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Mentor/Lab: Donnelly

Department: Neurobiology

Poster Session: AM
Location: 1

Category:
Neurology & Neurodegenerative Diseases

Title: Inducing Stress Granule Formation Using Optogenetics

Summary: The goal of this work is to generate light-induced SGs to study the role of these\nmembraneless organelles in ALS/FTD. Our work is the first to report the formation of functional membraneless organelles using light and demonstrates spatial and temporal control in their formation in the absence of cytotoxic cell stress. Employing this method allows us to broaden our understanding of the pathobiology underlying ALS and FTD and their neuropathologies.

Abstract: Amyotrophic lateral sclerosis (ALS) and Frontotemporal dementia (FTD) are progressive fatal neurological diseases caused by the loss of upper and lower motor neurons or cortical neurons respectively. The majority of diagnosed ALS and FTD patients are classified as having a sporadic phenotype with only a fraction of patients considered familial based on patient history. A molecular similarity between\nboth neurological diseases is the observed cytoplasmic aggregation of the RNA-binding proteins TDP-43 and FUS in the affected CNS tissue. In healthy cells these proteins are predominantly nuclear and traffic into and out of the cytoplasm. In ALS and/or FTD tissue they are absent from the nucleus and form cytoplasmic aggregates through currently unknown mechanisms. Current hypotheses suggest that impaired homeostasis of cell stress activated cytoplasmic granules called stress granules (SGs) may serve as sites that seed TDP-43 and/or FUS aggregation in disease and thus may promote disease progression. SGs form under periods of cell stress and function to prevent global protein synthesis to promote the upregulation of stress response genes until the stress is removed. Elucidating such an effect however has been problematic using current methods to form stress granules since prolonged treatment with extracellular stress is cytotoxic thus preventing the study of prolonged or repetitive stress granule formation on in the induction of ALS/FTD neuropathology. To overcome this we developed a novel method employing light-induced protein clustering to seed the core protein components. The goal of this work is to generate light-induced SGs to study the role of these membraneless organelles in the absence of toxic extracellular stressors. Employing this method we are able to broaden our understanding of the pathobiology underlying ALS and FTD and their neuropathologies. Our results demonstrate that the light induced SGs co-localize with endogenous stress granule components including G3BP1 Ataxin-2 PABPC1 TIAR eIF4G and eIF3H. Additionally the light-induced SGs sequester mRNAs and translation factors to inhibit global protein synthesis similar to endogenous SGs. Light-induced SGs can be controlled to induce prolonged or repetitive SG formation and light-induced SGs sequester with the ALS/FTD proteins TDP-43 and FUS. This body of work allows us to form functional SGs with great spatial and temporal control and in the absence of cytotoxic cell stress. This is the first report of the formation of functional membraneless organelles using light. We are currently using this tool to elucidate the role of SGs in TDP-43 and FUS aggregation and in ALS/FTD pathobiology.

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Department: Neurobiology

Poster Session: AM
Location: 2

Category:
Neurology & Neurodegenerative Diseases

Title: Disruption of nuclear import in C9ORF72 ALS

Summary: Amyotrophic Lateral Sclerosis (ALS) is a fatal disease in which motor neurons cells that control muscle die. My research investigates the role that proteins that handle moving substances around within cells play in this disease. I assess the amount of these proteins as well as their location in the disease versus normal cells.

Abstract: Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease characterized by both upper and lower motor neuron loss. 10% of patients exhibit familial ALS due to genetic mutations while 90% of patients have sporadic ALS and show no family history. C9ORF72 ALS is the most common known familial form of ALS. A mutation in chromosome 9 open reading frame 72 results in an expanded GGGGCC (G4C2) hexanucleotide repeat in the first intron of the gene. This G4C2 HRE undergoes RAN translation and yields five dipeptide repeat protein products (DPRs): GR- GP- GA- PR- and PA-repeats. Studies have shown that the GR protein product results in the cytoplasmic mislocalization of proteins such as TDP-43 which is predominantly nuclear in healthy cells. This is suggestive of nucleocytoplasmic transport impairment. Additional studies have also shown perturbed nuclear import in C9ORF72 ALS (Zhang and Donnelly et al 2015). Nucleocytoplasmic transport occurs through the nuclear pore complex a large protein embedded in the nuclear envelope. Proteins called karyopherins are the transport proteins responsible for carrying substances through this nuclear pore complex. One family of karyopherins is importins which bring substances from the cytoplasm into the nucleus. It has been shown that genetically modulating importins can be neuroprotective in C9ORF72 Drosophila models (Zhang and Donnelly et al 2015). Further support for the involvement of importins in nuclear import deficits in C9ORF72 ALS is provided by research showing that overexpression or deletion of genes coding for various importin proteins alters PR50 toxicity in yeast (Jovicic et al 2015). The presented work assesses the impact of both the C9ORF72 genotype as well as accumulation of DPRs on importins at the RNA and protein levels in models of C9ORF72 ALS. We found that both cellular expression and nucleocytoplasmic localization of various importins are altered in models of C9ORF72 ALS. Expression of a nuclear export accessory protein and transport factor was also shown to be altered in C9ORF72 ALS models. Investigation of the impairment of importins and a nuclear export accessory protein might lead to elucidation of the mechanism of TDP-43 mislocalization and cell death in C9ORF72 ALS. Combined with assessment of cellular toxicity overexpression or reduction of importin and transport factor levels might be implicated in the development of a novel therapeutic strategy for C9ORF72 ALS.

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Mentor/Lab: Donnelly

Department: Neurobiology

Poster Session: AM
Location: 3

Category:
Neurology &
Neurodegenerative
Diseases

Title: Cytoplasmic Nup62 seeds TDP43 aggregation

Summary: ALS and FTD patient tissue show a disruption in TDP43 structure and its location within cells. We found that another protein Nup62 can cause these changes in TDP43. Future studies of how Nup62 causes TDP43 disruption may explain why this happens in the disease and lead to new approaches for halting or preventing changes in TDP43.

Abstract: ALS and FTD are fatal neurodegenerative diseases that both present with cytoplasmic mislocalization and aggregation of TAR DNA-binding protein 43 (TDP43). TDP43 is an RNA and DNA binding protein that is predominantly located in the nucleus of healthy cells. However in ALS and FTD TDP43 is redistributed to the cytoplasm where it forms insoluble aggregates and these are pathologically hyperphosphorylated ubiquitinated and p62-positive. Several genetic mutations in the TDP43 gene have even been linked to familial ALS and FTD cases. TDP43 mutations have also been shown to cause neurotoxicity. In TDP43 Drosophila models neurotoxicity was reduced by mutating the phenylalanine-glycine (FG) domain of nucleoporin 50. The concentrated region of FG repeats in FG nucleoporins creates an area of hydrophobicity. A similar phenomenon is observed in the low complexity domain of TDP43. Therefore we sought to examine whether FG nucleoporins are associated with TDP43 aggregate formation. We hypothesized that these characteristics may favor interactions between FG nucleoporins and TDP43 that eventually yield insoluble TDP43 aggregates. Our studies revealed that the cytoplasmic accumulation of the FG nucleoporin Nup62 colocalizes with TDP43. These TDP43 aggregates are insoluble and mimic hallmark pathology typically observed in neurodegenerative diseases. Further characterization of the mechanism by which Nup62 seeds TDP43 aggregation may lend insight into the mechanism driving TDP43-aggregate formation in ALS and FTD.

First Author: Jacob Mann
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Mentor/Lab: Donnelly

Department: Neurobiology

Poster Session: AM
Location: 4

Category:
Neurology & Neurodegenerative Diseases

Title: RNA binding inhibits pathological TDP-43 aggregation

Summary: Amyotrophic lateral sclerosis (ALS) is a progressive and fatal neurodegenerative disorder characterized by selective loss of motor neurons that control the muscular system. Nearly every ALS patient (97%) shows aggregation or clumping of a protein called TDP-43 in dying cells suggesting a potential common mechanism of disease. Here we present a novel tool to control this clumping under the control of light to determine how this protein aggregates in disease and identify potential therapeutic options to prevent this pathological process.

Abstract: Amyotrophic lateral sclerosis (ALS) is a progressive and fatal neurodegenerative disorder characterized by selective loss of motor neurons in the cortex and spinal cord. While vast clinical and genetic heterogeneity has left pathogenic mechanisms of the disease largely unknown nearly every single ALS patient (97%) shares a similar pathological hallmark called TDP-43 proteinopathy. Predominantly a nuclear protein in healthy cells cytoplasmic TDP-43 inclusions are observed in postmortem tissue of patients and strongly correlate with areas of degeneration in the central nervous system. TDP-43 proteinopathy is also observed in Frontotemporal Dementia (~45%) Alzheimer's Disease (~30%) and Chronic Traumatic Encephalopathy (~85%) suggesting a potentially common mechanism of cell death across multiple neurodegenerative disorders. The mechanism by which TDP-43 aggregates in disease has remained elusive largely due to technological limitations that have prevented the probing of specific TDP-43 interactions within a cellular environment. Here we present a novel optogenetic-based system to selectively induce intracellular TDP-43 proteinopathy under the spatiotemporal control of light stimulation (optoTDP43). With this model we show that the formation of pathologically-relevant neurotoxic inclusions is driven by aberrant interactions between prion-like/low-complexity domains of TDP-43 that are antagonized by RNA-binding. Additionally exogenous RNA treatment is capable of preventing the induction of TDP-43 proteinopathy suggesting a potentially viable therapeutic avenue for the prevention or reversal of TDP-43 aggregation in neurodegenerative disease.

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Department: Neurobiology

Poster Session: AM
Location: 5

Category:
Neurology & Neurodegenerative Diseases

Title: A 2'-methoxyethyl stem-loop oligonucleotide targeting the RNA binding domains of TDP43 rescues cell viability in a photo-inducible model of TDP43 proteinopathy

Summary: The Donnelly lab and I demonstrated a rescue in human cell viability in vitro by targeting a pathological hallmark of ALS and FTD with a synthetic oligonucleotide technology.

Abstract: Amyotrophic Lateral Sclerosis (ALS) is an upper and lower motor neuron disease characterized by progressive and selective motor neuron degeneration and early death. Various genes have been identified in the familial form of ALS but these inherited mutations combine to account for only 5-10% of patients in the U.S. One common pathological hallmark in both familial and sporadic ALS however is the presence of cytoplasmic inclusions of TAR DNA Binding Protein 43 (TDP43)—a highly conserved predominantly nuclear protein containing two RNA recognition motifs (RRM1 and RRM2) and a low complexity domain (LCD). In fact 97% of all ALS cases present with pathological TDP43 inclusions as do 45% of frontotemporal dementia (FTD) cases—a neurodegenerative condition believed to share a common etiology to ALS. Interestingly these inclusions are also be found in Alzheimer's disease (AD) and Chronic Traumatic Encephalopathy (CTE) patient pathology.\nOver-expression of wild type TDP43 leads to the formation of cytoplasmic inclusions via its LCD. In addition familial mutations in the RRM region of the TDP43 is correlated with an increased propensity for cytoplasmic inclusion formation. \n\nThe Donnelly lab has established an optogenetic system for rapidly inducing TDP43 inclusion formation with blue light stimulation that involves the coupling a photo-active protein Cryptochrome 2 (Cry2) to TDP43 and fluorescent tag mCherry. The Cry-2 protein rapidly homo-oligomerizes when stimulated with blue light and quickly disaggregates when the stimulus is removed. This platform allows for unique spatiotemporal control by way of rapid inclusion formation and disaggregation at physiologically relevant translational levels. The platform demonstrates the recruitment of endogenous TDP43 protein into the inclusions. Our lab has optimized this Cry2_TDP43_mCh (OptoTDP43) construct in numerous cell culture systems and demonstrated that the protein inclusions induced by the system recapitulate the biochemical markers characteristic of the inclusions observed in patient pathology. \n\nEmpowered by our novel platform and research that has previously identified TG and UG dinucleotide repeating sequences has high affinity binders of TDP43's RRMs we hypothesize that stem-loop oligonucleotide designed to bind the RRM of TDP43 will sterically hinder its cytoplasmic homo-oligomerization and function as a neuroprotective agent when tested in vitro.

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Department: Neurological Surgery

Poster Session: AM
Location: 6

Category:
Neurology & Neurodegenerative Diseases

Title: Exploring Mitochondrial Dysfunctions in ALS using Human iPSCs derived Motor Neurons as a model

Summary: Correcting mitochondrial abnormalities could be a possible therapeutic strategy for ALS

Abstract: Amyotrophic lateral sclerosis (ALS) is fatal rapidly progressing disease characterized by loss of motor neurons (MNs). ALS is predominantly 90-95% sporadic while the other 5-10% of cases are familial in nature. The exact mechanisms responsible for sporadic ALS remains unidentified whereas within familial ALS cases various gene mutations have been identified as causal (SOD1 FUS TDP43 VCP etc). Although significant progress in understanding the molecular and genetic aspects of amyotrophic lateral sclerosis (ALS) has been made the exact and inclusive pathological mechanisms behind remain unknown. Until now studies have investigated the role of motor neurons in familial ALS. On the basis of these data two drugs (Riluzole and Edaravone) has been identified but only extend the life span by a few months. Therefore additional therapeutic targets need to be identified. We hypothesize that dysfunctional mitochondrial activity is a major factor triggering ALS. Elucidating patho-mechanisms related to mitochondria provides better understanding of ALS. Using established protocols we generated and differentiated patient-derived induced pluripotent stem cells (iPSCs) into neural progenitors (NPCs) and motor neurons (MNs) and confirmed them by ICC and RT-PCR. We further examined mitochondrial parameters (ROS MMP and protein import) at each developmental stage in the ALS cells along with controls. Our studies demonstrated that mitochondrial abnormalities found to be higher in ALS MNs in compare to their NPCs and iPSCs stages. Future studies will give insight to determine if correcting mitochondrial abnormalities is a possible therapeutic strategy for ALS.

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Mentor/Lab: Thathiah

Department: Neurobiology

Poster Session: AM
Location: 7

Category:
Neurology &
Neurodegenerative
Diseases

Title: Generation of knock-in mouse models with CRISPR/Cas9 genome editing: a method to study neurodegenerative diseases in vivo

Summary: Alzheimer's disease (AD) is one of the most significant medical and societal challenges of our time and yet no current intervention strategies can halt or modify the underlying disease course. Our lab identified the orphan G protein-coupled receptor (GPCR) GPR3 as a primary modulator of AD pathology. The current study provides proof of concept for the development of therapeutic agents to selectively inhibit βarr2 signaling in AD.

Abstract: G protein-coupled receptors (GPCRs) are the largest family of membrane proteins and the most common target for therapeutic drugs. Over 370 non-sensory GPCRs have been identified of which more than 90% are expressed in the central nervous system where they play important roles in cognition mood appetite pain and synaptic transmission through presynaptic and postsynaptic modulation of neurotransmitter release. A variety of GPCRs have been shown to be involved in various neurodegenerative diseases including the β2-adrenoceptor (β2-AR) in Alzheimer's disease (AD) dopamine receptors in Parkinson's disease (PD) and the Sigma-1 receptor in Amyotrophic Lateral Sclerosis (ALS). AD is one of the most significant medical and societal challenges of our time and yet no current intervention strategy can halt or modify the underlying disease course. Clinically AD is characterized by progressive memory loss personality disturbances and general cognitive decline. Neuropathologically the AD brain is characterized by the accumulation of amyloid-β (Aβ) the pathological phosphorylation and aggregation of tau and neuroinflammation. Aβ is derived from proteolysis of the β-amyloid precursor protein (APP) following sequential cleavage by the β- and γ-secretases. We identified the orphan GPCR GPR3 as a key modulator of γ-secretase activity and determined that β-arrestin 2 (βarr2) which belongs to a small family of multifunctional GPCR adaptor proteins specifically interacts with the γ-secretase complex and critically is required for the GPR3-mediated effect on Aβ generation. These results support the hypothesis that βarr2 is a critical link between GPCR dysfunction and Aβ generation in AD. Here we utilized a CRISPR/Cas9-mediated genome editing strategy to introduce defined point mutations in the C-terminus of murine Gpr3 to interfere with the interaction between GPR3 and βarr2. These studies will determine the putative in vivo consequence of selective abrogation of βarr2-dependent signaling in AD pathogenesis.

First Author: Julia Kofler
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Mentor/Lab: Kofler

Department: Pathology

Poster Session: AM
Location: 8

Category:
Neurology & Neurodegenerative Diseases

Title: Association of Alzheimer's disease genetic risk variants with pathology endophenotypes

Summary: Several new genetic risk factors for Alzheimer's disease (AD) have been identified in recent years. By analyzing the association of these risk genes with AD disease burden in postmortem human brain tissue we found that many of these genes modulate multiple AD-associated pathologies and co-morbidities. The findings from this study increase our understanding of how AD risk genes affect AD pathogenesis.

Abstract: Background:\nIn recent years genome-wide association studies (GWAS) have identified several genetic variants associated with increased risk for Alzheimer's disease (AD); however little is known about how and if these risk variants modulate the severity of AD pathology. To address this question we first aimed to test the association of known AD genetic risk variants with AD disease burden and severity of comorbid pathologies in a cohort of autopsy confirmed AD cases and second to perform a GWAS analysis on our pathology endophenotypes.\n\nMethods:\nAn autopsy cohort of 207 cases with moderate to severe AD pathology from the University of Pittsburgh ADRC was included. Quantitative immunohistochemical analyses using whole slide scanning and digital area fraction measurements were performed in the dorsolateral prefrontal cortex for beta-amyloid and p-Tau burden microglial density using Iba1 and microglial activation using HLA-DR antibodies. Cerebral amyloid angiopathy was rated as none mild moderate or severe. For alpha-synuclein and pTDP-43 pathologies staging systems were used based on extent and distribution of pathologic inclusions in standardized sections. Genotype information was obtained using Illumina Omni1-quad SNP arrays. \n\nResults:\nAll pre-defined AD risk genes showed nominally significant associations with at least one but often several of the pathology endophenotypes with several of the associations remaining significant after correction for multiple comparisons. HLA-DR area fraction was strongly associated with multiple SNPs in the HLA-DRB1 gene region at genome-wide significance level (p=1.86E-14) with minor allele homozygotes showing the highest protein expression. GWAS analysis for pathology endophenotypes revealed a genome-wide significant signal in SCYL3 for severity of TDP-43 pathology (p=3.61E-08). For all pathology endophenotypes several additional candidate markers at suggestive significance levels of p<1E-05 were identified. \n\nConclusions:\nAmyloid and tau burden and comorbid pathologies are variably associated with AD risk genotypes with many AD risk genes affecting multiple pathologies suggesting that these genes not only increase AD risk but also modulate disease burden. The findings from this study increase our understanding of how AD risk genes affect AD pathogenesis.

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Department: Neurobiology

Poster Session: AM
Location: 9

Category:
Neurology & Neurodegenerative Diseases

Title: Degeneration and Regeneration of Neural Circuits in the Mouse Olfactory Bulb

Summary: The olfactory bulb is one of only two regions in the mammalian brain where new neurons are continuously incorporated throughout adulthood. We are using the olfactory bulb as a model system to understand what makes particular neurons vulnerable to cell death and how newborn neurons can successfully replace those that were lost. Our work could help to design neural stem cell-based strategies to treat a range of neurological disorders such as Alzheimer's disease traumatic brain injury and stroke.

Abstract: Many neurological disorders involve the loss of particular populations of neurons. Transplantation of stem cell-derived neurons provides a potential therapeutic strategy to combat neuronal loss but we know little about how functional integration of new neurons can be promoted. In the mouse olfactory bulb (OB) new inhibitory interneurons generated from an endogenous population of stem cells in the subventricular zone (SVZ) incorporate into circuits throughout life providing an ideal model system in which to study this question. We have established an experimental strategy that enables us to study the degeneration and regeneration of OB circuits. Olfactory sensory neurons (OSNs) which provide the sole source of sensory input to the olfactory bulb are chemically ablated using methimazole (MMZ) without damaging their progenitor cells in the olfactory epithelium of the nose. Hence sensory input to the olfactory bulb is first abolished and then gradually restored over several weeks as OSNs in the nose are repopulated. In this study we focused primarily on OB dopaminergic neurons which are generated throughout life in the SVZ and are known to be particularly sensitive to sensory activity. In addition we investigated the possible role of microglia in degeneration and regeneration of OB dopaminergic neurons. Our preliminary results show that 7 days after MMZ administration the number of tyrosine hydroxylase-expressing neurons is significantly decreased while the number of microglia has increased relative to saline-injected control mice. Future work will address the properties of those dopaminergic neurons that are resilient to loss of sensory input how successful integration of newborn dopaminergic neurons into OB circuits can be promoted and the role of microglia in the degeneration and regeneration of OB dopaminergic neurons.

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Department: Neurobiology

Poster Session: AM
Location: 10

Category:
Neurology &
Neurodegenerative
Diseases

Title: G protein-coupled receptor kinases modulate γ-secretase function in Alzheimer's disease

Summary: Of the top ten leading causes of death worldwide Alzheimer's disease (AD) is the only one that we cannot prevent cure or slow down. Here we show that G protein-coupled receptor (GPCR) kinases (GRKs) play a significant role in modulating amyloid β(Aβ) generation. Further investigation into the mechanisms by which GRKs modulate Aβ generation will not only address a major challenge in understanding disease mechanisms in AD but will also provide new avenues for the development of potential therapeutic targets to mitigate and/or halt the neurodegenerative changes observed in this devastating neurodegenerative disorder.

Abstract: Alzheimer's disease (AD) is characterized by accumulation of the amyloid-β (Aβ) peptide which is generated by sequential cleavage of the β-amyloid precursor protein (APP) by the β- and γ-secretases and the pathological phosphorylation and aggregation of the microtubule-associated protein tau. Several G protein-coupled receptors (GPCRs) have been associated with multiple stages of APP proteolysis including GPR3 which our lab identified as a modulator of γ-secretase activity. We further determined the GPR3-mediated effect on γ-secretase activity and Aβ generation requires recruitment of the GPCR adaptor protein β-arrestin 2 (βarr2). GPCR kinases (GRKs) bind and phosphorylate GPCRs upon activation initiating βarr2 recruitment to the receptor and downstream signaling. Significantly evidence suggests that levels of GRK2 GRK3 and GRK5 are altered in the human AD brain. Despite these findings the putative involvement of GRKs in AD pathogenesis has not been investigated. To determine whether GRKs are involved in modulation of Aβ generation we utilized a CRISPR/Cas9 genome-editing strategy to delete each of the four ubiquitously expressed GRKs namely GRKs 2 3 5 and 6 in human embryonic kidney (HEK)293 cells. Interestingly we observed significantly lower Aβ generation in the GRK 3 knockout (KO) line compared to control cells yet no change in Aβ production in the GRK2 KO line or a GRK 2/3 double KO line. We did not observe an effect on the α- or β-secretase cleavage products in the GRK KO lines indicating that the effect onn Aβ generation in the GRK3 KO line is due to modulation of γ-secretase function. Ongoing studies are aimed at determining whether GRK3 modulates γ-secretase activity and Aβ generation via phosphorylation of specific GPCRs such as GPR3. In addition GRK3 may phosphorylate the γ-secretase directly independent of GPCR activation. Collectively these studies will determine the pathophysiological involvement of GRKs in the regulation of γ-secretase function and provide a potentially innovative therapeutic approach to treat AD.

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Department: Neurological Surgery

Poster Session: AM
Location: 11

Category:
Neurology & Neurodegenerative Diseases

Title: Sub-cellular Localization of Melatonin Receptor 1

Summary: Melatonin is a potent endogenous free radical scavenger and a well-known neuroprotector for patients affected by neurodegenerative diseases such as Huntington disease.\nOur lab has recently discovered that melatonin is synthesized in the mitochondrial matrix and that one of its receptors MT1 is localized on the mitochondria outer membrane. MT1 is a G-protein coupled receptor (GPCR) with a canonical plasma membrane localization. Its mitochondria outer membrane localization finding is changing our classical thinking of biological GPCR functions.\nThe goal of this project is to elucidate the molecular and cellular mechanisms that regulate MT1 receptor targeting to the mitochondria a critical first step for initiation of mitochondrial GPCR signaling. This information will provide important insights to develop new pharmaceutical targets for neurodegenerative diseases.

Abstract: Huntington's Disease (HD) is a neurodegenerative disease characterized by motor cognitive and behavioral abnormalities. The pathological changes that cause these symptoms are the result of the extension of a CAG trinucleotide repeat within the amino-terminal region of the Huntingtin gene (HTT). When the length of this repeated section exceeds 40 copies the result is the increased decay rate of certain neurons. In Huntington's Disease patients endogenous melatonin levels have been demonstrated to be low. Given the neuroprotective properties of melatonin low neuronal melatonin levels may contribute to neurodegeneration in this disease. In primary cerebrocortical neurons (PCN) an overexpression of the melatonin type 1 receptor (MT1) significantly reduces cell death induced by oxygen glucose deprivation and addition of melatonin results in additive neuroprotection as compared to wild-type PCN.\nThese data indicate that the over-expression of the MT1 receptor and the addition of melatonin have applications in neurodegenerative cell therapy. \nOur lab recently has shown that melatonin a hormone secreted by the pineal gland in neurons is synthesized in the mitochondrial matrix. In the same work our group also showed that the G-protein coupled receptor melatonin type 1 receptor (MT1) has a unique dual localization within the cell as a plasma membrane (PM) receptor and an intracellular mitochondrial outer membrane (MOM) receptor. The translocation signal responsible for this phenomenon is unknown. This project seeks to identify the mitochondrial and plasma membrane localization signal within the protein sequence and determine by which capacity they differ or coincide. We are investigating four variations of the protein amino acid sequence in human cells to identify the mechanism accountable for the translocation signal. One factor that may be significant is the N-linked glycosylation at the N terminus of the sequence. Another hypothesized factor of significance is the presence of two alternate start codons at position 86 and 106. The dual localization of MT1 may be due to the expression of two proteins from the same gene.

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Mentor/Lab: Hastings

Department: Neuroscience

Poster Session: AM
Location: 12

Category:
Neurology &
Neurodegenerative
Diseases

Title: Neurodegeneration induced by dysregulation of dopamine sequestration is rescued by restoration of vesicular packaging

Summary: The neurotransmitter dopamine is necessary for the control of motor output as evidenced by the development of motor deficits in Parkinson's disease resulting from the degeneration of dopaminergic neurons. Dopamine has the potential to act as an endogenous neurotoxin due to its chemical structure and reactivity within neurons and therefore might cause dopaminergic neurons to be vulnerable to degeneration in Parkinson's disease. Here we demonstrate that dysregulation of dopamine is sufficient to cause neurodegeneration and this can be prevented by restoring proper dopamine handling further implicating dopamine as a contributing factor in the pathogenesis of Parkinson's disease.

Abstract: Within dopaminergic (DAergic) neurons dysregulation of vesicular dopamine (DA) packaging results in increased cytosolic DA which is susceptible to oxidation and degradation: two processes that generate reactive metabolites and reactive oxygen species. There is significant evidence that deficits in vesicular packaging of DA contribute to the pathogenesis of Parkinson’s disease (Miller et al. 1999 Pifl et al. 2014) and animal models have demonstrated toxic consequences following dysregulation of vesicular DA packaging (Caudle et al. 2007 Chen et al. 2008). We have generated a viral vector (AAV2-shVMAT2) that dysregulates vesicular DA packaging by small-hairpin ribonucleic acid (shRNA) interference of rat vesicular monoamine transporter 2 (VMAT2) expression. Unilateral viral-mediated knock-down of VMAT2 results in increased cytosolic DA as evidenced by increased DA oxidation (27.5%) and turnover (64.6%) (paired t-test n=4 p<0.05). Dysregulation of DA packaging resulted in a 38.7% loss of DAergic neurons in the substantia nigra and a corresponding 29.8% loss of tyrosine hydroxylase (TH) intensity in the terminals (paired t-test n=5 p<0.05). These data suggest that dysregulation of DA sequestration is sufficient to induce neurodegeneration. To verify that the neurodegeneration was specific to dysregulation of DA and not an off-target effect of the AAV2-shVMAT2 itself we developed a viral vector (AAV2-muVMAT2) that expresses human VMAT2 with silent mutations resulting in VMAT2 transcript resistant to the shRNA-VMAT2. The mutant VMAT2 (muVMAT2) construct was first tested in vitro in a DAergic neuronal cell line derived from the midbrain of adult rat. Co-expression of muVMAT2 with the shVMAT2 construct decreased the endogenous rat VMAT2 mRNA but resulted in exogenous human VMAT2 mRNA and an overall\nincrease in VMAT2 protein expression. After cell culture verification the AAV2-muVMAT2 virus was made for in vivo experiments. When co-injected reintroduction of VMAT2 by AAV2-muVMAT2 restores VMAT2 protein and prevents neurodegeneration compared to a VMAT2 knock-down control that lost 36.17% of VMAT2 protein in transduced neurons (One-way ANOVA p<0.001) and lost 28.00% of DAergic neurons in the substantia nigra (One-way ANOVA p<0.05). These data confirm that neurodegeneration resulting from AAV2-shVMAT2 is specific to VMAT2 knock-down and further implicate the necessity of DA sequestration to maintain neuronal health in DAergic neurons.

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Department: Neuroscience

Poster Session: AM
Location: 13

Category:
Neurology & Neurodegenerative Diseases

Title: An opposing function of paralogs in balancing developmental silent synapse maturation

Summary: So called silent synapses are substrates to change the connection of cortical neurons during development. Here we show that two proteins that are associated with mental disorders regulate this process. Changes in the function of these proteins affects the developmental process and could indicate what goes wrong in neurodevelopmental disorders.

Abstract: The DLG-MAGUK family of proteins forms a central signaling hub of the glutamate receptor complex. Among this family some proteins regulate developmental maturation of glutamatergic synapses a process vulnerable to aberrations which may lead to neurodevelopmental disorders. As is typical for paralogs the DLG-MAGUK proteins PSD-95 and PSD-93 share similar functional domains and were previously thought to regulate glutamatergic synapses similarly. Here we show that they play opposing roles in glutamatergic synapse maturation. Specifically PSD-95 promoted whereas PSD-93 inhibited maturation of immature AMPA receptor-silent synapses in mouse cortex during development. Furthermore through experience-dependent regulation of its protein levels PSD-93 directly inhibited PSD-95's promoting effect on silent synapse maturation in the visual cortex. Thus controlling the pace of silent synapse maturation the opposing but properly balanced actions of PSD-93 and PSD-95 might be essential for fine-tuning cortical networks during developmental critical periods and imply aberrations in either direction of this process as potential causes for neurodevelopmental disorders.

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Mentor/Lab: Meriney

Department: Center for Neuroscience

Poster Session: AM
Location: 14

Category:
Neurology & Neurodegenerative Diseases

Title: A novel therapeutic approach to treat the neuromuscular weakness caused by Spinal Muscular Atrophy

Summary: Spinal Muscular Atrophy is a neurodegenerative disease that culminates in early childhood death via respiratory paralysis. The sole FDA-approved therapy for SMA uses antisense oligonucleotides (ASOs) which benefit patients that are able to access afford and tolerate the series of invasive ASO injections required for improvement in neuromuscular function but deficits persist despite treatment. We have developed a novel therapy to complement ASO treatment by independently and directly targeting neuromuscular function which would also help patients that are unable to receive or benefit from ASO administration.

Abstract: Spinal Muscular Atrophy (SMA) is the most common genetic cause of infant and childhood death. A null genetic mutation in the SMN1 gene causes ubiquitously low levels of Survival of the Motor Neuron (SMN) protein critical during activity-dependent neuromuscular development. Low SMN expression causes neuromuscular pathology severely reduced synaptic transmission and leads to neuromuscular denervation and subsequent α-motoneuron degeneration. The gradual loss of motoneurons results in muscular paralysis and culminates in early death due to respiratory failure. The only FDA-approved approach to treat SMA is to use antisense oligonucleotides (ASOs) to target a paralogous gene SMN2 to increase SMN protein expression. While SMA pathology is improved by centrally administered ASO treatment evidence suggests that ASOs have limited peripheral penetration and thus provide suboptimal benefit to neuromuscular junctions during the critical period of development. This incomplete rescue of the neuromuscular system will require long-term maintenance to ameliorate the progressive functional decline beyond childhood (after the requirement for high SMN expression in motoneurons is over). However many SMA patients lack access to ASO therapy due to medical costs treatment availability and immune rejection. New treatments should complement current therapy by targeting withstanding deficits via an SMN2-independent strategy. We have evaluated a novel treatment using a calcium channel agonist GV-58 in combination with a potassium channel blocker 34-DAP. In ex vivo recordings from SMNΔ7 mouse neuromuscular synapses GV-58 + DAP can increase the magnitude of transmitter released following action potential activity. Furthermore acute in vivo administration of GV-58 + DAP to PD10 SMNΔ7 mice increases grip strength compared to healthy littermates. Our novel treatment might be used in conjunction with current ASO therapy or as a stand-alone strategy to improve neuromuscular function in patients requiring SMN2-independent approaches to treat weakness.

First Author: Michel Modo
(Faculty)

Presenting Author: Jeffrey Moorhead
(Postdoctoral)

Mentor/Lab: Modo

Department: Radiology

Poster Session: AM
Location: 15

Category:
Neurology & Neurodegenerative Diseases

Title: Sub-additive effects of cell and physical therapy in a rodent model of stroke

Summary: Physical Therapy + Cell Therapy produce sub-additive effects leading to a mild improvement in functional recovery as opposed to either intervention alone. Physical Therapy helps to improve synaptogenesis and neural connections that were previously lost after stroke damage. Stem cell implantation does this as well. However the combined therapy does not yield improvements in neural connections as expected.

