My Itinerary

SATURDAY, OCT. 19, 2019

☆ Session 028 Peripheral Nerve Regeneration
Hall A

☆ Presentation 028.01 / A1 Increased ER-mitochondria tethering promotes axon regeneration
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Abstract
Molecular tethering between endoplasmic reticulum (ER) and mitochondria plays key roles in calcium buffering, lipid and ion exchange, and mitochondrial dynamics. However, making ER-mitochondria connection and its physiological roles in neurons are still unclear. Translocation of ER and mitochondria to the site of axon injury has been shown to facilitate axonal regeneration; however, the existence and physiological importance of ER-mitochondria tethering in the injured axons are unknown. Here, we show that glucose-regulated protein 75 (Grp75), a protein linking ER to mitochondria, is locally translated after delivering axonal injury. We find that overexpression of Grp75 in primary neurons increases ER-mitochondria tethering to promote regrowth of injured axons. Promoted contact between ER and mitochondria results in elevation of mitochondrial Ca2+ and ATP generation, thereby promoting regrowth of injured axons. Furthermore, our results demonstrate that overexpression of Grp75 in sciatic nerves of an animal facilitate axonal regeneration and behavioral recovery. Together, our findings suggest that increased ER-mitochondria tethering at axonal injury sites may provide a therapeutic strategy for axon regeneration.

☆ Session 030 Autism: Synaptic and Cellular Mechanisms I
Hall A

☆ Presentation 030.04 / A46 Autism-associated δ-catenin G34S mutation promotes GSK3β-mediated premature δ-catenin degradation inducing neuronal dysfunction
*S. KIM1, K. A. NIP1, M. SATHLER1, J. SHOU1; 1Dept. of Biomed. Sci., 2Colorado State Univ., Fort Collins, CO

Abstract
δ-catenin is a crucial component of a synaptic scaffolding complex, which regulates synaptic structure and function in neurons. Loss of δ-catenin function is strongly associated with severe autism spectrum disorder (ASD) in female-enriched multiple families. In particular, a G34S (Glycine 34 to Serine) mutation in the δ-cateningeine has been identified in ASD patients and suggested to exhibit loss-of-function. The G34S mutation is located in the amino terminal region of δ-catenin, where there are no known protein interaction domains and post-translational modifications. Notably, the Group-based Prediction System predicts that the G34S mutation is an additional target for GSK3β-mediated phosphorylation, which may result in protein degradation. Therefore, we hypothesize the G34S mutation accelerates δ-catenin degradation, resulting in loss of δ-catenin function in ASD. Indeed, we found significantly lower G34S δ-catenin levels compared to wild-type (WT) δ-catenin when expressed in cells lacking endogenous δ-catenin, which is rescued by genetic inhibition of GSK3β. By using Ca2+imaging in cultured mouse hippocampal neurons, we further revealed overexpression of WT δ-catenin is able to significantly increase neuronal Ca2+activity. Conversely, Ca2+activity remains unaffected in G34S δ-catenin overexpression, which is reversed by pharmacological inhibition of GSK3β using lithium. This suggests the G34S mutation of δ-catenin provides an additional GSK3β-mediated phosphorylation site, which could promote δ-catenin premature degradation, resulting in loss-of-function effects on neuronal Ca2+activity in ASD. In addition, inhibition of GSK3β activity is able to reverse G34S-induced loss of δ-catenin function. Thus, inhibition of GSK3β may be a potential therapeutic treatment for δ-catenin-associated ASD patients.

☆ Session 043 Cellular Mechanisms of Parkinson's Disease I
Hall A

☆ Presentation 043.09 / C83 Mammalian target of rapamycin complex 1 activated by astrocytic TRPV1 regulates the expression of neurotrophic factors in the MPP1-lesioned rat model of Parkinson's disease

1 activated by astrocytic TRPV1 regulates the expression of neurotrophic factors in the MPP1-lesioned rat model of Parkinson's disease.
Abstract
We have recently shown that Transient receptor potential vanilloid 1 (TRPV1) on astrocytes mediates production of neurotrophic factors (NTFs) in the MPP⁺-lesioned rat model of Parkinson's disease (PD). However, the precise molecular mechanisms are unknown. As mammalian target of rapamycin complex 1 (mTORC1) pathway can regulate the production of NTFs, we hypothesized that it could be involved in TRPV1-mediated production of neurotrophic factors on astrocytes in MPP⁺-lesioned rats. MPP⁺-increased expression of TRPV1, phosphorylated (p-) mTORC1 signaling molecules (p-p70S6K, p-p56, and p-4EBP1) and NTFs on astrocytes in the substantia nigra (SN) in vivo. The selective knockdown of astrocytic TRPV1 attenuated MPP⁺-induced increases in levels of p-p70S6K, p-p56, p-4EBP1, and NTFs in the SN. In addition, the selective knockdown of p70S6K or 4EBP1 in astrocytes decreased the levels of NTFs in the MPP⁺-lesioned SN, indicating the existence of TRPV1-mTORC1-NTFs signaling pathway. These results suggest that the mTORC1 signaling pathway is involved in the production of NTFs via astrocytic TRPV1 and might be a novel therapeutic target in the treatment of PD.

Session 044 Cellular and Circuit Mechanisms in Tauopathies
1:00 PM - 5:00 PM
Hall A

Presentation 044.03 / D6
Hiv glycoprotein gp120 induces tau hyperphosphorylation via cGMP-dependent kinase II

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Abstract
Over half of human immunodeficiency virus (HIV)-infected individuals suffer from HIV-associated neurocognitive disorders (HAND), including patients on the combination antiretroviral therapy (cART). As a result of more HIV-infected individuals surviving to older ages due to the efficacy of the treatment, they are at increased risk of developing neurodegenerative disorders. Alzheimer's disease (AD) is a chronic progressive neurodegenerative disorder characterized by two anatomical hallmarks, extracellular and intracellular protein aggregates: senile plaques and neurofibrillary tangles (NFTs), composed of beta-amyloid protein (Aβ) and hyperphosphorylated tau, respectively. Although recent studies indicate similar neuropathology between AD and HAND, little is known about mechanisms underpinning neurodegeneration in individuals with HIV. We quantify neuronal activity by monitoring Ca²⁺ dynamics using intracellular Ca²⁺ imaging after transfection with GCAMP, a genetically-encoded calcium sensor in cultured hippocampal neurons. HIV-induced tau phosphorylation (Ser202/Thr205) was measured by immunoblots of cultured cortical neurons. We also employ the Feline Immunodeficiency Virus (FIV) as a model to elucidate the molecular pathways underlying HIV-induced neuronal dysfunction, since it shares its structure, cell tropism, and pathology with HIV, including wide-ranging neurological deficits. Moreover, aged cats develop both amyloid deposits and tau pathology naturally, similar to humans; a feature lacking in all other animal models. We reveal that HIV and FIV envelope glycoproteins, gp120 and gp95, respectively, interact with the chemokine receptors and facilitate release of intracellular Ca²⁺. Significantly, gp120 and gp95 effects on calcium activity are dependent of the cGMP-dependent protein kinase I (cGKII) pathway, which increases Ca²⁺ release and synaptic activity. gp120 and gp95 were also able to induce tau protein hyperphosphorylation, which is dependent on the activation of p38-MAP kinase and cGKII, since addition of a p38 blocker (SB203580 10µM) or a cGKII inhibitor (KT5823 1µM) prevented both gp120 and gp95 effects on tau phosphorylation. Moreover, we reveal that human Aβ-specific immunoreactivity (using the 6E10 antibody) are higher in the hippocampal CA1 area of 2-year-old cat brains at 350 days post-infection of FIV. These results thus provide a novel neurobiological mechanism of cGKII-mediated synaptic hyperexcitation in HAND, leading to tau hyperphosphorylation.

Session 046 Cell Stress and Death Mechanisms
1:00 PM - 5:00 PM
Hall A

Presentation 046.22 / E17
Neuroprotective effect of gintonin, a ginseng-derived ingredient, against 3-nitropropionic acid-induced Huntington's disease-like behavioral, biochemical, and cellular alterations

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Abstract
Gintonin (GT), a ginseng-derived lysophosphatidic acid receptor ligand, regulates various cellular effects and suppresses inflammation. However, little is known about the potential value of GT regarding attenuation in the neurodegenerative diseases, such as Huntington's disease (HD). In this study, we investigated whether GT could ameliorate the neurological impairment and striatal toxicity in cellular or animal model of HD. Pretreatment with GT attenuated the severity of neurological impairment, lethality, mitochondrial dysfunction, apoptosis, microglial activation, and mRNA expression of inflammatory mediators in the striatum after 3-NPA-intoxication. Its action mechanism was associated with lysophosphatidic acid receptors (LPARs) and nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway activations and the inhibition of mitogen-activated protein kinases (MAPKs) and nuclear factor-κB (NF-κB) signaling pathways. These beneficial effects of GT were neutralized by pre-inhibiting LPARs with Ki16425 (a LPAR1/3 antagonist). Taken together, our findings firstly suggested that GT has beneficial effects in 3-NPA-induced striatal toxicity by antioxidant and anti-inflammatory activities through LPA. Thus GT might be an innovative therapeutic candidate to treat HD-like syndromes.

Session 047 Cellular Stress and Death Mechanisms
1:00 PM - 5:00 PM
Hall A
**Session 047.16 / E41** Lsm12-Epac1 pathway suppresses C9orf72 poly(GR)-induced neurodegeneration by establishing ran gradient for nucleocytoplasmic transport

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Abstract
Nucleocytoplasmic transport (NCT) defects have been implicated in neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS) or frontotemporal dementia (FTD) associated with C9orf72 mutations. Here we identify a neuroprotective pathway of *like Sm protein 12 (Lsm12)* and *Exchange protein directly activated by cyclic AMP (Epac1)* that suppresses NCT dysfunction by C9orf72-derived poly(glycine-arginine) proteins. Loss of Lsm12 function exacerbated neurodegeneration in Dro sophila models of the poly(GR)-induced ALS/FTD. Consistently, Lsm12 depletion in human neuroblastoma cells enhanced the poly(GR)-induced impairment of NCT while promoting the formation of nuclear poly(GR) granules. Overexpression of ALS-associated Lsm12 mutant comparably strengthened the poly(GR) toxicity, indicating dominant-negative effects. Transcriptome analyses further revealed that Lsm12 up-regulates Epac1 expression whereas Epac1 overexpression rescued NCT defects in Lsm12-deleted cells. In fact, Epac1 depletion dissociated Ran/importin β1 from cytoplasmic nucleopore complex, thereby dampening Ran gradient. These findings unveil a conserved role of the Lsm12-Epac1 pathway in the NCT-relevant pathogenesis of C9orf72-dependent ALS/FTD.

