plaque deposits fragments in much the same way when analyzed as the synthetic peptide does. While this provides information that may be applied to the identification and localization of amyloid-beta in senile plaque and in-tact tissue sections, we must still account for the ion suppression we see in the senile plaques which makes it difficult to see fragments which may appear at lower intensities. The addition of certain transition-metal salts (Cu(II), Zn(II), etc.) prior to analysis provide for the “cleaning” of spectra and allow the peptide fragments produced to be observed with much higher signal-to-noise than without the addition of the metal salts. We present a systematic study of different metal salts and their impact on the quality of the spectra obtained for both synthetic and isolated amyloid-beta. These optimized sample preparation methods will provide for simpler and more complete identification of the species in senile plaque samples and AD in-tact tissue samples.
Prediction of Thermal-Driven Human Performance from Brain Signals

Tapsya Nayak¹, Zijing Mao¹, Tinghe Zhang¹, Xiaojing Xu², Daniel J. Pack³, Bing Dong¹ and Yufei Huang¹
¹University of Texas at San Antonio
²University of Tennessee, Knoxville
³University of Tennessee, Chattanooga

ABSTRACT
Understanding how indoor environments affect human performance and developing methods to predict human performance in changing indoor environment have become highly important research topics that bear significant economic and sociological impact. Improving indoor environment in U.S. office buildings would result in a 0.5% to 5% increase in productivity, worth $12 - $125 billion annually. We conduct in this paper a comprehensive study of predicting thermal-driven indoor human performance using human brain signals collected by electroencephalography (EEG). Experiment was designed and performed to systematically measure human performance and brain signals during office work tasks and cognitive tasks. Correlations of frequency band (theta, alpha, and beta) powers of brain signals as well physiological signals with human performance measures during a typing task were investigated and prediction of performance using these brain and physiological signals were analyzed. The results show that brain signals have much higher correlations with performance and can achieve more than 15 fold reduction in prediction mean squared error compared with physiological signals. Further analysis revealed dissociations of power in alpha and theta power between high and low performance. These results establish brain signals as a new source for predicting thermal-driven performance. These results provide a promising mechanism for future work where a neuro-feedback can be implemented as a control signal to alter office environment to its new optimal settings to achieve higher human performance.
Design Deep learning models for Prediction of Rapid Serial Visual Presentation Events

Zijing Mao¹, Ehren Biglari¹, Vernon Lawhern¹,²,³, Brent J. Lance³, Kay Robbins¹ and Yufe Huang¹*

¹University of Texas at San Antonio
²DCS Corporation, USA,
³Translational Neuroscience Branch, U.S. Army Research Laboratory, USA

We report in this paper an investigation of deep learning (DL) specifically convolution neural network (CNN) methods for target prediction in time-locked rapid serial visual presentation (RSVP) experiment. We show higher performances for within-subject predictions on a small sample size by DL classifiers over the state-of-the-art algorithms: Bayesian linear discriminate analysis (BLDA) and xDAWN spatial filtering. In particular, our proposed region of interest (ROI) CNN model has achieved 6% better for AUC of ROC in binary RSVP tasks. Statistic test has been performed on 11 DL models with different filter design, indicating a local temporal filter combined with a ROI spatial filter, which is ROI CNN model, can achieve the best performance. For cross-subject predictions, we also show the advanced performance of DL over conventional machine learning algorithms. In this case, the designed global spatial filter (GSLT model) has shown the highest performance, 4% better of AUC comparing with the state of art BLDA. And our proposed ROI CNN also achieved competitive performance within 1% less than GSLT. In addition, by visualizing ERP features selected by ROI CNN comparing with the features selected by BLDA, we showed DL and BLDA have missed different part of features, indicate an ensemble of both may improve the performance. Finally, we also performed deconvolution of ROI CNN to show the reconstructed deep learning features choosing from activated hidden units from target/non-target EEG epochs. Our study suggests that deep learning is a powerful tool for RSVP target prediction and for brain computer interaction research in general.
Asynchronous UAV Control Using a SSVEP-based BCI