Abstract: A randomized control preclinical study was initiated to include adult male Sprague- Dawley rats that underwent transient middle cerebral artery occlusion (MCAo) a model of ischemic stroke. Success of MCAo was determined by T2-weighted magnetic resonance imaging (MRI). After exclusion of non-stroke and hemorrhagic animals rats with stroke were randomly assigned to the following conditions: MCAo only MCAo+NSCs MCAO+PT MCAO+NSCs+PT. Sham-operated animals served as healthy control to maintain blinding of experimenters. Groups subjected to NSCs or NSCs + PT received a perilesional NSC graft (450000 cells) at 2 weeks post-stroke. Each rat ran at 80% of its maximum capacity (determined by using the Bruce protocol) for 30 minutes 5 days/week. These parameters have previously been shown to optimize the effects of physical therapy by inducing positive oxidative physiological adaptations; opposed to 15 and 60 minutes of aerobic exercise a 30-minute time interval improves maximum capacity by 80%. Behavioral tests were performed by blinded researchers assessing bilateral asymmetry testing foot-fault testing and maximum capacity testing on a treadmill; following all groups for a span of 10 weeks. fMRI DTI and CBV MRI scans were acquired to assess recovery of brain tissue and functional neural connections between groups at 10-weeks post treatment. For fMRI acquisition an electrode was inserted subcutaneously in each forepaw and each paw was stimulated alternately for 5 minutes with a current of 1 mA over the duration of an hour with short periods of no stimulation to provide a resting-state intensity. DTI analysis was done using DSI Studio a tractography software three- dimensional maps of anatomical regions of interest (ROIs) were manually drawn on the MR images of pre and post scans to delineate the motor cortex (MC) somatosensory cortex (SMC) thalamus and striatum. Once the ROIs were drawn scalar indices of FA (Fractional Anisotropy and number of streamlines were recorded. Survival of transplanted cells in to the peri-infarct area was also assessed to determine if PT improved engraftment.

First Author: Jeffrey Moorhead
(Faculty)

Presenting Author: Jeffrey Moorhead
(Postdoctoral)

Mentor/Lab: Modo

Department: Radiology

Poster Session: AM
Location: 16

Category:
Neurology &
Neurodegenerative
Diseases

Title: Sub-additive effects of cell and physical therapy in a rodent model of stroke

Summary: The purpose of the study was to examine the effects of combined physical and cell therapy in motor & sensory recovery after stroke. Through behavioral testing and MRI analysis we concluding that Physical Therapy + Cell Therapy produce sub-additive effects leading to a mild improvement in functional recovery as opposed to either intervention alone.

Abstract: A randomized control preclinical study was initiated to include adult male Sprague-Dawley rats that underwent transient middle cerebral artery occlusion (MCAo) a model of ischemic stroke. Success of MCAo was determined by T2-weighted magnetic resonance imaging (MRI). After exclusion of non-stroke and hemorrhagic animals rats with stroke were randomly assigned to the following conditions: MCAo only MCAo+NSCs MCAO+PT MCAO+NSCs+PT. Sham-operated animals served as healthy control to maintain blinding of experimenters. Groups subjected to NSCs or NSCs + PT received a perilesional NSC graft (450000 cells) at 2 weeks post-stroke. Each rat ran at 80% of its maximum capacity (determined by using the Bruce protocol) for 30 minutes 5 days/week. These parameters have previously been shown to optimize the effects of physical therapy by inducing positive oxidative physiological adaptations; opposed to 15 and 60 minutes of aerobic exercise a 30-minute time interval improves maximum capacity by 80%. Behavioral tests were performed by blinded researchers assessing bilateral asymmetry testing foot-fault testing and maximum capacity testing on a treadmill; following all groups for a span of 10 weeks. fMRI DTI and CBV MRI scans were acquired to assess recovery of brain tissue and functional neural connections between groups at 10-weeks post treatment. For fMRI acquisition an electrode was inserted subcutaneously in each forepaw and each paw was stimulated alternately for 5 minutes with a current of 1 mA over the duration of an hour with short periods of no stimulation to provide a resting-state intensity. DTI analysis was done using DSI Studio a tractography software three-dimensional maps of anatomical regions of interest (ROIs) were manually drawn on the MR images of pre and post scans to delineate the motor cortex (MC) somatosensory cortex (SMC) thalamus and striatum. Once the ROIs were drawn scalar indices of FA (Fractional Anisotropy) and number of streamlines were recorded. Survival of transplanted cells in to the peri-infarct area was also assessed to determine if PT improved engraftment.

First Author: Catherine Ruff
(Graduate)

Presenting Author: Catherine Ruff
(Graduate)

Mentor/Lab: Ross

Department: CNUP

Poster Session: AM
Location: 17

Category:
Neurology &
Neurodegenerative
Diseases

Title: The contribution of NK1R interneurons in cerebral blood flow

Summary: Neurovascular coupling is a regional increase in blood flow to a brain area triggered by local neural activity. Cortical neurokinin 1 receptor neurons are a distinct subtype of inhibitory neurons that closely track the microvasculature and co-express neuronal nitric oxide synthase a potent vasodilator. We are investigating the role of NK1R neurons as a potential link between neural activity and local vasodilation.

Abstract: Catherine F Ruff Jay Couey Bryan M Hooks Alberto Vazquez* Sarah Ross*\nDepartment of Neurobiology University of Pittsburgh Pittsburgh Pennsylvania USA\n*Corresponding authors\n\nNeurovascular coupling (NVC) is a regional increase in blood flow to a brain area triggered by local neural activity. Although NVC is critical to normal brain function and its dysfunction is reported in many neuropathologies the underlying neural basis remains unclear. Here we report the generation of a neurokinin-1 receptor (NK1R)-creER mouse that selectively labels a subset of cortical inhibitory neurons that are ideally situated to regulate NVC. Using this genetic tool with a combination of imaging electrophysiology optogenetic techniques and in vivo laser Doppler flowmetry we found that NK1R cortical interneurons receive local excitatory input and their activation is sufficient for local vasodilation. Together these findings suggest that NK1R cortical inhibitory interneurons act as local integrators of neural activity to mediate neurovascular coupling providing important insight into the neural circuitry of NVC.

First Author: Eric Anderson
(Postdoctoral)

Presenting Author: Eric Anderson
(Postdoctoral)

Mentor/Lab: Pandey

Department: Pediatrics

Poster Session: AM
Location: 18

Category:
TBI, Concussion

Title: Traumatic Injury Induces Stress Granule Formation and Exaggerates Motor Dysfunction in ALS Models

Summary: Drosophila was used as a model to study traumatic brain injury (TBI) and to examine TBI influence on neurodegenerative symptoms. We show that TBI alters protein degradation pathways and enhanced neurodegenerative symptoms associated with ALS. Using proteomic analysis we identified novel pathways that are altered by TBI and are common in neurodegenerative diseases such as ALS/FTD.

Abstract: Traumatic brain injury (TBI) has been predicted to be a predisposing extrinsic factor for ALS and several other neurodegenerative disorders. We examined the contribution of traumatic brain injury (TBI) as an extrinsic factor and investigated if TBI influences the susceptibility of developing neurodegenerative symptoms in vivo. We found that traumatic injury leads to the induction of stress granules (SGs) in the Drosophila brain. The degree of SGs induction directly correlates with the level of trauma in flies. Furthermore we found that the level of mortality is directly proportional to the number of traumatic hits. Interestingly trauma-induced SGs are ubiquitin p62 and TDP-43 positive and persistently remain over time suggesting that SGs might be aggregates and exert toxicity in our fly models. TDP-43 pathology has been observed in ALS/FTD and several other related neurodegenerative diseases. Importantly mild and repetitive trauma in flies expressing ALS-linked genes such as FUS and expanded G4C2 repeats increased mortality and locomotion dysfunctions suggesting that mild trauma aggravate neurodegenerative symptoms associated with ALS. Furthermore we found elevated levels of high molecular weight ubiquitinated proteins and p62 with TBI suggesting that TBI may lead to defects in protein degradation pathways. Finally we performed proteomic analysis of the Drosophila brains and identified several candidate neuronal proteins that become altered in response to traumatic injury. Using bioinformatic analysis we identified potential molecular pathways that are perturbed due to traumatic injury in flies. We found alteration in major biological pathways such as nuclear transport synaptic transmission and RNA metabolism which has been previously implicated in ALS/FTD. We are testing these candidate proteins as potential modulators of traumatic injury in our fly models and we expect to better understand the role of trauma in ALS pathogenesis.

First Author: Hannah Bitzer
(Graduate)

Presenting Author: Hannah Bitzer
(Graduate)

Mentor/Lab: Kontos

Department: Orthopaedic Surgery

Poster Session: AM
Location: 19

Category:
TBI, Concussion

Title: Utility of Brief Symptom Inventory-18 (BSI-18) subset scores as a Predictor of Vestibular Impairment in Collegiate Athletes following Concussion

Summary: Concussions are becoming a prevalent injury in sports and the ability to correctly identify and manage athletes following concussion is paramount. The development of cost and time effective tools that identify athletes at risk for protracted recovery is critical when making treatment and return-to-play decisions. This analysis focuses on the utility of the BSI-18 and its subset scores as predictors of athletes with a vestibular profile following concussion. This is important because athletes with a vestibular profile are at an increased risk for protracted recovery and may need earlier intervention than those who do not have a vestibular profile.

Abstract: Introduction: There are roughly 11 concussion per 10000 athlete exposures (AE) in NCAA Division I collegiate athletes (Zuckerman Kerr et al. 2015). The purpose of this study was to collect data on collegiate athletes following concussion to understand the different concussion presentations the unique characteristics of collegiate athlete concussions and examine recovery outcomes. Research has shown that approximately 65% of athlete experience vestibular impairments following a concussion and that athletes with vestibular impairment tend to report higher symptoms and take longer to recover (Hoffer Gottshall et al. 2004 Naguib Madian et al. 2012).The ability to use cost-effective easy to administer assessments to predict athletes who may be at risk for vestibular dysfunction following concussion could be instrumental in the diagnosis and management of concussions in collegiate athletes. Methods: Participants were collegiate athletes between 18-23 years old (M=19.48 SD=2.63) with 47 males (56.6%) and 36 females (43.4%). There were a total of 83 concussion— 74 sport-related and 9 non-sport. Measures in the study included: the Vestibular/Ocular Motor screening (VOMs) the Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT) the Sport Concussion Assessment Tool 3 (SCAT3) the Brief Symptom Inventory 18 (BSI-18) and the Balance Error Scoring System (BESS). Each of the measures was completed within 48 hours of the injury and athletes were monitored until they were returned to play (i.e. recovered). For the purpose of this analysis we examined only the BSI-18 raw subset scores for anxiety (ANX) depression (DEP) and somatization (SOM) and examined four ImPACT composite scores: verbal memory visual memory visual motor speed and reaction time. In this analysis vestibular profile is defined as an individual having +2 symptom rating on any of the vestibular components of the VOMs from their baseline symptoms. Symptoms on the VOMs are headache dizziness nausea and fogginess which are self-reported on a 0 (none) to 10 (severe) scale. A series of Forward Wald logistics regressions were used to determine the independent and combined association of BSI-18 raw subset scores and ImPACT in relation to vestibular impairment and symptoms following concussion. Results: Researchers ran three Forward Wald logistic regressions to examine if BSI-18 subset scores (ANX DEP SOM) and the four components of the ImPACT test mentioned above are predictive of a positive vestibular profile in concussed collegiate athletes. The three analyses are as follows: 1) BSI-18 subset scores only; 2) ImPACT scores only and 3) BSI-18 subset scores and ImPACT scores. 1) The Forward Wald logistic regression model indicates that the raw somatization subset score on the BSI-18 is a significant predictor of a positive vestibular profile in recently concussed athletes [X2(1)=21.279 p <

.0001). The depression and anxiety subset scores are not predictive. BSI-18 SOM subset score is significant at the .01% level and athletes with a positive vestibular profile are 1.62 (95% CI: 1.279 2.05) times more likely to have a positive indication on their BSI-18 somatization subset score. The model explains 30.7% (Nagelkerke R2) of the variance in BSI-18 subset scores and correctly classifies 78.3% of athletes with a positive vestibular profile. 2) The Forward Wald logistic regression model indicates that ImPACT reaction time composite is a significant predictor of a positive vestibular profile in recently concussed athletes (X2(1)=9.51 p < .01). ImPACT verbal memory visual memory and visual motor speed composite scores are not significant predictors. The model explains 14.7% (Nagelkerke R2) of the variance in ImPACT scores and correctly classifies 67.5% of athletes with a positive vestibular profile. Athletes with a positive vestibular profile are 155.09 (95% CI: 2.84 8482.66) times more likely to have a higher reaction time score. 3) The Forward Wald logistic regression model indicates that ImPACT Visual Motor Speed Composite and BSI-18 SOM raw score are combined significant predictors of an athlete being diagnosed with a positive vestibular profile following concussion (X2(2)=25.55 p < .0001). The model explains 36.0% (Nagelkerke R2) of the variance in those ImPACT scores and BSI-18 subset scores and correctly classified 74.7% of athletes with a positive vestibular profile. Athletes with a positive vestibular profile were 1.58 (95% CI: 1.26 1.99) times more likely to have increased BSI-18 subset scores and were .93 (95% CI: .87 1.0) times more likely to have decreased visual motor speed composite. Conclusion: The BSI-18 may be useful screening tool to identify individuals who at risk for vestibular deficits following concussion. The analysis shows that while BSI-18 and ImPACT model explains more of the variance within the data (36%; 30.7%) the BSI-18 subset score only model correctly identifies more of the athletes with a positive vestibular profile compared to the BSI-18 and ImPACT model (78.3%; 67.5%). These individuals with higher BSI-18 subset scores may be at risk for a protracted recovery and may benefit from early intervention. More research is needed to examine the effectiveness of BSI-18 subset scores (e.g. anxiety depression somaticizing) in identifying concussed individuals experiencing psychological distress (e.g. irritability more/less emotional sadness) following concussion.

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(First Author Type)

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(Presenting Author Type)

Mentor/Lab: Kontos

Department: Orthopaedic Surgery

Poster Session: AM
Location: 20

Category:
TBI, Concussion

Title: Adolescent Post-Concussion Sleep Disturbances and its Relationship with Concussion Assessment Outcomes

Summary: This study analyzed the differences in clinical outcomes among adolescents with sport-related concussion and matched controls with and without sleep problems. The results reveal performance similarities between concussed individuals and controls with sleep problems. Furthermore the results highlight the need for more focused criteria for control enrollment in concussion studies.

Abstract: Adolescent Post-Concussion Sleep Disturbances and its Relationship with Concussion Assessment Outcomes\n\nNicholas A. Blaney Alicia Sufrinko PhD Hannah B. Bitzer Cyndi L. Holland MPH Michael W. Collins PhD Anthony P. Kontos PhD\n\nBackground: Sport-related Concussion (SRC) concussion is a heterogenous injury that results in diverse physical cognitive and emotional symptoms and impairments (e.g. cognitive vestibular) including sleep problems. Sleep problems are more complex than other concussion symptoms and can be challenging to study. Not only is sleep difficulty a symptom or consequence of SRC (Kostyun et al. 2015) but also a modifying factor for recovery following injury (Sufrinko et al. 2015). Sleep problems can be an iatrogenic effect of post injury management or secondary to anxiety (Wickwire et al. 2016) as well. Further sleep issues in healthy adolescents can lead to cognitive emotional and physical complaints that mimic concussion sequelae and many preexisting conditions such as anxiety and migraine are linked to sleep issues. Prior baseline and post concussion studies indicate athletes with inadequate sleep duration or sleep complaints pre injury perform worse on neurocognitive testing although it is unclear how this extends to post injury outcomes. As such it is vital to further examine how sleep problems affect performance on post-concussion assessment measures in both concussed and healthy adolescents. \n\nPurpose: To evaluate differences in clinical outcomes including neurocognitive testing and vestibular/oculomotor scores among adolescents with SRC and matched controls with and without sleep complaints on a concussion symptom scale. \n\nMethods: Fifty adolescents with a sport-related concussion diagnosed in the past 10 days were matched with 50 same sex same age healthy controls. Participants completed neurocognitive testing (i.e. Immediate Post-Concussion Assessment and Cognitive Test [ImPACT) vestibular/oculomotor screening (i.e. VOMS) and a concussion symptom scale (i.e. post concussion symptom scale [PCSS]). . All Participants from both groups were further categorized based on endorsement of one or more of sleep-related symptomology items on the PCSS. Thus four groups existed in this study: concussed with sleep problems(N=31) concussed without sleep problems (N=19) control with sleep problems (N=19) and controls without sleep problems (N=31). ANOVAs with Bonferroni correction for significant pairwise comparisons were used to compared groups on ImPACT and VOMS scores.\n\nResults: Between the two SRC groups the group endorsing sleep problems performed significantly worse on all ImPACT domains endorsed higher overall affective and cognitive/migraine symptoms and reported higher symptom burden on most of the VOMS exercises. When comparing the control groups the group reporting sleep problems indicated significantly higher affective symptoms and had an overall higher PCSS score. After cross-analyzing the SRC with sleep problems group to both control groups the SRC group reported higher symptom burden across all

VOMS exercises. The SRC with sleep problems group performed worse than the controls without sleep problems on visual memory visual-motor speed and reaction time components of ImPACT and reported higher overall affective and cognitive/migraine symptoms. When the same SRC group is compared to controls with sleep problems the SRC group performed worse on visual memory and had higher cognitive/migraine and PCSS scores. Lastly the SRC without sleep problems group endorsed higher symptom burden on the smooth pursuits and saccadic portions of VOMS and had higher cognitive/migraine and PCSS scores than controls without sleep problems. When compared to the controls with sleep problems the SRC without sleep problems group did not differ across all ImPACT PCSS and VOMS domains.\n\nConclusions: SRC with post-injury sleep problems was associated with lower neurocognitive scores higher symptom burden and a more provocative VOMS when compared to SRC without post-injury sleep difficulty. Another significant finding was the uniquely similar presentation on neurocognitive symptoms and vestibular/ocular evaluations between the SRC without sleep problems and the controls with sleep problems groups. Clinicians can use these new findings to assist in interpreting presenting concussion data. Lastly the higher symptom burden in the control with sleep problems group demonstrates the need for researchers to recruit controls that either do not have sleep problems or match concussed participants on baseline symptom cognitive and vestibular/ocular scores. \n\n\nReferences: \n\n1.) Kostyun R. O. Milewski M. D. & Hafeez I. (2015). Sleep disturbance and neurocognitive function during the recovery from a sport-related concussion in adolescents. Am J Sports Med 43(3) 633-640. doi:10.1177/0363546514560727\n\n2.) Sufrinko A. Pearce K. Elbin R. J. Covassin T. Johnson E. Collins M. & Kontos A. P. (2015). The effect of preinjury sleep difficulties on neurocognitive impairment and symptoms after sport-related concussion. Am J Sports Med 43(4) 830-838. doi:10.1177/0363546514566193\n\n3.) Wickwire E. M. et al. (2016). "Sleep Sleep Disorders and Mild Traumatic Brain Injury. What We Know and What We Need to Know: Findings from a National Working Group." Neurotherapeutics: 1-15.

First Author: Shaun Carlson
(Faculty)

Presenting Author: Shaun Carlson
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Mentor/Lab: Dixon

Department: Neurological Surgery

Poster Session: AM
Location: 21

Category:
TBI, Concussion

Title: Lithium improves striatal dopamine neurotransmission and synaptic dopaminergic protein abundance following traumatic brain injury

Summary: This study described the effects of lithium treatment on synaptic protein abundance and evoked dopamine neurotransmission in the striatum following traumatic brain injury.

Abstract: Experimental models of traumatic brain injury (TBI) recapitulate neurobehavioral impairments and the development of secondary injury sequela observed in TBI patients. Previous work from our lab shows that TBI reduces formation of the soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) complex protein machinery important for vesicular fusion contributing to impaired neurotransmission in the weeks post-injury. In the hippocampus lithium treatment increases SNARE monomeric protein abundance and SNARE complex formation and promotes the recovery of cognitive function after controlled cortical impact (CCI). However the effects of TBI on the SNARE complex formation have not been studied in the striatum a region exhibiting deficits in evoked dopamine neurotransmission. The objective of this study was to evaluate the effect of lithium treatment on SNARE complex formation and dopamine neurotransmission in the striatum. To test this anesthetized male Sprague-Dawley rats received CCI (2.7mm) or sham injury and injected daily (i.p.) with vehicle or 1.0mmol/kg/ml lithium chloride for 7d beginning 5 minutes post-injury. Daily treatment with lithium significantly improved high-potassium evoked striatal dopamine release at 7d post-injury (n=6-7/group). In a separate cohort animals received CCI or sham surgery as described and the brains were dissected at 7d post-injury and processed to produce synaptosomal lysates for immunoblotting (n=6/group). CCI significantly reduced cysteine string protein alpha VAMP2 and SNARE complex formation in striatal synapses. Treatment with lithium did not increase SNARE protein abundance or SNARE complex formation. However lithium increased the abundance of alpha synuclein D2 receptor and phosphorylation of tyrosine hydroxylase. These findings demonstrate treatment with lithium improves striatal neurotransmission and suggests that lithium may increase the abundance of multiple dopaminergic proteins after TBI.

First Author: Bianca Leonard
(Graduate)

Presenting Author: Bianca Leonard
(Graduate)

Mentor/Lab: Rossi

Department: Ophthalmology

Poster Session: AM
Location: 22

Category:
TBI, Concussion

Title: Fixational eye movements (FEMs) following concussion.

Summary: Precise measurement of tiny involuntary eye movements may be important for evaluating injuries and monitoring recovery in mild traumatic brain injury/concussion.

Abstract: Background: Concussion can affect ocular function including saccadic eye movements smooth pursuit convergence and accommodation (e.g. Mucha et al. 2014; Pearce et al. 2015). Fixational eye movements (FEMs) are the small involuntary movements that keep the eyes in constant motion when attempting to carefully point the eyes at a specific point in space. FEMs have been shown to be altered in neurological conditions such as Alzheimer's disease Parkinson's disease and mild cognitive impairment (Alexander et al. 2018). However little is known about FEMs following concussion. We used a retinal image-based eye tracker rather than one that tracked the pupil or Purkinje images allowing precise characterization of FEMs. \nPurpose: To examine FEMs using a tracking scanning laser ophthalmoscope (TSLO) in patients with concussion compared to controls. Our hypothesis is that FEMs are altered following concussion and may be useful for diagnosis or monitoring recovery.\nMethods: A total of 50 patients aged 13-29 years participated in the study. Fifty age-and gender-matched controls also participated. Preliminary data presented here represent data from 19 participants. FEMs were measured with a TSLO an image-based retinal-tracker with an accuracy of ~0.2 arcmin. All participants were each asked to perform a passive fixation task involving pointing their eyes to the corner of the imaging field which appeared as a red square on a dark background for 5 trials of 30 sec each. Concussion patients were imaged within 21 days of injury and again within 6 months after clearance to work/play. Concussion patients' FEMs were examined across these time points and compared to controls. Custom MATLAB software was used to generate eye motion traces at 480 Hz. Eye traces were analyzed to compute FEM statistics of microsaccades including: amplitude peak velocity peak acceleration and frequency. We also looked at other characteristics of fixation including blink rate and spread of fixation measured with the bivariate contour ellipse area (BCEA). All concussion patients underwent a full clinical concussion examination including Vestibular Oculo-motor Screening (VOMS) and Immediate Post-Concussion Assessment and Cognitive Test (ImPACT). Findings from the TSLO were compared to clinical testing for a multimodal representation of recovery in concussion patients of different mechanisms of injury such as sports-related injury motor-vehicle accident ground fall or assault. \nResults: Our preliminary results suggest that FEMs are altered in concussion patients. BCEA was increased by ~32% in comparison to control eyes indicating a larger spread of fixation in the concussed subjects. Concussion subjects made slower and smaller microsaccades as evidenced by microsaccade peak velocity and amplitude. Compared to concussion patients controls made ~14% more of their saccades with peak velocities greater than 50°/s and ~8% more of their saccades at amplitudes greater than 45 arcmin.\nConclusion: FEMs appear to be impaired following a concussion. Fixation is less accurate in concussion patients and the statistics of microsaccades are slower and of lower amplitude on average compared to controls. Precise measurement of FEMs may be useful for diagnosis of and monitoring of recovery in mild traumatic brain injury and concussion.

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Mentor/Lab: Kontos

Department: Orthopedic Surgery

Poster Session: AM
Location: 23

Category:
TBI, Concussion

Title: Preliminary examination of concussion in older adults

Summary: Little is known about concussion in the at-risk population of older adults. This study investigated 142 elderly individuals with concussion to better understand this injury in the elderly population

Abstract: Concussion is a significant health concern affecting millions of individuals each year. Surprisingly little is known about the characteristics of this injury in older adults who at-risk for this injury from falls and other mechanisms. We examined 142 de-identified patient charts of older adults to better characterize concussion in this at-risk population. We conducted a retrospective review of 142 de-identified patient medical records related to concussion care. Participants averaged 67.1 (SD= 6.1) years in age and included a majority of females (n=87; 61.3%). We recorded age gender concussion history migraine history motion sickness history psychiatric history learning disorder history employment status and educational background as well as concussion profile and ImPACT data. Data were recorded at intake visit and up to the seventh follow-up visit. Descriptive analysis including frequencies means and standard deviations was performed for the population. The average number of clinic visits across all participants in the study was 2.20 (SD= 1.45). Previous concussion history was present in 34/142 (23.9%) of participants. Migraine history was present in 30/142 (21.1%) participants motion sickness history in 30/142 (21.4%) and psychiatric history in 23/142 (16.2%). Concussion symptom severity scores at participants' first clinic visit averaged 48.1 (SD= 28.4 n=135) compare with 39.2 (SD= 25.1 n=79) at their final clinic visit. ImPACT Measures were compared for visit 1 (N=121) and at Last Visit/Clearance (N=74); all scores improved comparatively from Visit 1 to Last Visit/Clearance. Verbal Memory increases from 63.91 (19.08) to 69.09 (18.70) Visual Memory from 49.02 (12.84) to 51.65 (12.23) Visual-Motor Speed from 21.81 (7.04) to 24.77 (6.21) and Reaction Time decreased from 1.15 (0.52) to 0.93 (0.21). Older adults diagnosed with concussion showed improvement on ImPACT scores and their symptom severity scores decreased. Further research in this at-risk population is warranted to better inform clinical care for older adults following concussion.

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Presenting Author: Aaron Sinnott
()

Mentor/Lab: Kontos

Department: Sports Medicine and Nutrition, Orthopaedic Surgery

Poster Session: AM
Location: 24

Category:
TBI, Concussion

Title: Vestibular-Ocular Symptoms and Impairment among Collegiate Athletes within 3 days of Sport-related Concussion

Summary: The Vestibular/Ocular Motor Screening (VOMS) tool was designed to screen for vestibular impairment and symptoms following concussion but the differences between athletes with and without vestibular impairment on acute clinical measures following sport-related concussion (SRC) is unknown. 73 NCAA-D1 athletes completed the VOMS and commonly used clinical assessments <18 hours and 1-3 days after concussion. Athletes with initial vestibular symptoms and impairment within 18 hours of SRC experienced persistent deficits on VOMS than those without; performances on other clinical assessments were equal between groups within 18 hours of SRC.

Abstract: BACKGROUND: Sport-related concussion (SRC) is a heterogeneous brain injury characterized by a diverse presentation of symptoms and impairments1. Vestibular impairment and symptoms are common following SRC2 and are associated with greater symptom burden and worse clinical outcomes among high school and collegiate athletes3. The Vestibular/Ocular Motor Screening (VOMS) tool was designed to screen for these impairment and symptoms following SRC. Moreover we know little about differences between athletes with and without vestibular-ocular impairment/symptoms on common acute clinical measures such as balance cognitive and symptoms. PURPOSE: Compare commonly used clinical measures within 18 hrs and 1-3 days following SRC between collegiate athletes with and without vestibular-ocular impairment. METHODS: 73 NCAA-Division I collegiate athletes completed the Standardized Assessment for Concussion (SAC) Balance Error Scoring System (BESS) Post-concussion Symptom Scale (PCSS) and VOMS during a sideline evaluation <18 hrs post-injury and again at 1-3 days post-injury. Athletes were divided into vestibular-ocular symptoms/impairment (VESTIB) or no vestibular-ocular symptoms/impairment (NO VESTIB) based on their VOMS scores at 1-3 days post-SRC. A series of 2 (group) x 2 (time) ANOVAs were conducted to compare groups on preceding outcomes. RESULTS: 73 athletes (VESTIB=32 & NO VESTIB=41) completed the 1-3 day evaluation; 27 of which completed the <18 hrs evaluation (VESTIB=11 & NO VESTIB=16). Between-subjects effects were supported for worse SAC (26.19±2.42 vs. 27.29±2.18; p=.004) BESS (14.70±6.53 vs. 10.32±5.35; p=.003) PCSS severity (25.75±17.45 vs. 15.03±17.92; p=.013) and VOMS total symptom scores (65.81±40.62 vs. 29.85±37.23; p<.001) in VESTIB compared to NO VESTIB group at 3 days post-injury. A within-subjects effect was supported for VOMS symptoms improving from 18 hrs to 3 days post-injury for both groups (F1 20 =6.290; p=.021 ηp2= .239). CONCLUSION: Athletes with initial vestibular-ocular impairment/symptoms within 18 hrs of injury experienced persistent deficits on VOMS than those without. However performance on SCAT SAC BESS and VOMS symptoms were equivocal between athletes with and without vestibular-ocular impairment/symptoms <18 hrs post-injury.

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Presenting Author: Alexander Clark
(Graduate)

Mentor/Lab: Ikonomovic

Department: Neurology, Psychiatry

Poster Session: AM
Location: 25

Category:
Neuroprotection &
Treatment

Title: The Implications of Cerebral Vascular Amyloidosis on Blood Brain Barrier Integrity

Summary: It is believed that the Blood Brain Barrier (BBB) undergoes changes with amyloid present in the blood vessels of the brain. Using fluorescent tags for various cells and proteins (pericytes astrocytes endothelial cells tight junctions) that make up the BBB we have demonstrated decreased cell numbers and density in the presence of amyloid as well as changes in cell shape/localization.

Abstract: Background: Capillaries of the CNS possess the Blood Brain Barrier (BBB) which regulates movement of cells and molecules between the brain and blood.2 The BBB consists of astrocytic end feet endothelial cells and pericytes which all contribute to the Neurovascular Unit (NVU). After brain injury the NVU undergoes degenerative changes resulting in increased BBB permeability.4 Cerebral amyloid angiopathy (CAA) is defined as gradual deposition of amyloid-β (Aβ) peptide around cortical arterioles and meningeal vessels.5 The prevalence of CAA is 40-60% in 80-97-year-olds and it is greater in Alzheimer's disease (AD).25 CAA causes 5-10% of spontaneous intracranial hemorrhages.5 Despite this clinical significance temporal changes in NVU morphology due to CAA-associated vascular Aβ deposition have not been characterized sufficiently.\n\nHypothesis: The purpose of the study was to demonstrate that vascular amyloid pathology decreases BBB integrity resulting in altered PDGFR-β (pericyte) NG-2 (pericyte) AQP4 (astrocyte end-feet) ZO-1 (endothelial tight junction) and capillary density (endothelium) in a transgenic (Tg) mouse model of AD.\n\nMethods: The study used four experimental groups of mice: elderly control juvenile control elderly transgenic and juvenile transgenic (n = 5 mice per group). All Tg mice were APP/PS1 double mutants characterized by Aβ overproduction compared to C57Bl6 wild-type (Wt) which do not overproduce Aβ. Elderly were >400 days of age while juveniles were between 110-116 days at end of study. Five 40μm-thick coronal brain hemi-sections were chosen randomly at the level of the hippocampus. Using unbiased stereological principles 4 cortex regions of interest (ROI) were examined using the central sulcus and rhinal fissure as medial and lateral borders respectively. Overall 20 sites/mouse were sampled creating 100 sites per experimental group. The first experiment studied NVU constituents using IHF. We used lycopersicon esculentum agglutinin (Tomato Lectin) to distinguish blood-vessel endothelium.1 Sections were incubated in Tomato Lectin and 1° antibody for 20 hours at 4°C in 2° antibody for 90 minutes at RT and in a nuclear counterstain (DRAQ5) for 60 minutes at RT. In the second experiment capillary density was analyzed on Tomato Lectin processed sections dual-stained with X-34/6-CN-PiB. Both experiments were quantified using epi-fluorescence and stereological confocal microscopy techniques. NVU constituents were identified as fluorescent cell-bodies accompanied by ovoid endothelial "ghost" contours.3 Density was quantified using Stereo-investigator program "Space-balls" – a spherical probe virtually embedded in tissue to calculate length/region.3 \n\nResults: Confocal analysis of pericytes using PDGFR-β marker have been completed thus far. Tg elderly mice averaged 13 pericytes per ROI (our high-power selected regions) Tg juvenile averaged 16 pericytes per ROI Wt elderly averaged 25 pericytes per ROI and Wt juvenile averaged 43 pericytes per ROI. Preliminary analysis of epi-fluorescence imaging also suggests decreased contact between astrocytes/endothelium as well as increasingly tortuous capillaries in Tg mice.\n\nConclusions: The analyses support that there are changes in pericyte number and morphology in both normal aging and associated with amyloid

pathology. Ongoing investigations of NVU changes in response to amyloid will provide new critical information regarding: (1) quantification of PDGFR-β AQP4 and ZO-1 (IHF) (2) brain vasculature changes due to amyloid deposition (X-34/6-CN-PiB double-labeling) (3) correlations between brain circuitry changes and BBB morphology changes (future studies comparing in-vivo DTI to post-mortem histopathology). \n\nReferences: 1. 2018 C. H. H. et. al. (2018). "A novel method to visualize the three-dimensional organisation of the human cerebral cortical vasculature." Journal of Anatomy 232: 1025-1030. 2. Axel Montagne et. al. (2018). "Pericyte degeration causes white matter dysfunction in the mouse central nervous system." Nature Medicine 24(3): 326-337. 3. Gitte Nykjaer Nikolajsen et. al. (2015). "Quantitative analysis of the capillary network of aged APPswe/PS1dE9 transgenic mice." Neurobiology of Aging 36: 2954-2962. 4. Marion Bankstahl et. al. (2018). "Blood-Brain Barrier Leakage during Early Epileptogenesis Is Associated with Rapid Remodeling of the Neurovascular Unit." eNeuro 5(3): 1-18. 5. Olli S. Mattila et. al. (2015). "Cerebral amyloid angiopathy related hemorrhage after stroke thrombolysis: Case report and literature review." Neuropathology 35: 70-74.