**Session 049 Ischemic Stroke I**

**Session 049.01 / F27** Phosphorylation of Fbxw7 by Cdk5 causes decreased stability of Fbxw7 in glutamate mediated excitotoxicity

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Abstract
Fbxw7 is a component of the SCF^Fbxw7^ E3 ligase complex that regulates cell division and growth. So far, many of Fbxw7-related research have focused on cancer metabolism. However, it has been also reported that Fbxw7 regulates brain development and differentiation. Cyclin-dependent kinase 5 (Cdk5) is a brain-specific serine/threonine protein kinase that regulates brain development and neurodegeneration. In physiologic condition, Cdk5 is activated by its activator proteins, p35 and its physiological activity is appropriately regulated. However, in pathologic condition, Cdk5 is hyper-activated by p25 that is generated from cleavage of p35, resulting from calpain activation. Unlike p35, the generation of p25 is culpable for the aberrant hyper-activation of Cdk5, causing neurodegeneration. Therefore, decreased Cdk5/p25 activity was one target for alleviating neurodegeneration. Here, we discovered that F-box/WD repeat-containing protein 7 (Fbxw7) is a new substrate of Cdk5 and hyper-activation of Cdk5 was eventually linked to decreased stability of Fbxw7. We also observed decreased stability of Fbxw7 in various calpain-activating conditions; primary cultures of cortical neurons challenged with glutamate and rat brains received a middle cerebral artery occlusion (MCAO). Decreased levels of Fbxw7 led to increased levels of transcription factor AP-1 (c-Jun) that is a known substrate of Fbxw7, which could possibly lead to accelerated cell death by c-Jun-mediated apoptosis. Thus, our data reveal a novel Cdk5-Fbxw7-c-Jun death pathway and raise the possibility that maintenance of Fbxw7 may comprise a critical point of neuroprotection.

**Session 052 Somatosensation: Trigeminal Pain Circuits and Processing**

**Session 052.04 / H24** The role of TRPV1 in trigeminal ganglion and brain stem following dental pulp inflammation in rats


Abstract
Pulpitis produces significant changes in the peripheral nervous system, which induce hyperalgasia. However, the neuronal activity and TRPV1 expression following pulpal noxious stimulation have not yet been investigated in the central nervous system (CNS). The aim of the present study was to verify whether experimentally induced pulpitis activates the expression of TRPV1 and c-Fos, both peripherally and centrally. Acute pulpitis was induced in Sprague-Dawley rats via pulp exposure and application of complete Freund's adjuvant (CFA) (n=13). Saline-treated (n=13) rats and rats that did not undergo tooth preparation (n=13) served as control groups. Three days post-CFA or -saline application, face grooming activity was recorded, and the rats were then euthanized to allow for immunohistochemical analysis of the trigeminal ganglion (TG) and spinal trigeminal nucleus. We found significantly increased pain-like behavior and histological evidence of severe pulp inflammation in CFA-treated animals. C-Fos labelling and TRPV1 immunoreactivity in the TG were signicantly higher (both p<0.05) in the CFA group than in the control groups. In the spinal trigeminal nucleus, the immunoreactivity for c-Fos was absent in the intermediate region (trigeminal subnucleus interpolaris) in all animals, with comparable expression of TRPV1 among all groups. In contrast, neurons in the trigeminal subnucleus caudalis (TSC) exhibited significant c-Fos immunoreactivity in the CFA group. The expression of TRPV1 did not differ among the three groups, but the superficial laminae of the TSC exhibited significantly higher expression of TRPV1 than did the deep layers. These findings indicated that the TRPV1 channel was significantly involved in nociceptive signal processing in the peripheral nervous system, but not in the CNS, following acute pulp inflammation. Because pulpitis induced some neuronal activation at the brainstem levels, further studies are needed to identify additional transducers that mediate signal transmission from pulpal afferents to their central targets. This research was supported by the Basic Research Program through the National Research Foundation (NRF) funded by the Ministry of Science and ICT (2015R1C1A1A01053484 and 2017R1A2B3005753) and the Yonsei University College of Dentistry Fund (6-2014-0112).
**Presentation 071.06 / R16** Innervation of the parasympathetic nervous system visualization in human and modulation of chemogenetic activation/inhibition in mice

*C. NAMKOONG*,1, 2, W. SONG*, 3, D. CHEON*, 4, J. HWANG*, 5, H. KIM*, 6, 7


**Abstract**

The liver is innervated by both the sympathetic and the parasympathetic nervous system. Human liver parasympathetic nerves are well characterized in the neuroanatomical pattern in the human liver is unknown. In the present study, we investigated the parasympathetic innervation of human and mouse liver by passive tissue clearing method for 3D-images. We optimized passive clearing method and immunofluorescent labeling of parasympathetic neurons in the human liver and mouse tissue. In addition to visualizing of parasympathetic nerve in the liver. We performed liver passive clearing and immunohistochemistry analysis to confirm 3D-anatomical interaction of parasympathetic neurons and hepatocytes. The images show the complex and dense neuronal circuit in the liver. We next investigated the role of parasympathetic in the regulation of liver glucose metabolism by chemogenetic methods using DREADDs (designer receptors exclusively activated by designer drugs). We confirm that our chemogenetic virus and mouse model is working by electrophysiology of DMV neurons showing that CNO activates the neurons. Acute activation of neurons in the DMV region results in increasing hepatic lipogenesis and gluconeogenesis. These results suggest that specific activation/inhibition of parasympathetic neurons to might be involved in the regulation of lipid and glucose metabolism.

Key words: Liver, Parasympathetic, Chemogenetics.

**Presentation 071.07 / R17** Comprehensive overview of full thickness enteric nervous system

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**Abstract**

The gastrointestinal tract is contains Mucosa, Submucosa, Muscularis Propria, Serosa. Enteric nervous system that neural network in gastrointestinal tract is known as 2parts: Submucosal Plexus and Myenteric Plexus. Myenteric Plexus is well known, especially with a number of methods of evaluation; Neuron cell body count, glia cell count, nerve type. However, Submucosal Plexus and other layers' neuronal structure is not well known yet. We investigated the cholinergic enteric nervous system structure with ChAT Cre Tomato Mouse using clearing method for 3D-images. in addition to visualizing of mesenteric nerve and method of evaluation. The images show complex and dense cholinergic neuronal structure. In this research, We discovered each layers' cholinergic enteric nerve structure in gastrointestinal tract.

**Presentation 072.04 / T6** A skin thermal surge following cocaine injection: Mediation of peripheral dopamine receptor


1Daegu Haany Univ., Daegu, Korea, Republic of; 2Acupuncture, Moxibustion& Meridian Res. Center, Div. of Standard Res., Korea Inst. of Oriental Med., Daejeon, Korea, Republic of

**Abstract**

Drug addiction has become a worldwide problem, affecting the people of every country in the world. While most studies for drug addiction have been focused on central nervous system including the mesolimbic dopamine (DA) system, peripheral phenomena or the underlying mechanisms are largely unknown. Our preliminary study found that systemic injection of cocaine induced a phenomenon of thermal surge in peripheral skin. Thus, the present study investigated whether the skin thermal surge following cocaine injection is caused by activation of peripheral DA receptor or mesolimbic DA system. The male Sprague-Dawley rats were anesthetized with pentobarbital sodium and peripheral skin temperature was measured using a K-type thermocouple microprobe or an infrared thermal camera. After recording basal temperature for 10 min, animals were given an intraperitoneal injection of cocaine and monitored for up to 30 min after injection. To investigate the mediation of peripheral or central DA receptors, Domperidone (10 mg/kg) or L741,626 (3 mg/kg) was administered 10 min before cocaine.
infrared thermal imaging displayed that the thermal increase was dominant in the distal areas of forelimb and hind limbs, compared to body skin. The temperature increases were blocked by systemic injection of nonspecific or peripheral D2 antagonist. Direct injection of cocaine into brain did not produce thermal changes in skin. These results suggest that a thermal surge in skin following cocaine injection is associated with activation of peripheral D2 receptor, but not central DA receptor.

**Session 087** Schizophrenia: Animal Models and Genetic Studies

**Presentation 087.06 / AA2** Identification of low-level brain somatic mutations in dorsolateral prefrontal cortex underlying schizophrenia

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**Abstract**

Genetic factors are considered as important for etiology of schizophrenia (SCZ), however, most cases of SCZ are known as sporadic. Many researchers have tried to find the genetic cause of SCZ using DNA extracted from the patients' blood. As a result, some related genes and copy number variations were found. However, only up to 5% of cases can be explained by these variations.

One major finding in the pathology of SCZ is the hypofrontality which indicates reduced metabolic activity in prefrontal cortex, especially in DLPPC. Moreover, recent study shows strong correlation between SCZ disease gene expression and DLPPC. This fact lead us to suspect that somatic mutations in DLPPC might cause the SCZ symptoms.

First of all, we performed 500x deep whole exome sequencing on matched DLPPC and peripheral tissues of 26 healthy controls and 27 SCZ patients which are provided by Stanley Medical Research Institute. We found average 4.9 and 6.0 in DLPPC and 8.6 and 7.3 mutations in peripheral tissues of SCZ and controls. The pattern of somatic mutations was not significantly different in SCZ and controls. This result means randomly developed mutations in important genes in neurons can induce psychiatric disease. Surprisingly, ingenuity pathway analysis shows that these mutated genes detected only in DLPPC of SCZ are enriched on canonical pathways which are known as disrupted in SCZ, related to glutamate and dopamine receptor signaling.

To examine the functional role of deleterious somatic mutations in the DLPPC of SCZ, we tested missense mutations in GRIN2B which detected in two cases. GRIN2B is very well-known genes which is related to SCZ. We found that both mutations lead disruption of GRIN2B localization but not its own expression pattern through primary culture experiment. This may affect patients' DLPPC activity and cause malfunction of synaptic plasticity and memory function and this should be studied more to figure out which neuronal connection has affected. Overall, our study suggests new insight into genetic architecture and molecular genetic cause of psychiatric disease. Studies to find out the factors which break neural activity may induce severe symptoms of SCZ need to be proceed to understand the causes of SCZ symptoms and develop infallible cure.