L. Meriño1, P. Kolar1, T. Nayak1, G. Hall1, D. Pack2 and Y. Huang1

1University of Texas at San Antonio
2University of Tennessee

Autonomous control of external devices using brain control interface (BCI) in real world situations, i.e. recreation, rehabilitation or exploration, still remains a challenge. This work demonstrates the use of non-invasive Electroencephalography (EEG) signals and special visual stimulus to create a Steady-State Visual Evoked Potential (SSVEP) BCI. The SSVEP-based BCI allows an individual to control an Unmanned Aerial Vehicle (UAV) in this case a consumer quadcopter (AR Drone). Asynchronous control was achieved by using six actuation commands by detecting 'command' brain state and hover by detecting 'idle' brain state. Actuation commands programmed were: forward, back, left, right, up and down. ‘Idle’ state detection was implemented by using a novel technique called likelihood ratio test, which is based on Baye’s Ratio. To test the robustness, detection accuracy of this system and quantify user control of the system, we recorded from 42 subjects offline and 6 subjects online. We achieve an accuracy of 90% for stimulus detection and 80% accuracy with 'idle' state detection. The shortest epoch time window used was 3.5 seconds. Currently, the use of BCI applications in real world either on healthy or disable participants is limited due to restricted autonomous control. By detecting 'Idle' state gives the BCI user superior control not only over the system but also in a 3D environment, for instance in obstacle avoidance and error corrections. This gives the user the ability to judge the environment the external device is in and then generate appropriate command. In situations when the external device is in a visually restricted environment, the user can generate commands by using visual feedback from the camera attached to the drone.
Abnormal accumulation of brain metals is a key feature of Alzheimer’s disease (AD). Formation of amyloid-β plaque cores (APC) is related to interactions with biometals, especially Fe, Cu and Zn, but their particular structural associations and roles remain unclear. Using an integrative set of advanced transmission electron microscopy (TEM) techniques, including spherical aberration-corrected scanning transmission electron microscopy (Cs-STEM), nano-beam electron diffraction, electron holography and analytical spectroscopy techniques (EDX and EELS), we demonstrate that Fe in APC is present as iron oxide (Fe3O4) magnetite nanoparticles. Here we show that Fe was accumulated primarily as nanostructured particles within APC, whereas Cu and Zn were distributed through the amyloid fibers. These results were also confirmed by synchrotron based scanning transmission X-ray microscopy. Remarkably, these highly organized crystalline magnetite nanostructures directly bound into fibrillar Aβ showed characteristic superparamagnetic responses with saturated magnetization with circular contours, as observed for the first time by off-axis electron holography of nanometer scale particles. This work was supported by Welch Foundation and Semmes Foundation. Facilities of Kleberg Advanced Microscopy Center (KAMiC), NIH RCMI Nanotechnology and Human Health Core (5G12RR013646-12) and NIH RCMI Biophotonics Core (G12MD007591) at UTSA.
Abstracts

HDAC6 Inhibition Effectively reverses Chemotherapy-Induced Peripheral Neuropathy.

Jiacheng Ma¹, Karen Krukowski¹, Olga Golonzhka², Tanuja Gutti¹, Matthew Jarpe², Cobi J. Heijnen¹ and Annemieke Kavelaars¹
¹University of Texas MD Anderson Cancer Center
²Acetylon Pharmaceuticals

Chemotherapy-induced peripheral neuropathy (CIPN) characterized by pain and numbness is one of the most commonly reported side-effects of cancer treatment. The presence of CIPN can limit the dosage and interfere with the selection of chemotherapeutics, delay further treatment cycles, or in the worst scenario lead to early termination of treatment. Despite daunting facts about the high prevalence and severity of CIPN, there is less known about its underlying mechanism or effective treatment. HDAC6, a microtubule-associated deacetylase, plays an important role in the regulation of α-tubulin-dependent intracellular transport. Inhibition of HDAC6 has been shown protective in several neurological disorders through enhancing α-tubulin acetylation, and thereby improving axonal transport of mitochondria. In the current study, we aim at investigating that if inhibition of HDAC6 could prevent and/or reverse cisplatin-induced peripheral neuropathy. We show that pharmacological inhibition of HDAC6 with the selective HDAC6 inhibitor ACY-1083 both prevented and reversed cisplatin-induced mechanical allodynia. In addition, ACY-1083 reversed established spontaneous pain as well as numbness induced by cisplatin. Mechanistically, ACY-1083 treatment increased α-tubulin acetylation in neuronal tissues. More importantly, ACY-1083 restored the impaired mitochondrial motility induced by cisplatin in primary cultures of DRG neurons in vitro, and restored mitochondrial function and content in the distal tibial nerves in vivo. ACY-1083 also restored intra-epidermal nerve fiber (IENF) density in cisplatin-treated mice. Our results strongly indicate that HDAC6 inhibition protects against cisplatin-induced peripheral neuropathy, and the protective effects are likely exerted through enhancing mitochondrial transport and improving mitochondrial bioenergetics in the distal sensory axons.
Nasally Administered Mesenchymal Stem Cells Promote Recovery from Cisplatin-Induced Cognitive Deficit and Neurological Dysfunction

Gabriel S. Chiu, Nabila Boukelmoune, Sahar Rizvi, Annemieke Kavelaars and Cobi J. Heijnen
University of Texas M.D. Anderson Cancer Center

Cognitive impairments are common side effects of chemotherapy treatment that may persist after the secession of intervention. Here, we tested the effects of nasal mesenchymal stem cell (MSC) administration on the neurotoxic side effects of cisplatin treatment. Adult C57Bl/6J mice were treated with saline or cisplatin (2.3 mg/kg) for two cycles. One million MSC were administered intranasally at 48h and 96h after the last injection of cisplatin. MSC administration promoted recovery in cognitive function as measured in the novel object/place recognition (NOPR), Y-maze, and the Puzzle Box tests. Additionally, MSC promoted recovery from cisplatin-induced decrease in functional network efficiency as measured in resting state fMRI. Synaptic mitochondrial function was also normalized by MSC treatment as measured in the Seahorse XFe 24 Analyzer. MSC administration after cisplatin treatment promoted doublecortin (DCX)+ cells in the subventricular zone (SVZ) and the dentate gyrus (DG) of the hippocampus suggesting increased neurogenesis. Furthermore, MSC promoted recovery from white matter damage as measured by myelin basic protein (MBP) fibers. Administration of MSC after chemotherapy treatment promoted recovery from cisplatin-induced cognitive impairment and restored mitochondrial function as well as white matter damage and the loss of DCX+ cells. Our data suggest that treatment with MSC may represent a realistic therapeutic strategy for the prevention of chemotherapy-induced cognitive impairment.