First Author: Brian Edwards
(Postdoctoral)

Presenting Author: Brian Edwards
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Mentor/Lab: Davis

Department: Neurobiology

Poster Session: AM
Location: 26

Category:
Neuroprotection &
Treatment

Title: Immune checkpoint protein PDL1 is expressed in sensory and sympathetic neurons and is regulated by inflammatory growth factors and in a model of pancreatic cancer.

Summary: These studies reveal neuro-immune interactions in the context of inflammatory disease and cancer.

Abstract: Introduction. Identification of immune checkpoint proteins (proteins that regulate homeostasis of the immune system) have revolutionized cancer therapies. These proteins are responsible for preventing immune response from becoming overly aggressive and damaging host tissue as well as preventing the development of autoimmune diseases. While important during responses to normal infections this self-regulation can also produce a pro-tumorigenic environment that allows slow growing cancers to escape immunosurveillance and to continue to grow and metastasize. One of the best-known checkpoint protein pairs is PD-1 (programmed cell death protein 1) and PDLI (programmed death-ligand). PD-1 is expressed on regulatory T-cells and when bound by its ligand PDL1 (often expressed on tumor cells) PD-1 activation causes T-cell death or suppression of T-cell signaling such that the immune system does not attack the tumor. It has long been known that neural-immune interactions are critical for optimal function of the immune system and that sensory neurons express a wide range of genes that are normally associated with both the adaptive and innate immune response. Here we examined whether these checkpoint points are expressed on peripheral nervous system neurons and whether they are regulated by an inflammatory cytokine (artemin) known to regulate sensory and sympathetic neurons as well as in a genetic model of pancreatic ductal adenocarcinoma (PDAC).\nMethods. The level of PDL1 and PD1 mRNA was measured in whole sensory and sympathetic ganglion using RT-qPCR. Transcripts for both genes were also measured in single sensory DRG and nodose neurons innervating the colon and pancreas. These measurements were made in wildtype mice in transgenic mice that overexpress artemin in the skin (ARTN-OE mice) and in a genetic mouse model of PDAC in which mice contain the most common mutations found in human PDAC patients and in which all mice develop pancreatic tumors that metastasize to other organs. RNAscope in situ hybridization was used to confirm cellular localization in DRG neurons in wildtype and ARTN-OE mice. \nResults. In whole DRG and sympathetic ganglia (celiac superior cervical and lumbar chain) PDL1 mRNA expression was 2-4 fold higher than for PD1. In contrast whole nodose ganglia contained 16 fold more mRNA for PD1 than PDL1. However on the single cell level for visceral afferents projecting to the pancreas only PDL1 mRNA could be detected. Single cell analysis of colon afferents also indicated high levels of PDL1 especially for colon afferents arising from the nodose ganglion (PD1 was not examined). This data suggests that while PDL1 and PD1 mRNA can be found in sensory and sympathetic ganglia single cell analysis will be required to determine whether these genes are expressed on neurons and/or other cell types in the ganglion (e.g. it is know that immune cells are present in sensory ganglia and that the complement of immune cells changes in disease states). Interestingly in the single cell analysis of colon afferents we found that PDL1 mRNA is highest in afferents arising from the nodose ganglia and these afferents are distinct from all other colon afferents by high levels of expression of the P2X2 ATP receptor. PDLI mRNA expression is also high in naïve wildtype DRG neurons that project to the pancreas skin muscle and bladder. For the

pancreatic afferents these cells also contain high levels of mRNA for other express genes associated with neurogenic inflammation including: TRPV1 (a non-selective cation channel associated with inflammatory pain) CGRP (a peptide neuromodulator that produces vasodilation) TrkA (a receptor for NGF) and interferon □ receptor 2. \nIn mice that overexpress the neurotrophic factor artemin a cytokine increased during disease and inflammation whole ganglion analysis showed that PDL1 mRNA expression was increased 3 fold in the celiac ganglia 7 fold in DRG and 18 fold in nodose ganglion. No change was seen in PD1 mRNA expression. In the PDAC mice single cell analysis revealed that as the disease progressed from precancer (PanIN lesions) to cancer the level of PDL1 dropped dramatically. Our working hypothesis is that prior to the appearance of overt cancer high level of PDL1 in afferents helps to moderate the immune response preventing regulatory T-cells from recognizing and responding to the developing cancer. Support of this comes from our previous studies that show that sensory denervation prevents development of cancer at its earliest disease stages (Saloman et al. 2016 PNAS). \nConclusions. The work presented here shows that PDL1 is also normally expressed on a number of different neurons in the peripheral nervous system (PNS) and is regulated in neurons by an inflammatory cytokine (artemin) as well as in a genetic mouse model of pancreatic adenocarcinoma (PDAC). These observations suggest that immunomodulation of checkpoint proteins via PNS mechanisms could play a central role in inflammatory disease and cancer.

First Author: Ronald Fortunato
(Graduate)

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(Graduate)

Mentor/Lab:

Department: Mechanical Engineering, Bioengineering

Poster Session: AM
Location: 27

Category:
Neuroprotection &
Treatment

Title: Computational modeling of arterial wall tissue to quantify uniaxial tissue failure properties

Summary: Using computational models we gain insight about tissue mechanics. This insight is important in understanding and then predicting both behavior and failure of soft tissues. Using structural models designed from tissue physiology makes it each to see the effect of structural components such as collagen networks on tissue response and failure.

Abstract: Biomechanical failure of arterial tissue such as rupture of aneurysms in cerebral arteries can be a rapid and deadly event. These pathologies motivate us to understand the failure mechanics of both healthy and diseased tissues. While uniaxial tensile experiments are commonly used to evaluate biomechanical failure properties of tissues diverse protocols exist for testing. These protocols can potentially impact the stress state within the specimen and confound data interpretation. The objective of this work is to use in silico methods to determine the sensitivity of the failure properties to the choice of these testing conditions. In particular we employed the nonlinear cohesive volumetric finite element method to model the failure process in uniaxial experiments. Inputs required for this method are intrinsic strength as well as fracture toughness. While we observed insignificant changes in failure properties based on protocol we observed the important role of fracture toughness in the post-peak response.

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(First Author Type)

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Mentor/Lab:

Department: Neurological Surgery

Poster Session: AM
Location: 28

Category:
Neuroprotection &
Treatment

Title: Melatonin regulates neurodegeneration by inhibiting immune response in differentiated neurons

Summary: Melatonin is a naturally occurring free radical scavenger and well documented in neuroprotection. Absence of endogenous melatonin leads to accumulation of ROS and MMP loss. Elevated ROS and hypopolarized mitochondria activate immune response which results in synaptic and neuritic degeneration and finally neuronal cell death.

Abstract: Melatonin is a naturally occurring free radical scavenger and well documented in neuroprotection. To identify the mechanism of melatonin-regulated neuroprotection we developed CRISPR/CAS9 mediated Arylalkylamine N-acetyltransferase (AANAT) knockout (KO) N2a cells. AANAT is a rate-limiting enzyme in the synthesis of melatonin from serotonin. Wild type (WT) and AANAT KO N2a cells were differentiated into mature neurons by the exposure of retinoic acid. Our studies has revealed that differentiated AANAT KO cells have lower number of synapses with decreased average neurite length and neurite numbers. Moreover differentiated AANAT KO N2a cells have elevated reactive oxygen species (ROS) and significant loss in mitochondrial membrane potential (MMP) with increased mitochondria permeability transition (MPT). Interestingly when AANAT KO cells were treated with exogenous melatonin during differentiation the synaptic degeneration neuritic length neuritic numbers MMP ROS were rescued. Further our studies has identified that AANAT KO differentiated neurons have increased secretion of inflammatory markers (IL1β IL6 IL-18 TNFα IFNα IFNβ) which is inhibited by exogenous melatonin exposure. In conclusion AANAT KO leads to absence of endogenous melatonin which in turn to results in accumulation of ROS and MMP loss. Elevated ROS and hypopolarized mitochondria activate immune response which results in synaptic and neuritic degeneration and finally neuronal cell death.

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(Postdoctoral)

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Mentor/Lab: Aizenman

Department: Neurobiology

Poster Session: AM
Location: 29

Category:
Neuroprotection &
Treatment

Title: Molecular neuroprotection induced by zinc-dependent expression of\nhepatitis C-derived protein NS5A targeting Kv2.1 potassium channels

Summary: Here we present data demonstrating the proof of concept of an innovative strategy to deliver a neuroprotective agent "on-demand." We believe this strategy may prove to be useful in limiting neuronal cell loss in neurodegenerative diseases such as Alzheimer's and Parkinson's.

Abstract: Abstract\nWe present the design of an innovative molecular neuroprotective strategy and provide in vitro proof-of-concept for its implementation relying on the injury-mediated activation of an ectopic gene construct. As oxidative injury leads to the intracellular liberation of zinc we tapped onto the zinc-activated metal regulatory element (MRE) transcription factor 1 (MTF-1) system to drive expression of the hepatitis C protein NS5A previously shown to be neuroprotective by preventing cell death-enabling Kv2.1-mediated cellular potassium loss. We demonstrate rapid expression of MRE-driven products in rat cortical neurons in tissue culture and report that NS5A expression driven by a slowly evolving excitotoxic stimulus functionally blocks injurious enhanced Kv2.1 potassium currents and improves neuronal viability. We suggest this form of "on-demand" neuroprotection could provide the basis for a tenable therapeutic strategy to prevent neuronal cell death in neurodegeneration.

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Department: Neurobiology; Pittsburgh Institute for Neurodegenerative Diseases (PIND)

Poster Session: AM
Location: 30

Category:
Neuroprotection & Treatment

Title: Disruption of Kv2.1 somatodendritic clusters with a cell-permeant peptide based on the Proximal Restriction and Clustering domain of Kv2 channels is neuroprotective following acute Middle Cerebral Artery occlusion.

Summary: Kv2.1 potassium channels are inserted into the neuronal plasma membrane following injury and play a major role in mediating the programmed cell death pathway. Here we show that by disrupting specific sites of pro-apoptotic Kv2.1 channel insertion with specifically engineered cell-permeant peptides we are able to reduce neuronal cell death following cerebral ischemia in mice. This work suggests that targeted disruption of pro-apoptotic Kv2.1 potassium channel insertion may be a viable neuroprotective therapeutic strategy in the context of ischemic stroke.

Abstract: Hypothesis:\nKv2.1 K+ channels are delayed-rectifying voltage-gated ion channels widely expressed on the plasma membrane of mammalian neurons. They function primarily to regulate neuronal excitability but are involved in a range of physiologic and pathophysiologic processes. Notably Kv2.1 K+ channels play a major role in the apoptotic cell death program. Following injury Kv2.1 channels are inserted at specific plasma membrane-endoplasmic reticulum (PM-ER) sites known as Kv2.1 clusters – areas of concentrated somatodendritic non-conducting Kv2.1 channels. Pro-apoptotic insertion of Kv2.1 channels allows for increased outward K+ currents that set the stage for caspase and nuclease activation culminating in cell death. Furthermore our recent studies have shown that disruption of these Kv2.1 clusters at PM-ER junctions with the C-terminus of the cognate channel Kv2.2 (Kv2.2 CT) is protective against oxidative injury in vitro. Importantly this prevention of channel insertion occurs without changes in channel activation kinetics. Thus we hypothesize that disruption of Kv2.1 channel clusters with a cell-permeant peptide based on a critical region of Kv2.2 CT responsible for clustering may be a neuroprotective strategy by preventing pro-apoptotic channel insertion following acute ischemic injury.\n\nMethods:\nLiterature review of Kv2.1/Kv2.2 Proximal Restriction and Clustering (PRC) domain for was performed to identify the critical residues of Kv2.2 CT that likely disrupt Kv2.1 surface clusters. GenScript (Piscataway NJ) was contracted to synthesize this peptide with a TAT-linkage to enable cell-permeability (TAT-DP-2). Kv2.1 cluster dispersal was investigated by confocal imaging of transfected rat primary cortical neurons on a Nikon A1+ microscope. Patch-clamp electrophysiology was used to measure Kv2.1 K+ currents in vitro. In order to assess neuroprotection in vivo a 50 min Middle Cerebral Artery occlusion (MCAo) model in mice was utilized to generate a reproducible infarct.\n\nResults:\nWe found that Kv2.1 K+ channels were significantly declustered following 2-3 h exposure of TAT-DP-2 when compared with scrambled control (TAT-DSc-2) or vehicle treatment in a manner consistent with Kv2.2 CT-mediated declustering (Vector 0.17 ± 0.01 Kv2.1 clusters/μm2 n = 21 vs. Kv2.2CT 0.06 ± 0.01 Kv2.1 clusters/μm2 n = 6 ***p = 0.0007; TAT-DSc-2 0.18 ± 0.03 Kv2.1 clusters/μm2 n = 8 vs. TAT-DP-2 0.08 ± 0.01 Kv2.1 clusters/μm2 n = 16 **p < 0.007). TAT-DP-2 treatment also prevents increases in K+ channel current density following excitotoxic injury with TBOA in vitro when compared with vehicle or scrambled control peptide treatment (Vehicle 68.6 ± 0.79 pA/pF n = 17 vs. Vehicle + TBOA 162.5 ± 18.6 pA/pF n = 14 ***p = 0.0002; TAT-DSc-2 71.4 ± 10.3 pA/pF n = 16 vs. TAT-DSc-2 + TBOA 130.8 ± 9.4 pA/pF n = 14 **p = 0.003; TAT-DP-2 66.9 ± 4.8

pA/pF n = 14 vs. TAT-DP-2 + TBOA 63.4 ± 11.4 pA/pF n = 14 ns). Most importantly intraperitoneal injection of TAT-DP-2 at one and six h following acute MCA stroke in mice significantly reduced cerebral infarct ratio (viable area/infarct area) when compared to a scrambled control peptide (TAT-DSc-2 0.12 ± 0.001 n = 9 vs. TAT-DP-2 0.07 ± 0.02 n = 8 *p = 0.03). \n\nConclusions:\nOur results indicate that TAT-DP-2 may be a viable neuroprotective therapeutic method for reducing cerebral infarct volume following acute cerebral ischemia. This likely occurs by direct disruption of Kv2.1 surface clusters at ER-PM junctions which prevents apoptotic Kv2.1 K+ channel insertion increases in outward K+ currents and cell death following injury. Ongoing work focuses on further evaluating the mechanism of TAT-DP-2 mediated neuroprotection both in vitro and in vivo as well as to measuring its behavioral impact on neurological function following injury.

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Mentor/Lab: Aizenman

Department: Neurobiology

Poster Session: AM
Location: 31

Category:
Neuroprotection &
Treatment

Title: Neuroprotection by small molecule inhibition of Kv2.1/syntaxin interaction

Summary: Previously we presented the discovery of a short protein sequence capable of improving stroke outcomes in a mouse model. This story continues here as we utilized virtual simulations to describe how this treatment works and screened for small molecules capable of similar benefits. En route to these findings we unexpectedly re-organized a current model of brain and liver cell secretion.

Abstract: The cell death-enabling loss of cytoplasmic K+ following neuronal injury is mediated by a large increase in the number of Kv2.1 potassium channels in the plasma membrane. This phenomenon relies on the binding of Kv2.1 to syntaxin 1A (syntaxin) via a 9-amino acid sequence within the channel's proximal c-terminus (C1aB; HLSPNKWKW). Previous results showed that competitively disrupting the Kv2.1/syntaxin interaction using a blood-brain-barrier permeable peptide containing the C1aB sequence can effectively improve neuronal viability following in vivo injury. Here guided by molecular dynamic simulations we predict and experimentally validate the C1aB structural elements mediating the cell death promoting interaction between Kv2.1 and syntaxin. Critical for this binding is the aromatic ring stacking between C1aB W7 and syntaxin F34 the latter of which is a known peripheral component of the Mammalian UNCoordinated 18 (munc-18) binding site. Leveraging these findings we virtually screened a database of 26 million commercially available compounds identifying the small molecule F5722-8410 (F5; 3-[3-(13-benzothiazol-2-yl)phenyl]-1-[(34-dimethoxyphenyl)methyl]urea) as a putative inhibitor of the C1aB/syntaxin binding. We provide biochemical confirmation that F5 can effectively displace both Kv2.1 C1aB and munc-18 from syntaxin. Importantly we also demonstrate that F5 suppresses cell death promoting Kv2.1 currents and provides neuroprotection without affecting intrinsic electrical or synaptic properties of cortical neurons. Collectively our findings reveal an important molecular component of syntaxin's role in neuronal cell death and validate a highly relevant cellular target for neuroprotective therapeutics.

First Author: David Baranger
(Postdoctoral)

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Mentor/Lab: Forbes

Department: Psychiatry

Poster Session: AM
Location: 32

Category:
Psychiatry:
Addiction

Title: Convergent evidence for predispositonal effects of brain volume on alcohol consumption

Summary: There is a lot of evidence that heavy alcohol use damages the brain but it is less clear whether moderate alcohol use has any negative effects. We found that while alcohol use and brain volume are correlated all the evidence points in the direction of this correlation being driven by what we call 'shared predisposition'. That is moderate alcohol consumption does not shrink the brain instead there are genetic factors that simultaneously drive reduced brain structure and increased alcohol consumption.

Abstract: Background: There is growing evidence that alcohol abuse results in reduced brain volume. However it remains unclear whether moderate alcohol consumption similarly impacts the brain.\n\nMethods: We used 3 neuroimaging samples: Duke Neurogenetics Study (DNS; N=1303); Human Connectome Project (HCP; N=897); Teen Alcohol Outcomes Study (TAOS; N=238). We sought first to identify replicable gray matter volume correlates of alcohol consumption across the DNS and HCP. Family-based analyses were conducted to determine whether such associations are attributable to shared genetic or environmental influence. Analyses of longitudinal data tested whether brain volume was prospectively predictive of alcohol use initiation or consumption. Bioinformatic analyses of public databases examined the association of genetic risk for alcohol consumption with gene expression in the brain.\n\nResults: Whole-brain analyses (DNS) found 8 clusters where greater alcohol consumption predicted reduced volume. Two of these - right insula and right superior/middle frontal gyrus – were independently replicated (HCP). Family-based analyses (HCP) revealed that the correlation between alcohol consumption and volume is attributable to shared genetic but not environmental influence. Frontal gyrus volume predicted future consumption in the DNS and in a longitudinal adolescent sample (TAOS) frontal gyrus volume prospectively predicted the initiation of alcohol use. Bioinformatic analyses found that genes expressed in the frontal cortex are significantly enriched for associations with alcohol consumption and that genetic risk is replicably predictive of gene expression in the frontal cortex. \n\nConclusions: We identify a replicable association of alcohol consumption with reduced volume of the middle/superior frontal gyrus and insula which is largely attributable to shared genetic risk factors and is prospectively predictive of alcohol use. Bioinformatic analyses show that shared predisposition is biologically plausible. This work suggests that reduced volume and alcohol consumption share causal genetic risk factors and that moderate alcohol consumption does not lead to reduced brain volume.

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Mentor/Lab: McClung

Department: Psychiatry

Poster Session: AM
Location: 33

Category:
Psychiatry:
Addiction

Title: Astrocyte molecular clock function in the nucleus accumbens is important for reward-related behavior

Summary: Addiction has long been associated with disruptions in circadian rhythms and interestingly circadian genes appear to play an important role in reward regulation. However most research to date has primarily been neuron-oriented. Here we demonstrate circadian astrocyte function in a key reward region of the brain is also important for reward-related behavior.

Abstract: Cocaine addiction is widely prevalent in the United States with tremendous social and economic burdens. Unlike other substance use disorders there are currently no FDA approved treatment options. Given the lack of successful therapeutics it is important to better understand the cellular and molecular level changes following cocaine use and how these changes may establish and/or reinforce addiction. While most research efforts to date have primarily focused on neuronal based changes in the brain's reward circuitry increasing evidence suggests astrocytes may also play a critical role in the addiction process. Astrocytes are a highly abundant glial cell type important for numerous modulatory and support functions in the brain. Notably recent studies in rodent models demonstrate exposure to cocaine self-administration and extinction leads to significant reductions in astrocyte morphology and function in the nucleus accumbens (NAc) a key reward region of the brain. Moreover rodents with altered gliotransmission show disrupted reinstatement of both cocaine self-administration and conditioned place preference. Despite these recent advances in understanding it is still unclear how and by what mechanisms astrocytes may contribute to the regulation of reward. One potential mechanism may be through astrocyte molecular clock function and their regulation of circadian rhythms. Several recent studies have demonstrated the importance of astrocyte molecular clock function for maintenance of both circadian rhythmicity in the suprachiasmatic nucleus (SCN) the brain's master pacemaker and behavior. Work from our lab and others have extensively demonstrated the functional importance of the circadian molecular clock in the NAc and upstream ventral tegmental area (VTA) for regulation of reward. However no studies to date have explored the role of circadian astrocyte function specifically in the NAc. Therefore we sought to investigate the role astrocyte molecular clock function may play in NAc-regulated behaviors. To do so we induced a functional mutation in BMAL1 a core molecular clock protein specifically in NAc astrocytes by injecting an AAV8-GFAP-Cre virus into the NAc of Bmal1f/f mice. Mice were then assessed across a range of behaviors testing both exploratory drive and cocaine reward. Interestingly loss of NAc astrocyte molecular clock function lead to a significant increase in exploratory drive across three different assays. Moreover mice also displayed a significant reduction in cocaine conditioned place preference. Taken together these preliminary data suggest astrocyte molecular clock function in the NAc may be important for overall NAc function. Future studies will aim to investigate the molecular mechanisms underlying this phenotype.

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Mentor/Lab: Torregrossa

Department: Psychiatry

Poster Session: AM
Location: 34

Category:
Psychiatry:
Addiction

Title: Cue extinction after cocaine self-administration is more effective in rats exhibiting goal-directed behavior than habitual behavior

Summary: Drug-associated stimuli can induce drug cravings and increase risk of relapse so reducing cravings caused by these stimuli is a prominent goal in substance use disorder research. Although exposure therapy shows promising reductions in drug seeking in animal models of goal-directed drug self-administration results have been modest in human studies where drug use may be more habitual. This experiment examines the effects of cue extinction an animal model of exposure therapy on rats trained to self-administer cocaine using more goal directed or more habitual behavioral response strategies.

Abstract: Cue exposure therapy a memory-manipulation therapy that involves repeated exposure to drug-associated stimuli in the absence of the drug has shown promising results in reducing cue-induced drug seeking in animal models of addiction but results are less pronounced in human research. The lack of efficacy of clinical research could be because human drug seeking may have more habitual components that are often not captured by animal models of addiction. Therefore in the present study we examined whether our model of cue exposure has differential efficacy in rats trained under two schedules of reinforcement that facilitate either goal-directed or habitual behavior respectively. Rats were trained to self-administer IV cocaine for 20 days under different schedules of reinforcement and then were given a control procedure exposed to a number of cues that has previously been effective in goal-directed rats (120) or an excessive number of cues (240). Rats underwent a reinstatement test following cue exposure and western blot analysis was performed on tissue from brain regions associated with goal-directed (dorsomedial striatum) and habitual (dorsolateral striatum) behavior. In rats trained to self-administer cocaine on a schedule that facilitates goal-directed responding 120 and 240 cues reduced drug seeking but only 240 cues reduced drug seeking in rats trained on a schedule that facilitates habitual responding. Western blot analysis revealed increased expression of proteins involved in synaptic plasticity in the dorsolateral striatum of rats trained on a schedule facilitating habitual responding compared to those trained on a schedule facilitating goal-directed responding. Overall the present study suggests that rats using more habitual response strategies are less susceptible to the effects of cue extinction than rats using more goal-directed response strategies.

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Department: Psychiatry

Poster Session: AM
Location: 35

Category:
Psychiatry:
Addiction

Title: Circadian- and sex-dependent increases in intravenous cocaine self-administration in Npas2 mutant mice

Summary: Addiction affects about 8% of the population aged 12 and older every year and the development of substance dependence is associated with disruptions in circadian rhythms and alterations in circadian genes. Here a mutation in the circadian gene Npas2 increases addiction-related behaviors in rodents most notably increasing drug taking. Interestingly these effects are different in males and females and across time of day but further research is required to understand how Npas2 regulates cocaine intake.

Abstract: The development of substance dependence is associated with disruptions in circadian rhythms and circadian genes. In mice a dominant negative mutation in circadian locomotor output kaput (CLOCK) increases both cocaine reward and self-administration. Interestingly our previous studies found that a mutation in its suggested paralogue neuronal PAS domain protein 2 (NPAS2) show a decrease in cocaine reward. However the role of NPAS2 in cocaine self-administration remains unknown. Here we performed intravenous cocaine self-administration using male and female mice with a mutation in Npas2 during the light or dark phase. Mice first acquired an operant response for food and then were implanted with an indwelling jugular catheter. After recovery mice acquired cocaine self-administration and then dose-response testing was conducted both at a fixed ratio and progressive ratio schedule. While the Npas2 mutation did not impact acquisition of a food-reinforced response it surprisingly enhanced acquisition of a cocaine-reinforced response particularly in females. More specifically Npas2 mutant mice took more infusions of cocaine and acquired the response faster. The reinforcing properties of cocaine were also increased in mutant mice whereas motivation was only moderately increased in females. Interestingly these sex differences became greater during the dark phase with Npas2 mutation increasing cocaine intake as well as the reinforcing and motivational properties of cocaine extinction responding and cue-induced reinstatement. These results suggest that NPAS2 affects reward in a circadian-dependent manner. Importantly females appear to be more impacted by the Npas2 mutation particularly during the dark phase. Further research is required to understand why and how NPAS2 regulates cocaine intake across phase and in a sex-dependent manner.

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Mentor/Lab: McClung

Department: Psychiatry

Poster Session: AM
Location: 36

Category:
Psychiatry:
Addiction

Title: Strain Differences of Molecular Circadian Rhythms in Primary Fibroblasts

Summary: Our study demonstrates strain and sex differences of molecular circadian rhythms in cultured primary fibroblasts derived from the CC/DO founder strains. Heritability estimates suggest that circadian parameters were strongly attributed to strains.

Abstract: Recent genome-wide studies have been successful in revealing novel genetic mechanisms regulating the phase amplitude and robustness of the molecular clock. High-throughput cell-based screen approaches may be valuable for discovering potential genetic modifiers and variants influencing molecular clock function. Extensive variations of period and other circadian phenotypes are present between inbred and wild-derived strains of mice suggesting the molecular clock is genetically heterogeneous. Powerful biological tools for investigating the genetics of complex traits are the Collaborative Cross (CC) and Diversity Outbred (DO) mouse populations. The DO genome harbors more than 45 million unique polymorphisms and allelic combinations which provides expansive genetic and phenotypic variation enabling high-precision genetic analyses. As part of the Center for Systems Neurogenetics of Addiction our goal is to utilize these mouse lines to identify variations in circadian phenotypes that associate with addiction-related traits and ultimately identify the genes underlying these associations. Thus far we have used primary fibroblasts from the founder lines of CC and DO mice composed of 5 inbred (A/J C57BL/6J 129S1/SvlmJ NOD/ShiLtJ and NZO/HiLtJ) and 3 wild-derived (CAST/EiJ PWK/PhJ and WSB/EiJ) strains to examine strain differences in molecular rhythms. Following transfection with lentivirus expressing luciferase fused to the Bmal1 promotor Bmal1-dLuc rhythms were compared among strains. In comparison with C57BL/6J the period of Bmal1-dLuc rhythms was significantly shorter for 129S1/SvlmJ WSB/EiJ and CAST/EiJ in females but significantly longer for A/J and PWK/PhJ in males. Moreover we also observed that the amplitude of the rhythms was significantly higher for WSB/EiJ in both males and females by ~3-fold and for 129S1/SvlmJ in males by ~4-fold relative to C57BL/6J. Heritability estimates were 56% for the period and 27% for the amplitude suggesting that circadian parameters were attributed to strains. Behavioral studies related to impulsivity addiction-like behavior and other phenotypes are ongoing in the Center and our results will be incorporated in the future to determine significant associations between these molecular rhythm phenotypes and variations in behavior.

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(Postdoctoral)

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(Postdoctoral)

Mentor/Lab: Torregrossa

Department: Psychiatry

Poster Session: AM
Location: 37

Category:
Psychiatry:
Addiction

Title: Working memory training reduces drug-seeking in abstinence for the cannabinoid WIN 55212-2

Summary: Cognitive training on tasks that engage executive functioning such as a working memory task may help maintain abstinence in individuals with substance use disorders. In this study we used a rodent model of behavior to demonstrate that working memory training blunts cannabinoid-seeking in abstinence. Ongoing studies focus on the underlying neurobiological mechanisms involved in mediating these effects.

Abstract: Evidence from clinical and preclinical studies suggests that cognitive training may promote resistance to the development of problem drug use or dependence. Training in tasks that improve working memory response inhibition and goal-directed learning may also serve as a treatment option to promote continued abstinence in individuals with substance use disorders. In rodent models of cannabinoid self-administration rats will self-administer the synthetic cannabinoid WIN 55212-2 (WIN) show cue-induced reinstatement of WIN-seeking and show incubation of WIN craving after 30 days of abstinence. We hypothesized that cognitive training on a working memory task prior to WIN exposure would blunt this elevation of drug-seeking during abstinence. To test this hypothesis rats were trained on a delayed-match-to-sample working memory task. During this task rats learn to nose poke into one of 5 illuminated sample ports to receive a sucrose pellet reward. After the rat nosepokes into a specific sample port 3 adjacent ports are presented and the rat must choose the originally sampled port. Rats in the experimental group (WM) completed a cognitively taxing version of the task that engaged their working memory during a 0 – 24s delay period before the choice phase. Animals in the control (CON) group did not experience a delay before the choice phase and thus did not have to utilize their working memory. Next all rats were trained to self-administer WIN (12.5µg/kg/infusion) during 2-hour sessions for 14 days. Rats were then tested in abstinence for working memory performance and WIN-seeking over 35 days. Rats were classified into high- and low-drug taking groups for further analysis based on WIN intake during self-administration. We found that CON rats took significantly more WIN than WM animals and showed increased WIN seeking in abstinence. This effect was most pronounced in CON animals that stably self-administered higher amounts of WIN throughout the end of self-administration. Both WM and CON animals showed decreases in working memory or control task accuracy when tested in abstinence after WIN self-administration. Thus cognitive training on a working memory task prior to WIN self-administration has a protective effect against the subsequent expression of high levels of drug craving during abstinence. Ongoing studies will continue to investigate the involvement of the prefrontal cortex in mediating this effect.

First Author: M. Catalina Camacho
(Graduate)

Presenting Author: Maria Camacho
(Graduate)

Mentor/Lab: Perlman

Department: Center for Neuroscience; Psychiatry

Poster Session: AM
Location: 38

Category:
Psychiatry: Emotion and Affective Disorders

Title: Neural Architecture Supporting Active Emotion Processing in Children: A Multivariate Approach

Summary: Children are still developing how they process emotions an important part of how we interact with each other and the world around us. Using machine learning we examined the differences in how children (compared to adults) process movie clips during fMRI scanning. We found that while children show more activation in sensory processing and integration regions of the brain adults activated in regions associated with emotion regulation pointing to a shift in processing style across development.

Abstract: Background: Adaptive emotion processing is critical for nearly all aspects of social and emotional functioning. There are distinct developmental trajectories associated with improved emotion processing with a protracted developmental course for negative or complex emotions. The specific changes in neural circuitry that underlie this development however are still scarcely understood. We employed a multivariate approach in order to elucidate distinctions in complex naturalistic emotion processing between childhood and adulthood.\nMethod: Twenty-one adults (M±SD age=26.57±5.08 years) and thirty children (age=7.75±1.80 years) completed a free-viewing movie task during BOLD fMRI scanning. This task was designed to assess naturalistic processing of movie clips portraying positive negative and neutral emotions. Multivariate support vector machines (SVM) were trained to classify age groups based on neural activation during the task. \nResults: SVMs were able to successfully classify condition (positive negative and neutral) across all participants with high accuracy (61.44%). SVMs could successfully distinguish adults and children within each condition (ps<0.05). Regions that informed the age group SVMs were associated with sensory and socio-emotional processing (inferior parietal lobule) emotion regulation (inferior frontal gyrus) and sensory regions of the temporal and occipital lobes. \nConclusions: These results point to distributed differences in activation between childhood and adulthood unique to each emotional condition. In the negative condition specifically there is evidence for a shift in engagement from regions of sensory and socio-emotional integration to emotion regulation regions between children and adults. These results provide insight into circuitry contributing to maturation of emotional processing across development.