**Session 089** Connectomics Analytics I

**Presentation 089.02 / BB2** Enhanced and unified anatomical labeling for a common mouse brain atlas

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**Abstract**

Anatomical atlases in standard coordinates are necessary for the interpretation and integration of research findings in a common spatial context. For mouse, the most commonly used brain atlases are Franklin and Paxinos (FP) atlas based on histological staining of a single mouse brain and the common coordinate framework (CCF) 3D digital atlas from the Allen Institute for Brain Science. However, these atlases have accumulated inconsistencies in anatomical delineations and nomenclature, creating confusion among neuroscientists. To overcome these issues, we adopted the FP labels into the CCF to merge two labels in the single atlas framework. We used cell type specific transgenic mice and an MRI atlas to adjust and further segment our labels. Moreover, new segmentations were added to the dorsal striatum using cortico-striatal connectivity data. We digitized our anatomical labels based on the Allen ontology to facilitate integration of our labels as a neuroinformatics tool, created a web-interface for visualization, and provided tools for comprehensive comparisons between Allen and FP labels. Our open-source labels provide an neuroinformatics platform for future neuroanatomical studies and signify a key step towards a unified mouse brain atlas.

**Session 120** Potassium Channels I

**Presentation 120.14 / B63** Trafficking and localization of Kv2.1-HCN2 channel complexes in neurons

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**Abstract**

The voltage-gated potassium channel Kv2.1 has a critical role in regulating neuronal membrane excitability and is localized to plasma membrane clusters on the soma, proximal dendrites, and axon initial segment (AIS). Hyperpolarization activated cyclic nucleotide-gated channel 2 (HCN2) is localized to the soma, dendrites, and axon terminals in neurons, and these localizations show differences among neuronal cell types. HCN2 channel is implicated in neuropathic pain, febrile seizure, and depression.
and contributes spontaneous rhythmic activity in brain. Here, we show that Kv2.1 channels affinity-purified from rat brain are associated with HCN2 channels using mass spectrometry. HCN2 and Kv2.1 channel expressions reveal a different distribution among the distinct regions of the brain. Co-expression of HCN2-WT and Kv2.1 in heterologous cells results in plasma membrane localization, while HCN2-N380Q, a trafficking-defective mutant, retains Kv2.1 in the endoplasmic reticulum. In hippocampal neurons, HCN2-WT dramatically reconstitutes the large somatodendritic and axonal clusters of Kv2.1 in plasma membrane, whereas HCN2-N380Q significantly leads to disruption of the clustering and AIS specific localization of Kv2.1. Thus, these results suggest that HCN2 channel regulates the surface localization and axonal trafficking of Kv2.1 in neurons.

**Presentation 126.15 / B6A**
Nav channel beta3 regulates the expression and localization of Kv3.1b channels in neurons

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Abstract
Voltage-gated K⁺ channel Kv3.1b play a crucial role in regulating fast-spiking properties of neurons and is widely expressed in the dendrites, the somatodendritic region, and the axonal nodes of Ranvier in neurons. It has been reported that balance activity of Kv3 and Nav channels is important for inducing and maintaining fast-spiking. Here, we show that Navβ3, an auxiliary subunit of Nav channels, is a part of the Kv3.1b channel complex in rat brain using mass spectrometry. Co-expression of Navβ3 results in changes in the steady-state expression levels and stability of Kv3.1b channels. Interestingly, Kv3.1b and Navβ3 are differentially expressed between distinct regions of the brain and have a different expression pattern during brain development. Navβ3 regulates Kv3.1b channel trafficking to the cell surface and reduces the localization and expression of Kv3.1b in dendrites in hippocampal neurons. In addition, Navβ3 dramatically decrease the current densities of Kv3.1b channel in a voltage-dependent manner and induces a hyperpolarizing shift in the voltage dependence of steady-state inactivation. Therefore, these data suggest an unexpected role for Navβ3 in regulating the biophysical characteristics and localization of Kv3.1b channel.

**Session 122 Structural Plasticity and Circuit Remodeling II**

**Presentation 122.10 / C6**
Visualization of micro RNA distribution at the functional states of dendritic spines

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Abstract
microRNAs (miRNAs), small non-coding RNA, have emerged as critical regulators of synapse development and plasticity through their control of gene expression. However, we still do not know the distribution and role of miRNAs at dendritic spines which major loci of excitatory inputs and synaptic plasticity accompanying structural changes. Brain-specific miR-134s likely regulate the morphological maturation of spines, but their subcellular distributions and functional impacts have rarely been assessed. Here, we adapted atomic force microscopy (AFM) to visualize in situ miR-134s, which indicated that they are mainly distributed at nearby dendritic shafts and necks of spines. The abundance of miR-134s varied between morphologically and functionally distinct spine types and their amounts were inversely correlated with their postulated maturation stages. Moreover, spines exhibited reduced contents of miR-134s when selectively stimulated with beads containing a brain-derived neurotrophic factor (BDNF). From these results, in situ visualizations of miRNAs provided unprecedented insights into the “inverse synaptic-tagging” roles of miR-134s that are selective to inactive/irrelevant synapses and potentially a molecular means for modifying synaptic connectivity via structural alteration.

**Presentation 126.16 / D13**
Extracellular vesicles: Where the amyloid precursor protein carboxyl-terminal fragments accumulate and amyloid-beta is not generated

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Abstract
The amyloid β precursor protein (APP) is a single-pass transmembrane protein whose proteolysis by α- and β-secretases generates α- and β-carboxyl-terminal fragments (APP-CFTFs), respectively. γ-secretase cleavage of APP-CFTFs generates amyloid-β (Aβ), the major component of the amyloid deposits in the brain of Alzheimer’s disease patients. The involvement of extracellular vesicles (EVs) in Aβ amyloidosis was proposed because full-length APP, APP cleaving enzymes, APP-CFTFs, and a minute fraction of Aβ were identified in association with EVs. Here we undertook to determine whether in addition to Aβ binding to EVs in the extracellular space as was previously shown, EVs are a source of Aβ. We investigated the processing of APP in exosome-enriched EVs isolated from the brain of wild-type and APP overexpressing Tg2576 mice, aged 4 to 6 months. EVs were isolated from brain extracellular space using a method developed in our laboratory. The EVs were incubated in human CSF for different time periods at 37°C and analyzed by Western blotting. We found that APP was enzymatically processed in isolated brain EVs following 24h incubation, generating APP-CFTFs. We not only confirmed the presence of the α- and β-secretases, ADAM10 and BACE1 in the EVs, but also found the presence of all the γ-secretase subunits. Interestingly, treatment of EVs with the γ-secretase inhibitor, L-685, did not affect the levels of APP-CFTFs, suggesting no further processing of APP-CFTFs in EVs. Lastly, we found a decrease in the level of the 4 kDa monomeric Aβ accompanied by an increase in the level of Aβ signals at 8-9kDa following 24h incubation. This indicates the recruitment of EV-associated Aβ into dimers, which have been suggested as a building block of toxic assemblies. As a result, our data show that while exosomes are not a major source of Aβ generation, it seeds oligomeric Aβ.
**Session 128** Neurodegenerative Disorders and Injury I

8:00 AM - 12:00 PM

**Hall A**

**Presentation 128.06 / E7 Genetic and non-genetic factors for sleep and inhibitory control**

*E. B. SALDES, P. R. SABANDAL, A. ARZOLA, K. A. HAN; Univ. of Texas at El Paso, El Paso, TX*

Abstract

Dysfunctional executive functions are associated with brain disorders such as attention deficit hyperactivity disorder (ADHD), autism, dementia, substance abuse and addiction. However, the underlying neural and cellular mechanisms responsible remain unclear. To address this, we screened for novel genetic factors important for inhibitory control using a Go/No-Go test in *Drosophila melanogaster*. We found that *Shaker* and *Hyperkinetic*, which encode potassium channels, and *kekkon5*, which codes for a cell adhesion molecule with tyrosine kinase activity and important for synaptic plasticity. To identify the neural site where these genes play roles in inhibitory control, we knocked them down in either all neurons or a subset of neurons including mushroom body (MB) and central complex neurons known to be important for high order brain functions. We also explored non-genetic factors influencing inhibitory control. Previous studies indicate that loss of sleep increases mistakes in the human subjects performing the Go/No-Go test, which is used to assess impulsivity. In addition, approximately 60-80% of adults with ADHD show sleep anomaly. Consistently, *Shaker* and *Hyperkinetic* mutants have abnormal sleep, suggesting a role of sleep in inhibitory control. We disrupted sleep in wild-type flies, which resulted in impaired inhibitory control. This supports the notion that abnormal sleep causes impulsivity. This study will begin to clarify the mechanism by which genetic and non-genetic factors affect inhibitory control.

**Presentation 128.24 / E25 Scully in aging-associated loss of memory and inhibitory control**

*P. R. SABANDAL, A. ARZOLA, C. M. SIERRA, N. M. DELGADO, E. B. SALDES, K.-A. HAN; Biol. Sci., Univ. of Texas At El Paso, El Paso, TX*

Abstract

Alzheimer's disease and related dementias (ADRD) are characterized by progressive cognitive decline including augmented memory loss and dysfunctional executive function. Although numerous studies have identified several key pathophysiological changes such as mitochondrial dysfunction, cholinergic neurodegeneration and aggregation of β-amyloid (Aβ), the underlying mechanisms are elusive. This is due to the fact that ADRD involves heterogenous genetic and non-genetic risk factors (e.g. aging, social stress and sleep perturbation). Yet, how these diverse risk factors interplay to cause ADRD is still unclear and our study aims to fill this knowledge gap. To address this, we conducted an unbiased functional genetic screen to identify novel ADRD genes that interact with non-genetic factors, particularly aging and social stress, by measuring premature inhibitory control dysfunction as an endophenotype in the *Drosophila* model. One of the genes that we identified is Scully. It is the fly homolog of 17-β-hydroxysteroid dehydrogenase 10 (HSD17B10), which is a multifunctional mitochondrial enzyme binding to Aβ peptides and thereby being associated with Alzheimer's disease. The Scully-deficient flies exhibit aging-dependent loss of inhibitory control as well as enhanced memory loss compared to control flies. The progress of this study will be presented including Scully's roles in mitochondrial homeostasis, cholinergic neurodegeneration and amyloidogenesis. The findings from this study will advance our understanding of the ADRD pathogenesis mechanisms and possibly uncover unique therapeutic targets.