First Author: Melissa Nance
(Graduate)

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Mentor/Lab: Forbes

Department: Psychiatry

Poster Session: AM
Location: 39

Category:
Psychiatry: Emotion and Affective Disorders

Title: Subjective Anhedonia: Examining Coherence across Measures and Association with Neural Response to Reward

Summary: Anhedonia (loss of interest/pleasure) is an important symptom that emerges in disorders like depression bipolar disorder and schizophrenia. Self-report data about feeling pleasure and looking forward to things was collected from teens aged 13-19 using a number of surveys and compared with their brain responses while playing a game in an fMRI. Teens who reported looking forward to things less in daily life showed different brain activity in a region of the brain called the Thalamus when given a chance to win money in the game they played.

Abstract: Affective disorders and psychotic disorders together comprise a large portion of serious mental illnesses and both classically include anhedonia (a diminished ability to experience or drive to seek out pleasurable experiences). Anhedonia may prove to be an important target for treatment and must be investigated using methods that connect real-world experiences and tested neuroimaging paradigms. Multiple measures have been used to assess anhedonia and investigating coherence among these measures can reveal a consistent factor with relevance to clinical and neural mechanisms of mental illness.This project relies on data from the Development of Anhedonia Study an ongoing longitudinal study of 145 adolescents aged 13-19. A subset of 113 adolescents (56 % female; age M=15.2) were used for this project. A number of widely used psychometrically sound scales were employed to measure anhedonia; including the TEPS SHAPS Chapman- Physical PANAS Pleasure Scale for Children BIS/BAS and AES . An exploratory factor analysis was conducted to create composite operationalization of subjective anhedonia. Participants also completed an fMRI scan involving a guessing task with monetary rewards which included anticipation and outcome conditions. Anhedonia factor scores were independent variables in regression analyses with reward processing. Analyses were conducted in SPM12 at a threshold of p<.001 with FWE cluster correction. Two factors emerged—Anticipation Anhedonia and Enjoyment Anhedonia—accounting for 58.86% of variance in all items. Subsequent analyses showed that greater Anticipation Anhedonia was related to lower response to reward anticipation in the Thalamus (k=294 T=5.8 p <.005). These early findings confirm that anhedonia measures can converge into an interpretable limited set of factors and that those factors are related to function in reward circuitry. Anhedonia deserves continued attention as a feature with close connections to reward processing and future work will address independent confirmation of these factors and their associations with the emergence of illness.

First Author: Orma Ravindranath
(Graduate)

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Mentor/Lab: Luna

Department: Psychology

Poster Session: AM
Location: 40

Category:
Psychiatry: Emotion and Affective Disorders

Title: Effects of Emotional Context on Cognitive Control from Adolescence Through Adulthood

Summary: Cognitive control abilities improve from the teenage years into adulthood but only in specific emotional contexts. However while baseline connectivity between emotional and cognitive brain regions also does not change from the teen to adulthood these connections within an emotional context become stronger through this transition possibly due to greater arousal associated with negative emotion in adulthood.

Abstract: Introduction: Mood disorders often emerge during adolescence indicating important maturational changes in brain regions supporting emotional processing at this time (Paus Keshavan & Giedd 2008; Jennifer H. Pfeifer et al. 2011). Previous studies suggest that during adolescence emotion may have a distinct influence on brain function including effects on engaging cognitive control (Hardin et al. 2009). Many of these studies have examined effects of emotional stimuli within individual task trials. However in reality emotion is experienced as a state which may have unique effects through development. Here we were interested in probing changes from mid-adolescence to adulthood of emotional state on cognitive control by examining changes in connectivity between the amygdala a primary hub for emotional processing and cortical regions known to support cognitive control. Thus we used an affective inhibitory control fMRI task and resting state fMRI to probe the developmental effects of emotional state interacting with the inhibitory aspect of cognitive control.\nMethods: 50 participants (age range: 14-31 years 25 females) completed a standard antisaccade (AS) fMRI task in a 3T scanner. Most trials included a positive negative or neutral sound except for control trials which were silent. All subjects also completed a 5-minute resting state scan in the same session. Outside of the scanner subjects completed valence and arousal ratings of all sounds that played during the task. fMRI data were preprocessed using a pipeline including slice time correction motion correction skill stripping wavelet despiking field map unwarping warping to standard MNI space and smoothing using a 4 mm FWHM Gaussian kernel. Resting state data additionally underwent bandpass filtering and global signal regression. To obtain background connectivity data task-related effects were estimated and then removed using multiple linear regression. All analyses were conducted with sex as a covariate of no interest.\nResults: Arousal and valence ratings indicated that adults perceived negative stimuli as more “arousing” than adolescents while other stimuli were perceived similarly across age. Error rates of AS responses decreased with age at the trend level when averaging across trial types. When considering age-related changes in error rate by trial type results showed significant age-related decreases in error rate specific to the negative condition only. While reaction time (RT) of correct AS responses did not change with age across all trials there was a significant age-related decrease in RT within the silent condition only. Background connectivity reflecting emotional context revealed age-related increases between a bilateral amygdala seed and the precuneus frontal pole and dorsal anterior cingulate cortex. In contrast resting state connectivity (no emotional context) analyses revealed no significant age-related changes in amygdala connectivity with these brain regions.\nConclusion: Results indicate that cognitive control abilities improve from mid-adolescence to adulthood but only in some emotional conditions. However while baseline connectivity (as demonstrated by resting state) between amygdala and frontoparietal regions does not change from mid-adolescence to adulthood these connections

within an emotional context become more strongly coupled through this transition possibly due to greater arousal associated with negative trials in adulthood.

First Author: Kevin Sullivan
(Postdoctoral)

Presenting Author: Kevin Sullivan
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Mentor/Lab: Ganguli

Department: Epidemiology

Poster Session: AM
Location: 41

Category:
Psychiatry: Emotion and Affective Disorders

Title: Depressive Symptoms on the Decline in Older Adults: Birth Cohort Analyses from the MoVIES and MYHAT Studies

Summary: Population trends in depression in children and younger adults appear to be rising but trends in older adults are less understood. We observed that more recently born older adults (post-1920) exhibited significantly fewer symptoms of depression than earlier born older adults (pre-1920) even when accounting for age sex education dementia antidepressant usage.

Abstract: Depression in older adults is related to adverse health outcomes and lower quality of life. However many older adults with depressive symptoms do not meet the clinical threshold for Major Depressive Disorder (MDD) or may be precluded from a diagnosis due to presence of debilitating chronic disease such as dementia. Studies suggest that prevalence of MDD and depressive symptoms is increasing in children and younger adults but little is known about population trends in depressive symptoms in older adults over age 65. To investigate this we pooled data from two large prospective community-based epidemiological studies of older adults in Western Pennsylvania between 1987-Present. We identified four birth cohorts of sufficient sample size: 1902-1911 (n=305) 1912-1921 (n=1202) 1922-1931 (n=1051) 1932-1941 (n=669). In both studies a modified Center for Epidemiological Studies Depression Scale (mCESD) was used to determine presence of symptomatic depression (>= 5 symptoms) at each wave of examination. The percentage of participants in each birth cohort who had at least one study visit with symptomatic depression was 23.0% for the 1902-1911 cohort 19.1% for the 1912-1921 cohort 16.0% for the 1922-1931 cohort and 15.2% for the 1932-1941 cohort. In a shared parameter model that jointly modeled depressive symptoms and attrition the 1922-1931 and 1932-1941 cohorts were significantly less likely to report depressive symptoms than the 1902-1911 cohort (p<.01). Specifically when compared to our oldest cohort (1902-1911) we report 55% lower odds of symptomatic depression in the 1922-1931 cohort and 65% lower odds in the 1932-1941 cohort. Models were adjusted for follow-up time baseline age sex education dementia diagnosis and antidepressant medication use. Understanding trends in older adult mental health will improve patient care for chronic conditions which are highly prevalent in this population.

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Department: Psychiatry

Poster Session: AM
Location: 42

Category:
Psychiatry:
Circadian

Title: ClockΔ19 mutation leads to increased oxidative damage to parvalbumin interneurons and impairs perineuronal net development

Summary: Impairments in the body's natural 24 hour rhythms are present in bipolar disorder. Therefore we use a mouse that has altered 24 hour rhythms to determine how this affects adolescent brain development.

Abstract: Introduction: The molecular clock is intimately involved in the regulation of cellular redox state and multiple studies suggest that increased levels of oxidative stress and redox dysregulation may be key features in the pathophysiology of bipolar disorder. Therefore we investigated the relationship between molecular clock dysfunction oxidative stress and the frontal cortical development in ClockΔ19 mice a robust model of bipolar mania. \nMethods: At postnatal day 20 40 and 90 female wildtype and ClockΔ19 mice (4-5 in each group) were anesthetized with ketamine xylazine and transcardially perfused. Quantitative fluorescence microscopy was used to determine levels of oxidative stress as measured by 8-hydroxy-2'-deoxyguanosine (8-oxo-dG) levels. GABAergic parvalbumin (PV) expressing interneurons show a distinct maturation of perineuronal nets during adolescence that protect them from oxidative stress and lock in important synaptic connections. Therefore we measured PV expression and Wisteria floribunda agglutinin staining a marker of perineuronal nets in ClockΔ19 and WT mice. mRNA expression of genes involved in the endogenous antioxidant system and DNA repair were also measured. Furthermore another cohort of WT and ClockΔ19 mice were given the antioxidant N-acetylcysteine beginning at postnatal day 5 and oxidative stress PV expression and perineuronal net formation were assessed as described above at postnatal days 20 40 60 and 90.\nResults: While there was no significant difference in 8-oxo-dG fluorescence at postnatal day 20 or 40 we found that adult ClockΔ19 mice display a cell-type specific increase in 8-oxo-dG fluorescence intensity in PV interneurons within the anterior cingulate cortex and pre-limbic region. Furthermore ClockΔ19 mice show decreased PV expression and decreased staining for perineuronal nets at postnatal day 40 and into adulthood. Adult ClockΔ19 mice also show decreased expression of a key enzyme involved in DNA damage repair. Preliminary data suggests that treatment with the antioxidant N-acetylcysteine is able to ameliorate some of the deficits observed in ClockΔ19 mice.\nConclusion: The decreased PV expression and perineuronal net formation from adolescence into adulthood suggests a delay in critical period closing in the ClockΔ19 mice. Given that adult ClockΔ19 mice display increased oxidative stress in PV interneurons in adulthood but not earlier we hypothesize that the increase in oxidative stress observed in adult ClockΔ19 mice may be due to an impairment in the endogenous antioxidant system allowing oxidative stress to accumulate particularly within fast spiking PV interneurons.

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Mentor/Lab: Cameron

Department: Behavioral and Community Health Sciences, Psychiatry

Poster Session: AM
Location: 43

Category:
Psychiatry:
Circadian

Title: Are Adverse Childhood Experiences and Poor Sleep Associated with Lower Cognitive Achievement and Poorer Social-Emotion Skills in Urban Low-Income Preschool Children?

Summary: Working For Kids: Building Skills™ (WFK) an education program based on the principles of developmental neuroscience is designed to teach the general public — particularly those living in stressed communities — about healthy childhood brain development in a fun and interactive way. This study was conducted as a feasibility study to determine whether the program would be well accepted by families with young children receiving social services and if it would be possible in these communities to assess changes in children's brain development by measuring cognitive development social-emotional development sleep and oxidative stress levels.

Abstract: Children who have faced significant early life stress are at a much higher risk of poorer outcomes in terms of education physical health mental health and economic success in the workplace. Increasing the availability of supportive and enriching experiences can improve children's outcomes but in stressed communities there is often little knowledge of how to help children strengthen the many brain pathways they need for important life skills. The Working For Kids: Building Skills™ (WFK) educational platform was designed based on principles of developmental neuroscience to educate the general public about how to strengthen children's brain pathways for a variety of cognitive skills and social-emotional skills. In this feasibility study 23 families were recruited from four Allegheny County Family Support Centers. Baseline measures were collected including Demographic and Adverse Childhood Experience (ACEs) questionnaires; surveys on child cognitive development and social-emotional development; and surveys (i.e. the CSHQ) regarding sleep time timing and quality. Direct assessments of cognitive function were also collected using the NIH Toolbox tests [Dimensional Change Card Sort Test (DCCS) and Picture Vocabulary Test (PVT)]. Parent-child interactions were scored in 10-minute videos of parents and children playing together. A 7-day sleep log was obtained. We found that 22 of 23 children had sleep scores in the clinical sleep problem range and children with more sleep problems had later bed times (rho=0.838 p=0.002) and later wake times (rho=0.8 p=0.0045). There was a significant negative correlation between sleep quality and performance on the DCCS (rho=-0.50 p=0.04) and PVT (rho=-0.46 p=0.03) such that children with poor sleep showed poorer cognitive performance. Poor sleep was also correlated with elevated social-emotional problems measured on the ASQ-SE questionnaire (rho=0.59 p=0.01). Exposure to adverse childhood experiences in neither the children nor the parents were correlated with children's cognitive performance. However high ACE exposure in parents was negatively correlated with the level of reciprocity in parent-child interactions (rho=-0.323 p=0.042). We conclude that it is feasible to study various measures of brain development in children living in stressful circumstances and important relationships emerge between levels of stress exposure and sleep with both cognitive and social emotional development in children. We are currently studying how these measures change over a one-year period after parents receive the Working For Kids education.

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Mentor/Lab: Ahmari,
Gittis

Department: Neurobiology

Poster Session: AM
Location: 44

Category:
Psychiatry:
OCD

Title: Increased supplementary motor inputs to central striatum play a role in compulsive behavior

Summary: Orbitofrontal cognitive circuits have long been implicated in Obsessive-Compulsive Disorder but some evidence also suggests involvement of supplementary motor circuits. Our work in a OCD-relevant mouse model of compulsive behaviors suggests that an increased influence of supplementary motor regions in a normally cognitive-driven circuit may play a role in compulsive behaviors. These findings highlight a possible role of motor circuits in the generation and treatment of abnormal repetitive behaviors.

Abstract: Obsessive-Compulsive Disorder (OCD) is defined by the presence of obsessive intrusive thoughts and compulsive behaviors linked to these thoughts. Although the exact neuronal mechanisms leading to the development and expression of these symptoms are unclear hyperactivity in LOFC and caudate is consistently observed in OCD patients at baseline and with symptom provocation. Homologous corticostriatal circuitry has been shown to be dysregulated in the Sapap3-KO OCD mouse model. Specifically hyperactivity in central striatum spiny projection neurons (SPNs) has been correlated with compulsive grooming in this model but it is unclear what specific cellular and synaptic mechanisms lead to this hyperactivity. \nTo determine if increased intrinsic excitability plays a role in SPN hyperactivity in Sapap3-KOs we examined intrinsic properties in SPNs in the central striatum. We found no differences in intrinsic properties suggesting that dysfunction underlying SPN hyperactivity is not at the level of the striatum. To assess whether cortical inputs were increased onto SPNs in Sapap3-KOs we injected channelrhodopsin2 (ChR2) into LOFC and recorded optogenetically-evoked synaptic responses. Contrary to our expectations LOFC inputs were weaker onto SPNs. To further understand what other cortical inputs may be influencing SPN activity we used retrograde fluorogold tracing to look for alternative sources of increased excitatory input in Sapap3-KOs . We discovered that M2 cortex which is thought to be homologous to primate supplementary motor regions sends projections to central striatum that overlap with those from LOFC. By conducting optogenetic slice physiology experiments we found that M2-evoked EPSCs were increased onto SPNs in the central striatum of Sapap3-KOs relative to WTs. In vivo NpHR-mediated inhibition of M2 reduced compulsive grooming behavior in Sapap3-KOs but not WT littermates suggesting that hyperactivity in M2-CS circuits may lead to abnormal behavioral selection in Sapap3-KOs. Ongoing experiments are 1) using retrograde-Cre and diO-NpHR to specifically inhibit M2-CS projections and 2) developing optogenetic paradigms that will allow us to selectively inhibit these projections during motor planning which may be more relevant to the theorized role of M2.\nOur data suggest that shifting primary cortical control of central striatum from LOFC to M2 may lead to compulsive/ abnormal repetitive behaviors through excessive selection of maladaptive behavior patterns. These results highlight the possible role of supplementary motor areas in the generation of abnormal repetitive behaviors which may lead to a conceptual shift in both clinical and preclinical OCD research.

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Mentor/Lab: Ahmari

Department: Psychiatry

Poster Session: AM
Location: 45

Category:
Psychiatry:
OCD

Title: ¬Investigating the effects of EAAT3 overexpression on OCD-relevant behaviors in mice

Summary: Obsessive compulsive disorder (OCD) is a common and debilitating mental illness and current treatment options for are insufficient for many patients with OCD. In order better understand this disorder and potentially develop new treatments we created a mouse model based on genetic findings from human patients. These mice display behaviors that may have relevance for OCD such as increased repetitive stereotypies following drug administration and increased anxiety-like behaviors.

Abstract: Obsessive Compulsive Disorder (OCD) is a debilitating psychiatric disorder characterized by intrusive obsessive thoughts and compulsive behaviors. The etiology of OCD is unknown but twin and family studies show a significant role for genetics with multiple studies identifying association of polymorphisms in the SLC1A1 gene with OCD. The most common of these OCD-associated polymorphisms increases expression of the encoded protein – excitatory amino acid transporter-3 (EAAT3). To directly test the effect of increased EAAT3 levels on OCD-relevant behaviors we used the Flexible Accelerated STOP Tetracycline Operator-knockin (FAST) system which combines cre flippase and tTA technology to manipulate gene expression in a cell-type and temporally specific manner. Slc1a1-overexpressing (OE) mice were created by breeding Slc1a1-tetO mice with CamKII-tTA hemizygotes. The resulting progeny show increased striatal EAAT3 expression (as measured by Western blot) that is normalized in a dose-dependent manner by doxycycline. Slc1a1-OE mice with increased EAAT3 expression throughout development show increased stereotypies compared to tTA-negative littermate controls following administration of a high dose of amphetamine (8mg/kg) (genotype main effect F(243) = 39.06 p < 0.0001 n=20 WT 25 Hemi). In addition these mice show an increase in anxiety-like behavior spending significantly less time in the open arms of the elevated plus maze (unpaired t-test p=0.02 n=20 WT 25 Hemi) and less time in the center region of the open field (unpaired t-test p=0.04 n=20 WT 25 Hemi). In a second cohort Slc1a1-OE mice were raised on doxycycline to ensure normal EAAT3 expression during development; doxycycline was then removed to increase EAAT3 expression specifically in adulthood. Adult Slc1a1-OE mice also show an increase in amphetamine-induced stereotypies compared to littermate controls (genotype main effect F(236) = 14.962 p < 0.0001 n=17 WT 17 Hemi). In contrast adult Slc1a1-OE mice do not have increased anxiety-like behavior relative to littermate controls. This suggests EAAT3 overexpression differentially impacts anxiety-like and stereotypic behaviors through different circuit mechanisms at different developmental timepoints. Ongoing experiments are investigating this question using cFos immunohistochemistry and in vivo calcium imaging.

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Mentor/Lab: Ahmari

Department: Psychiatry

Poster Session: AM
Location: 46

Category:
Psychiatry:
OCD

Title: Fear processing in the SAPAP3 knockout mouse model of OCD

Summary: Obsessive-compulsive disorder is a debilitating mental disorder characterized by intrusive thoughts and repetitive behavior. Evidence suggests that patients with OCD display abnormal fear processing. Using a genetic mouse model of OCD we examine the potential neural mechanisms of these altered fear responses.

Abstract: Obsessive-compulsive disorder is a debilitating mental disorder characterized by intrusive thoughts and repetitive behavior. One theory of OCD pathogenesis is that patients form maladaptive fearful associations with neutral stimuli leading to maintenance of fear and avoidance. While human behavioral and imaging studies have provided evidence for this theory investigation of the possible underlying neural mechanisms has been limited. We therefore turned to SAPAP3 KO mice a model that displays perseverative grooming and anxiety-like behavior. Using a 3-shock Pavlovian fear conditioning paradigm [three pairs of a 20-second tone (5kHz 75dB) co-terminating with a 2-second shock (1mA)] we found that SAPAP3-KOs have an enhanced fear conditioning response compared to WT mice (time x genotype interaction: $F(3\ 51) = 4.89$ $p = 0.005$). To exclude the possibility that altered pain signaling contributed to this enhanced fear response we tested for pain sensitivity using Hargreaves and von Frey tests. No differences between genotypes were observed (Hargreaves: $p = 0.19$ $t = 1.34$ $df = 48$; von Frey: $p = 0.34$ $t = 0.97$ $df = 48$) indicating that enhanced fear conditioning in SAPAP3-KOs is not due to differences in pain sensitivity. To begin to explore the neural correlates of the elevated freezing response we broadly examined candidate regions that might contribute to differential fear processing using the immediate early gene cFos. A second cohort was perfused 60 minutes after the final fear conditioning tone and cFos+ cell density was acquired for regions previously related to fear conditioning. No differences in cFos+ cell density were observed between KOs and WTs when all regions tested were included in a repeated measures model. However after correcting for multiple comparisons cell density correlations between regions within each genotype reveal that cell densities in the prelimbic cortex (PL) and basolateral amygdala (BLA) were significantly positively correlated in KO but not WT mice. Furthermore cell density in the central amygdala (CeA) was significantly positively correlated with most regions (e.g. PL BLA periaqueductal grey bed nucleus of the stria terminalis) in KO but not WT mice. These data indicate that SAPAP3 KO mice display elevated cFos+ cell density correlations between fear-associated brain regions (i.e. PL BLA CeA) after fear conditioning compared to WT mice suggesting a potential circuit mechanism for the elevated fear conditioning response observed in KOs. Ongoing experiments are testing this hypothesis using in vivo fiber photometry to measure calcium activity in the PL and BLA during fear conditioning.

First Author: Xiaojun Li
(Graduate)

Presenting Author: Xiaojun Li
(Graduate)

Mentor/Lab: Ahmari

Department: Psychiatry

Poster Session: AM
Location: 47

Category:
Psychiatry:
OCD

Title: Using in vivo calcium imaging to assess the role of lateral orbitofrontal cortex in compulsive behaviors in OCD-relevant mouse model

Summary: Patients with obsessive-compulsive disorder (OCD) are often troubled by compulsive behaviors. This study examines the neural mechanisms of compulsive behaviors in a mouse model with OCD-relevant compulsive grooming. Using miniature microscopes to record activity in individual brain cells in freely moving animals we found that animals with disorganized grooming behaviors have an increased proportion of responsive neurons during grooming.

Abstract: Introduction: Disrupted corticostriatal circuits are consistently observed in patients with obsessive-compulsive disorder (OCD). Neuroimaging studies in OCD patients have identified hyperactivity of the lateral orbitofrontal cortex (lOFC) during provocation of symptoms and this is normalized following successful treatment. In the Sapap3-knockout (KO) mouse model optogenetic stimulation of lOFC has also been shown to alleviate OCD-relevant perseverative grooming. By using miniature microscopes for in vivo calcium imaging in Sapap3-KO mice we sought to further describe specific patterns of lOFC activity associated with compulsive behaviors.\nMethods: Sapap3-KO mice (n = 14) which exhibit compulsive over-grooming phenotype and wild-type (WT) control littermates (n = 12) were injected with a virus encoding fluorescent calcium indicator (AAV5-hysn-GCaMP6f) and implanted with gradient-index (GRIN) lens in the lOFC to visualize neural activity during grooming assessment tests. Calcium imaging and behavioral data were synchronized and calcium-dependent fluorescence was aligned to the start and end of grooming bouts as well as transitions within grooming bouts. \nResults: Grooming analysis demonstrated significant heterogeneity in the severity of compulsive grooming in Sapap3-KOs. Half of the KOs (n = 7/14) with grooming time greater than 30% of the session duration shows a compulsive grooming pattern whereas KOs with grooming time less than 30% (n = 7/14) behave more similarly to WTs than to high-grooming KOs. In WTs and KOs with normal levels of grooming the majority of bouts (60.6% in low-grooming KOs 63.2% in WTs) are continuous without interruption. In contrast KOs with high levels of compulsive grooming have a higher proportion (53.3%) of bouts that are interrupted by transitions between different types of grooming and are generally more disorganized in their grooming. Preliminary analysis of neural data (n = 5 KO 6 WT) suggests that a larger proportion of lOFC cells are modulated by the start (p=0.02) and end (p=0.08) of grooming in KOs then in WTs however the amplitude of response in modulated neurons is similar between the genotypes. Ongoing analysis will focus on neural activity associated with transitions between grooming types.\nConclusion: Compulsive grooming in a subset of Sapap3-KOs is associated with specific changes in the organization of grooming. Preliminary analysis suggests that lOFC hyperactivity described in OCD patients may be a consequence of increase in the proportion of neurons modulated during compulsive behavior rather than an increase in the neural activity in modulated neurons.

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Mentor/Lab: Ahmari

Department: Psychiatry

Poster Session: AM
Location: 48

Category:
Psychiatry:
OCD

Title: Using in vivo calcium imaging to study prefrontal cortex contributions to OCD-relevant behavioral dysfunction in the Sapap3 knockout mouse model

Summary: Patients with OCD show abnormal brain activity in the prefrontal cortex however the patterns of activity change differ when patient symptoms are evoked (hyperactivity) vs when patients are asked to make flexible decisions (hypoactivity). To determine the precise changes in neural activity in prefrontal cortex associated with different behaviors relevant to OCD we used in vivo calcium imaging with miniature microscopes in a genetic mouse model. This approach allows neural activity of individual brain cells to be directly compared during different OCD-relevant behaviors to determine if distinct or overlapping populations contribute to different types of OCD-relevant behaviors.

Abstract: Background:\nFunctional neuroimaging studies have strongly implicated prefrontal cortex (PFC) dysfunction in the pathophysiology of obsessive compulsive disorder (OCD). However the mechanisms by which this gives rise to OCD symptoms are unclear with hyperactivity typically observed at baseline and during symptom provocation whereas impaired recruitment of PFC is observed across a variety of neurocognitive paradigms including reversal learning. This raises the question of whether overlapping or distinct populations of neurons contribute to these different patterns of neural activity and associated symptoms. This can now be addressed using newly developed miniature microscopes for in vivo calcium imaging in freely moving rodents which allow neural activity of individual neurons to be compared between different paradigms relevant to the cognitive impairments (i.e operant reversal learning) and symptoms (i.e. compulsive grooming) observed in OCD. \nMethods:\nAll studies were performed in Sapap3 knockout mice (KOs) which have previously been shown to display OCD-relevant compulsive grooming and littermate wildtype (WT) controls. Neural activity was measured in medial PFC (mPFC) using Inscopix miniature microscopes (n=6 KO/3 WT males; 9 KO/5 WT females) and aligned to specific behavioral events during reversal learning (correct/incorrect responses reward retrieval) and compulsive grooming (initiation and termination of grooming bout).\nResults:\nWe have recently demonstrated that Sapap3 KOs show impairments in reversal learning (repeated measures ANOVA p<0.001). Approximately half of KOs (17/36) are unable to acquire a reversed contingency during 5 days of training whereas the other half perform similarly to controls. This heterogeneity in Sapap3 KOs was unrelated to severity of compulsive grooming. Preliminary analysis of calcium imaging suggests that the proportion of neurons in mPFC that are modulated by grooming is increased in Sapap3 KOs (11% vs 3%; p=0.004) with no change in the mean amplitude of neural responses. In contrast there appear to be a similar number of cells modulated by correct and incorrect responses during reversal learning in WT and KO mice. However poor reversal learning in KO mice is associated with reduced amplitude of modulation in cells that are suppressed by the new correct response whereas KO mice with good reversal performance show changes in the profile of neural modulation in cells that are activated by new correct responses relative to WT and poor reversing KOs. Ongoing analysis will compare activity of individual neurons during compulsive grooming and reversal learning using longitudinal tracking to determine whether distinct or overlapping neural populations are associated with these behaviors. \nConclusions:\nOur studies are among the first to describe OCD-relevant cognitive impairments in a transgenic mouse model. Ongoing

analysis of in vivo calcium imaging data should provide new insight about the specific patterns of neural dysfunction in the PFC associated with compulsive grooming and cognitive impairment relevant to OCD.

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Mentor/Lab: Sweet

Department: Psychiatry

Poster Session: AM
Location: 49

Category:
Psychiatry:
Schizophrenia

Title: MAP2 Immunoreactivity Deficit is Conserved Across the Rostro-Caudal Axis of Cerebral Cortex in Schizophrenia

Summary: Microtubule-associated protein 2 (MAP2) is a cytoskeletal protein that contributes to neuronal structure through the regulation of microtubule dynamics which in turn has a critical role in proper synaptic function. Schizophrenia is a mental disorder highlighted by both abnormalities in synaptic function and reduction in the immunoreactivity of MAP2 which may reflect changes in MAP2 structure and function. Here we assessed MAP2 immunoreactivity in various cortical areas using post-mortem tissue from subjects with schizophrenia to determine if this is an internally-consistent abnormality and found that MAP2 reductions exist globally within-subject.

Abstract: Several postmortem studies have reported decreases in the immunoreactivity (IR) of microtubule-associated protein 2 (MAP2) in diverse cortical and subcortical regions of the schizophrenic (SZ) brain. However whether the effect is global or regionally-specific remains unclear. We characterized the within-subject patterns of MAP2-IR in SZ cortex across the rostral-caudal axis by measuring MAP2-IR levels in deep layer 3 of dorsolateral prefrontal cortex (DLPFC) lateral intraparietal cortex (LIP) and primary visual cortex (V1). Postmortem tissue containing each cortical region was derived from 20 pairs of SZ subjects and healthy controls matched by age sex and postmortem interval. MAP2-IR was assessed by quantitative fluorescence microscopy. MAP2-IR was significantly reduced in SZ subjects relative to controls at V1 and LIP with DLPFC showing a strong trend toward reduction (V1: $F139 = 4.6185$ $p = 0.03906$; LIP: $F139 = 5.5845$ $p = 0.0240$; DLPFC: $F139 = 4.1352$ $p = 0.0501$). Mean MAP2-IR levels varied significantly with region in control subjects but not in SZ. Correlation analysis revealed that MAP2-IR pairwise decreases are persistent across the three regions. These findings demonstrate that MAP2-IR is reduced in SZ across cerebral cortex on a within-subject basis. A generalized model of MAP2-IR deficit in SZ has implications for therapeutic development and future investigations of MAP2 pathology.

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Mentor/Lab: McClung

Department: Psychiatry

Poster Session: AM
Location: 50

Category:
Psychiatry:
Schizophrenia

Title: Molecular rhythms in the human prefrontal cortex in subjects with schizophrenia

Summary: Schizophrenia is a debilitating psychiatric disorder that is associated with significant disturbances in circadian rhythms. We used a time-of-death analysis of RNA sequencing data to compare gene expression rhythms in the human prefrontal cortex of schizophrenia subjects to control subjects. Gene expression rhythms in the prefrontal cortex of schizophrenia subjects are largely distinct from controls resulting in altered transcript levels at night.

Abstract: Schizophrenia is a debilitating psychiatric disorder that is associated with significant disturbances in circadian rhythms including altered sleep/wake cycles and disrupted peripheral gene expression rhythms. Furthermore circadian rhythm disruptions are known to precipitate mood and psychotic episodes and current treatments for psychiatric disorders lead to stabilization of rhythms that likely contribute to their therapeutic efficacy. A recent study from our group used a time-of-death analysis of microarray data and found age-dependent changes in gene expression rhythmicity in the human prefrontal cortex. In the current study we aimed to extend these studies into psychiatric disease cohorts. We utilized a time-of-death analysis of RNA sequencing data from the CommonMind Consortium to compare gene expression rhythms in the human dorsolateral prefrontal cortex (dlPFC) of schizophrenia subjects to comparison control subjects. We first established rhythmic genes in a cohort of 104 control subjects and then independently analyzed a matched cohort of 46 schizophrenia subjects and 46 comparison subjects. We discovered that approximately 18% of the transcripts in the dlPFC are rhythmic and many of these genes are similar to those identified in a previous microarray study from a different cortical region. Interestingly there was a small degree of overlap between rhythmic transcripts in control and schizophrenia subjects. Moreover transcripts from schizophrenia subjects displayed a distinct pattern of rhythmicity with most genes showing a peak in expression during the day and a trough at night compared to controls in which transcripts peaked at various times of day. Many of the transcripts that are only rhythmic in schizophrenia subjects are associated with mitochondrial function with daytime peaks in expression matching the overall expression levels of controls and the nighttime trough falling below control levels. Furthermore many of the changes in gene expression between schizophrenia and control subjects are only observed in subjects that died at night. These data suggest that gene expression rhythms in the dlPFC of schizophrenia subjects are largely distinct from controls resulting in altered transcript levels at night. Ongoing studies will determine the specificity of these results across brain regions including the nucleus accumbens.

First Author: Matthew Rannals
(Postdoctoral)

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Mentor/Lab: Urban

Department: Neurobiology

Poster Session: AM
Location: 51

Category:
Psychiatry:
Schizophrenia

Title: Targeted translatome profiling using in utero gene transfer identifies ion channel pathophysiology in a brain development model of transcription factor 4 (TCF4) function

Summary: Healthy brain development is remarkably robust to the genetic differences across the DNA of individuals but the diagnosis of many mental health disorders can now be traced back to particular DNA variations. By altering the genetic instructions of a developing brain in our model system we have found that changes in a gene (TCF4) linked to both autism and schizophrenia disrupts the ability of brain cells to send signals correctly. Using a technique that lets us tag the DNA instructions that these dysfunctional cells are using we have been able to identify the specific signaling problem in these brain cells and then reverse their function back to the level found in a normal healthy brain.

Abstract: The normal development of the brain results from a genetic program that is highly regulated and remarkably robust. Understanding the functional pathophysiology that results from the dysfunction of genes associated with mental health disorders can illuminate the key developmental aspects of generating and regenerating cells in the healthy brain. Transcription Factor 4 (TCF4) is a clinically pleiotropic gene associated with schizophrenia and the rare autism spectrum disorder (ASD) Pitt-Hopkins syndrome (PTHS). Contactin Associated Protein Like 2 (CNTNAP2) is one of the largest genes in the human genome and encodes a neurexin family protein also associated with schizophrenia and autism as well as epilepsy ADHD and intellectual disability To gain insight about the neurobiology of TCF4 we created an in vivo model of PTHS by suppressing Tcf4 expression in rat prefrontal neurons immediately prior to neurogenesis. This cell-autonomous genetic insult attenuated neuronal spiking by increasing the afterhyperpolarization. At the molecular level using a novel technique called iTRAP that combined in utero electroporation and translating ribosome affinity purification we identified increased translation of two ion channel genes Kcnq1 and Scn10a. These ion channels candidates were validated by pharmacological rescue and molecular phenocopy. Remarkably similar excitability deficits were observed in prefrontal neurons from a Tcf4+/tr mouse model of PTHS. Thus we identify TCF4 as a regulator of neuronal intrinsic excitability in part by repression of Kcnq1 and Scn10a and suggest that this molecular function may underlie pathophysiology associated with neuropsychiatric disorders. Our continued work on CNTNAP2 aims to investigate the hypothesis that this gene shares with TCF4 and other ASD genes downstream targets and common molecular pathways controlling critical aspects of normal brain development.

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Department: Center for Neural Basis of Cognition

Poster Session: PM
Location: 1

Category:
Sensory - Vision

Title: The Representation of Orientation and Identity in Human Ventral Face Processing Areas as Measured by Intracranial Electroencephalography

Summary: This study uses Intracranial Electroencephalography to examine the relationship between representations of face orientation as well as identity in Human Ventral Face Processing Areas. In our results we find support for representation of face orientation as well as orientation dependent representations of identity in a study spanning 13 patients with a total of 43 electrodes using stimuli from the Karolinska Directed Emotional Faces dataset.

Abstract: Faces can be recognized across a remarkable degree of transformations including viewpoint which greatly shifts the position and orientation of facial features. Primate electrophysiology studies provide evidence that identity and facial orientation representations evolve along a three level hierarchy across the monkey face patch system. These levels proceed from viewpoint dependence at the lowest level mirror-symmetry at the mid-level and viewpoint invariance at the highest levels. In the human brain face identity processing is thought to involve a distributed network of several brain areas including the occipital face area (OFA) and fusiform face area (FFA). FMRI studies in humans have begun to shed light as to how the levels of face viewpoint coding are reflected in the human face processing system however many questions still remain.\n\nTo help resolve these questions we recorded intracranial electroencephalography (iEEG) data from 13 patients with a combined total of 43 electrodes in the OFA and/or FFA. The stimulus set is composed of 40 unique identities (20 male + 20 female) each with 5 different emotional expressions presented either straight facing away (left or right) 90 degrees or facing tilted (right or left) 45 degrees. Using nearest centroid classifiers we can reliably predict face orientation in 11 out of the 13 patients. Evidence for mirror symmetric coding (confusion between left and right facing away faces and significant classification between straight away and tilted in a 3-way classifier) was seen in 6 out of 13 patients. Significant identity classification was seen when all orientations are present in training/test data in all 13 subjects. However when a viewpoint was left out of the training sample for the classifier identity classification fell to chance for that viewpoint suggesting the identity code was viewpoint dependent.\n\nThese results suggest that the OFA and FFA code for both viewpoint and identity however the identity representation was viewpoint dependent despite some broad mirror generalization for faces. Further analyses will examine how these effects spatially distribute across these face processing areas and how they evolve over time.

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Mentor/Lab: Cohen

Department: Neuroscience

Poster Session: PM
Location: 2

Category:
Sensory - Vision

Title: Using pharmaceuticals to study how cognition affects perception

Summary: Cognitive processes such as attention and learning improve our vision at different time scales yet affect populations of neurons in a very similar way. Using this framework we aim to test how commonly used stimulants and pharmaceutical drugs change perceptual performance as well as neuronal population activity using a visual change-detection task.

Abstract: Using pharmaceuticals to study how cognition affects perception \n\nBrittany S. Bowes Amy M. Ni and Marlene R. Cohen \n\nDepartment of Neuroscience and Center for the Neural Basis of Cognition University of Pittsburgh Pittsburgh PA 15260 USA\n\n\n\nWe showed recently that cognitive processes that improve perceptual performance such as arousal spatial attention and learning affect neuronal populations in visual cortex in similar ways even while acting on very different time scales. This work led to a strong hypothesis that perceptual performance can be predicted by simple signatures of neuronal population activity regardless of how performance is at a particular level. Here we develop a framework to test this hypothesis using commonly used stimulants such as caffeine as well as pharmaceutical drugs used to treat Attention Deficit Hyperactivity Disorder (ADHD) such as methylphenidate and amphetamine. Our goal is to compare their effects on performance on perceptual tasks and on neuronal population activity with those caused by cognitive processes such as arousal attention and learning. \n\nWe measured the effects of pharmaceuticals on the performance of rhesus monkeys during a visual change-detection task that manipulates spatial attention.\nUsing an approach inspired by signal detection theory we measured effects of these stimulants on several measures of visual perceptual performance including sensitivity (d') criterion (c) spatial bias and the effects of a randomly administered bonus reward which affects general cognitive processes like arousal and motivation. Our preliminary results suggest that stimulants affect these measures in ways that are similar to but dissociable from the effects of cognitive processes. Understanding the effects of stimulant drugs on behavioral performance as well as on the activity on neuronal populations in future studies may answer fundamental questions about the neuronal mechanisms underlying perceptual performance as well as clinical questions about the different behavioral and neuronal effects of these commonly prescribed drugs. \n\n\n \nSupport:\nNIH R00EY020844\nNIH RO1EY022930\nSimons Foundation\nSloan Foundation\nWhitehall Foundation\nMcknight Foundation\nKlingenstein-Simons Fund

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Mentor/Lab: Cui

Department: Bioengineering

Poster Session: PM
Location: 3

Category:
Sensory - Vision

Title: Effect of neuro-adhesive L1 coating on long-term neural recording quality in the visual cortex of mice

Summary: L1 a neuronal specific cell adhesion molecule has been shown to promote neuron adhesion and reduce the initial microglia activation and the chronic gliosis when covalently immobilized to the surface of neural implants. Chronic implantation of L1-coated electrodes in mice showed significantly improved recording quality and longevity compared to the control groups. This study demonstrated that the L1 coating is a promising approach to achieving long lasting and stable neural interface.

Abstract: It is commonly assumed that the success of long-term functionality of implanted microelectrodes into the cortex for electrophysiological recording and stimulation depends on the stability of the interface between neural tissue and electrodes. The possible cause for electrode failure is the inflammatory host tissue response and neuronal loss in the surrounding microenvironment around the recording sites. L1 a neuronal specific cell adhesion molecule has been shown to promote neuron adhesion and reduce the initial microglia activation and the chronic gliosis when covalently immobilized to the surface of neural implants. In this study the chronic recording performance of L1-coated NeuroNexus neural electrode arrays was evaluated in vivo by implanting coated probes into V1m cortex of WT male mice. Electrophysiological recording evaluation showed significantly improved single-unit yield from the L1-coated groups from week 2 to the end of the 16 week experiment compared to the control groups. The effect of L1 on microglial activation and astrogliosis was evaluated with immunohistochemistry. Quantitative image analysis demonstrated significantly reduced expression of Iba-1 (microglia marker) and GFAP (astrocyte marker) within 50 μm and 110 μm of the insertion site respectively compared to the control probes at 16 weeks. These results suggest that the L1 surface coating improves chronic recording performance by reducing gliosis in the electrode-tissue interface. Further study will investigate the specific interaction between L1 and glial cells to determine the mechanism of action. Nevertheless the L1 coating is a promising approach to achieving long lasting and stable neural interface.

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Mentor/Lab: Gandhi

Department: Bioengineering

Poster Session: PM
Location: 4

Category:
Sensory - Vision

Title: Population dynamics of delay period activity during a saccade task

Summary: We are investigating the dynamics of neural population activity in the superior colliculus during visual-to-motor transformation using machine learning techniques such as decoding and clustering. This will allow us to better understand the times at which neural activity reflects a visual or movement preparation signal.

Abstract: The superior colliculus (SC) is a midbrain structure crucial for the generation of fast eye movements or saccades. SC neurons are known to encode multiple types of signals. For instance aptly named visuomotor SC neurons increase their firing rates following stimulus onset and when generating a motor command. This multiplexing of visual and motor information is most apparent in the activity of SC neurons during a delayed saccade task. The paradigm temporally dissociates the visual and motor epochs and consequently reveals two distinct bursts of activity that are widely thought to be visual- and movement-related respectively. However the structure of population activity during the delay period i.e. between visual target onset and eye movement onset is not as well characterized. SC activity during the delay period likely reflects cognitive processes transformations of signals from a sensory to motor reference frame and movement preparation. To investigate the structure of neural activity during the delay period we recorded SC activity from two male rhesus macaques (Macaca mulatta) with a multi-contact laminar probe while they performed a standard delayed saccade task to a target placed either in the population's response field or in the diametrically opposite direction. We sought to characterize the evolution of SC activity throughout the trial with clustering and decoding techniques. We first performed a clustering analysis of population activity seeking any systematic trends across the delay period and used this clustering approach to inform our decoding analyses. Population spike counts in sliding windows during the delay period were fed into a logistic regression classifier trained on predefined activity windows (baseline visual delay motor or other) and the decoder returned the most likely category to which the neural activity belonged. A general trend emerged: activity early in the delay period was often classified as visual but late in the delay period as motor with a smooth transition between the two categories. Overall this preliminary analysis shows that SC population activity during the delay period is not static but rather reflects a dynamic transition between two multiplexed signals.

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Department: Neurological Surgery

Poster Session: PM
Location: 5

Category:
Sensory - Vision

Title: Endogenous pre-stimulus activity modulates category tuning and influences perceptual behavior

Summary: Using direct recording from category sensitive regions in the cortex we demonstrated that endogenous activity modulates category tuning and influences perceptual behavior in a regionally specific manner on a trial-to-trial basis in the category sensitive regions.

Abstract: Perception of sensory inputs is modulated by shifts in endogenous ongoing brain activity. Specifically previous studies have tied endogenous pre-stimulus neural activity to behavior in sensory tasks. However it remains unclear whether the endogenous activity modulates neural coding and category tuning in visual processing and if this modulation of tuning provides a neural pathway for behavioral modulation. To address these questions we collected intracranial electroencephalography (iEEG) data from a large cohort of 32 patients while viewing visual images. We analyzed the iEEG data recorded from 246 channels showing category-selectivity for 6 different categories of visual stimuli: faces human bodies words places tools and scrambled images. We hypothesized that pre-stimulus activity modulates the degree of category tuning in response to visual stimuli and the aspect of pre-stimulus activity that modulates category tuning correlates with behavior. To test this a generalized linear model was trained to classify the category of the stimuli and the accuracy was compared for a model that used the post-stimulus activity alone and one that conditioned the post-stimulus classification on the pre-stimulus activity. The results showed that the inclusion of pre-stimulus activity improved the classification accuracy indicating that category-selectivity was modulated by pre-stimulus activity in category sensitive regions. Furthermore the aspect of the pre-stimulus activity that modulated category tuning correlated with behavior in a 1-back task. We then examined the temporal and spatial specificity of the pre-stimulus effects. Pre-stimulus modulation were seen to be very localized suggesting the effect seen was not due to fluctuations in overall arousal or global attention. They were also seen to fluctuate greatly from trial-to-trial suggesting the effects were not related to slow fluctuations in neural activity such as infra-slow fluctuations seen in resting state. Taken together these results demonstrate that endogenous activity modulates category tuning in a regionally specific manner on a trial-to-trial basis in the category sensitive regions. This modulation provides a potential neural basis for perceptual variation arising from shifts in endogenous ongoing activity.

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Mentor/Lab: Gandhi

Department: Bioengineering

Poster Session: PM
Location: 6

Category:
Sensory - Vision

Title: Characteristics of saccades to moving targets

Summary: We investigated the main characteristics of saccades that catch moving targets including: peak velocity duration latency and saccadic error in four non-human primates. We compared the effect of direction (inward and outward) and speed (15-45 deg/s) across these characteristics both within and across the subjects and found the results to be very idiosyncratic.

Abstract: The world is a dynamic environment filled with non-stationary sensory information that can be crucial to survival. Animals extract relevant information from their surroundings by aligning their gaze on both stationary and moving objects. Saccades rapid eye movements have been used to study sensory motor and cognitive processes in primates. The metrics and kinematics of saccades to stationary targets have been well characterized through countless studies. However there have been relatively few in-depth studies that describe the kinematics of saccades to moving targets called interceptive saccades across a broad range of target speeds and directions. The goal of this study is to provide an understanding for how kinematics of saccades to stationary and moving targets vary as a function of target speed and trajectory. We recorded saccade kinematics from four rhesus monkeys who performed a delayed saccade task in which the delay duration starting target location moving target direction (inward and outward) and target speed (range: 15 to 45 deg/s) were varied randomly to elicit saccades with a broad spectrum of amplitudes and directions. Trials using stationary targets placed along the moving target paths were randomly interleaved with trials using moving targets. Eye position was recorded using magnetic search coils or an eye-tracker system. Preliminary analysis suggests that main sequence properties for monkeys may be more idiosyncratic than previously observed. Of the four subjects two showed little to no difference in their main sequence properties between saccades to stationary and moving targets as the peak velocity and duration of amplitude-matched saccades were similar. This effect was maintained across different moving target parameters (speed and direction). The other two subjects showed distinct differences: peak velocity was attenuated and duration was longer for amplitude-matched saccades to moving targets. For all subjects saccade latency for interceptive saccades was similar to saccades to stationary targets. Saccadic error the error of the animal's gaze relative to the target location at saccade end increased as a function of saccade eccentricity and target speed and in general was greater for trials with a moving target. Since all four subjects performed the same task the range in kinematics for interceptive saccades most likely reflects subject-to-subject variability. These results therefore reveal a potential diversity in strategy used by different subjects to process a moving stimulus and direct the line of sight toward it.

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Presenting Author: Lily Kramer
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Mentor/Lab: Cohen

Department: Neuroscience

Poster Session: PM
Location: 7

Category:
Sensory - Vision

Title: The Behavioral Relevance of Communication Between Macaque Brain Areas

Summary: We are examining the the neuronal mechanism underlying the bidirectional relationship between belief and perception in different behavioral contexts utilizing non-human primate behavioral and electrophysiological data. Through the use of change discrimination and rule switching tasks we can gain insight into the inter-area communication that may contribute to this relationship.

Abstract: Our beliefs affect our ability to perceive while perceptual information conversely affects our decision-making and influences our beliefs. When we hold beliefs how do we decide which information is pertinent to us? In turn at what point do our beliefs change when presented with opposing information? We will attempt to address the neuronal mechanism of evolving belief and its effect on perception in two steps: 1. By examining a belief's influence on the communication of perceptual information in areas V1 and V4. 2. By examining perception's impact on belief representation and communication in V4 and 7a. The information communicated between brain areas could be of great significance given that many studies show coordinated activation in a network of brain areas during cognitive tasks. It has been found that visual spatial attention affects the information shared between V1 and MT possibly through changes to the synaptic weights between neurons in these areas. This finding suggests that inter-area communication could be crucial to the selective processing of behaviorally relevant information. We implanted multi-electrode arrays in areas V1 and V4 of one rhesus monkey and recorded neuronal activity while the animal performed a change discrimination task. This task required the monkey to indicate which feature of a visual stimulus was changing and how it was changing by making a saccade to one of two targets. We trained another rhesus monkey to perform a rule-switching change discrimination task while we collected behavioral data. This task required the monkey to determine which feature change was relevant in each trial (the rule) and saccade to the target that described how that specific feature changed while the relevant rule switched stochastically throughout the session. The behavioral data acquired from the change discrimination task will allow us to examine how perceptual information is selectively processed when it is behaviorally relevant or not and the neuronal population data will give insight into how/if the communication between V1 and V4 changes accordingly. The behavioral data obtained from the rule-switching task will enable us to examine how the subject's belief about which rule is behaviorally relevant is shaped by perceptual information.

First Author: Pilar Montes Lourido
(Postdoctoral)

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Mentor/Lab: Sadagopan

Department: Neurobiology

Poster Session: PM
Location: 8

Category:
Sensory - Auditory

Title: Cortical mechanisms supporting complex sound processing

Summary: Understanding how the brain processes sounds in realistic conditions

Abstract: We recognize complex sounds such as speech accurately, reliably, and in real-time, despite the widely varying listening conditions in which we encounter these sounds. We aim to determine the algorithms and neuronal mechanisms underlying rapid and accurate sound recognition in real-world conditions. We focus on the categorization of vocalizations in the face of two sources of real-world variability: 1) production variability, which is the within- and between-subject variability with which sounds are produced, and 2) environment variability, which encompasses the noise, reverberations, and other sounds added by the acoustic environment. We use Guinea pig (GP) vocalizations as an experimental model to address these questions in naturalistic settings. We first show using an information theoretic model that calls can be categorized while generalizing across production variability by detecting smaller, optimal features. These model features predict some nonlinear cortical response properties at the single-neuron level, and population transformations between auditory processing stages. Consistent with this model, we find critical transformations to sound representation that occur between layer 4 (L4) and layer 2/3 (L2/3) of primary auditory cortex (A1). To understand the mechanisms underlying environment invariance, we first used pupillometry to determine the threshold of call detection in noise. In electrophysiological experiments, we found that at these signal-to-noise ratios, environment-invariance also increases between thalamus and A1 L2/3. These results suggest that a dense, non-invariant representation of complex sounds in thalamus and A1 L4 is transformed into an invariant and sparse representation in A1 L2/3. Ongoing experiments using novel optogenetic methods to address the mechanisms underlying this transformation will be discussed. Funding: NIDCD R01DC017141, Pennsylvania Lions Hearing Research Foundation, Samuel and Emma Winters Foundation.

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Mentor/Lab: Oswald

Department: Neuroscience

Poster Session: PM
Location: 9

Category:
Sensory - Olfactory

Title: Inhibitory circuits that gate associative synaptic plasticity in olfactory cortex

Summary: This work shows the inhibitory circuit into the piriform cortex that promotes an association link between olfactory sensorial inputs and intracortical signaling through the establishment of an LTP associative.

Abstract: The piriform cortex (PC) plays a role in the combinatorial representation of odorant features from the olfactory bulb (OB) as well as associating odors with information coded from other cortical areas. OB afferents as well as intracortical inputs form synapses on the apical dendrites of pyramidal cells of PC. Long-term potentiation of the intracortical synapse is achieved by co-stimulation of the lateral olfactory tract (LOT) coming from the OB and the intracortical fiber tracts in Layer 1B. It has been shown that this associative LTP is highly dependent of intrinsic inhibition. However the inhibitory circuits that gate LTP has not been elucidated. In this study we explored the inhibitory circuits that modulate associative LTP induction in anterior piriform cortex (APC) by using a combination of optogenetic tools and electrophysiological recordings. Three inhibitory interneuron classes were evaluated; somatostatin (SST) cells that inhibit pyramidal cell (PC) dendrites parvalbumin cells (PV) that inhibit PC somas and vasoactive intestinal peptide cells (VIP) that are postulated to inhibit both SST and PV cells. Our results reveal three main findings. First inactivation of SST cells but not PV cells promotes associative LTP induction. Second VIP cells inhibit both SST and PV cells in olfactory cortex. Third activation of VIP cells promotes associative LTP. These findings support a model in which VIP cells inhibit SST cells and thus disinhibit PC dendrites to promote LTP induction. Interestingly our preliminary results suggest an additional functional difference between L2 and L3 PCs. Associative LTP is gated by the VIP-SST disinhibitory circuit in L2 but not in L3 PCs. Our work proposes a disinhibitory circuit gates associative LTP in APC and also suggests different circuits are involved the modulation of synaptic plasticity in distinct layers of piriform cortex.

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Presenting Author: Christopher Cover
(Graduate)

Mentor/Lab: Poplawsky

Department: Radiology

Poster Session: PM
Location: 10

Category:
Sensory - Olfactory

Title: High resolution odor mapping in the awake mouse olfactory bulb using noninvasive BOLD and contrast-enhanced fMRI

Summary: Functional MRI (fMRI) noninvasively measures brain activity and is a useful tool to examine whole brain function or dysfunction in preclinical rodent models of disease. However anesthesia is often administered to keep animals still during fMRI studies which can change brain function and bias our observations. We propose an fMRI technique that enables rodents to be scanned in the awake state during odor stimulation; and show consistency between awake fMRI responses and previously reported activity patterns in the olfactory bulb.

Abstract: Anesthetics are commonly administered in rodent preclinical fMRI to eliminate motion induced magnetic susceptibility artifacts. However many have pharmacokinetics that influence neurovascular coupling pathways thus reducing or eliminating the hemodynamic BOLD (blood oxygenation level dependent) signal. We propose that an awake imaging platform can eliminate confounds of anesthesia improving spatio-temporal sensitivity and strength of the fMRI signal. To determine this we analyzed its' ability to elucidate previously reported 2-deoxy-glucose histological and fMRI odor maps in the olfactory bulb. One C57BL/6 mouse was acclimated to the scanner environment in a custom-built MRI-compatible head and body restraint system prior to scans in a 9.4-T Bruker horizontal bore magnet. Gradient echo planar imaging and compressed-sensing fast low angle shot pulse sequences were used for BOLD and MION contrast-enhanced cerebral blood volume (CBV) imaging at high spatial resolutions (94 x 94 x 300 μm3). Scan paradigms consisted of a block design: 2-min odor off 1-min odor presentation of 5% amyl-acetate (AA) or 2-hydroxactephenone (2HA) in a mineral oil solution followed by a 2-min odor off recovery period. Reliable activation maps were obtained for AA and 2HA across multiple scans for BOLD and CBV. Regions of activation for amyl-acetate in the olfactory bulb were: dorsolateral and ventromedial which is consistent with prior literature. Regions of activation in the olfactory bulb for 2-HA were: dorsolateral and medial. Average BOLD signal intensities ranged from 2.5-3.5% for AA with average CBV signal intensities being 2.5-5% for AA. MION enhanced CBV compared to BOLD provided stronger signal intensities (2.5-3.5% vs. 2.5-5% respectively) and more consistent activation maps. Initial results suggest that our current model for awake mouse fMRI can capture specific odor maps within the mouse olfactory bulb. This project though still requiring a lot of development has laid the initial groundwork for an awake mouse fMRI platform that can be extended into awake mouse whole-brain analysis for both task and resting-state fMRI.

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Presenting Author: Monica Liu
(Graduate)

Mentor/Lab: Weber

Department: Bioengineering

Poster Session: PM
Location: 11

Category:
Sensory - Touch

Title: Effect of surface texture on the encoding of touch pressure and shear in the glabrous skin of a rhesus macaque

Summary: Sensation of texture arises from activity of neurons in the periphery. These neurons encode various features of a tactile stimulus such as roughness. We found that neurons encode the interaction between stimulus movement and texture better than either the stimulus movement or the texture alone.

Abstract: Cutaneous mechanoreceptors in the skin encode information about the mechanics of touch allowing humans to perceive grip force as well as object properties such as shape weight and texture. Understanding the interaction between parameters such as force of contact and surface properties such as roughness will yield insight into how the nervous system can extract object-specific information such as texture. Tactile signals originate from mechanoreceptors in the skin innervated by nerve fibers whose cell bodies are located in the dorsal root ganglia (DRG). To elucidate how aspects of texture and touch mechanics are encoded in DRG neurons we implanted penetrating multielectrode arrays in the C6 C7 and C8 DRG of two anesthetized rhesus macaques. We identified cutaneous and proprioceptive units via manual palpation of the arm and hand and delivered textured tactile stimuli via a handheld probe that was used to apply normal and shearing forces to the palm and fingers. The probe contained a force transducer to measure the normal and shear forces. Any of several interchangeable tips was attached to the end of the probe each containing a different material spanning a range of roughnesses. The\nspiking activity of small populations of DRG neurons was recorded as the probe was brushed repeatedly over specific locations on the finger-pads and palm. This allowed us to examine how populations of neurons in the DRG encode contact parameters such as force and scanning speed as well as object properties such as texture. Activity of individual neurons was modulated with changes in both texture and force and the applied texture could be predicted from the activity of a small population of neurons. However texture could not be accurately predicted from force suggesting that mechanoreceptors do not encode force of the stimulus alone. Force data also could not predict firing rates of individual neurons but force data along with texture and interactive effects between force and texture improved firing rate prediction. This suggests that individual cutaneous mechanoreceptors encode both texture and contact forces. Although the mechanisms for distinguishing texture from force remain unclear it is possible that under active conditions the brain relies on efference copy signals to discriminate object-specific properties (i.e. texture) from motion-dependent components (i.e. force and speed of contact).

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Mentor/Lab: Fields

Department: Anesthesiology and Perioperative Medicine / Division of Pain Medicine

Poster Session: PM
Location: 12

Category:
Sensory - Pain

Title: Optimizing conditioned analgesia for translational applications

Summary: Past experiences strongly impact the perception of pain. In this study we show that repeatedly pairing a visual cue with pain relief eventually gives the cue alone a pain-relieving effect. This conditioned pain relief technique could be used to improve pain control following surgery.

Abstract: Introduction - Pain and pain relief are strongly affected by learning. Classical conditioning techniques have been used in experimental settings to produce analgesia. In healthy volunteers visual or auditory cues (conditioned stimuli CS) can be paired with an analgesic manipulation (unconditioned stimulus UCS) to elicit conditioned analgesia. Despite these discoveries the key characteristics of the CS and UCS required for optimal analgesia are largely unknown including which modality of cue (visual auditory or audiovisual) is most effective. Cue optimization in healthy volunteers will allow for more rapid translation of conditioned analgesia as an adjunctive non-pharmacologic therapy in clinical populations. \nHypothesis – In healthy volunteers multimodal audiovisual cues elicit greater analgesia than auditory or visual cues in a novel conditioned analgesia paradigm using offset analgesia.\nMethods –Eighty-one healthy volunteers were randomized into one of four groups based on CS: (1) a visual CS (blue field with “pain relief”) (2) an auditory CS (simple tone) (3) an audiovisual CS (combination of the visual and auditory CS) and (4) a non-contingently paired control group. In all groups the UCS was an endogenous analgesic phenomenon known as offset analgesia evoked with a complex heat stimulus delivered using a cutaneous thermode applied to the volar surface of the forearm. During a training phase UCS and CS were paired 9 times in each group with CS varying by group. Conditioned analgesia was measured by presenting the CS during a simple suprathreshold heat stimulus without offset analgesia. Other within-subject controls included target CS novel CS and no CS test conditions. A 2-way repeated measures ANOVA model with post-hoc testing was used to measure differences within and across subject groups.\nResults – Following training in the test phase both visual and audiovisual CS presentation during a noxious heat stimulus resulted in significant decreases in pain measured on COVAS. Interestingly there was no significant decrease in pain in the auditory group. Importantly there was no decrease in pain in the non-contingent control group. The magnitude of conditioned analgesia in the visual group was large – comparing the visual and non-contingent control groups showed a mean difference in pain intensity in the test phase of 27.6 mm 95% CI 7.6 mm – 47.5 mm adjusted p=0.0036.\nConclusions – Visual and audiovisual groups demonstrated evidence of conditioned analgesia although there was no significant difference between the two groups. Auditory stimuli were not sufficient to elicit conditioned analgesia. Moreover using offset analgesia as a UCS in this novel paradigm was effective in eliciting conditioned analgesia.\nSignificance – Visual conditioning cues can elicit significant analgesia in the conditioned analgesia paradigm described above. The tested paradigm could potentially be used in clinical contexts as an opioid-sparring adjunct. One area of interest is in patients requiring intravenous patient-controlled analgesia (PCA)-delivered opioids for post-operative pain management. \nResearch / Grant Support – Financial support provided by the Foundation for Anesthesia Education and Research “Research Fellowship Grant” (B.A.) and Research Scholar Funds from the UCSF Department of Anesthesia and Perioperative Care (B.A.).

First Author: Michael Chiang
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Mentor/Lab: Ross

Department: Neurobiology

Poster Session: PM
Location: 13

Category:
Sensory - Pain

Title: Lateral parabrachial nucleus mediates separable aspects of the nociceptive response

Summary: The lateral parabrachial nucleus (LPBN) is thought to mediate affective and motivational components of the pain response but what the outputs of this nucleus encode remains unclear. Distinct subsets of the LPBN project to different downstream targets and their optogenetic activation drive uniquely distinct aspects of the nociceptive response. Projections to extended amygdalar structures are primarily aversive while outputs to hypothalamic or periaqueductal gray drive defense behavior that promote escape from nociceptive stimuli.

Abstract: Pathological pain is a widespread condition that comprises severe and emotionally unpleasant nociceptive sensations. This pain affect is believed to arise from the spino-parabrachial pathway via the lateral parabrachial nucleus (LPBN). However the role of distinct projections from the LPBN in the pain response is poorly understood. Here we show that two anatomically distinct subregions of the lateral parabrachial nucleus projects to different downstream targets and the optogenetic activation of these pathways generates aversive responses with behavioral phenotypes unique to each projection. The external lateral and dorsal lateral parabrachial nucleus collateralize respectively within either the extended amygdala or hypothalamus and periaqueductal gray. Photostimulation of terminals within the extended amygdala induced only robust avoidance behavior whereas explosive locomotor behavior was observed in both the hypothalamus and periaqueductal gray terminal photoactivation. Only LPBN – PAG photostimulation reduced tail flick in response to noxious heat. Taken together this suggests that LPBN pathways encode separable aspects of the nociceptive response. Understanding this neural circuitry will yield insight into how the brain generates pain and help identify novel therapeutic targets that can potentially modulate pain with reduced adverse effects.

First Author: Andrew Cooper
(Postdoctoral)

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Mentor/Lab: Taylor

Department: Anesthesiology

Poster Session: PM
Location: 14

Category:
Sensory - Pain

Title: The effect of peripheral nerve injury on neuropeptide Y1 receptor expression in interneuronal populations within the dorsal horn of the mouse spinal cord

Summary: Nerve injury results in long-lasting neuropathic pain that is inadequately treated by conventional analgesics. A potential target for novel analgesics is the neuropeptide Y1 receptor however it is currently unclear which pain processing circuits in the spinal cord contain this target. Here we have examined the populations of neurons containing the Y1 receptor in the spinal cord before and after nerve injury in mice.