**Session 135** Stroke I

8:00 AM - 12:00 PM

**Hall A**

**Presentation 135.03 / H31 Changes in the coupling of slow-waves with spindles tracks motor recovery after stroke**

*K. KIM1, S.-J. WON2, A. HISHINUMA1,2, L. GUO1, S. J. WON1, K. GANGULY1,2; 1Dept. of Neurol., Univ. of California San Francisco, San Francisco, CA; 2Neurol. and Rehabil. Service, San Francisco Veterans Affairs Med. Ctr., San Francisco, CA*

Abstract

There is growing evidence that sleep can promote motor recovery after stroke, but little is known about the underlying mechanisms. Importantly, the precise temporal coupling of spindles (10-15 Hz) to slow-waves activity (SW; <1 Hz) during non-rapid-eye-movement (NREM) sleep has been proposed to support memory consolidation in healthy cortical areas (e.g., prefrontal cortex and primary motor cortex). Here we tested the hypothesis that such sleep dynamics are important for recovery after stroke. Here, we show that the temporal coupling of spindles to SW tracks motor recovery after stroke and can be a target for modulation of recovery. In rats, the temporal coupling of spindles to SW measured in the local field potential of the penisileon cortex after a lesion to the primary motor cortex, was increased over rehabilitation days after stroke; such restoration of sleep dynamics was closely related to the recovery of motor performance. In addition, motor deficits involving arm and hand movements were more severe in rats with a large stroke area compared to rats with a small stroke area, and the quality of temporal coupling of spindles to SW predicted the two degrees of stroke. Interestingly, the duration of sleep after rehabilitation training was closely correlated with motor task offline gains. Taken together, our results suggest that sleep, in general, and the restoration of the precise temporal coupling of spindles to SW, in specific, are important for recovery of upper-limb function after stroke.

**Session 161** Hippocampus: Intrinsic Hippocampal Circuits

8:00 AM - 12:00 PM

**Hall A**

**Presentation 161.03 / W14 Impairment of cognitive function under Hyper-Gravity in rats**

*E. B. SALDES, P. R. SABANDAL, A. ARZOLA, C. M. SIERRA, N. M. DELGADO, E. B. SALDES, K.-A. HAN; Biol. Sci., Univ. of Texas At El Paso, El Paso, TX*

Abstract

Alzheimer's disease and related dementias (ADRD) are characterized by progressive cognitive decline including augmented memory loss and dysfunctional executive function. Although numerous studies have identified several key pathophysiological changes such as mitochondrial dysfunction, cholinergic neurodegeneration and aggregation of β-amyloid (Aβ), the underlying mechanisms are elusive. This is due to the fact that ADRD involves heterogenous genetic and non-genetic risk factors (e.g. aging, social stress and sleep perturbation). Yet, how these diverse risk factors interplay to cause ADRD is still unclear and our study aims to fill this knowledge gap. To address this, we conducted an unbiased functional genetic screen to identify novel ADRD genes that interact with non-genetic factors, particularly aging and social stress, by measuring premature inhibitory control dysfunction as an endophenotype in the *Drosophila* model. One of the genes that we identified is Scully. It is the fly homolog of 17-β-hydroxysteroid dehydrogenase 10 (HSD17B10), which is a multifunctional mitochondrial enzyme binding to Aβ peptides and thereby being associated with Alzheimer's disease. The Scully-deficient flies exhibit aging-dependent loss of inhibitory control as well as enhanced memory loss compared to control flies. The progress of this study will be presented including Scully's roles in mitochondrial homeostasis, cholinergic neurodegeneration and amyloidogenesis. The findings from this study will advance our understanding of the ADRD pathogenesis mechanisms and possibly uncover unique therapeutic targets.
Communication

Session 167 Human Long-Term Memory: Medial Temporal Lobe I
Hall A

Presentation 167.03 / Y37 Differential effect of human hippocampal stimulation on memory enhancement with theta rhythm
*S. JUN1, S. LEE1, J. KIM2, C. CHUNG3;

Abstract
How the direct hippocampal electrical stimulation affects episodic memory has not been well characterized. To characterize it, we applied 50 Hz electrical stimulation to the hippocampus during the encoding phases of each task, and recorded intracranial EEG (iEEG) from 10 epilepsy patients who performed two different verbal memory tasks, including paired associative memory and single item memory. Hippocampal stimulation modulated memory performance in a task-dependent manner: associative memory performance was enhanced, while item memory performance was impaired. In addition, subjects with poorer baseline memory improved much more by stimulation. On iEEG from the hippocampus during non-stimulation encoding blocks, the associative memory task elicited stronger theta oscillations than item memory. Also during retrieval, stimulation-induced memory enhancement was linked to increased theta power. These results suggest that: 1) hippocampal stimulation enhances associative memory but not item memory because it engages greater hippocampal theta activity and that 2) increased hippocampal theta may be a neural mechanism for memory enhancement.

Session 190 Pain and Itch Behavior, Circuitry, and Novel Techniques
Room S106

Presentation 190.08 Genetic dissection of ascending spinal pathways for affective touch and pain
*S. CHO1, J. HACHISUKA2, M. A. BRETT1, H. R. KOERBER1, S. E. ROSS1, D. D. GINTY1;
1Neurobio., Harvard Med. School/HHMI, Boston, MA; 2Neurobio., Univ. of Pittsburgh/Pittsburgh Ctr. for Pain Res., Pittsburgh, PA

Abstract
The anterolateral system consists of tracts that ascend within the anterior and lateral part of the spinal cord white matter and conveys touch, pain, and temperature information from the periphery to multiple regions in the brain. The spinoparabrachial (SPB) tract terminates in the lateral parabrachial nucleus (PBN) of the pons, a main brain target of the anterolateral system that relays multimodal sensory signals to higher brain centers. The projection neurons in the anterolateral system, including SPB neurons, are attractive therapeutic targets for pain treatment because nociceptive signals emanating from the periphery channel through these spinal projection neurons. However, the subdivisions and organizational logic of the anterolateral pathway are poorly understood. Here we show that two projection neuron populations that express structurally related GPCRs, NK1R (Neurokinin 1 receptor) and GPR83, form parallel ascending circuit modules that are anatomically, physiologically, and functionally distinct. We found that GPR83-expressing SPB neurons are uniquely sensitive to cutaneous mechanical stimulation and receive strong synaptic inputs from both high- and low-threshold primary mechanosensory neurons. Remarkably, the axons of the NK1R- and GPR83-expressing SPB neurons terminate in a partially segregated manner within the PBN, and optogenetic stimulation of the axon terminals of these two neuronal populations induces distinct patterns of escape locomotion and autonomic responses. Moreover, while activation of NK1R-expressing SPB neurons elicits aversive behavioral responses, the valence associated with activation of GPR83-expressing SPB neurons is either positive or negative depending on stimulus intensity; low-intensity stimulation is appetitive whereas high-intensity stimulation is aversive. Overall, our findings support a model in which the PBN, receives touch, pain, and temperature information from physiologically and anatomically distinct SPB circuit motifs and broadcasts somatosensory signals to other brain regions to generate proper behavioral responses to changes in the physical world.

Session 205 Mechanisms of Bi-Directional Glia-Neuron Communication
Hall A

Presentation 205.07 / C25 Ultrasonic neuromodulation via astrocytic TRP1
*S.-J. OH1
KIST, Seoul, Korea, Republic of
Abstract
Low-intensity, low-frequency ultrasound (LILFU) is the next-generation, non-invasive brain stimulation technology for treating various neurological and psychiatric disorders. However, the underlying cellular and molecular mechanism of LILFU-induced neuroremodulation has remained unknown. Here we report that LILFU-induced neuroremodulation is initiated by mechanical activation of TRPA1 channels in astrocytes. The Ca²⁺ entry through TRPA1 causes a release of gliotransmitters including glutamate through Best1 channels in astrocytes. The released glutamate activates NMDA receptors in neighboring neurons to elicit action potential firing. Our results reveal an unprecedented mechanism of LILFU-induced neuroremodulation involving mechanosensitive TRPA1 as a unique sensor for LILFU and glutamate-releasing Best1 as a mediator of glia-neuron interaction. These discoveries should prove to be useful for optimization of human brain stimulation and ultrasonogenetic manipulations of TRPA1.

Session 206 Molecular and Cellular Mechanisms of Demyelinating Disorders
Hall A

Presentation 206.14 / C61 Quantifying myelination of single neurons using spatial light interference microscopy (SLIM)


Abstract
Deficient myelination in the central nervous system is associated with neurodevelopmental complications, Alzheimer's disease and temporal lobe epilepsy. Furthermore, deficient remyelination is thought to underlie neurodegeneration in multiple sclerosis patients. Although both neurons and oligodendrocytes have been extensively studied individually, their interactions are still incompletely understood. New techniques are needed to further study the intricacies of this interplay in terms of cellular and molecular dynamics. Spatial Light Interference Microscopy (SLIM) is a quantitative imaging technique that generates phase maps related to the dry mass content of the sample. Recently, we have assessed myelin content in piglet brain tissue using color SLIM, which combines phase maps with corresponding color images. In this study, we examined the ability of SLIM to quantify myelination at the single axon level. We imaged 18 sets of cocultures comprising hippocampal neurons and oligodendrocytes, of varying densities over two weeks. After imaging, the cocultures were fixed and stained for both myelin and intermediate filament, using antibodies specific to proteolipid protein (PLP) and neurofilament (NF) respectively. Registering the resulting immunofluorescent images with dry mass videos allowed the evaluation of myelin development throughout the course of neuron-oligodendrocyte interaction. Preliminary analysis has shown that the proximity and contact of oligodendrocytes contributes to normal axonal mass and diameter. In summary, we have quantified myelin development from its inception in oligodendrocytes to its periodic insulation of axons. These results will provide insight on the details of myelin transport, as well as improve the sensitivity and validity of further myelin quantifications in neuronal cultures and brain tissues.