Abstract: Aims:\nPeripheral nerve injury results in long-lasting neuropathic pain and current analgesic strategies suffer from inadequate efficacy and a range of adverse effects including abuse and addiction potential. This can be partially attributed to a limited understanding of nociceptive circuitry within the superficial dorsal horn (DH) of the spinal cord. Amongst potential novel analgesic targets are spinal neurons expressing the neuropeptide Y (NPY) Y1 receptor (Y1R). Endogenous NPY exerts a tonic inhibition of nociceptive signaling following nerve injury (Solway et al. 2011) and intrathecal administration of NPY has also been shown to attenuate neuropathic pain; this activity is diminished following the application of Y1R-specific antagonists (Intondi et al. 2008; Kuphal et al. 2008). Y1Rs are expressed by a heterogeneous population of largely excitatory interneurons and projection neurons in the rodent spinal cord and are most predominant in laminae I-III of the dorsal horn (Brumovsky et al. 2005; Fu et al. IASP Yokohama 2016). Multiple distinct sub-populations of excitatory interneuron have been identified (Todd 2017); however it is unclear which express the Y1R and how these integrate into neuronal circuits. Therefore we investigated Y1R expression with various neurochemically defined interneuron populations. Specifically we tested the hypothesis that spared nerve injury (SNI) alters the phenotype of Y1R-expressing interneurons within the DH of mice.\n\nMethods:\nAll procedures were approved by the University of Kentucky IACUC in accordance with AVMA and IASP guidelines. Adult male Npy1r-eGFP mice (RRID: MMRRC_010554-UCD underwent either sham or spared nerve injury (SNI) surgery (n = 3/group). Before and 14 days after surgery mechanical withdrawal thresholds were assessed via the application of von Frey filaments to the plantar surface of the hindpaw using the up-down method. Then following perfusion-fixation spinal cords were collected and 30 µm L4-5 lumbar sections (5-6 per animal) were immunostained for the neurochemical markers of DH interneuron populations Tlx3 (T-Cell Leukemia Homeobox 3; excitatory interneurons) Pax2 (Paired Box 2; inhibitory interneurons) nNOS (neuronal nitric oxide synthase) calretinin or PKCγ (Protein kinase C gamma) (distinct interneuron subpopulations). Co-labelling of these markers with Y1R-associated eGFP fluorescence was then quantified within regions of the superficial DH (laminae I-III) innervated by transected sciatic nerves (medial; M) and the spared sural nerve (centro-lateral; CL) (Corder et al. 2010) and compared between sham and SNI groups.\n\nResults:\nY1R-eGFP-expressing neurons predominately localized within the superficial laminae of the DH. SNI induced a significant decrease in mechanical withdrawal threshold but did not alter the number of Y1R-eGFP-expressing cells within the DH even after we segregated our quantification within the mediolateral region innervated by the transected sciatic nerves (M) or the spared sural nerve (CL). Over half of observed Y1R-expressing neurons within the DH could be classified as excitatory; Y1R co-labelled extensively with Tlx3

immunofluorescence in M (49.4 ± 3.8%) and CL (54.5 ± 2.9%) regions. This differs from the rat in which greater than 95% of Y1R-expressing neurons also express Tlx3 (Fu et al. IASP Yokohama 2016). A small percentage of Y1R neurons also were found to co-express markers of the distinct excitatory interneuron populations calretinin (M: 4.8 ± 1.1%; CL: 8.3 ± 1.7%) and PKCγ (M: 18.3 ± 1.9%; CL: 12.6 ± 1.8%). In contrast little if any Y1R-Pax2 co-labeling was present (M: 1.5 ± 1.2%; CL: 0.8 ± 0.4% Y1R+ cells also expressing Pax2). There was also negligible co-expression of Y1R and the inhibitory interneuron sub-population marker nNOS (M: 0.2 ± 0.2%; CL: 0.3 ± 0.3% of Y1R+ cells also expressing nNOS in M and CL regions respectively). Notably SNI did not alter Y1R co-labeling with any of these markers with the exception of PKCγ in contrast to our previous findings in the rat in which we observed a significant decrease in Tlx3 and an increase in Pax2 Y1R co-labeling. A significant increase in both the number of cells displaying PKCγ immunofluorescence and percentage of Y1R+ neurons also expressing PKCγ was observed following SNI in both the M and CL regions of the DH both ipsilateral and contralateral to the nerve injury. \n\nConclusions:\nWe found that Y1R is expressed within a heterogeneous population of largely excitatory interneurons in the mouse DH. By and large peripheral nerve injury did not change these patterns of expression however did increase the number of PKCγ-expressing neurons. Colocalization differs from mouse versus the rat. Y1R may present a novel target for spinally-directed analgesics in patient populations whose pain syndromes display a resistance to conventional analgesic therapies.\n\nAcknowledgements:\nFunded by R01NS45954-12 awarded to BKT

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Mentor/Lab: Gold

Department: Neurobiology

Poster Session: PM
Location: 15

Category:
Sensory - Pain

Title: Using GCaMP6 forthe Assessment of Activity of Nociceptive Afferents

Summary: The fluorescent indicator of neuronal activity known as GCaMP6 is a tool increasingly used to indirectly assess activity of neurons in the peripheral neurons by measuring cytosolic calcium levels. While GCaMP6 is a potentially powerful means to measure neuronal activity on a large scale the diversity of neuronal subtypes in the periphery and the way that these cells regulate cytosolic calcium may limit its utility. In this study we assess the relationship between neuronal firing cytosolic calcium levels and GCaMP6 activity in subpopulations of peripheral neurons.

Abstract: Aim of Investigation\nIn the absence of light-sensitive tools that enable direct assessment of activity in large populations of neurons investigators have turned to genetically-encoded Ca2+ indicators such as GCaMP based on the assumption that changes in cytosolic Ca2+ ([Ca2+]c) can be used as an indirect measure of neural activity. Three versions of one of later generations of GCaMP--GCaMP6 have been optimized for sensitivity (GCaMP6s) speed (GCaMP6f) or a balance between the two (GCaMP6m) via manipulations of the kinetics of Ca2+ binding. A number of investigators are already using GCaMP6 to address fundamental questions about the coding of sensory information by primary afferents. However the heterogeneity among primary afferents with respect to firing frequency the regulation of [Ca2+]c and the relationship between the two may pose unique challenges in the application of this technology as a surrogate for neural activity. In this study we sought to further define the relationship between neural activity and [Ca2+]c among subpopulations of sensory neurons as well as the relative utility of the GCaMP6 isoforms in the assessment of changes in [Ca2+]c and neural activity. \nMethods\nAcutely dissociated rat trigeminal ganglion (TG) neurons were infected with AAV9-CAG-GCaMP6s -CAG-GCaMP6m or -CAG-GCaMP6f. GCaMP expression was monitored over time. During imaging Fura-2 was used in combination with GCaMP6 imaging to enable quantification of the relationship between changes in GCaMP6 fluorescence and [Ca2+]c. High K+ (30 mM) and electrical stimulation were used to increase [Ca2+]c. Using these approaches a series of questions were addressed: (i) What is the infection efficiency across subpopulations of neurons defined by soma size IB4 binding and capsaicin sensitivity? (ii) What is the dynamic range of each of the GCaMP isoforms and is this influenced by afferent subpopulation? (iii) Among subpopulations of afferent neurons are there differences between GCaMP6 isoforms with respect to the ability to enable detection of a single action potential but also to enable resolution of action potentials across a range of stimulus frequencies? (iv) Finally are there levels of GCaMP6 expression at which changes in the regulation of [Ca2+]c can be detected?\nResults\nOur preliminary data shows that single spikes are resolved in approximately 80% of cells across the range of cell sizes using GCaMP6f and 6m. We also find that while decay times are similar between Fura-2 and GCaMP6f at 1Hz these values are up to 3s longer for GCaMP6f at 0. 5Hz across different neurons of different sizes. With GCaMP6m it was possible to resolve spike frequencies up to 2. 0 Hz (68%) while GCaMP6f enabled resolution of spike frequencies up to 10 Hz. Further with GCaMP6f it was possible to generate “tuning curves” for individual neurons where the peak increase in Ca2+ varied as a function of stimulation frequency 2 and 10 Hz. Ongoing studies are designed to further answer the questions posed in the outset of this study. \nConclusions\nThe tremendous signal to noise afforded by GCaMP6 enables resolution of single

spikes in the majority of sensory neurons as well as coding at low frequencies of activity. Nevertheless our preliminary results highlight the care that must be taken in the interpretation of negative results with this research tool. Additionally the inverted “U”-shaped stimulus response data must be taken into consideration in the interpretation of changes in peak-evoked changes in fluorescence.

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(Graduate)

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Mentor/Lab: Albers

Department: Neurobiology

Poster Session: PM
Location: 16

Category:
Sensory - Pain

Title: The role of colon epithelium in visceral pain signaling

Summary: Our studies show how colon epithelial cells communicate with sensory nerves in the colon. These experiments will provide new insight into how epithelial cells contribute to sensory signaling in normal and inflammatory disease states. This knowledge may significantly improve our understanding of pathological changes that occur in inflammatory bowel diseases and the basis of the chronic pain that accompanies these disorders.

Abstract: Visceral hypersensitivity and pain are common debilitating symptoms of inflammatory bowel diseases (IBD). This hypersensitivity is thought to be mediated in part by primary afferent neurons innervating the colon. Evidence shows that epithelial cells in the colon may contribute to changes in afferent excitability and thus also have a role in behavioral hypersensitivity. Our recent studies showed that in an ex vivo colon-nerve electrophysiological preparation optogenetic stimulation of colon epithelial cells alone initiated robust action potential firing in sensory fibers. This led us to examine the behavioral implications of selective epithelial activation. Optogenetic mouse models were developed to selectively activate either colon afferents or colon epithelial cells. This was achieved by expressing channelrhodopsin (ChR2) under the villin (protein specific to colon epithelium) promoter. In another mouse line ChR2 was expressed under the TRPV1 promoter to allow laser activation of primary afferent neurons. These mice were used to compare epithelial-induced responses and responses to direct activation of primary afferent neurons. A laser-balloon device was custom made to deliver colorectal distension (CRD) and laser stimuli in the colon. This device was inserted transanally and visceral sensitivity was measured using electromyographic recording of visceromotor responses (VMR). Blue laser stimulation in Vil-ChR2 mice showed that activation of colon epithelial cells alone can elicit visceromotor responses. Responses were also measured to 60 mmHg noxious CRD stimulus and ChR2-mediated direct activation of colon afferents. Including all laser presentations Vil-ChR2 mice displayed responses 65% of the time whereas TRPV1-ChR2 mice responded 97% of the time. The latency to response to laser was longer in Vil-ChR2 mice than in TRPV1-ChR2 mice. These data provide the first in vivo evidence that the colon epithelium can directly influence visceral sensation and nociception (in the absence of mechanical stimulation). Responses to activation of epithelium alone were comparable to responses to colorectal distension stimuli. The latency to response to epithelial stimulation is consistent with our electrophysiological experiments and suggests chemically mediated communication between epithelial cells and colon afferents. Further experiments will explore how epithelial-neuronal communication changes with colon inflammation and whether epithelial cell inhibition can attenuate visceral hypersensitivity.

First Author: Pranav Prasoon
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Mentor/Lab: Taylor

Department: Anesthesiology

Poster Session: PM
Location: 17

Category:
Sensory - Pain

Title: Co- Expression and potential interaction of neuropeptide Y receptor 1 (Y1) and mu-opioid receptors (MOR) in the superficial dorsal horn of the spinal cord

Summary: Most of studies investigated opioid receptors interaction (Such as MOR and DOR) and their pain inhibitory synergy. There is little knowledge about Y1 and MOR interaction and their pain inhibitory endogenous synergy. We investigated the cellular site potentially involved in the synergistic analgesic effect of MOR and Y1 receptors. To examine whether MOR and Y1 coexist in the same neurons or there is a synaptic interaction between neurons differentially expressing MOR and Y1. This idea is further support by our lab findings related to behavioral and pharmacological study which showed the endogenous synergy pain inhibition between mu opioid receptors and Y1 receptors (Unpublished data).

Abstract: Background: Substantial evidence indicates that both NPY and opioid peptides inhibits spinal pain transmission. Both are widely expressed in GABAergic interneurons in the dorsal horn. Intrathecal administration of Y1 antagonist (BIBO 3304) enhanced thermal hyperalgesia to CFA induced inflammatory model. Morphine binds to a mu-opioid receptor and attenuates pain.

First Author: Diogo Santos
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Mentor/Lab: Taylor

Department: Anesthesiology

Poster Session: PM
Location: 18

Category:
Sensory - Pain

Title: GluN2 and GluN3 receptor-mediated pain sensitization is tonically inhibited by endogenous mu opioid receptors

Summary: NMDA receptors are expressed in the central nervous and participate in the transition from acute to chronic pain. Using a post-surgical model of pain the current project shows for the first time that three NMDA subtypes modulate and may be targets for the treatment of chronic pain.

Abstract: Background: Blockade of endogenous opioid receptors with naltrexone (NTX) reinstates pain hypersensitivity when conducted months after the resolution of hyperalgesia. The latent sensitization (LS) underlying this phenomenon is mediated in part by NMDA receptors and may contribute to the transition from acute to chronic pain (Corder et al Science 2013). However the contribution of specific NMDA subtypes to LS is unknown. Aim: To evaluate the contribution of GluN2A GluN2B and GluN3 subtypes to NTX-induced pain reinstatement. Methods: C57BL male mice (20-25g) were submitted to a plantar incision model (PIM). On day 21 after PIM mice were pre-treated with a 5µL intrathecal injection of the GluN2A antagonist PEAQX (3-100 ng/) GluN2B antagonist Ro 25-6981 (0.01-10 µg/) or the GluN3 antagonist TK30 (30-300 ng/). NTX (3 mg/kg s.c.) was administered 15 minutes later. Mechanical hypersensitivity was assessed with von Frey filaments. Results: PEAQX prevented NTX-induced pain reinstatement in a dose-dependent manner with a peak effect from 30 to 120 minutes after injection (p < 0.05 n=8). Ro 25-6981 prevented NTX-induced pain reinstatement at 90 minutes after injection (p < 0.05 n=8). TK30 prevented NTX-induced pain reinstatement at 60 minutes after injection (p < 0.05 n=8). Conclusion: NMDAR subtypes GluN2A GluN2B and GluN3 modulate NTX-induced pain reinstatement and are important targets to better understand the mechanism from acute to chronic pain.\nAcknowledgements: NIH DA37621 and NS45954-12 to BKT

First Author: Junichi Hachisuka
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Mentor/Lab: Hachisuka

Department: Neurobiology

Poster Session: PM
Location: 19

Category:
Sensory - Pain

Title: Neural circuit basis for the inhibition of itch by counter stimuli

Summary: Counter stimuli such as noxious mechanical and thermal stimuli activate dynorphin expressing inhibitory interneurons in the superficial dorsal horn to inhibit the transmission of itch from the spinal cord to the brain.

Abstract: Scratching and other counter stimuli are known to inhibit itch but the neural circuit mechanisms remain unclear. Previous work from our lab suggested the involvement of a population of inhibitory interneurons that express dynorphin as those involved in this inhibition. Here we tested this idea using a combination of patch clamp recording dorsal horn neurons natural stimulation of the skin and ontogenetic manipulation. We find that DynorphinCre (DynCre) neurons receive respond to noxious mechanical and thermal stimulation. In addition optogenetic activation of DynCre neurons decreased the amplitude of root-evoked EPSCs in lamina I spinoparabrachial (SPB) tract neurons which send noxious information to the brain. Finally activation of DynCre neurons blocked action potentials in SPB neurons in response to itch stimulation. These data suggest that counter stimuli such as noxious mechanical and thermal stimuli activate dynorphin expressing inhibitory interneurons in the superficial dorsal horn to inhibit the transmission of itch from the spinal cord to the brain.

First Author: Kimberly Meerschaert
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Presenting Author: Kimberly Meerschaert
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Mentor/Lab: Davis

Department: Neurobiology, Pittsburgh Center for Pain Research

Poster Session: PM
Location: 20

Category:
Sensory-Motor - Internal

Title: Neuroimmune genes are differentially expressed in visceral afferents innervating the colon: a single cell RT-qPCR analysis

Summary: Organs receive sensory neurons from two different areas in the nervous system. The molecular profile of these neurons show they are distinct populations and probably play different roles in neuroimmune interactions.

Abstract: Aim of Investigation: Unlike somatic structures visceral organs receive sensory innervation from primary sensory neurons arising from two different regions of the neuroaxis. The reason for this dual innervation remains a mystery. Thoracic and upper abdominal viscera receive innervation from thoracolumbar spinal afferents (that travel with sympathetic splanchnic nerves) and from afferents arising in the nodose ganglia (and travel in the vagus nerves) whereas lower abdominal and pelvic organs are innervated by thoracolumbar and lumbosacral spinal afferents (and run with sympathetic and parasympathetic splanchnic nerves respectively). Hypotheses for this dual innervation include: a) that different levels of innervation are involved in different qualitative aspects of pain b) that different levels are important for the integration of autonomic function or c) that different levels play complementary roles in immune modulation. The first step in discerning the role of these different afferents is to characterize the molecular identity of afferents from different levels innervating the same organ. This was accomplished by creating a molecular profile of colon afferents from thoracolumbar lumbosacral and nodose ganglia using single cell RT-qPCR. \n\nMethods: Visceral afferents were back-labeled using fluorescently tagged cholera toxin beta injected into the colon. The nodose ganglia thoracolumbar (T12-L2) and lumbosacral (L5-S1) dorsal root ganglia (DRG; aka spinal ganglion) were dissected and dissociated for single cell pickup. Individual fluorescent cells were identified and extracted for single cell RT-qPCR. Cells were clustered according to their relative transcription level using an unbiased clustering method (weighted pair group method with arithmetic mean).\n\nResults: A total 96 colon afferents from the nodose ganglia thoracolumbar DRG and lumbosacral DRG were run for 44 genes. The first surprising finding was that nearly all colon DRG afferents contained mRNA coding for tyrosine hydroxylase an enzyme typically associated with sympathetic postganglionic fibers. This enzyme is required for the production of catecholamines (e.g. norepinephrine and dopamine) although there is little or no evidence that these neurons make any of these neurotransmitters. Also of note colon afferents from the nodose ganglia were clustered distinctly from colon afferents from the DRG ganglia. Major differences included higher levels of expression (both number of cells and intensity) in DRG afferents for mRNAs for Calca (the precursor of CGRP) GFRa3 (the co-receptor for artemin a cytokine associated with inflammatory pain) TRPA1 (a non-selective ion channel implicated in inflammatory pain) and TrkA (the NGF receptor also associated with chronic inflammatory pain). In contrast DRG afferents from the thoracolumbar and lumbosacral levels did not cluster into separate groups. Finally numerous receptors involved in neuroimmune interactions were found in both vagal and spinal colon afferents and these also were expressed at different levels in DRG and nodose afferents. For example programmed-death ligand 1 (PDL1) an important immune checkpoint protein was found in higher levels in nodose afferents compared to spinal afferents. Interleukin-4 receptor subunit a (Il4ra) an important anti-inflammatory cytokine and part of the Th2 response was higher in expression in

spinal afferents compared to nodose afferents. Numerous other immune related genes including interferon alpha receptor 1&2 C-X-C motif chemokine receptor 2 interferon gamma receptor 1&2 and the interleukin-1 receptor type 1 were expressed at various levels in both DRG (all levels) and nodose neurons. \n\nConclusions: Our analysis of colon afferents from the nodose ganglia thoracolumbar and lumbosacral DRG revealed unique molecular profiles in visceral afferents. Most importantly colon afferents from the nodose were molecularly distinct from DRG colon afferents with respect to immune gene expression suggesting different that this dual innervation plays a role in coordinating immune responses at least for visceral organs. The next step will be to determine how this differential gene expression affects the behavior of immune cells under different pathological conditions such as inflammatory diseases and cancer.

First Author: Kristen Smith-Edwards
(Postdoctoral)

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Mentor/Lab: Davis

Department: Neurobiology

Poster Session: PM
Location: 21

Category:
Sensory-Motor - Internal

Title: In vivo and ex vivo GCaMP imaging of enteric circuits for the use of optogenetic stimulation to regulate colon motility\nKristen M. Smith-Edwards Sarah A. Najjar Brian S. Edwards Kathryn M. Albers Brian M. Davis

Summary: There are numerous GI disorders that result in colon dysmotility and mapping the functional connections among enteric subpopulations of cells would provide the means to precisely control colon motility. With the recent advances in optogenetic tools (GCaMP channelrhodopsin ChR2) we now have the capabilities to report and manipulate activity in specific molecular populations of cells. Our lab has employed optogenetic techniques in both ex vivo and in vivo colon preparations to reveal the neural mechanisms underlying colon motility and build a functional map of the ENS connectome.

Abstract: The gut is equipped with its own local nervous system the enteric nervous system (ENS) which can function autonomously to regulate colon motility. In addition there are extrinsic nerve pathways that coordinate activity between distant regions of the gastrointestinal (GI) tract and allow the central nervous system (CNS) to regulate GI functioning. There are numerous GI disorders that result in colon dysmotility and mapping the functional connections among enteric subpopulations of cells would provide the means to precisely regulate colon motility. To reveal the neural mechanisms underlying colon motility our lab has employed optogenetics (e.g. GCaMP ChR2) in ex vivo (n=30) and in vivo (n=10) colon preparations in which the intrinsic ENS circuits and extrinsic pathways to the colon remain intact. We used mice that express the genetically-encoded calcium indicator GCaMP to image spontaneous and evoked calcium signals in enteric neurons and correlated this activity to evoked colon contractions. We also used mice that express the blue-light activated ion channel channelrhodopsin (ChR2) to activate specific subpopulations of enteric neurons while recording the effect on whole colon motility patterns. Electrical stimulation (100μs 20Hz 1sec) of the colon either 5mm anal or oral to the imaging field activated distinct ascending (i.e. those traveling from the anal to oral end of the colon) and descending neural circuits respectively that produced different patterns of contractility. Additionally activation of extrinsic parasympathetic fibers via ventral root stimulation mimicked the neural responses and contractions produced by stimulation anal to the imaging field indicating that extrinsic parasympathetic input from the CNS engages ascending excitatory enteric circuits to promote colon motility. However activation of extrinsic sensory neurons via dorsal root stimulation only produced responses when the spinal cord was intact suggesting that extrinsic sensory neurons indirectly influence enteric neuron activity via spinal reflexes. Recordings of whole colon motility patterns revealed that spontaneous waves of propagating contractions (colonic migrating motor complexes CMMC) occur regularly every 5 minutes. Blue light stimulation of excitatory choline acetyltransferase (ChAT)-expressing enteric neurons (ChAT-ChR2 mice) was able to trigger CMMCs however this was not always reproducible and appeared to depend on the location of light stimulation. Overall our lab is beginning to construct a functional and predictive map of the ENS connectome in mice with healthy colons. Future studies will use mouse models of GI motility disorders to determine which subpopulations of enteric neurons are altered and whether optogenetic stimulation can be used to correct motility patterns.

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Mentor/Lab: Gandhi

Department: Bioengineering

Poster Session: PM
Location: 22

Category:
Sensory-Motor

Title: Ventral premotor control of head and eye movements

Summary: Neural activity in the ventral premotor cortex influences unrestrained head and eye movements. This activity seems to differentiate between effectors used (eye or head) and in some cases the order of the effector.

Abstract: We redirect our visual axis to a stimulus of interest through a coordinated set of movements with our eyes and head. The specific properties of these gaze shifts are task dependent and rely on the initial head-in-space and eye-in-head positions. It is known that the premotor cortex plays a role in complex movements involving several muscle groups. In particular a region of the ventral premotor cortex (PMv) projects polysynaptically to extraocular and neck muscles through a pathway that bypasses the frontal eye field (FEF) and primary motor cortex (M1) (Billig and Strick Program No. 371.05/LL12 SFN 2012). This relatively direct route suggests that PMv activity influences eye and/or head movements. Thus we developed a paradigm in which a Rhesus monkey (Macaca Mulatta) was trained to produce an eye-only movement followed by a head-only movement the same movements but in the reverse order or a gaze shift without constraints on the effectors of action. We also incorporated in the design systematic control of initial eye-in-head and head-in-space positions as well as requirements to produce ipsiversive contraversive and centering movements because all of these factors have been associated with PMv function in previous physiological and/or anatomical studies. Neural activity in PMv was recording with single as well as laminar electrodes. Based on our current dataset a majority of PMv cells exhibited enhanced activity ~100-200 ms before the movement onset and notably this activity returned to near baseline levels before movement onset. Furthermore many cells responded to ipsiversive movements corroborating anatomical findings which show that PMv projects to neck muscles bilaterally. Additionally a sub-population of cells responded to the first effector in the movement regardless whether it was eye or head potentially indicating the onset of a movement but remaining agnostic of which effector is used to execute that movement. These observations are consistent with the notion that there is a neural code in PMV which coordinates the movements (in this case head-unrestrained gaze shifts) across multiple effectors and muscle groups.

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(Faculty)

Mentor/Lab: Richardson

Department: Neurological Surgery

Poster Session: PM
Location: 23

Category:
Motor

Title: Neuronal firing in the subthalamic nucleus encodes segmenting of motor sequences

Summary: We investigate the contribution of a deep-brain nucleus the STN to the production of speech. We find evidence that neural activity in the STN participates in the timing of speech utterances such as syllables within a word. This finding has important implications for current models of speech production and for development of brain-machine interfaces to aid in novel therapies in movement disorders.

Abstract: The basal ganglia has been implicated in the implementation of “chunking” of motor sequences that is necessary for learning and execution of complex behaviors. This allows for an efficient representation of complex motor sequences as well as their optimization during learning. Speech can be understood in terms of sequence chunks at several hierarchical levels of analysis: (1) individual articulator movements (2) phonemes (3) syllables and (4) words. In order to investigate the involvement of the subthalamic nucleus (STN) in the encoding of these speech chunks we recorded extracellular unit activity from the STN of Parkinson’s disease patients undergoing deep brain stimulation electrode implantation. Subjects were asked to listen to audio recordings of consonant-vowel syllable triplets presented through earphones and repeat them during STN recordings and simultaneous electrocorticographic (ECoG) recordings from articulatory sensorimotor cortex. We hypothesized that STN neuronal activity is patterned to designate the boundaries and the duration of individual speech at these levels of granularity; and that phase synchronization between STN spiking and oscillatory activity in sensorimotor cortex is modulated by throughout the motor sequence. Consistent with our previous findings we observed that speech induced both increases (165 ± 11% of baseline firing rate in 24 units) and decreases (68 ± 3% of baseline firing rate in 23 units) in the firing rate of STN neurons (55 units recorded from 6 subjects). Furthermore we observed that speech-related firing rate increases were either phasic (i.e. temporally aligned with one or more individual syllables in the spoken response) or tonic (i.e. temporally aligned with the entire spoken response) while speech-related firing rate decreases were tonic. This finding provides preliminary evidence for STN encoding of motor sequences at the syllable- and word-level. In addition we observed phase synchronization between STN spiking and oscillatory activity in sensorimotor cortex at rest. Further analyses will address speech-related changes in cortico-subthalamic phase synchronization and the encoding of motor sequence chunks in these networks.

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(Graduate)

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(Graduate)

Mentor/Lab: Gharbawie

Department: Bioengineering

Poster Session: PM
Location: 24

Category:
Motor

Title: Motor cortex's intrinsic connections revealed with intracortical microstimulation and optical imaging in squirrel monkeys

Summary: We investigated the local connectivity within the forelimb representation of the primary motor cortex of squirrel monkeys. We found that intrinsic connectivity preferentially linked zones that controlled similar muscle groups in the arm and hand. This result implies that intrinsic connectivity within M1 is not heavily involved in coordination between arm and hand muscles.

Abstract: Contiguous zones within the primary motor cortex (M1) forelimb representation control the arm and the hand. Arm/hand coordination requires precise spatial and temporal synchronization of neural activity within the M1 forelimb representation. Although intrinsic connections are the densest and most direct communication networks in M1 their organization and role are not known. The present study aims to identify the principles that govern the spatial organization of intrinsic connectivity within the M1 forelimb representation. In three squirrel monkeys motor output at many sites spatially distributed throughout the forelimb representation was mapped using intracortical microstimulation (ICMS). Effective connectivity of M1 sites was identified using ICMS (150 biphasic pulse train 0.2 ms pulse width 300 Hz 60 μA) and concurrent optical imaging of intrinsic signal (630 nm illumination). Functional connectivity of M1 sites was identified using optical imaging of spontaneous activity (resting state). The connectivity of each site was overlaid onto the motor map. The connectivity of sites in the distal forelimb representation tended to be localized to within 2-3 mm of the site and preferentially targeted M1 zones with distal forelimb motor output. The connectivity of sites in the proximal forelimb representation had a similar cluster of connectivity around each site in addition to patchy connectivity at distances of up to 7mm from the site. Similar to distal sites the connectivity of proximal sites preferentially targeted M1 zones with proximal forelimb output. We therefore conclude that intrinsic M1 connectivity is preferentially biased toward M1 zones that target similar muscle groups. This spatial organization of intrinsic M1 connectivity suggests that this connectivity is likely specialized for controlling neural activity of the arm or the hand and less likely to be involved in arm/hand coordination.

First Author: Nick Chehade
(Graduate)

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(Graduate)

Mentor/Lab: Gharbawie

Department: Neurobiology

Poster Session: PM
Location: 25

Category:
Motor

Title: Arm and Hand Muscle and Kinematic Activity During a Reach-to-Grasp Task

Summary: We trained a non-human primate to perform a reach-to-grasp task while recording muscle and kinematic activity of the arm and hand. Building models of these signals revealed earlier peaks for proximal muscles and joints corresponding to reaching and later peaks for distal muscles and joints corresponding to grasping.

Abstract: In order to understand how the brain controls arms and hands the relationship between movement parameters (e.g. joint kinematics muscle activity) and neural activity must be investigated. Recording neural modulations joint kinematics and muscle activity in an awake behaving subject is the best way to investigate these relationships. However obtaining all of these signals in tandem poses practical issues. We propose robust repeatable models of muscle and kinematic activity of the arm and hand in order to eliminate the need to obtain these signals simultaneously. We trained a non-human primate (NHP) to perform a reach-to-grasp task on three different sized grasp objects and one non-grasp object presented at the same location. EMG signals of the biceps triceps deltoid digit flexors wrist flexor digit extensors and wrist extensor were recorded from percutaneous electrode insertions. LED markers were placed on the arm and hand of the NHP to track kinematic changes in 3D. Three LEDS on the shoulder four on the forearm two on the wrist two on the hand and one on the digit were used to construct vectors to calculate joint angles of the shoulder elbow wrist and digit. Our findings demonstrate that muscle and kinematic signals modulate earlier in the task (during the reach phase) for proximal muscles and joints while distal muscles and joints modulate later (during the grasp phase). Additionally distal muscles and joints express condition dependent variations whereas proximal muscles and joints tend to not. Our results reveal that EMG signals of a muscle modulate its activity earlier than kinematic activity for its respective joint. In future work these temporal models of joint angles and muscle activity can be used to correlate neural recordings obtained from the NHP performing the same task in order to better understand how the brain is encoding complex movements.

First Author: Benjamin Chernoff
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Mentor/Lab: Mahon - CMU

Department: Psychology

Poster Session: PM
Location: 26

Category:
Motor

Title: Intra-operative direct electrical stimulation of the left Frontal Aslant Tract disrupts sentence planning but does not affect articulation

Summary: Producing a sentence requires several components including planning working memory and the actual motor process of articulation. Patients with damage to a recently discovered nerve pathway called the Frontal Aslant Tract (FAT) exhibit speech production impairments but there has been no psycholinguistics research to elucidate which of those components break down when the FAT is damaged. We used a novel sentence planning experiment in the operating room with a patient undergoing awake surgery to remove a brain tumor and we found that direct electrical stimulation of the FAT affected his ability to plan phrases within the sentence without disrupting his ability to articulate individual words demonstrating that the FAT is crucial for planning.

Abstract: Benjamin L. Chernoff Max H. Sims Susan O. Smith Webster H. Pilcher & Bradford Z. Mahon\n\nSentence planning unfolds at multiple levels of processing including planning of the\nmessage syntagmatic and syntactic relations and positioning of morphophonological elements. Patients with damage to a recently discovered white matter pathway in the brain the left Frontal Aslant Tract (FAT) exhibit impaired sentence production and dysfluent speech in the absence of impairments to semantic processing lexical access articulation or non-speech motor function (e.g. limb or orofacial apraxia). We propose that the left frontal aslant tract is a key pathway for integrating syntagmatic and positional-level planning during sentence production. We refer to this as the 'Syntagmatic Constraints On Positional Elements' (SCOPE) hypothesis. A core prediction made by the SCOPE hypothesis is that disruption of the FAT should specifically disrupt sentence production at phrasal boundaries with no impairment for articulation. We test this prediction by measuring sentence production latencies in a patient undergoing direct electrical stimulation (DES) mapping of the frontal aslant tract during an awake craniotomy to remove a left hemisphere brain tumor. The patient produced cued sentences such as 'The red square is above the yellow circle' and we measured the intra-word and inter-word durations as a function of stimulation (on off and location relative to the tract). We found that stimulation significantly prolonged intra-word pauses before the start of the noun phrases and at the verb while intra-word durations internal to noun phrases were if anything shorter in the context of stimulation compared to without stimulation. Stimulation of the frontal aslant tract had no effect on articulation time. These results provide initial support for the SCOPE hypothesis and motivate novel directions for future research to explore the functions of this recently discovered component of the language system.

First Author: Anna Chrabaszcz
(Postdoctoral)

Presenting Author: Anna Chrabaszcz
(Postdoctoral)

Mentor/Lab: Richardson, Fiez

Department: Psychology

Poster Session: PM
Location: 27

Category:
Motor

Title: Representation of speech and vocal tract articulators in the subthalamic nucleus and the sensorimotor cortex

Summary: Speech production constitutes a complex motor behavior involving precise coordination of various vocal tract articulators. The sensorimotor cortex appears to represent them somatotopically however it is still largely unknown how articulatory movements are encoded at the subcortical level. In this poster we present new data comparing how sensorimotor cortex and the subthalamic nucleus may represent vocal tract articulators.

Abstract: The sensorimotor cortex appears to be somatotopically organized to represent the vocal tract articulators such as lips tongue larynx and jaw. How speech and articulatory features are encoded at the subcortical level however remains largely unknown. We analyzed electrocorticography (ECoG) recordings from the sensorimotor cortex (SMC) and simultaneous local field potential recordings from the subthalamic nucleus (STN) of 11 patients with Parkinson's disease during implantation surgery for deep brain stimulation. Patients read aloud words and pseudowords presented on a computer screen. The initial consonant of the stimuli involved articulation primarily with the tongue or the lips. We observed significant increases in high gamma (60–150 Hz) power throughout the STN for the speech articulation window similar to the high gamma response in the SMC. The magnitude of the STN response varied along the dorsal-ventral trajectory of the electrodes with greater high gamma power observed dorsally. Consistent with previous studies high gamma response in the SMC revealed a spatial topography according to the primary articulator involved in the production of the consonant (tongue or lips). In contrast the STN high gamma response varied depending on the articulator type but showed no clear spatial topography. The results demonstrate the simultaneous involvement of the SMC and the STN activity in speech production and indicate that these two regions may represent speech-related movement at the level of articulators differently.

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Mentor/Lab: Richardson

Department: Neurosurgery

Poster Session: PM
Location: 28

Category:
Motor

Title: Local field potentials in the human subthalamic nucleus predict scaling of speech production.

Summary: Direct brain recordings have shown that the basal ganglia is involved in the scaling of limb movements; however it is unknown if the same is true for speech movements. \n We explored the relationship between direct human brain recordings and measurements of speech gain. Results suggest that the basal ganglia is important for modulating speech movements.

Abstract: The basal ganglia have been implicated in speech motor control but their role is unclear. In limb movement tasks intra-operative electrophysiology studies reveal a role for basal ganglia in movement scaling. Here we explore the relationship between an indirect measure of scaling in speech articulation (acoustic formant-frequency ratio) and population-scale neuronal signals from the human subthalamic nucleus (STN). LFPs were recorded from the macroelectrode as 14 patients with Parkinson's disease (PD) underwent intra-operative recording during STN deep brain stimulation (DBS) implant surgery. Cued by visual orthography patients read aloud a list of consonant-vowel-consonant words as their utterances were recorded for acoustic analysis. LFP's were separated into canonical spectral bands and analyzed for changes relative to baseline recordings. Using correlation and mixed effects models we examined the relationship of theta beta and gamma band power (z-scores) with the formant ratio (FR) an acoustic measurement of the second formant frequency (F2) during /i/ versus /u/ (as in he vs. who) that provides a relative estimate of the amplitude of tongue movement during articulation. Compared to baseline theta power (4-8 Hz) significantly increased following the visual cue low beta power (13-20 Hz) and high beta power (20-30 Hz) decreased following the visual cue and gamma power (50-90 Hz) increased during speech. The average theta band z-score during speech was significantly correlated with FR ($r = 0.337$ $p = 0.0415$) as was low beta ($r = -0.53$ $p = 0.00068$); high beta was only correlated to FR with non-parametric analysis (spearman's $rho = -0.451$ $p = 0.0051$). Gamma power however did not correlate significantly with FR. We then applied mixed effects models across the task using each band as a fixed effect and subject and recording session as random effects. The effect of theta power in predicting FR was significant for time points during speech [0.0725 s - 0.13 s peak beta = 0.057]; low beta power was also significant 0.26 s before speech onset to 0.7 s after speech onset; high beta power was also significant across the task. Effects remained significant when including the Unified Parkinson's Disease Rating Scale as a random effect (theta: fixed effect = 0.059 $p = 0.001$; low beta: fixed effect = -0.048 p < 0.026). These results provide evidence that the STN participates in speech articulation and contributes to scaling of articulatory movements. Theta and beta oscillations may contribute synergistically to speech scaling These relationships may represent theoretical 'internal models' of movement and have implications for treatment of speech deficits with DBS

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Mentor/Lab: Richardson

Department: Neurological Surgery

Poster Session: PM
Location: 29

Category:
Motor

Title: Differential modulation of neural activity in the ventral lateral nucleus of the thalamus during speech production

Summary: Thalamus functions as a relay center between cerebral cortex and subcortical structures yet its involvement in speech rarely has been studied directly. By recording electrophyisological signals from the ventral lateral nucleus of the thalamus we studied neural activity modulation in the thalamus during speech production.

Abstract: Both basal ganglia-thalamo-cortical and cerebello-thalamo-cortical circuits contribute to speech motor control and language processing. The thalamus functions as a relay center in both circuits yet its involvement in speech production rarely has been studied directly. The posterior part of the ventral lateral nucleus (VLp) mainly receives inputs from the cerebellum and sends outputs to the motor cortex while the anterior part of the ventral lateral nucleus (VLa) primarily relays information between the globus pallidus and the premotor cortex; both regions are encountered during implantation of deep brain stimulation (DBS) leads into the Vim nucleus. We recorded spoken acoustics and simultaneous local field potentials (LFPs) in the ventral lateral nucleus of the thalamus (VL) in 12 essential tremor subjects while they performed an intra-operative speech task during DBS surgery. On each trial subjects were asked to name a consonant-vowel-consonant syllable when it appeared on the screen. LFP signals were spectrally decomposed and power values were normalized relative to the baseline period. Recording locations were determined using the Lead-DBS toolbox and contact locations were categorized to VLa and VLp. High Gamma (70-150 Hz) activation and beta (13-30 Hz) desynchronization were observed during speech indicating active participation of thalamus in speech production. The increase in high gamma power was locked to speech onset (30/47 contacts Pearson correlation p < 0.01 FDR corrected) while beta desynchronization was locked to presentation of the visual cue (35/39 contacts Pearson correlation p < 0.01 FDR corrected) suggesting that oscillations within these frequency bands encode different aspects of the speech task. Furthermore we observed that the strength of power changes during speech were dependent on recording location within the nucleus. High Gamma activation during speech was greater in electrode contacts that were localized to the more posterior part of VL than those localized to the more anterior part of VL (p< 0.05) indicating functional heterogeneity of VL in speech control. These results provide support for the involvement of VL in speech motor control and establish a novel methodological framework to test neurophysiological models of speech production.

First Author: Digna de Kam
(Postdoctoral)

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(Postdoctoral)

Mentor/Lab: Torres-Oviedo

Department: Bioengineering

Poster Session: PM
Location: 30

Category:
Motor

Title: The size and direction of performance errors during sensorimotor adaptation regulate the carryover of motor learning across contexts

Summary: We studied the effect of performance error size and direction on the carryover of locomotor learning from walking on the split-belt to overground walking. Our results show that positive errors facilitate carryover possibly because they induce more learning whereas negative errors mitigate it because they enable subjects to recall the appropriate motor pattern according to the environmental conditions at hand.

Abstract: Movement patterns learned in one context partly carry over to untrained contexts. This carryover is limited by contextual cues such as large performance errors that promote linking of motor patterns to the context in which they were learned. We investigated the extent to which different strategies to reduce error size promote the carryover of locomotor learning to an untrained context. To this end we reduced performance errors (i.e. asymmetric step lengths) on a split-belt treadmill moving the legs at different speeds with either an explicit or an implicit strategy. In the explicit case subjects were instructed where to place their feet with visual feedback whereas in the implicit case subjects simply walked while we gradually introduced the split-belt perturbation (600 strides ramp). These two groups were compared to a control group experiencing large performance errors through a semi-abrupt split-belt perturbation (40 strides ramp). Carryover of locomotor learning was quantified by step length asymmetry aftereffects in the overground context. Smaller errors during adaptation resulted in reduced aftereffects overground (implicit p=0.017 explicit p=0.022). This was surprising given previous work showing a negative association between error size and carryover of motor learning (Torres-Oviedo and Bastian 2012).\nThus we tested the effect of two factors that were distinct between our studies: error direction or error magnitude. This was done by contrasting the overground aftereffects of our control group to: 1) a large-error group experiencing errors in the same direction as but of even greater magnitude than the control group and 2) an opposite-error group experiencing errors of the same magnitude but in opposite-direction as the control group. We found that the large-error group did not exhibit larger after effects than controls however errors in the opposite direction substantially reduced overground aftereffects (p<0.01). \nIn sum errors experienced when the perturbation is introduced (positive errors) or removed (negative errors) have opposite effects on carryover of motor learning across contexts. Positive errors facilitate carryover possibly because they induce more learning whereas negative errors mitigate it because they enable subjects to recall the appropriate motor pattern according to the environmental conditions at hand.

First Author: Carly Sombric
(Graduate)

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Mentor/Lab: Torres-Oviedo

Department: Bioengineering

Poster Session: PM
Location: 31

Category:
Motor

Title: Cognitive and motor switching are associated in older adults

Summary: Cognitive and motor switching abilities are impaired with healthy aging. This study specifically identifies that these abilities are related in older adults. This finding suggests that older adults may benefit from motor and cognitive strategies during physical rehabilitation.

Abstract: Aging impairs our ability to switch actions based on the context in the motor and cognitive domains. Specifically older adults have greater difficulty switching actions in cognitive tasks such as set shift tasks (e.g. Van Asselen and Ridderinkhof 2000) and in motor tasks such as switching motor patterns when transitioning between two different walking contexts (Sombric et al. 2017). Here we ask if these cognitive and switching abilities were associated and potentially share similar neural processes as we age. To this end we characterized cognitive switching on 11 healthy older (76.5+/-2.77 years old 6 women) and younger adults (21.7+/- 3.47 years old 7 women) with a task similar to Wisconsin Card Sorting. We also characterized motor switching in these individuals by quantifying their ability to disengage locomotor patterns specific to a novel split-belt treadmill (that moves their legs at different speeds) when walking over ground. We found that motor and cognitive switching were positively correlated in older adults ($R^2=0.83$ $p=0.001$) such that individuals that were better at switching actions in the cognitive task were also better at switching walking patterns in the motor task. On the other hand this relation was not found in younger individuals ($R^2=0.15$ $p=0.67$). This age-mediated difference was found even if the averaged switching ability in the motor ($p=0.07$) and cognitive domains ($p=0.54$) were not different between groups. We also confirmed previous results (Sombric et al. 2017) indicating that older adults were more forgetful than young during the motor learning process ($p=.035$) but reached similar steady-state behavior as young individuals ($p=0.929$) before walking overground. Thus treadmill-specific locomotor pattern was performed equally well in both groups before we assessed their switching ability. Taken together our results indicate that the relation between cognitive and motor switching was the only aspect predominantly different between age groups. This suggest that the neural basis for switching actions according to the contexts is shared between motor and cognitive domains in older individuals due to age-related neural changes. Our findings also suggest that training to explicitly change actions with cognitive tasks may improve motor switching in older adults.

First Author: Jing He
(Postdoctoral)

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(Postdoctoral)

Mentor/Lab: Stauffer

Department: Systems Neuroscience

Poster Session: PM
Location: 32

Category:
Systems

Title: Transcriptional characterization of single cells from Rhesus macaque brains

Summary: The brain is made-up of many different types of cells and an accurate description of these is critical to understanding normal brain function and disease. Here we use a new technology to capture 'transcriptomes' – the sets of messages cells use to make proteins – from thousands of individual brain cells in parallel. We classify cell types based on the similarity of their transcriptomes. These results will tell us what cell types are present in the brain what genes they use and perhaps identify ways to selectively target brain circuits with advanced therapeutic measures.

Abstract: A comprehensive characterization of the brain cell types is a necessary foundation for understanding the neural basis of cognition and behavior. Single-cell and single-nuclei RNA sequencing (scRNAseq and snRNAseq respectively) can provide transcriptional profiles for thousands of cells in parallel. When coupled with advanced computational methods these techniques can be used to identify and characterize the cellular composition of brain regions. Moreover they can reveal rare transcripts that may provide enhance/promoter regions to enable targeted gene delivery. These powerful techniques are just now being applied to mouse and human brains yet few attempts have been made to characterize transcriptional profiles for nonhuman primates (NHPs). NHP are the neuroscientific animal model with the greatest anatomical and cognitive homology to human. Therefore NHP studies are the cornerstone of systems neuroscience and a stepping stone to translational applications of gene therapy. Massively parallel scRNAseq / snRNAseq provides an ideal platform to characterize NHP brains and identify rare transcripts that might enable cell type-specific access to this critical animal model. Here we set out to measure the transcriptional profiles of cell types in three brain regions that have undergone significant development during the evolution of primates the retina the prefrontal cortex (PFC) and the striatum. We tested different isolation protocols in 8-10 months old rats and used real time PCR to identify important transcripts (DRD1 DRD2 and TH) and optimize the dissociation of adult neurons. We then dissected the retina PFC and striatum from a 5-year-old Rhesus macaque. We dissociated the neurons and the nuclei and used a 10x Genomics Chromium controller sorted the resulting suspensions into single droplets to capture the transcriptomes and sequenced to average depth of 80000 reads per cell. We quantified the read count per gene and per cell and the performed similarity-based imputation to reduce the technical noise in the gene expression matrix. Afterwards we used a variety of dimensionality reduction and computational clustering techniques to identify distinct cell types. For each cell type we found present we were able to identify the marker genes whose expression defined that cell type and the biological processes that these markers genes were statistically enriched for. We will describe preliminary results of our analysis into the cell type composition of NHP brain.

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Department: Bioengineering

Poster Session: PM
Location: 33

Category:
Systems

Title: Left-right brain connectivity - how cells drive MRI functional signals

Summary: We investigated how left-right brain connectivity drives MRI functional signals

Abstract: The interhemispheric circuit connecting the left and the right mammalian brain plays a key role in integration of bilateral signals from the body. The information transfer is carried out by modulation of simultaneous excitation and inhibition. Hemodynamic studies of this circuit are inconsistent since little is known about the vascular response to mixed excitation and inhibition. We investigated the variability in hemodynamic responses driven transcallosally during optogenetic and somatosensory activation in rats. In order to compare different aspects of the response we used multimodal approach employing electrophysiology hemoglobin-based optical intrinsic signal BOLD and CBV-weighted fMRI. In half of the experiments optogenetic stimulation of the cell bodies evoked a predominant post-synaptic inhibition in the other hemisphere accompanied by metabolic oxygen consumption and reduction of CBV without functional hyperemia. When the same stimulation resulted in post-synaptic excitation we observed robust hemodynamic response. Optogenetic suppression of the postsynaptic excitation abolished the coupled functional hyperemia. We also observed differences in the neurovascular response based on the stimulation site – cell bodies versus distal projections. Light stimulation at distal projections evoked consistently a metabolic response without hyperemia. Our findings suggest that functional hyperemia requires signals originating from the cell body and that hemodynamic response variability appears to reflect the balance between the post-synaptic excitation and inhibition. This work aims to bridge the gap between cellular approaches and whole brain functional imaging. The end goal is to understand both the fundamental principles of brain function as well as the biological basis of BOLD fMRI signals.

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Mentor/Lab: Johnson

Department: Neuroscience

Poster Session: PM
Location: 34

Category:
Systems

Title: Functional and Biochemical Investigation of Inter-subunit Interactions in NMDA Receptor Transmembrane Regions

Summary: N-methyl-D-aspartate receptors are receptors in the brain cells which mediate communication between brain cells by allowing flow of ions across the membrane and are central to essential basic nervous system functions including learning and memory. These receptors are composed of 4 different types of subunits (two obligatory GluN1 subunits with two GluN2 (A-D) and/or GluN3 (A-B) subunits) and each subunit has some conserved residues. Here we specifically investigated and elaborated on the functional and structural consequences of altering a conserved amino acid tryptophan (W) on receptor properties.

Abstract: NMDA receptors (NMDARs) are excitatory glutamate and glycine-gated ion channels that form functional receptors by pairing of two obligatory GluN1 subunits with two GluN2 (A-D) and/or GluN3 (A-B) subunits. Each functional receptor is divided into four domains: extracellular N-terminal domain (NTD) extracellular ligand-binding domain (LBD) trans-membrane domain (TMD) and the intracellular C-terminal domain (CTD). The TMD of each subunit is composed of three membrane spanning regions (M1 M3 and M4) and a re-entrant pore-forming loop (M2). Within the M2 region of TMD of each subunit lies a highly conserved tryptophan (W) residue. The effects of mutating the conserved W have subunit-dependent effects: e.g. mutating the conserved W in the GluN2B subunit (GluN2B (W607)) strongly reduces channel block by Mg2+ whereas mutation of the homologous W in GluN1 (GluN1 (W608)) or in GluN2A (GluN2A (W606)) subunits has only a modest effect on Mg2+ block. We hypothesized that the subunit-dependent effects of conserved W mutations could be due to varied interactions with residues in the M3 region of the adjacent subunit. To investigate intersubunit interactions we performed a cysteine-substitution study using computational modeling electrophysiological and biochemical techniques. Based on a structural NMDAR model we predicted that M634 in the M3 region of the GluN1 subunit is adjacent to GluN2A(W606). We found that GluN1/2A(W606C) receptors exhibit nearly normal Mg2+ block whereas both GluN1(M634C)/2A and GluN1(M634C)/2A(W606C) receptors show severely-decreased Mg2+ block. In contrast GluN1/2B(W606C) receptors exhibit greatly decreased Mg2+ block as do GluN1(M634C)/2B(W606C) receptors whereas GluN1(M634C)/2B receptors exhibit nearly normal Mg2+ block. We found electrophysiological but not biochemical evidence of coupling between GluN1(M634) and GluN2A(W606) and no evidence of coupling between GluN1(M634) and GluN2B(W607). Previously we showed electrophysiological evidence of coupling between GluN1(W608) and GluN2A(S632). Here we added further electrophysiological and biochemical evidence for coupling of GluN1(W608) and GluN2A(S632). Overall we conclude that intersubunit interactions of adjacent M2 and M3 regions powerfully regulate NMDAR properties. This study has broader implications to understanding the functional and structural characteristics of NMDARs which are involved in myriad nervous system disorders.

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Mentor/Lab: Lewis

Department: Psychiatry

Poster Session: PM
Location: 35

Category:
Systems

Title: Development of GABA receptor transcripts in layer 3 pyramidal and parvalbumin neurons in monkey visual and prefrontal cortices

Summary: Detailed molecular studies into typical development of primate brain microcircuitry across multiple scales of organization are critical for understanding developmental deviations that contribute to cognitive dysfunction and the development of schizophrenia.

Abstract: Background: Visuospatial working memory (vsWM) is a key cognitive function impaired in schizophrenia. vsWM requires information transfer among cortical regions including visual and prefrontal cortices via layer 3 pyramidal neurons whose activity is regulated by GABAergic parvalbumin (PV) neurons. In primates vsWM performance improves through adolescence and certain measures mature earlier in visual cortex (V2) than prefrontal cortex (PFC). Phasic GABA neurotransmission undergoes protracted postnatal maturation in the PFC with a progressive shift from □2 (GABRA2)- to □1 (GABRA1)-subunit containing GABAA receptors which is important for neural oscillations underlying vsWM. However whether the pattern and timing of these GABRA1 and GABRA2 messenger RNA developmental trajectories is conserved across different cells types and cortical regions has not been examined. Here we tested whether this developmental molecular shift in pyramidal and PV neurons occurs earlier in V2 than PFC. Understanding the timing of molecular changes during typical postnatal development may provide insight into how deviations from the typical trajectory could increase schizophrenia risk.\n\nMethods: Rhesus monkey V2 and PFC tissue from neonatal prepubertal late-pubertal and adult ages was labeled by fluorescence in situ hybridization for DAPI (cell nuclei) PV (GABA neuron marker) or vGLUT1 (pyramidal neuron marker) GABRA1 and GABRA2.\n\nResults: In pyramidal neurons the GABRA1/GABRA2 ratio expression increased across all ages both in V2 and PFC. In V2 there was a significant increase in the ratio from prepubertal to late-pubertal ages. In contrast in PFC the ratio rose significantly from prepubertal to late-pubertal and from late-pubertal to adult ages. For PV neurons the ratio increased across all ages. Both in V2 and PFC the increases were similar from neonatal to prepubertal ages.\n\nConclusions: Findings for GABRA1/GABRA2 mRNA trajectories in layer 3 pyramidal neurons support the hypothesis that V2 achieves adult levels of expression earlier than PFC. However these findings appear to be specific to pyramidal neurons as they were not detected in PV neurons. This difference suggests that vsWM abnormalities and possible schizophrenia risk related to GABA receptor expression levels may be cell type-specific.

First Author: Ryan Phillips
(Postdoctoral)

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Mentor/Lab: Rubin

Department: Mathematics

Poster Session: PM
Location: 36

Category:
Systems

Title: Short-term Plasticity of GABAergic Synapses in the Substantia Nigra Pars Reticulata

Summary: This work uses a data-driven computational model to explore the role of short-term synaptic dynamics in regulating neuronal activity in the substantia nigra pars reticulata a primary output nuclei of the basal ganglia.

Abstract: The substantia nigra pars reticulata (SNr) is one of the primary output nuclei of the basal ganglia (BG) and receives converging synaptic inputs from the direct and indirect pathways. Due to this convergence the SNr is thought to be important structure that integrates and relays encoded behavioral information from upstream structures within the BG. \n\nConsistent with this idea abnormal activity within the SNr is associated with parkinsonian symptoms seizures and impaired decision making. Therefore understanding how the SNr integrates inputs from these two pathways may be critical for understanding basal ganglia function. \n\nThe projections from indirect and direct pathways form synapses at distinct locations on SNr neurons and are known to undergo short-term plasticity. Striatal neurons of the direct pathway preferentially form synapses on the distal dendrites of the SNr neurons and undergo synaptic facilitation (12). In contrast neurons from the external segment of the globus pallidus of the indirect pathway form basket-like synapses around the somas of SNr neurons and undergo synaptic depression (13). The functional significance of the location of these synapses is unclear; however these spatial characteristics may influence their short-term plasticity properties. GABAA synapses are prone to breakdown of the reversal potential (EGABA) mediated by increases in the intracellular Cl- concentration [Cl-]i (4). Due to the differences in size and in the distribution of the Cl- extruder KCC2 we hypothesize that dendritic and somatic compartments may have different susceptibilities to breakdown of EGABA which may contribute to differences in the properties of direct and indirect pathway synapses on SNr neurons.\n\nTo test this hypothesis we constructed a novel conductance-based model of an SNr neuron with dendritic and somatic compartments. After establishing that the model's dynamics matches a range of experimental observations on SNr firing patterns we used the model to investigate the effects of [Cl-]i dynamics on EGABA and short-term synaptic plasticity. We show that GABAA- and KCC2-mediated fluctuations in [Cl-]i can explain many aspects of the short-term plasticity seen with GABAergic inputs from the direct and indirect pathways in the SNr. Integration of GABAA receptor-mediated synaptic inputs to somatic and dendritic compartment is not unique to SNr neurons and therefore these results may have implications for other brain regions. \n\n\n\n1) Connelly William M. et al. "Differential short-term plasticity at convergent inhibitory synapses to the substantia nigra pars reticulata." Journal of Neuroscience 30.44 (2010): 14854-14861.\n2) Von Krosigk M. et al. "Synaptic organization of GABAergic inputs from the striatum and the globus pallidus onto neurons in the substantia nigra and retrorubral field which project to the medullary reticular formation." Neuroscience 50.3 (1992): 531-549.\n3) Smith Y. and J. P. Bolam. "Convergence of synaptic inputs from the striatum and the globus pallidus onto identified nigrocollicular cells in the rat: a double anterograde labelling study." Neuroscience 44.1 (1991): 45-73.\n4) Raimondo Joseph Valentino Henry Markram and Colin J. Akerman. "Short-term ionic plasticity at GABAergic synapses." Frontiers in Synaptic Neuroscience 4 (2012): 5.

First Author: Kathryn Rothenhoefer
(Graduate)

Presenting Author: Kathryn Rothenhoefer
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Mentor/Lab: Stauffer

Department: Neurobiology

Poster Session: PM
Location: 37

Category:
Systems

Title: Rare Rewards Enhance Dopamine Prediction Error Responses

Summary: Rare rewards disproportionately affect behavior likely through neural learning mechanisms. Here we show they enhance dopamine reward prediction error responses a well-known neural teaching signal. This effect on dopamine neurons may be the neural basis for the amplified psychological effects of rare events.

Abstract: Rare events can be highly salient and they often have an exaggerated effect on behavior. The neural mechanisms for such behavioral effects are not known but likely involve neural learning signals such as the phasic responses of dopamine neurons. Phasic dopamine responses code for reward prediction errors (RPEs). According to the standard reinforcement learning account of dopamine responses RPEs are calculated as the value of received rewards minus the average (mean) value of prior outcomes. Thus the predicted value is simply formalized as the mean of past outcomes. This formalism does not account for the higher statistical moments (variance skewness kurtosis etc.) of reward outcome distributions. Here we set out to investigate if the 'shape' of reward-size distributions influences the responses of dopamine neurons. In particular we held the RPE constant while we manipulated the probability of rewards drawn from the tails of reward size distributions. In a simple reward prediction task dopamine neurons responded more strongly to rewards that were delivered infrequently than to identical rewards delivered more regularly. This difference persisted even when the mean of past outcomes was identical. Furthermore this difference could not be adequately explained by shifting the mean – which would occur if the animals assigned different subjective values to the different reward-size distributions. Thus rare rewards appear to enhance the dopamine prediction error response. This result suggests that the activity of dopamine neurons reflects higher moments of reward outcome distributions. In a corresponding choice task the rate at which animals learned the mean reward value was dependent on the shape of the reward size distributions. The enhanced response of dopamine neurons to rare rewards may underlie this differential learning rate and provides a candidate neural mechanism to explain the exaggerated effects of rare events on behavior.

First Author: Christopher Cover
(Graduate)

Presenting Author: Christopher Cover
(Graduate)

Mentor/Lab: Vazquez

Department: Radiology

Poster Session: PM
Location: 38

Category:
Imaging

Title: Optimizing Dynamic Changes in Neuronal and Hemodynamic Connectivity Calculated in Awake Mice Expressing GCaMP

Summary: Even at rest the brain has been shown to be functionally active with communication occurring between regions that change in states of disease. Accurately capturing this information has required optimized algorithms capable of inferring neuronal activity with minimal data. This project explores the parameters required for two algorithms sliding window correlation and dynamic conditional correlation algorithms to accurately capture dynamic neuronal activity from regional blood flow in a mouse's brain.

Abstract: Algorithms like sliding window correlation (SWC) and dynamic conditional correlation (DCC) have emerged to examine complex fluctuations in information flow across brain regions during resting-state functional magnetic resonance imaging (rs-fMRI). Since the fMRI BOLD signal (blood oxygen level dependent) indirectly represents neuronal activity it is necessary to determine the minimum temporal and spatial scales to which BOLD data can inform researchers and clinicians about neuronal connectivity. In this study we investigated the temporal properties in which short dynamic changes in the hemodynamic connectivity captures short dynamic changes in neuronal connectivity. Wild field optical mapping (WFOM) simultaneously captured 5-minutes of resting-state neuronal and OIS-BOLD activity in six transgenic GCaMP3 awake mice. Data analysis consisted of dynamic functional connectivity (DFC) calculations performed between brain regions within the imaging modality. To compare correspondence between GCaMP and OIS-BOLD DFC measurements temporal coherence was calculated by testing for significant relationships between the correlation coefficients of the same node-pairs (15 node-pairs t>2.2 or r>0.5 for p<0.05). To determine the impact of noise on GCaMP and BOLD DFC calculations the time-series data was systematically filtered at and temporally binned for SWC and DCC respectively. To determine the minimum window size to capture DFC for SWC window size was systematically varied. Dynamic analysis of OIS-BOLD and GCaMP data for SWC and DCC showed a trend of higher frequency data inclusion (5-2.5 Hz) resulting in a greater degree of connectivity between hemodynamic and neural activity achieving significance (r>0.5) at smaller windows (5-35's) and bin sizes (2-5 data points) than low frequency data (0.5-0.1 Hz; 35-50's and 10-50 data points respectively). Preliminarily we have shown that inclusion of higher frequency OIS-BOLD data more reliably captures neuronal activity at small-window sizes with an optimal window length for SWC between 5-35's and temporal sampling of 2-5Hz (binning 2-5) for DCC.

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(Graduate)

Presenting Author: Matthew Bambino
(Graduate)

Mentor/Lab: Jacob

Department: Pharmacology, Chemical Biology

Poster Session: PM
Location: 39

Category:
Imaging

Title: Diazepam Down-regulates Gephyrin Scaffolding and Reduces Synaptic Availability of α2γ2 GABAARs

Summary: Benzodiazepines (BZD) are prescribed clinically in the treatment of seizure disorders anxiety and insomnia to calm down the brain by working with the inhibitory neurotransmitter gamma-aminobutyric acid (GABA); however individuals quickly develop drug tolerance. Here we studied the classical BZD diazepam (DZP) and its effects on how the GABA type A receptor (GABAAR) moves around the cell and is assembled. We found that exposure to DZP decreases the expression of a key scaffolding protein called gephyrin and reduces the availability of GABAARs that readily bind BZD both of which likely contribute to drug tolerance.

Abstract: Benzodiazepines (BZD) are prescribed clinically in the treatment of seizure disorders anxiety and insomnia as they potentiate the inhibitory actions of the neurotransmitter gamma-aminobutyric acid (GABA). BZD bind and positively modulate the heteropentameric GABA type A receptor (GABAAR) at the interface of the γ2 subunit with adjacent α1 2 3 or 5 subunits. Unfortunately the duration of BZD efficacy is critically hampered by tolerance with mechanisms that remain poorly understood. Prior work from the lab showed a significant decrease in α2 subunit containing GABAARs and enhanced lysosomal targeting in neurons within 24 h of BZD treatment. In contrast using immunofluorescence and biochemical experiments we found that treated with the classical BZD diazepam (DZP) presented no substantial change in surface or synaptic levels of γ2-GABAARs. However both γ2 and the post-synaptic scaffolding protein gephyrin showed diminished total protein levels following a single DZP treatment in-vitro with enhanced phosphorylation of gephyrin Ser270 and increased generation of gephyrin cleavage products. Moreover we found DZP simultaneously enhanced synaptic exchange of both γ2 containing GABAARs and gephyrin using fluorescence recovery after photobleaching techniques. Together these findings implicate specific downregulation of assembly and surface trafficking of α2γ2 GABAAR. To address this question we developed and used live-imaging and florescence resonance energy transfer (FRET) measurements of surface localized α2γ2 GABAAR. FRET measurements using a donor α2 pH-sensitive green fluorescent protein (α2pHGFP) and acceptor fluorescently tagged γ2Cherry showed a reduction in surface trafficked receptors. Validation of FRET measurements included acidic saline (MES) perfusion washes to quench surface membrane fluorescence of α2pHGFP and subsequent NH4Cl washes (pH 7.4) to restore synaptic puncta and reveal intracellular pools of α2γ2 GABAARs. As an additional control we used β3pHGFP (donor) and β3Cherry (acceptor) measurements to confirm FRET efficacy within a receptor as it is critically dependent on distance. FRET from two non-adjacent β subunits was drastically decreased compared to α2γ2 FRET emissions as a result of increased distance. Thus DZP exposure elicits down-regulation of gephyrin scaffolding and reduces synaptic availability of BZD sensitive GABAAR via multiple trafficking processes likely contributing to drug tolerance.

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Presenting Author: Yasin Karimi
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Mentor/Lab: Chamanzar - cmu

Department: Electrical and Computer Engineering, CMU

Poster Session: PM
Location: 40

Category:
Imaging

Title: In situ Ultrasonically Tunable Virtual Relay Lens for Non-invasive Micro-endoscopy

Summary: In this work we exploited ultrasonic waves generated by a ultrasonic phased-array to perform deep optical imaging in scattering media. As an alternative to invasive implantable endoscopes we developed and demonstrated experimentally in biological tissue phantoms the effectiveness of a non-invasive tunable virtual relay lens. Moreover we showed reconfigurable light patterning in turbid media (up to optical thicknesses of ~ 52 MFP).

Abstract: We present a novel technique for sculpting tunable virtual optical relay lenses in a medium by using acoustic interference patterns. Ultrasonic waves generated by a cylindrical piezo-transducer array alter the local density of modulated medium thus sculpting a refractive index contrast profile in situ that modulates the phase front of light wave similarly to a graded-index lens. Optical parameters of the virtual lens such as numerical aperture and focal length can be dynamically tuned by controlling the amplitude of the driving signal. We experimentally demonstrate the effectiveness of this method in relaying microscopic images (minimum feature size = 22 μm) through transparent and scattering media including biological tissue phantoms where the sculpted lens counteracts the effect of scattering. The results prove that this technique can be used for optical imaging and light delivery through optically thick media without peer thus serving as a unique non-invasive alternative to commonly used invasive implantable endoscopes. We furthermore demonstrate the phase front of the incoming optical waves can be modulated to focus light in multiple points deep into the medium to form arbitrary patterns of light illumination as well as multipoint parallel imaging. These patterns can be reconfigured by changing the ultrasound interference pattern e.g. by exciting higher-order azimuthal modes of the ultrasonic array. An incident beam of light can be fragmented into multiple beamlets and the formed discrete shapes can be reconfigured in real-time by controlling the frequency and phase of the ultrasound array elements. In this work we demonstrate experimentally that this technique can be used to perform high-throughput imaging in turbid media. We have experimentally shown active light patterning in tissue phantom with the optical thickness of 52 MFP.

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Mentor/Lab: Luna

Department: Psychology

Poster Session: PM
Location: 41

Category:
Imaging

Title: Striatal hyper-activation underlies adolescent substance use risk: a functional nueroimaging meta-analysis

Summary: The current project integrated data from 22 brain imaging studies and determined that adolescents who show increased activity in brain regions supporting reward and motivation may be at increased risk for problematic substance use.

Abstract: Prominent neurodevelopmental theories suggest adolescent substance use risk is driven by an enhanced reward drive mediated by the ventral striatum and poor inhibitory control mediated by lateral prefrontal cortex. Here we formally test this 'dual risk' model by performing a meta-analysis of 22 functional neuroimaging studies representative of approximately 1080 subjects (484 female mean age = 16.06).\n\nCoordinates of activation differences (N=179) associated with adolescent substance use risk (family history of substance use disorder and prospective prediction of initiation and escalation) were extracted from studies identified through a systematic literature search (PubMed Google Scholar Scopus). Multilevel kernel density analysis was used to identify brain regions most consistently associated with adolescent substance use risk. Implicated neurobehavioral systems (RDoC Matrix version 4) were quantified through spatial similarity with neurosynth concept maps. \n\nResults showed that risk groups were most reliably differentiated by activation differences in the pre-SMA associated with the RDoC subconstruct of 'monitoring' and the striatum (dorsal and ventral) associated with the RDoC subconstruct of 'reward'. Follow-up analyses revealed at-risk adolescents had hyper-activation in the striatum while cortical areas were inconsistent in the sign of activation difference. No significant activation differences were observed in lateral prefrontal cortex nor did any results implicate the RDoC subconstruct of 'response inhibition'\n\nChallenging current 'dual-risk models' these results suggest striatal hyper-activation and reward-reactivity is the primary feature of adolescent substance use risk with relatively less contribution from cortical regions supporting inhibitory control.