Session 213 Parkinson's Disease: Molecular Mechanisms
Hall A

Presentation 213.13 / E40 The effects of valproic acid on neuroinflammation in LRRK2 R1441G mice

- Y. PARK, S. SONG, T. KIM, H. NOH, S. KANG, H. SEO;
- Hanyang Univ., Seoul, Korea, Republic of

Abstract
Numerous studies have shown that activated microglia release pro-inflammatory markers and results in dopaminergic neuronal degeneration in Parkinson's disease (PD). Some of histone deacetylase (HDAC) inhibitors are reported neuroprotective in various neurodegenerative diseases. We previously studied that valproic acid (VPA), pan inhibitor of HDAC, alleviated neuroinflammation in Alzheimer's disease. In this study, we hypothesized that HDAC inhibition decrease the expression of pro-inflammatory markers and increased the survival of dopaminergic neurons in PD model. To determine the effects of VPA on neuroinflammation, the activated microglial cells in substantia nigra (SN) and striatum (ST) were counted by immunohistochemical staining using anti-iba-1 antibody. Consequently, we found that VPA decreased the number of activated microglia in ST of LRRK2R1441G mice and altered the histone acetylation related expression levels of pro-inflammatory markers including Fc gamma receptors (FcyRs) in LRRK2R1441G mice and LPS-induced activated microglia, BV2 cells. In addition, VPA improved non-motor PD symptoms, which were detected by time spent in center from open field test and cognitive behaviors from elevated plus maze test. These data suggest that the regulation of histone acetylation through neuroinflammatory responses can be future therapeutic targets of PD to recover not only nigrostriatal pathway but also mesocorticolimbic pathway of dopaminergic system.

Session 220 Preclinical and Clinical Studies in Peripheral Nerve Injury and Neuropathic Pain
Hall A

Presentation 220.11 / I27 Substance P is an important mediator for acupuncture effects

- Col. of Korean Medicine, Daegu Haany Univ., Daegu, Korea, Republic of; 2Korean Med. Fundamental Res. Div.ion, Korea Inst. of Oriental Med., Daejeon, Korea, Republic of

Abstract

Spatial Light Interference Microscopy (SLIM) is a quantitative imaging technique that generates phase maps related to the dry mass content of the sample. Recently, we have assessed myelin content in piglet brain tissue using color SLIM, which combines phase maps with corresponding color images. In this study, we examined the ability of SLIM to quantify myelination at the single axon level. We imaged 18 sets of cocultures comprising hippocampal neurons and oligodendrocytes, of varying densities over two weeks. After imaging, the cocultures were fixed and stained for both myelin and intermediate filament, using antibodies specific to proteolipid protein (PLP) and neurofilament (NF) respectively. Registering the resulting immunofluorescent images with dry mass videos allowed the evaluation of myelin development throughout the course of neuron-oligodendrocyte interaction. Preliminary analysis has shown that the proximity and contact of oligodendrocytes contributes to normal axonal mass and diameter. In summary, we have quantified myelin development from its inception in oligodendrocytes to its periodic insulation of axons. These results will provide insight on the details of myelin transport, as well as improve the sensitivity and validity of further myelin quantifications in neuronal cultures and brain tissues.
Abstract
Acupuncture has been used to treat a variety of diseases and symptoms for more than 2,500 years. Our previous study showed that acupoints are identical to neurogenic spots arising from the release of neuropeptides such as substance P (SP) from activated small diameter sensory aferents in the dermatome associated with visceral disorders. The neuropeptide SP may be an important mediator for the initiation of acupuncture effect. To explore the roles of SP in producing therapeutic effects of acupuncture, the present study investigated in a rat model of immobilization-induced hypotension whether the acupuncture effects at acupoints is closely associated with elevation of cutaneous SP level during neurogenic inflammation. When plasma extravasation from neurogenic inflammation was examined by exploring the leakage of intravenously injected Evans blue dye (EBD) to the skin, extravasated EBD began to appear at acupoints on the wrist, gradually accumulated and fully saturated within 15 min after EBD injection. Significant increase of SP over acupoint in hypertensive rats were observed, compared to control. Injections of either SP or capsaicin produced anti-hypertensive effects, which was reversed by injecting an SP antagonist into acupoints on the wrist. Moreover, single fiber recording displayed that local injection of SP into acupoint increased the sensitivity of A- and C-fibers in response to acupuncture stimulation. In addition, the rate of discharge of wide-dynamic response (WDR) neurons in spinal cord significant increased following intradermal SP treatment in naïve rats but decreased following intradermal SP antagonists in hypertensive rats. Therefore, our findings suggest that SP is an important mediator in the development of acupuncture effects.

Diffusion Tensor Imaging allows to study ethanol-associated behaviors including sedation, tolerance, euphoria, behavioral disinhibition and sensitization. To identify the mechanism by which social environment affects ethanol responses, we compared the socially isolated versus socially enriched conditions in the wild-type Canton-S flies. We found that socially isolated flies were less sensitive to the sedative and euphoric effects of ethanol compared to socially enriched flies. To pinpoint whether the effect of social environment on sedation and euphoria is due to the social experience during housing or at the time of ethanol exposure, we compared the following conditions: (1) singly housed/singly exposed versus group housed/singly exposed and (2) singly housed/group exposed versus group housed/group exposed flies. We found that group exposed flies consistently displayed greater ethanol-induced euphoric response compared to singly exposed flies regardless of housing conditions. This suggests that the social environment during ethanol exposure, but not housing, is the major factor influencing the euphoric response. We will present the progress of this study and the role of dopamine D2 receptor as a key factor mediating social environment information. Findings of this study may have novel implications for social environment-dependent alcohol use or addiction.

Abstract
When a brain receives ambiguous stimuli, a perceptual decision often spontaneously alternates between two possible states. Such perceptual switching, characterized as bistable perception, is observed to occur quasi-periodically, with frequency varying across individuals. Complex cognitive functions might be involved in this bistable perception, but in some studies (Laubrock et al., 2008; Martinez-Conde et al., 2013) it was suggested that oculomovement may solely drive periodic perceptual switches. This is because eye movement often appears as an oscillatory pattern during perceptual decision. However, whether eye movement can induce perceptual decision, or if it is merely a consequence of perception is still subject to debate. In this study, we hypothesized that oculomovement may induce an active perceptual decision for ambiguous stimuli. We performed a human psychophysics experiment with simultaneous eye tracking, using three bistable stimuli— racetrack, rotating cylinder, and Necker cube. We observed that eye gaze continuously oscillates slowly (period 1-10 s) during bistable perception. Moreover, the period of oscillation matched that of the perceptual switch in individuals. Using eye-gaze trajectory measurement only, we were able to predict when individuals would make perceptual switches. With the previous notion that switching frequency of bistable perception is strongly correlated with the sensory integration time of an individual (Choi and Paik 2019), our results suggest that slow rhythmic oculomovement may control the temporal dynamics of sensory integration and induce active interpretation of ambiguous sensory information.

Diffusion Tensor Imaging allows to study ethanol-associated behaviors including sedation, tolerance, euphoria, behavioral disinhibition and sensitization. To identify the mechanism by which social environment affects ethanol responses, we compared the socially isolated versus socially enriched conditions in the wild-type Canton-S flies. We found that socially isolated flies were less sensitive to the sedative and euphoric effects of ethanol compared to socially enriched flies. To pinpoint whether the effect of social environment on sedation and euphoria is due to the social experience during housing or at the time of ethanol exposure, we compared the following conditions: (1) singly housed/singly exposed versus group housed/singly exposed and (2) singly housed/group exposed versus group housed/group exposed flies. We found that group exposed flies consistently displayed greater ethanol-induced euphoric response compared to singly exposed flies regardless of housing conditions. This suggests that the social environment during ethanol exposure, but not housing, is the major factor influencing the euphoric response. We will present the progress of this study and the role of dopamine D2 receptor as a key factor mediating social environment information. Findings of this study may have novel implications for social environment-dependent alcohol use or addiction.
Abstract

The human primary auditory cortex (PAC) occupies major parts of the Heschl's gyrus (HG). The macro-anatomical geometry of HG, however, is highly variable across individuals and provides only rough indication of the position and extent of PAC. In the current study, we aimed to construct an automated pipeline for defining PAC of the human auditory cortex. We combined myelin density and curvature information derived from magnetic resonance imaging (MRI) to better indicate the extent of PAC.

We have developed an automated pipeline defining the human primary auditory cortex (comparable to the core area in non-human primates) using myelin density and curvature information from magnetic resonance images. In the current study, we aimed to further parcellate the surrounding belt area using resting-state functional magnetic resonance imaging (rs-fMRI) and verify the consistency of parcellation with diffusion tensor imaging. We started with the early auditory cortex defined by HCP multi-modal parcellation atlas as the initial region of interest. Within the ROI, a Gaussian mixture model clustering was applied to the myelin density map (cluster size of two). This process yielded two subdivisions, highly myelinated center (putative core) and less myelinated surrounding (putative belt). The curvature information was then applied to adjust the putative core area. To incorporate the prior knowledge that PAC corresponds close to HG, we drew a line in between HG and Heschl's sulcus. The two resulting subcompartments of the putative core were then obtained until they had spatial overlap. Finally, the subcompartment located on HG was selected as PAC. From ten participants, we calculated the mean surface area of PAC defined by our pipeline. The mean from the left hemisphere was 2,524 mm$^2$ (SD, 651 mm$^2$) and from the right hemisphere was 2,470 mm$^2$ (SD, 344 mm$^2$). The size of PAC area reported in previous studies range from 1,329 to 2,172 mm$^2$. Our method defined the extent of PAC greater than others because we intended to include all the primary architectonic areas, for example, the core area of non-human primates, which includes A1, R and RT. Here, we developed a fully automated pipeline to objectively define the human PAC using structural MRI data, and the outcomes were comparable to the previous studies suggesting the reliability of our pipeline.

Presentation 252.24 / BB54 Parcellation of the belt area in the human auditory cortex using multi-modal magnetic resonance imaging

*H. S. LEE, 1, B.-Y. PARK, 2 K. BYEON, 3 H. PARK, 4 D. POEPPEL 5
1Max Planck Inst. For Empirical Aesthetics, Frankfurt am Main, Germany; 2Sungkyunkwan Univ., SUWON-SI, Korea, Republic of; 3SKKU, Suwon, Korea, Republic of; 4Neurosci., Max-Planck Institute For Empirical Aesthetics, Frankfurt, Germany

Abstract

Over a dozen subregions are defined in the non-human primate auditory cortex. The translation of these areas onto the human brain, however, remains unclear. Recently the Human Connectome Project (HCP), using magnetic resonance images, has successfully delineated 180 areas per hemisphere in humans which includes the auditory cortex roughly subdivided into five compartments. Further delineation and comparisons to non-human primate auditory cortex remain to be explored. We have developed an automated pipeline defining the human primary auditory cortex (comparable to the core area in non-human primates) using myelin density and curvature information from magnetic resonance images. In the current study, we aimed to further parcellate the surrounding belt area using resting-state functional magnetic resonance imaging (rs-fMRI) and verify the consistency of parcellation with diffusion tensor imaging. We started with the early auditory cortex defined by HCP multi-modal parcellation atlas as the initial region of interest. Within the ROI the core area was defined by our automated process and then excluded. The time series of all vertices in the remaining belt area that surround the core were extracted. Then three independent components were computed from the time series data. These components were identified in the anterior, medial, and posterior clusters within the belt area. Tractography was performed with the seed of each identified cluster using diffusion tensor imaging (deterministic) to assess the anatomical connections. The anterior subregion had connections to the prefrontal cortex including the primarily orbito- and medial-frontal and secondarily dorsolateral prefrontal cortices. The posterior subregion was connected to the visual cortex. The medial subregion showed connections both with the prefrontal and visual cortices. Our findings suggest that functionally distinct subregions within the belt area in humans show distinct anatomical connectivity patterns. These results might provide new insights on exploring the subregions of the belt area in the human auditory cortex.