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(Faculty)

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Mentor/Lab: Vogt

Department: Anesthesiology

Poster Session: PM
Location: 42

Category:
Imaging

Title: Modulation of human memory by midazolam and ketamine during painful stimulation

Summary: Summary: We investigated memory encoding of auditory items paired or not paired with acute painful stimuli under midazolam (Mdz) and ketamine (Ket) using fMRI in humans. Pain did not significantly affect recognition memory but both drugs impaired but did not eliminate recognition memory which was more pronounced for Mdz compared to Ket. Preliminary fMRI analyses suggested that both drugs modulate activity in the hippocampus and amygdala.

Abstract: Introduction: The interacting effects of anesthetics and acute pain on memory encoding have not been well-characterized. There is evidence that amygdala (fear) activity is not blocked by anesthetics while viewing aversive images [1]. We investigated memory encoding of auditory items paired or not paired with acute painful stimuli under midazolam (Mdz) and ketamine (Ket) using fMRI in humans. We hypothesized that both agents would blunt learning and impair memory encoding. We also sought to determine brain areas that mediate memory encoding for these distinct agents.\n\nMethods: These preliminary data include 11 healthy adults (6 male) mean (sd) age = 24.7 (4.1) years. MRI scanning was at 3 T 1 s temporal resolution. A list of 90 words was played 3 times (random order) and participants classified each (e.g. alive or not) while response times (RTs) were recorded. Thirty of the words were consistently followed by a 1 s painful (rated 7/10) electrical stimulation. Either drug was then administered via target-controlled infusion to effect-site concentrations expected to be equi-amnestic. The same experimental procedures were repeated with a new word list. During next-day memory testing accuracy and confidence in recognition were determined [2] and these responses were tabulated for each experimental condition. Preliminary group average fMRI maps were generated using SPM 12.\n\nResults: Compared to saline RTs were slowed by Mdz and further slowed by Ket (Figure 1). There was a significant interaction between pain and anesthetic with different pain vs. non-pain RT time profiles seen under Ket and Mdz compared to saline. Pain did not significantly affect recognition memory (Figure 2) so results were collapsed across pain condition. Both drugs impaired but did not eliminate recognition memory which was more pronounced for Mdz compared to Ket. Preliminary fMRI analyses suggested that both drugs modulate activity in the hippocampus and amygdala. \n\nDiscussion: We have developed an experimental framework for assessing the influence of pain on learning and memory at baseline and under sedation. We describe preliminary behavioral and neuroimaging effects for two drugs. Additional data should allow more definitive conclusions for the interacting effects of acute pain and distinct anesthetics on human memory.

First Author: John Wu
(Postdoctoral)

Presenting Author: John Wu
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Mentor/Lab: Escolar

Department: Pediatrics

Poster Session: PM
Location: 43

Category:
Imaging

Title: Histopathological findings confirm in vivo diffusion-MRI measurements in a Krabbe disease patient

Summary: One young patient with a neurodegenerative disease had an MRI exam shortly before her death and an autopsy short after her death. The results of the two exams are consistent and both show she had more disease burden in one brain region than the other.

Abstract: Introduction: There have been some doubts about the ability of in vivo MRI to assess myelination in human brains. In this work we aim to address this concern by comparing quantitative diffusion-based MRI measurements with postmortem histopathological findings in one Krabbe disease patient. Krabbe disease is a pediatric leukodystrophy where diffusion MRI has shown some promise to evaluate the white matter integrity. In this case study the patient received disease-modifying umbilical cord blood transplantation at a young age and received autopsy shortly after the MRI scan. In the context of neurodegeneration in Krabbe disease lower fractional anisotropy (FA) derived from MRI indicates disorganization of myelin sheath and lower level of normal myelin.\n\nMethod: Diffusion tensor imaging (DTI) was obtained on a 16-year-old female Krabbe patient two weeks before her death. Alignment of the patient DTI image to a normal atlas was performed such that four white matter tracts could be delineated (left and right corticospinal tracts via internal capsule genu and splenium of the corpus callosum). FA measures were calculated along these specific tracts and compared with a population of 6-year-old normal children. The formalin-fixed right hemisphere of the postmortem brain was serially sectioned in the coronal plane and representative sections of the white matter were stained with Luxol Fast Blue to assess myelination status. \n\nFindings: The findings from MRI and histopathology are shown in the figures below (left panel: corticospinal tract; right panel: posterior corpus callosum). The corticospinal tract showed moderate to severe reduction in density of myelinated axons and accordingly low FA values compared to normal. The posterior corpus callosum had better preserved myelinated axons and relatively high FA values.\n \nConclusion: In this case study we were able to demonstrate that the quantitative DTI-based measures along specific white matter tracts were consistent with histopathological examination of the myelin level. The corticospinal tract had more severe reduction in myelin as indicated by the FA values and the myelin stain as compared to the posterior corpus callosum. This evidence enhances the validity of using MRI in assessing the white matter integrity in the context of a pediatric neurodegenerative disease.

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Mentor/Lab: Kozai

Department: Bioengineering

Poster Session: PM
Location: 44

Category:
Technology & Techniques

Title: Microelectrode implantation induces pericyte reactivity and vascular bed reorganization as revealed by two-photon microscopy

Summary: Neural electrode implantation in the brain induces tissue responses that can alter device performances and function. Following electrode insertion in the mouse cortex in vivo fluorescent imaging was used to observe changes in the dynamics of pericytes which are cells that reside along brain vessels and are responsible for blood-brain barrier maintenance. Changes in pericyte behavior as well as structural changes to the vascular bed were observed in response to electrode implantation providing further insight into the dynamics of the foreign body response commonly elicited from neural interfaces.

Abstract: Integration of neural interfaces with minimal tissue disruption in the brain is ideal to develop robust tools that can address essential neuroscience questions and combat neurological deficiencies. However implantation of intracortical devices provokes severe tissue inflammation which requires a high metabolic demand to support a complex series of cellular events mediating tissue degeneration and wound healing. Pericytes peri-vascular cells involved in blood-brain barrier maintenance vascular permeability waste clearance and angiogenesis have recently been implicated as significant participators in neurodegenerative disease. While the intimate relationship between pericytes and the vascular bed have been explored under other diseased states its behavior following microelectrode implantation which is responsible for direct blood vessel disruption and permeability is currently unknown. Using two-photon laser scanning microscopy NG2+ vascular pericytes labeled by a red fluorescent reporter (Cspg4-Ds.Red) were observed during microelectrode implantation. Non-functional 4-shank microelectrode probes were inserted into the adult mouse cortex and imaged every 12 hours for a minimum of 2 weeks following insertion. Reactive changes in pericyte morphology and structural changes to the vascular bed were monitored around implanted electrode shanks. No obvious changes were noted in pericyte structure within the first 24 hours following insertion. Over time morphological deformations in pericyte soma coincided with the formation of new blood vessels within the vicinity of the electrode. These new blood vessels displayed a significantly larger diameter compared to pre-injury capillaries indicating an increase in blood flow perfusion following microelectrode implantation. Beginning 5-7 days following injury fluorescent pericyte coverage of the tissue area surrounding the electrode increased independent of angiogenesis suggesting potential encapsulation of the device. Preliminary data suggests that alterations in the physiological behavior of vascular-bound pericytes is attributed to insertion of a microelectrode array. Since pericytes are important facilitators of blood-brain barrier restoration it is possible their reactivity is induced by vasculature damage sustained during implantation. These novel insights on the fluctuating tissue dynamics around neural interfaces within the brain provide an additional framework for analysis in an effort to improve long-term device stability and performance.

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(Graduate)

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Mentor/Lab: Chamanzar - cmu

Department: ECE

Poster Session: PM
Location: 45

Category:
Technology & Techniques

Title: Parylene Waveguide Neural Probes for Optogenetic Stimulation

Summary: To be able to fully understand the brain neuroscientists need a toolset for direct light delivery to illuminate neuron clusters. High-density neural probes fabricated in rigid substrates such as Silicon are able to perform this function but the mechanical mismatch between the device and surrounding tissue results in inflammation and glial scarring and hence reduced performance over time. Here we demonstrate optical neural probes fabricated in the flexible and biocompatible polymer Parylene C which hold the promise of chronic interfacing with the brain for high resolution light delivery to stimulate and image neurons.

Abstract: A full understanding of brain function requires a neural interfacing platform capable of single unit stimulation and recording of individual neurons in a neural circuit for which high-density compact optical neural probes using waveguides to deliver light are a promising solution. Currently available optical waveguide probes use rigid materials and substrates such as Silicon Silicon Nitride and Oxides. However these rigid probes lose performance over time due to glial encapsulation resulting from their mechanical mismatch with the surrounding tissue. A flexible biocompatible polymer-based optical waveguide platform is desired to minimize tissue damage during chronic implantation. We demonstrate for the first time a flexible high-density array of optical waveguides made entirely in biocompatible polymers Parylene C and PDMS ($\Delta n = 0.239$) for light delivery deep into tissue. Unlike traditional end-firing optical neural probes our waveguides utilize integrated micromirrors to achieve 90-degree input/output coupling for illumination volumes orthogonal to the probe axis. The waveguide platform is compact (5 – 30 μm) < 5 dB/cm (at

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Mentor/Lab: McClung

Department: Psychiatry

Poster Session: PM
Location: 46

Category:
Technology & Techniques

Title: Using Optogenetics to Determine the Role of the Suprachiasmatic Nucleus in Mood Regulation

Summary: Disruptions in circadian rhythms rhythms that repeat approximately every 24 hours commonly occur in people with mood disorders. The suprachiasmatic nucleus (SCN) in the brain drives and synchronizes bodily rhythms but it is unclear whether perturbing SCN neural activity affects mood. Here we are studying the mood-like effects of dampening or advancing SCN activity in mice.

Abstract: Individuals suffering from mood disorders often display circadian rhythm disruptions including dampened and/or phase shifted rhythms. Recent work indicates that disrupting molecular rhythms in the suprachiasmatic nucleus (SCN) affects mood-like behavior suggesting that the SCN plays a causal role in mood disorders. However it is unknown whether disrupting SCN neural activity rhythms affects mood or anxiety-like behaviors. Here our goal was to determine whether chronically dampening or advancing SCN neural activity rhythms affects depression and anxiety-like behavior. Channelrhodopsin-2 (ChR2) expression in the SCN was obtained by crossing mice expressing Cre recombinase in GABAergic neurons with mice expressing Cre-dependent ChR2. Optic fibers were implanted above the SCN and mice were individually housed to measure activity and/or body temperature rhythms by telemetry or piezoelectric sensors. To determine the effects of SCN-mediated dampening of rhythms we unpredictably stimulated (1 h 10 ms pulse width 8 Hz) the SCN during the dark phase. To determine the effects of chronically advancing rhythms free-running mice received 1 h stimulations every three days late (CT21) into their active phase. Depression and anxiety-like behaviors were assessed using a battery of tests. Unpredictable stimulation of the SCN during the dark phase dampened the amplitude of activity and body temperature rhythms. Interestingly chronic unpredictable stimulation of the SCN during the dark phase increased anxiety-like behavior. Stimulating the SCN at CT21 decreased the period of activity rhythms. Chronic stimulation at CT21 also dampened the amplitude of rhythms. Consistent with the unpredictable stimulations correlations were observed between the amplitude of rhythms and behavior in chronically phase-advanced mice. Overall our findings thus far suggest that dampened SCN neural activity rhythms increase anxiety-like behavior. Ongoing studies will determine the effects of chronically delaying SCN neural activity rhythms.

First Author: Jordan Williams
(Postdoctoral)

Presenting Author: Jordan Williams
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Mentor/Lab: Schwartz

Department: Systems Neuroscience Institute

Poster Session: PM
Location: 47

Category:
Technology & Techniques

Title: Prolonged functional optical sensitivity in non-human primate motor nerves following Cyclosporine-based immunosuppression and AAVretro-mediated expression of ChR2

Summary: Peripheral optogenetics presents a gene therapy that allows us to stimulate muscle activity with light rather than traditional electrical stimulation. While this approach has potential benefits over electrical stimulation for patients with disorders such as spinal cord injury in restoring their ability to move their own muscles a patient's own immune system may actually fight this gene therapy rendering it ineffective. In this work we present a simple approach to dampen the immune system in order to prolong the utility of this gene therapy in a monkey model.

Abstract: Peripheral optogenetic stimulation of motor activity offers enticing advantages over traditional functional electrical stimulation for the purposes of reanimating paralyzed muscles. When facilitated by intramuscular injection of viral gene therapy constructs however the process of transducing light sensitive ion channels along motor nerves faces several challenges including uptake of the virus at the neuromuscular junction as well as evasion of both virus and expressed gene products from the immune system. These hurdles to successful peripheral motor gene therapy are often amplified when attempting to translate these techniques to non-human primates. In this study we examined the efficacy of a systemic immunosuppression regimen and use of a designer adeno-associated virus (AAV) variant in prolonging functional opsin expression in targeted peripheral nerves of a macaque. Using a simple regimen of daily oral cyclosporine and either an intramuscular or intraneural injection of AAVretro-hSyn-ChR2-GFP we observed functional intraneural expression of ChR2 via EMG activity locked to optical stimulation of a targeted nerve for up to 24 weeks post-injection. Throughout this experiment we observed a gross timeline of expression including an initial increase of ChR2 expression over 9-13 weeks followed by an eventual decline after cessation of the immunosuppression regimen. These preliminary results suggest a potential strategy for successful translation of peripheral motor gene therapy to human subjects as well as motivation for further investigation validation and refinement of this immunosuppression regimen and viral vector.

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Department: Electrical and Computer Engineering

Poster Session: PM
Location: 48

Category:
Technology & Techniques

Title: Steeltrode: A Hybrid Parylene- Stainless steel Probe for Recording from Non-human Primate Brain

Summary: Given the similarity to the human brain study of Non human primate (NHP) brains is important for understanding brain function in humans. However realizing probes suitable for recording neuronal activity in an NHP brain poses an engineering challenge due to the material strength required to insert a long and narrow probe into brain tissue not achievable due to the brittleness of Silicon- a common material platform for neural probes. We are presenting our work on developing mass producible high density probes in hybrid Parylene-stainless steel platform which offers remarkable mechanical and chemical properties particularly suitable for NHP probes.

Abstract: To understand the neural basis of brain function the ability to record from neurons across different brain areas with high spatiotemporal resolution is fundamentally important. While there has been significant recent improvements in the design of high-density probes for rodents recording from a non-human-primate (NHP) brain is still limited to recording using low density hand assembled and expensive neural probes. Most rodent neural probes are based on Silicon which is a well-developed material platform for neural interfaces. However given the brittleness and fragility of Silicon it not suitable for NHP probes which require mechanical strength during insertion into deep cortical regions of the brain. Compared to Silicon stainless steel has higher durability modulus of resilience and bio-compatibility which makes it a promising material platform for NHP probes. However micromachining of stainless steel has not been developed as much as Silicon microfabrication which benefits from decades of academic and industrial research. For this reason the commercially available stainless steel probes are mostly manually assembled and therefore are constrained in terms of channel density and process throughput and yield. In this work we discuss a novel microfabrication process to realize lithographically-defined thin-film on stainless steel substrate probes. We designed 4-12 cm long and 250 μm wide neural probes with 30-128 low impedance channels in a hybrid stainless steel and Parylene C platform.Our long form factor probes realized through highly scalable high-throughput process are capable of large-scale high-resolution recordings from deep seated brain areas in NHPs which can potentially enable development of novel therapeutic and clinical interventions for human.

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(Graduate)

Presenting Author:
()

Mentor/Lab: Ghuman

Department: Psychology

Poster Session: PM
Location: 49

Category:
Technology & Techniques

Title: Intracranial EEG recordings from face-selective temporal cortex show enhanced response to contralateral face information

Summary: Seeing a face activates the brain most strongly in portions of the right hemisphere, but the time course of neural activity in both halves of the brain is not well understood. We worked with 8 epilepsy patients to record brain activity from electrodes directly implanted into their brain while they viewed images of face halves on the right or left side of a computer screen. Our results show that both sides of the brain respond most strongly to images of faces that are located in the opposite part of the visual field, i.e. face information in the left half of the visual field will quickly drive activity in the right hemisphere of the brain.

Abstract: Despite behavioral and neuropsychological evidence for a right hemisphere bias for face processing, and a corresponding left hemifield advantage for faces, neurally much remains unknown about the division of labor in face processing between the right and left fusiform. In particular, there remain gaps in our understanding of the role of bilateral face-selective areas in contributing to dynamic representation of face information. To clarify the effects of visual hemifield on bilateral fusiform dynamics, we recorded intracranial encephalography (iEEG) data from 8 patients with electrodes placed directly on right and/or left face-selective temporal cortex. While fixating, participants completed a gender discrimination task in response to 16 face halves presented individually to the right or left of fixation. Using the local field potential (LFP), we found that electrodes placed in both right and left temporal cortex show an enhanced response to face halves presented in the contralateral visual hemifield. This difference between contra- and ipsilateral face halves emerges within the first 50 ms after stimulus presentation, with both fusiform hemispheres showing an early peak at ~160 ms. We further examine these dynamics by using a machine learning classifier to decode face identity, showing that identity decoding between contralateral face halves is enhanced and earlier occurring when compared to ipsilateral face halves. Together, these results highlight both early and persistent differences in the hemispheric representational dynamics of face processing based on visual hemifield of stimulus presentation.

First Author: Matthew Boring
(Graduate)

Presenting Author:
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Mentor/Lab: Ghuman

Department: Neurological Surgery

Poster Session: PM
Location: 50

Category:
Technology & Techniques

Title: Cross-validating source localized MEG and iEEG using single trial decoding of fine-grained information processing dynamics in the fusiform gyrus during visual perception

Summary: Magnetoencephalography (MEG) is a non-invasive brain imaging modality that captures the magnetic fields generated by groups of neurons inside the brain. However, the sensitivity of MEG and its accuracy in determining what part of the brain a signal is coming from has been debated. This work demonstrates that MEG has remarkably high sensitivity to subtle brain activity and can be used to localize where these signals are originating, which makes it an excellent tool for studying neurological diseases.

Abstract: Previous studies have demonstrated the agreement between magnetoencephalography (MEG) and intracranial electroencephalography [iEEG] data when localizing epileptic foci, as well as the course spatial and spectral similarity of simultaneously recorded MEG and iEEG data during reading. However, little work has been done to determine if subtle information processing dynamics captured by single trial decoding in the ventral visual stream by source-localized MEG and iEEG data are conserved across modalities and subject populations. This work sought to determine the similarity of these signals by applying multivariate decoding to task-related MEG data source-localized to the fusiform gyri in healthy participants and iEEG data recorded from fusiform gyri of patients with intractable epilepsy. Using both word and face stimuli, we show that MEG data source-localized to the left and right fusiform gyri corroborates our previous iEEG findings. MEG and iEEG both demonstrated similar dynamic shifts in which stimuli could be decoded from each other during the trial. For example, when decoding individual words from activity anatomically and functionally localized to the visual word form area, visually dissimilar words could be decoded at approximately 150-250 ms, while visually similar words could not be decoded until 250-350 ms in both MEG and iEEG. Also, when decoding emotion from activity anatomically and functionally localized to the left and right fusiform face area, an early and late peak in decoding accuracy (at approximately 150-250 and 250-350 ms) was found in both MEG and iEEG, though iEEG was able to show that these two peaks localized to different parts of the fusiform. The results from both experiments argue for temporally distinct stages of processing in the ventral visual stream, the first involving a gist-level representation of visual stimuli and the second more fine-level representation. The agreement between MEG and iEEG data demonstrates the sensitivity of MEG to task-induced changes in neural activity, the similarity of these changes in neural signals between MEG and iEEG, and the spatial correspondence of these effects in source-space. Despite these similarities, iEEG was more sensitive to task-induced changes in activity, which manifested as increased decoding accuracy, and had a higher spatial resolution, which manifested as separability decoding timecourse at mid- versus posterior fusiform electrodes, but not in the MEG fusiform sources. Taken together, this study shows that MEG and iEEG are valuable complimentary tools: MEG being useful to generalize iEEG results to larger, healthy populations and iEEG useful for increasing the signal to noise ratio and spatial resolution of MEG findings.

First Author: Jianjun Meng
(Postdoctoral)

Presenting Author: Jianjun Meng
(Postdoctoral)

Mentor/Lab: He

Department: Biomedical Engineering

Poster Session: PM
Location: 51

Category:
Technology & Techniques

Title: 3-dimensional Brain-computer Interface Control through Simultaneous Overt Spatial Attentional and Motor Imagery Tasks

Summary: Through the combination of the two strategies (motor imagery MI and overt spatial attentional modulation OSA) a substantial portion of the recruited subjects were capable of robustly controlling a virtual cursor in 3D space by a noninvasive electroencephalography (EEG) based brain-computer interface.

Abstract: It is of significance and great interest to move the noninvasive electroencephalography (EEG) based brain-computer interface (BCI) beyond the one-dimensional (1D) or two-dimensional (2D) controls. The conventional motor imagery based modulation of brain rhythms provides relatively easy and intuitive way for 1D or 2D controls however three-dimensional (3D) control or even beyond is challenging based on solely motor imagination. 3D BCI control is vital for efficient robotic arm or prosthetic control. In this study we propose a paradigm based on parietal brain rhythm modulation named overt spatial attentional (OSA) orientation and combine this paradigm with the conventional motor imagination (MI) to formulate a novel 3D BCI control based on endogenous EEG modulation. OSA modulation was shown to provide comparable control to conventional MI modulation in both one- and two- dimensional tasks. Furthermore this work provides evidence for the functional independence of traditional MI and OSA as well as an investigation into the simultaneous use of both. Using this newly proposed BCI paradigm sixteen participants successfully completed a 3D eight target control task. Nine of these subjects further demonstrated robust 3D control in a twelve target task significantly outperforming the information transfer rate achieved in the 1D and 2D control task (29.7±1.6 bits/min). Through the combination of the two strategies (MI and OSA) a substantial portion of the recruited subjects were capable of robustly controlling a virtual cursor in 3D space. The proposed novel approach could broaden the dimensionality of BCI control and shorten the training time.

First Author: Maxwell Wang
(Graduate)

Presenting Author: Maxwell Wang
(Graduate)

Mentor/Lab: Ghuman

Department: Neurosurgery

Poster Session: PM
Location: 52

Category:
Technology & Techniques

Title: Effect of Deep Brain Stimulation on Cortical Connectivity

Summary: Deep brain stimulation (DBS) is an effective and increasingly popular method of treating various brain pathologies and has become a widely used standard of care for advanced Parkinson's disease and other movement disorders if pharmacological treatments are ineffective. However its mechanism and effects on the brain remain largely unknown. Here we utilize magnetoencephalography recordings and graph theoretical analysis to measure network-level differences in cortical activity between when the deep brain stimulation is on and when it is off in these patients.

Abstract: Deep brain stimulation (DBS) is an effective and increasingly popular method of treating various brain pathologies and has become a widely used standard of care for advanced Parkinson's disease and other movement disorders if pharmacological treatments are ineffective. However its mechanism and effects on cortical activity remain largely unknown. Clinically understanding its neural effects can help direct efforts to optimize symptom management while minimizing side-effects. Scientifically DBS represents a unique opportunity to understand how information is propagated throughout the brain from a pertubation paradigm rather than an observatory one. Here we combine magnetoencephalography recordings from 11 individuals with DBS for treatment of Parkinson's disease or essential tremor and graph theoretical analysis to measure the network-level differences in cortical activity between when the deep brain stimulation is on and when it is off in these patients. The results show that DBS primarily modulates cortical response in the high beta frequency band (26-31 Hz) consistent with previous studies of DBS using intraoperative recordings while the electrodes are implanted. A network of regions that increase their connectivity in the high beta band in response to DBS were identified which include somatosensory and motor regions frontal regions and occipitotemporal regions. Taken together these results illustrate the therapeutic mechanism of DBS through modulation of the somatomotor system and potentially suggest a role for broader frontal and occipitotemporal regions in non-motor side effects of DBS. Future translational studies may try to leverage magnetoencephalography to tune DBS programming to maximize therapeutic effects by optimally modulating the somatomotor network and minimize side effects by reducing frontal and occipitotemporal response.

First Author: Otilia Stretcu
(Graduate)

Presenting Author: Mariya Toneva
(Graduate)

Mentor/Lab: Mitchell

Department: Machine Learning, CNBC

Poster Session: PM
Location: 53

Category:
Technology & Techniques

Title: Context Matters: Modeling Single Repetition Question-Answering in the Brain

Summary: It is a well-known fact in neuroscience that two presentations of the same stimulus do not elicit the same brain activation. We hypothesize that much of what is considered "noise" in single-repetition brain activity data is variation that can be explained given the right analytical tools. We propose a methodology that enables the study of the sources of variation across repetitions and use it to investigate how context affects brain activity recorded using MEG during a question-answering task.

Abstract: It is a well-known fact in neuroscience that two presentations of the same stimulus do not elicit the same brain activation. Often neuroscientists attribute these differences to "noise" in the signal of interest which they aim to remove by averaging across repetitions. Such averaging reduces the already-small sample sizes and limits the variability of stimuli in fixed-length experiments. We hypothesize that much of what is considered "noise" in single-repetition data is variation that can be explained given the right analytical tools. We propose a methodology that enables the study of the sources of variation across repetitions and use it to investigate how context affects brain activity recorded using MEG during a question-answering task. We find that 550−800ms post stimulus onset the differences in brain activity across repetitions correlate significantly with the differences in the contexts of these repetitions. We additionally show that incorporating information about the context of a stimulus improves the prediction of single-trial brain data by an average of 10% across subjects. Our work provides a framework to characterize the variation across single trials as an important step towards understanding how brain activity is generated.

First Author: Regina Calloway
(Graduate)

Presenting Author: Regina Calloway
(Graduate)

Mentor/Lab: Perfetti

Department: Psychology

Poster Session: PM
Location: 54

Category:
Learning

Title: A study the study: Individual differences in using indefinite and definite articles as cues for structure building

Summary: More- and less-skilled readers use indefinite (a/an) and definite article (the) cues differently for anticipating upcoming text information. The difference measured in an ERP component may stem from differences in adaptation to reading environments.

Abstract: Text comprehension requires integration of meanings within and across sentences. However sentence boundaries mark an occasion for the reader to begin a new structure—integration with prior meanings is not immediately required in the absence of a strong retrieval cue to a text segment in memory. In an ERP study we investigate a grammatical cue for integration the definite article. We varied whether definite (the) or indefinite articles (a/an) occurred at sentence-initial positions and whether the article was followed by a repeated noun. Evidence for lexical-semantic facilitation while reading a repeated noun was observed as a right-lateralized centro-parietal N400 effect. A left-lateralized N400 effect marked co-referential integration. An increased frontal LPC occurred when higher skilled readers encountered new nouns following indefinite articles. Reversing this pattern lower-skilled comprehenders showed increased positivity for repeated nouns after indefinite articles. Results show readers' sensitivity to cues for co-referential integration and new structure building that may be driven by differential adaptations to reading environments.

First Author: Xiaoping Fang
(Graduate)

Presenting Author: Xiaoping Fang
(Presenting Author Type)

Mentor/Lab: Perfetti

Department: Psychology

Poster Session: PM
Location: 55

Category:
Learning

Title: ERP evidence for rapid meaning access to newly learned words

Summary: Novel spoken words were paired with verbal definitions describing either action or non-action meanings.\nDifferences in ERPs between novel action and non-action words were first observed around recognition point suggesting a very early semantic category effect and rapid meaning access.

Abstract: Previous studies have shown that meaning access to novel words can become automatic especially after overnight consolidation. This is usually indicated by the emergence of semantic priming or interference between novel and existing words one or more than one day following the initial learning. The current study aimed to examine the automaticity of meaning access in a more direct way through observing ERPs to novel words that were assigned sensor-motor meanings. While previous studies have used pictures or videos to provide direct sensorimotor input we taught the novel words with definitions. Participants learned novel words associated with either action or non-action (i.e. static visual) meanings across multiple sessions of training over three days reaching ceiling performance in both cued-recall and recognition tests. On the fourth day they performed a meaning judgment task on novel words and existing words presented in auditory modality while ERPs were recorded. The results showed an early semantic effect among novel words as indicated by a larger negativity for action words than non-action words within N1 and P2 time windows. In contrast the effect emerged relatively later in existing words (after 300ms). Although novel words and existing words overall were indistinguishable before 500ms we observed larger frontal negativity and parietal positivity for novel words than existing words within 500-700ms. While the difference in the latency of semantic effects between novel and existing words is likely to be driven by the difference in the uniqueness point of spoken words the very early effect observed on novel words suggests that specific meaning features are activated rapidly (and arguably automatically) during the processing of the spoken word even though meanings had been learned through definitions. Furthermore episodic retrieval is involved when such activation is not sufficient to support confident meaning judgments about novel words.

First Author: Paola Hernandez-Chavez
(Postdoctoral)

Presenting Author: Paola Hernandez-Chavez
(Postdoctoral)

Mentor/Lab:

Department: Center for Philosophy of Science

Poster Session: PM
Location: 56

Category:
Learning

Title: Methodological Principles of Dysfunctions in Cognitive Neuroscience: How to Improve Them

Summary: 1. Facing difficulties when explaining dysfunctions. 2. A taxonomy of methodological principles applied to dysfunctions. 3. Subtleties of Neuroimaging studies (PET fMRI etc.).

Abstract: This work aims to contribute to the identification of some sources of difficulties when we think about dysfunctions. I put forward six methodological principles permeating our ideas of how cognition is organized and what happens when something is broken.\n(1) Modularity of Cognition. The idea that cognition is composed of specialized mechanisms characterized by being hardwired domain-specific encapsulated fast automatic etc.\n(2) A logic of Subtraction. Once it is assumed that cognition is modular a recurring tactic is counting back to track down partition of functions.\n(3) Reverse Engineering. Components are disassembled to analyze how the parts work and contribute to the overall functioning. \n(4) Residual Normality. This is a common insight consisting in asserting that a dysfunction originates from a disruption or deviation from the standard norms leaving untouched all the remaining elements of the system.\n(5) Double Dissociation. This is a method employed for distinguishing related but separated cognitive processes; a useful tool when you want to assess the functional independence of cognitive processes. \n(6) The Force of Genes. A heavyweight is given to genetic factors disregarding the fact that genes are multiply realizable. Genetic predispositions can be scarce broadly or disruptively expressed.\nAs long as we are clear about where the problems come from and which are the guiding principles for thinking about dysfunctions we can design better experimental protocols to understand human brain functioning.

First Author: Griffin Koch
(Graduate)

Presenting Author: Griffin Koch
(Graduate)

Mentor/Lab: Coutanche

Department: Psychology

Poster Session: PM
Location: 57

Category:
Learning

Title: Investigating how neural representations during encoding predict later recall

Summary: This study investigates the brain's activity while viewing video clips of animals. Within particular regions of interest video clips which were subsequently remembered showed more similarity than clips which were subsequently forgotten.

Abstract: As we progress through our lives we are constantly inundated with stimuli and information. Our brains however do not encode all of the possible information available to us. Even among the information we encode only a fraction is later successfully recalled. In this study we investigate how brain activity during encoding differs for information that is and is not recalled. Participants viewed brief video clips of animals while undergoing a functional magnetic resonance imaging (fMRI) scan and then answered a series of behavioral questions that measured memory performance. We employ univariate and multivariate techniques to compare neural representations for individual video scenes and ask how these vary by measures of individual differences such as tendencies to encode information in a certain form and participant memory performance. Regions such as the parahippocampal gyrus posterior medial cortex anterior cingulate cortex as well as the ventral and dorsal default mode networks showed more neural similarity for remembered than not remembered information. Additionally neural activation within the right anterior and posterior cingulate cortex could be used to successfully predict subsequent memory performance.

First Author: Michael Ward
(Graduate)

Presenting Author: Michael Ward
(Graduate)

Mentor/Lab: Ghuman

Department: Neurological Surgery

Poster Session: PM
Location: 58

Category:
Learning

Title: Anterior Temporal Naming Area: a Patch Near the Anterior Tip of the Fusiform Causally Linked to Reading and Language

Summary: The ventral anterior temporal lobe has been studied within the context of language processing for decades yet the precise role of this region is debated. Our electrophysiology and imaging studies provide convergent evidence for a new word selective patch near the anterior fusiform gyrus that is causally tied to naming and language.

Abstract: The role of the ventral anterior temporal lobe in language processing remains unclear. In particular electrical disruption of regions stretching along much of the ventral temporal cortex has been shown to affect naming. Here we present intracranial electrophysiology direct cortical stimulation and 7T fMRI results that describe a new word sensitive region near the anterior tip of the fusiform gyrus which we dub the anterior temporal naming area. In 5 neurosurgical epilepsy patients undergoing intracranial electroencephalography electrodes near the left anterior fusiform exhibited word sensitivity over five other categories of visual stimuli (faces bodies houses hammers and phase-scrambled images). For 2 patients those same electrodes also displayed sensitivity to non-words such as letter strings and pseudo words. Direct cortical stimulation was administered to 2 patients (P1 and P2) disrupting word and picture naming when applied to the word sensitive electrodes in both individuals and resulted in item circumlocution for P1. Additionally the word selectivity demonstrated in our intracranial and stimulation studies is consistent with 7T fMRI findings in healthy controls which display preferential orthographic sensitivity versus line drawings of objects anterior to the visual word form area near the anterior fusiform. Taken together our results strongly suggest the presence of a word sensitive patch near the anterior tip of the fusiform gyrus that is critical for naming and language but not conceptual knowledge per se.