Presentation 254.03 / BB81 Decoding the functional role of the ventral tegmental area-olfactory tubercle dopamine circuit via integration of electrochemical and chemogenetic techniques

*R. BHIMANI, C. E. BASS, J. PARK
Univ. at Buffalo, Buffalo, NY

Abstract

The olfactory tubercle (OT), a limbic structure located at the ventral most portion of the ventral striatum, receives dense dopamine (DA) innervation from the ventral tegmental area (VTA) and plays a pivotal role in the reinforcing effects of drugs of abuse. However, due to its anatomical location and proximity to neighboring DA rich brain structures (e.g. nucleus accumbens, caudate putamen), functional characterization of OT-DA has been limited. In order to overcome such challenges, recent genetic techniques such as Designer Receptors Exclusively Activated by Designer Drugs (DREADDs), have facilitated the understanding of the functional roles of complex brain circuits. DREADDs are synthetic G-protein coupled receptors that can be delivered to neurons via gene transfer and allow for the excitation or inhibition of neuronal activity through pharmacologically inert ligands such as Clozapine-N-Oxide (CNO). In this study, we used a viral targeting system to restrict DREADD expression to VTA-DA neurons and employed in vivo fast-scan cyclic voltammetry (FSCV) to determine how CNO modulates DA transmission and associated behavioral outputs in awake behaving rats. We further compared these findings with a retrograde intersectional viral approach to selectively modulate VTA-DA projections neurons that innervate the OT. Through immunohistochemical and electrochemical evidence, we demonstrate how chemogenetic modulation of VTA-DA neurons impacts sub-second changes in DA transmission in the OT and compared the effects of global and discrete sub-populations of VTA-DA neuron modulation. These findings will provide a novel understanding of the VTA-DA-OT circuit and how it is linked to various brain functions as well as psychiatric and neurodegenerative diseases.
Abstract
Episodic memory (EM) is a key cognitive function that enables us to recall details of past experiences, including content ("what"), space ("where"), and time ("when"). While humans can effortlessly remember a spatiotemporally continuous episode, a detailed understanding of the neural mechanisms underlying temporal binding of memory components is still unclear. The hippocampus is widely known for its role in spatiotemporal representations including EM, but the prefrontal cortex (PFC) also plays an important role and is of interest due to its accessibility using a wide range of methodologies for measuring and modulating neural activity. In this study, we used a high-density portable functional infrared spectroscopy (fNIRS) system to investigate PFC activity in an EM task that required the temporal binding of "what" and "where" information. Subjects (n=15) were asked to perform a computer-based EM task in which they were asked to place a subset of available objects in a subset of available locations in a specific temporal order (encoding) and, then, re-enact that entire sequence after a delay (retrieval). We dissociated EM temporal binding into three trial types: (1) what-when binding, (2) where-when binding and (3) what-where-when binding (full EM). In the full EM trial, subjects successfully recognized objects and locations (what) but made more errors when recalling their temporal order. In the componential trials (what-when or where-when binding), however, behavioral performance in both recognition and temporal binding were at ceiling. Multi-class SVM based on multi-depth fNIRS channels could classify each trial type and memory process (demo/encoding/retrieval) with an accuracy of more than 80%. Overall PFC activation was greater in the full EM trial than the componential conditions during encoding and retrieval period (what: t(17)=2.38, p=.023 / where: t(17)=3.94, p=.001), particularly in the right PFC (what: t(17)=2.84, p=.011 / where: t(17)=2.87, p=.011). Interestingly, full EM showed a tendency toward higher activation than both of the componential conditions in dorsolateral PFC (what: t(17)=1.92, p=.071 / where: t(17)=2.85, p=.011), but higher activation during full EM in ventrolateral PFC was only observed in comparison with what-when condition, not with the where-when condition. (what: t(17)=2.15, p=.046 / where: t(17)=0.96, p=.35) Our study provides insight into how PFC activity varies with temporally-bound memory components in episodic memory. Such knowledge could be applied to the assessment of memory-related neural activity in a wide range of experimental and clinical settings, using portable fNIRS systems.
Abstract
Corticospinal excitability measured by motor-evoked potentials (MEPs) is modulated by polarity-dependent transcranial direct current stimulation (tDCS). Specifically, anodal- and cathodal-tDCS applied to the motor cortex (return electrode: supraorbital cortex) increases and decreases the amplitude of MEPs elicited by transcranial magnetic stimulation (TMS), respectively. Yet, it remains unknown how tDCS polarity modulates cortical reactivity and its relationship with corticospinal excitability. The recent development of combined TMS and electroencephalography (EEG) enables us to probe altered brain network dynamics. Here we performed a crossover, double-blind, sham-controlled TMS-EEG study with three tDCS conditions (anodal/cathodal tDCS, and sham) to examine the causal role of cortical reactivity in corticospinal excitability. We recruited 18 healthy right-handed participants (male, 18-35 years old; free of neurological or psychiatric illness) and applied TMS pulses on the hand area of the left precentral gyrus based on individual magnetic resonance imaging (3 Tesla, T1-weighted). We first identified resting motor threshold (RMT) and then applied 100 TMS pulses with 120% intensity relative to RMT over a period of 5 minutes. We collected MEPs and 128-channel EEG data before and after tDCS administration for 10 minutes. We found anodal and cathodal tDCS significantly increased and decreased MEP ratio (post/pre) in “stimulation condition” (F(2,28)=255, p<0.0001) using a linear-mixed effect model with factors “stimulation condition” and “session”. This result replicates and confirms previous findings of bidirectional modulation of corticospinal excitability with tDCS. To investigate cortical reactivity in the EEG data, we removed the TMS-induced artifact from -10 to 20ms relative to stimulation onset and calculated the TMS-evoked potential (TEP) components (P25, N45, P60, N100, P180, N280) with respect to the TMS onset. We found that the P25, N45, P60 TEP components are significantly modulated by tDCS. No other TEP components exhibited such modulation by stimulation condition (all p>0.05). Importantly, the modulation of the component by tDCS were correlated for P25 TEP component (r=0.022), cathodal tDCS (r=0.51, p=0.032), but not for sham tDCS (r=0.15, p=0.54). Together, our findings demonstrate (1) a clear effect of tDCS on corticospinal excitability, (2) the positive cortical reactivity at 25ms (P25) drives the change in corticospinal excitability induced by tDCS. These results provide a strong foundation for future neurophysiology-based examination of tDCS and its effect of motor excitability.

**Session 292** Alzheimer’s Disease: Omics Approaches
Hall A

**Presentation 292.14 / E24** Functional screening of miR126 targets in *in vitro* and *in vivo* AD models
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1Hanyang Univ., Seoul, Korea, Republic of; 2McLean Hospital, Harvard Med. Sch., Belmont, MA

Abstract
Alzheimer’s disease (AD) is chronic neurodegenerative disease caused by loss of neurons and synapses in several brain regions including entorhinal cortex and hippocampus. Alteration of the expression of micro RNA (miRNA) a small non-coding RNA, has been studied for pathologic process of several neurodegenerative diseases, as it functions in RNA silencing and post-transcriptional regulation of gene expression. One of the miRNAs, miR126 has been reported as a novel pathological marker of various neurodegenerative diseases such as Parkinson’s disease (PD) and AD, but its pathophysiological targets are poorly understood. In this study, we predicted several genes as potential targets of miR126, using network topologic analysis. To determine transcriptomic changes, we screened the targets of miR126 using next generation sequencing (NGS) analysis in cholinergic neurons after Lenti-miR126 overexpression under AD-like pathological environment induced by amyloid beta 42 (Aβ-42). The selected genes from this screening analysis were functionally evaluated in *in vitro* AD cell model. The function of various target genes of miR126 in this study can reveal the pathophysiological mechanisms and potential therapeutic approaches in AD.

**Session 293** Synaptic Dysfunction in Alzheimer’s Disease: In Vivo Models II
Hall A

**Presentation 293.16 / F10** Loss of Presenilin function in inhibitory neurons causes impairments of memory, synaptic plasticity and age-dependent neurodegeneration
*J. KANG*, S. LEE, J. SHEN;
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Abstract
Mutations in the *Presenilin* (PSEN1 and PSEN2) genes are the major genetic cause of Alzheimer’s disease (AD). Inactivation of Presenilin (PS) in excitatory neurons of the postnatal mouse forebrain results in memory and synaptic impairment as well as age-dependent neurodegeneration. Although the function of interneurons and the oscillatory network activities they regulate are altered in AD, the role of PS in inhibitory neurons is unknown. Here we generated inhibitory neuron-selective *PS* cDKO mice, in which PS is selectively inactivated by Cre recombinase expressed under the control of the Gad2 promoter. Western analysis confirmed reduction of PS1 in the cerebral cortex and the striatum, in which ~95% of neuronal cells are GABAergic medium spiny neurons. Interestingly, IN-PS cDKO mice show significant spatial learning and memory deficits in the Morris water maze, as indicated by significant increases of latency during training and reduced quadrant occupancy in post-training probe trials. Furthermore, paired-pulse facilitation, frequency facilitation, and long-term potentiation are enhanced in the Schaffer collateral pathway of IN-PS cDKO mice at 2 months of age. Importantly, we found age-dependent neurodegeneration in IN-PS cDKO mice, similar to excitatory neuron-specific PS cDKO mice. The number of inhibitory neurons is reduced in the cerebral cortex and the striatum of IN-PS cDKO mice at the age of 9 months but is unchanged at 3 months, relative to littermate controls. Consistent with these findings, the number of apoptotic cells labeled by active caspase-3 immunoreactivity and the TUNEL assay is increased in the cerebral cortex of IN-PS cDKO mice at the age of 9 months. Neuronal loss in IN-PS cDKO mice is also accompanied with gliosis as shown by elevated GFAP and Iba1 immunoreactivity. These findings demonstrate essential roles of PS in synaptic plasticity, learning and memory, and neuronal survival in adult interneurons.

**Presentation 293.12 / F6** Cleavage of neural cell adhesion molecules by BACE1 is spatio-temporally regulated *in vivo*

Abstract
...
Abstract
β-site amyloid precursor protein cleaving enzyme 1 (β-secretase 1, BACE1) cleaves amyloid precursor protein (APP) to initiate the generation of amyloid beta peptides (Aβ). Studies strongly suggest that Aβ is associated with synaptic dysfunction and neuronal loss in Alzheimer's disease (AD). Thus, BACE1 is considered a prime therapeutic drug target for lowering Aβ levels in the AD brain. However, very recently, two clinical trials using different BACE1 inhibitors in patients with prodromal or preclinical AD were halted due to the worsening of cognitive functions, most likely owing to mechanism-based side effects.

In addition to APP, several neuronal proteins, including the neuronal cell adhesion molecule L1-like protein (CHL1) have been identified as BACE1 substrates and validated in vivo. We report here, for the first time, that neuronal cell adhesion molecule 1 and 2 (NCAM1 and NCAM2, respectively) are BACE1 substrates in vivo. Neuronal cell adhesion molecules have been shown to regulate formation, maturation, and maintenance of synapses. Since synaptic loss is one of the earliest signs of AD, the relationship between NCAMs and AD has been studied intensively. Interestingly, reduced synaptic NCAM1 and NCAM2 levels were reported in AD brains.

BACE1-mediated processing of NCAM1, NCAM2 and CHL1 was analyzed in the olfactory bulb and hippocampus of wild type mice and BACE1+/− mice at three different ages (postnatal day 10 (P10), 4 and 12 months). NCAM1 was cleaved in the olfactory bulb of wild type but not BACE1+/− mice at all ages analyzed. Instead, NCAM1 was processed by BACE1 in olfactory bulb at 4 and 12 months of age but not at P10 in wild type mice. Moreover, CHL1 was processed by BACE1 in olfactory bulb at P10 and 4 months of age but not at 12 months of age in olfactory bulb. In the hippocampus, NCAM1 and NCAM2 BACE1-mediated processing was detected only in synaptosomes but not in total homogenates. In contrast, CHL1 processing was clearly detected in both hippocampal homogenates and synaptosomes.

We also found that NCAM2 but not NCAM1 is sequentially cleaved by BACE1 and γ-secretase in vitro. Next, we identified and validated the BACE1 cleavage site of NCAM1 and NCAM2 by mass spectrometry and site-directed mutagenesis. Taken together, our data demonstrates that the regulation of BACE1-mediated processing of neuronal cell adhesion molecules (CHL1, NCAM1, and NCAM2) depends on the regions of brain, age, and subcellular localization in vivo. Supporting the concept of BACE1 may play important roles in physiological functions by regulating the proteolysis of substrates spatio-temporally.

Session 295 Alpha-Synuclein Models and Mechanisms I
Hall A
8:00 AM - 12:00 PM

Presentation 295.07 / F33 Transneuronal Propagation of Pathologic α-synuclein From the Gut to the Brain Models Parkinson's Disease

*K. KIM1, S.-H. KWON2, T.-I. KAM3, N. PANICKER4, S. S. KULIPAGounder1, S. LEE1, J. LEE1, W. KIM1, M. KOOK1, C. A. FOSS2, C. SHEH1, S. KULIPARIN1, P. J. PASRICA1, G. LEE1, M. G. POMPER1, V. L. DAWSON1, T. M. DAWSON1, H. KO1
1Inst. for Cell Engin., 2The Russell H. Morgan Dept. of Radiology and Radiological Sci, 3Ctr. for Neurogastroenterology, Dept. of Med., Johns Hopkins Univ., Baltimore, MD; 4Dept. of Pharmacol. and Toxicology, Univ. of Alabama at Birmingham Sch. of Med., Birmingham, AL, 5Dept. of Nuclear Med., Shanghai Jiao Tong Univ. Affiliated Sixth People's Hosp., Shanghai, China

Abstract
Analysis of human pathology led Braak to postulate that α-synuclein (α-syn) pathology could spread from the gut to brain, via the vagus nerve. Here, we test this postulate by assessing α-synucleinopathy in the brain in a novel gut-to-brain α-syn transmission mouse model, where pathological α-syn preformed fibrils were injected into the duodenal and pyloric muscularis layer. Spread of pathologic α-syn in brain, as assessed by phosphorylation of serine 129 of α-syn, was observed first in the dorsal motor nucleus, then in caudal portions of the hindbrain including the locus coeruleus, and much later in basolateral amygdala, dorsal raphe nucleus, and the substantia nigra pars compacta. Moreover, loss of dopaminergic neurons, motor and non-motor symptoms were observed in a similar temporal manner. Truncal vagotomy and α-syn deficiency prevents the gut-to-brain spread of α-synucleinopathy and associated neurodegeneration and behavioral deficits. This study supports the Braak hypothesis in the etiology of idiopathic PD.

Presentation 295.11 / F37 Endogenous astrocytic CDNF protects dopamine neurons in AAV-AS3T-α-synuclein rat model

*K. KYOUNG1, J. JANG2, A. HONG3, Y. CHUNG2, B. JIN1,2
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Abstract
Abnormal alpha synuclein (α-syn; SNCA) is one of the components within Lewy body characterized by Parkinson's disease (PD). AS3T mutant α-syn induces mitochondrial autophagy and macroautophagy leading to cell death. Cerebral dopaminergic neuronal cell death in α-synucleinopathy is considered a result of α-synuclein toxicity. Endogenous astrocytic CDNF protects dopaminergic neurons in the substantia nigra. This study supported the first description of CDNF-mediated protection of dopaminergic neurons in a mouse model of PD.

Session 297 ALS and Motor Neuron Disease
Hall A
8:00 AM - 12:00 PM

Presentation 297.01 / G11 Two axes of CHCHD10 dominant toxicity: TDP-43 and PINK1

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Abstract
Mutations in coiled-coil-helix-coiled-coil-helix-domain containing 10 (CHCHD10) have been identified as a genetic cause of
Alzheimer’s disease (AD), the most common cause of dementia, leads to neuronal damage and deterioration of cognitive functions in aging brains. Recently, both astrocytes and microglia acquiring reactive properties are involved in the AD progression. However, there are challenges to discover molecular and intercellular mechanisms of astrogliosis and microgliosis in AD progression due to the lack of appropriate model systems that accurately reflect AD-related immunity in human brains. We previously presented effective human AD brain models by tri-culturing human APP neurons, astrocytes, and microglia in a 3D microfluidic platform, which closely reconstructs key aspects of AD, β-tau signature, and neuroinflammatory. Here, the AD model was employed to clarify the molecular mechanisms of crosstalk between astrocytes and microglia contributing to neurotoxic inflammation in AD environments. We found the increased reactivity of astrocytes in response to AD producing excessive H$_2$O$_2$ (5.7 fold) and proinflammatory cytokines (IL-6, IFN-γ, TNF-α) compared to healthy models. The promoted neuronal damages in the co-cultured AD models were confirmed by increased phosphorylated tau (pTau) expression (2.2 fold) and LDH level (3.6 fold) compared to healthy models. The addition of either H$_2$O$_2$ scavenger or astrocyte-specific MAO-B inhibitor effectively prevented the taupathy and neurodegeneration validating that the major neuro toxic factor was the oxidative stress from the reactive astrocytes. To investigate the involvement of microgliosis in the AD progression, we added microglia to the AD models and found the elevated neurotoxic effects by observing increased pTau expression (1.3 fold) and decreased cellular viability (1.3 fold) compared to healthy models. Further single culture study with microglia was performed to explore the potential underlying mechanisms of microgliosis, which may exacerbate the neurodegeneration in AD. We found that synergistic effects of H$_2$O$_2$ and IL-6, found in reactive astrocytes in AD models, on M1 microglial polarization (6.5 fold). In addition, the combined treatments of H$_2$O$_2$ and IFN-γ triggered NO production (2.0 fold) from microgliosis. Currently, we are examining the intercellular pathways of astrocyte-driven microgliosis that promote neuronal damages in the co-cultured AD models were confirmed by increased phosphorylated tau (pTau) expression (5.7 fold) and proinflammatory cytokines (IL-6, IFN-γ, TNF-α) compared to healthy models. The promoted neuronal damages in the co-cultured AD models were confirmed by increased phosphorylated tau (pTau) expression (2.2 fold) and LDH level (3.6 fold) compared to healthy models. The addition of either H$_2$O$_2$ scavenger or astrocyte-specific MAO-B inhibitor effectively prevented the taupathy and neurodegeneration validating that the major neuro toxic factor was the oxidative stress from the reactive astrocytes. To investigate the involvement of microgliosis in the AD progression, we added microglia to the AD models and found the elevated neurotoxic effects by observing increased pTau expression (1.3 fold) and decreased cellular viability (1.3 fold) compared to healthy models. Further single culture study with microglia was performed to explore the potential underlying mechanisms of microgliosis, which may exacerbate the neurodegeneration in AD. We found that synergistic effects of H$_2$O$_2$ and IL-6, found in reactive astrocytes in AD models, on M1 microglial polarization (6.5 fold). In addition, the combined treatments of H$_2$O$_2$ and IFN-γ triggered NO production (2.0 fold) from microgliosis. Currently, we are examining the intercellular pathways of astrocyte-driven microgliosis that promote neuronal damages in AD brains, which may offer a promising target for drug discovery in AD.

Non-invasive imaging of inflammasome activation enables rapid and spatiotemporal detection of Alzheimer’s disease

Abstract

Alzheimer’s disease (AD) is the most common form of dementia among the elderly and the number of individuals with AD continues to increase. To develop effective therapeutics in AD, many scientists have been focusing on the development of novel drugs. However, the development of drugs has been known to fail. This failure could possibly be attributed to the administration of the treatment at a late stage in the disease progress. Thus, it is important to establish early diagnosis methods which can predict the risk of AD for effective prevention and treatment. Inflammasomes play a critical role in diverse inflammatory disorders, such as AD. Inflammasomes can be activated by various pathogenic insults and induces secretion of IL-1β after cleavage by active caspase-1, an executing protease of the inflammasome complex. Therefore, direct imaging of active caspase-1 in vivo may provide enormous advantages for diagnosis, drug discovery, and therapeutic monitoring in AD. Here, we developed an activatable fluorescence probe, comprised of caspase-1-specific cleavable peptide bridging a near-infrared fluorescence dye and a quencher, for visualization of active caspase-1. This novel caspase-1 probe is biocompatible and can be efficiently delivered into cells and tissues, and specifically emit fluorescence upon caspase-1 activation as assessed in vitro and in vivo inflammatory conditions. We demonstrated efficient in vivo imaging of caspase-1 activation in AD. Significant fluorescence emitted from the inflamed sites, as well as their draining lymph nodes, can be detected by macroscopic imaging analysis within 30 min after systemic injection of the probe. This novel synthetic probe could be applied for efficient and rapid detection of caspase-1 activity in a spatiotemporal way by non-invasive imaging and revolutionize the current paradigm for diagnosis and therapeutics in AD.
Our brain has the ability to learn about rewarding sensory stimuli through synaptic modifications of the associated circuits (reward-based learning). These changes depend on the sensory stimuli and the associated reward which is typically delayed. This temporal difference creates a conundrum, the so called “distal reward problem”: How does the brain know which synapses are responsible for the reward among those that were active during the waiting period? A theoretical solution is “synaptic eligibility traces”, silent and transient synaptic tags that can be converted into long-term synaptic strength changes by reward-linked neuromodulators. Previously in visual cortical slice preparation, we showed distinct synaptic eligibility traces for long-term potentiation (LTP) and depression (LTD), which are transformed by retrograde norepinephrine and serotonin signals, respectively. In the present work, we show evidence demonstrating the functional role of synaptic eligibility traces in the plasticity of visual responses in vivo using whole cell patch clamp recording and optical imaging of the intrinsic cortical signal. First, optogenetic activation of norepinephrine or serotonin projections in a temporally retrograde manner induced rapid and selective potentiation or depression of the associated visual response, respectively. Secondly, interfering with the conversion of synaptic eligibility traces prevented the rapid change of visual response by neuromodulators. Furthermore, we tested these ideas in a more “natural” setting, and found that preventing the conversion of eligibility traces also prevented ocular dominance changes induced by monocular deprivation. These results suggest that the conversion of synaptic eligibility traces by neuromodulators has a functional role in visual cortical plasticity via reward based learning mechanisms.

Abstract

Lateral ankle sprains have been reported as the most common injury in physically active populations. Poor postural control following the lateral ankle sprain is a key factor for chronic ankle instability, which is characterized by the feeling of the ankle giving way along with residual signs and symptoms for months to years. Up to 74% of acute lateral ankle sprain (ALAS) patients suffer chronic ankle instability with persistent postural control deficits. Recently, neuroimaging studies have shown that ligamentous injuries cause neural adaptation in the central nervous system (CNS), and such altered cortical activation may be underlying mechanisms for chronic ankle instability. However, to date, there is a limited study that identifies the centrally mediated neural adaptation in ALAS patients during a postural control task. Thus, the purpose of this case-control study was to identify the cortical activation pattern in ALAS patients compared with healthy controls during the bipedal balance task. A total of 10 subjects participated (5 ALAS patients, 5 healthy controls). Electro cortical activations over the frontal (Fz), parietal (Pz) and occipital (Oz) cortices were recorded using a 64-channel of Electroencephalograph (EEG) during a total of 12 trials of 10 second-bipedal balance task with eyes open. Theta (4-8 Hz) and alpha-2 (10-12 Hz) frequency bands power and total center of pressure path length (tCOP) were calculated for electro cortical activation and balance, respectively. We found that there was no significant difference in tCOP between groups during the bipedal-balance (*p=0.099, ALAS: 13.73 ± 3.66, control: 10.23 ± 5.80cm). However, the ALAS group showed greater parietal theta (Pz; p=0.003, ALAS: 0.28±0.03, control: 0.20±0.03) and less frontal alpha-2 (Fz; p=0.038, ALAS: 0.15±0.06, control: 0.24±0.05) compared to the control group. Theta frequency in the parietal cortex plays a key role in situational awareness to external stimuli, while less frontal alpha-2 power indicates more excitatory responses in the frontal cortex, which is the area for the cognitive decision-making process for motor tasks. These preliminary results suggest that ALAS patients were able to maintain postural stability similar to the healthy individual but different electro cortical activation patterns, indicating that ALAS patients demand more neural recruitment than the healthy individuals to process and integrate internalized attention and proprioceptive deafferented input.

Abstract

The maladaptation in reward-value dependent shifting between goal-directed and habitual actions may underlie multiple psychopathologies such as addiction, obsessive compulsive disorders, impulsivity and some decision-making disorders. Dorsomedial striatum (DMS) has been spotlighted because of its role in goal-directed behaviors orchestrated by neurons within the DMS via adenosine signaling. However, how astrocytes, the major modulator of extracellular adenosine levels, contribute to the neuronal synaptic activities and the sequential behavioral shifts remains largely unknown. Utilizing the Inscopix endomicroscopy/fiber photometry in vivo calcium imaging and the cell type specific activation of designer receptors exclusively activated by designer drugs (DREADDs), we confirmed that GFAP-driven activation of hM3Dq DREADDs increases intensity and frequency of calcium signaling in the DMS astrocytes of ALDH1L1-GCaMP6s expressing mice. We found
that this chemogenetic activation of the DMS astrocytes increase and decrease neuronal excitability of direct pathway Medium Spiny Neurons (dMSNs) and indirect pathway Medium Spiny Neurons (iMSNs), respectively. Specifically, it reduced the frequency of spontaneous excitation postsynaptic currents (sEPSCs) in dMSNs, whereas it increased the amplitude of the sEPSCs and decreased the frequency of spontaneous inhibitory postsynaptic currents (sIPSCs) in iMSNs. The changes in sEPSCs and sIPSCs induced by astrocytic activation were significantly inhibited in the DMS of mice lacking ethanol-sensitive adenosine transporter, ENT1 (equilibrative nucleoside transporter 1, Slc29a1); NTB1, an ENT1-specific blocker, also reduced the chemogenetic-evoked synaptic events, suggesting that ENT1 is, at least partly, required for astrocytic adenosine release. In the devaluation tests of reward seeking by within-subject instrumental nose-poking paradigm, which mice shift between goal-directed and habitual actions according to outcome value change, the chemogenetic activation of DMS astrocytes shifted the habitual behaviors to the goal-directed actions in sucrose-reward seeking in the ENT1 WT mice, but not in the ENT1 KO mice. When the ENT1 expression in the DMS is rescued by injection of GFAP-driven ENT1 expressing AAV into the DMS of the ENT1 KO mice, the behavioral shift was restored by the chemogenetic activation. Together, our results indicate that astrocyte-mediated adenosine signaling in the DMS determines goal-directed and habitual actions by selectively regulating specific synapses suggesting that reward-seeking behavior results from the interaction of neurons and astrocytes.

Presentation 372.20
Glia-Neuron Interactions in Diseased Brain

Session 366
Genetic and Neural Mechanisms for Development Disorders
Hall A

Presentation 366.10 / A67
Alteration in the intracellular cross-talk between mitochondria and exosome in the developmental disorder
* B. HA, J. HEO, Y.-J. JANG, T.-S. PARK, K.-H. LIM, S.-J. JEONG;
Korea Brain Res. Inst., Daegu, Korea, Republic of

Abstract
Extracellular vesicles (EV) including exosomes are considered as emerging tools for biomarkers screening and drug/gene delivery in diagnostic and therapeutic strategies, respectively, because they include tissue-specific and disease-related molecules such as lipids, proteins and RNAs. Exosomes, 50-150 nm nano-sized vesicles, are secreted by cells and important mediators of intercellular communications. In central nervous system, various evidences show that exosomes can transfer pathogens such as prion protein (PrP), α-synuclein, amyloid β (Aβ) and phosphorylated tau. Recent findings reveal that mitochondrial component including mtDNA can be packaged in exosome and thus be horizontally transferred between cells. It has been observed that intact mitochondria or their components can be transferred between cells in disease conditions such as cancer, stroke, and lung injury. However, until now, it is not elucidated the intracellular transferring mechanism between mitochondria and exosome in the developmental disorders yet. In this study, we performed the protein profiling in exosome derived from either the brain or primary neuron/astrocyte of the developmental disorders. Various mitochondrial components were detected in exosomes isolated from the brain and primary neuron/astrocyte prepared from the mouse model. Our findings show that mitochondrial proteins were remarkably decreased in disease mouse models which was confirmed by analysis with mitotracker and qRT-PCR for mtDNA/nDNA ratio as well as gene expression related to mitochondrial biogenesis. In conclusion, these results suggest that the intracellular trafficking system between mitochondria and exosome is altered under the developmental dysfunction and exosomes-derived mitochondrial components have a possibility as potential diagnostic/prognostic/therapeutic targets.
Abstract

Chronic inflammation in the hypothalamus has been proposed as a key pathological factor that alters feeding behaviors and energy homeostasis associated with obesity and diabetes. Emerging evidence suggests that metabolic shift from oxidative phosphorylation to glycolysis contributes to neuroinflammatory responses and pathophysiology of diverse neurological disorders. We report that streptozotocin-or high fat diet-induced diabetes enhanced hypothalamic expression and activity of pyruvate dehydrogenase kinase (PDK), a key regulatory enzyme in mitochondria, that caused glycolytic metabolic shift along with substantial inflammatory activation in the hypothalamus. Genetic ablation or inhibition of hypothalamic PDK attenuated diabetes/obesity-induced neuroinflammatory hallmark in the hypothalamus and food/calorie intake. Moreover, dysregulation of hypothalamic neuropeptidergic circuitry involved in the regulation of feeding behavior was improved by deficiency or inhibition of hypothalamic PDK. Studies using primary astrocytes revealed that PDK plays a critical role in altered glycolytic metabolism and inflammatory activation of glial cells, which favor hypothalamic inflammation in vivo. Collectively, these findings unveil a novel role of PDK in regulating metabolic and inflammatory pathways that contribute to hypothalamic manifestations of diabetes and obesity.

✿ Session 373 Microglial Activation in Disease States

1:00 PM - 5:00 PM

✿ Presentation 373.24 / C35 Targeting microglial Gi DREADD for the inhibition of chronic pain

*M.-H. YI1, Y. LIU1, K. LIU1,4, T. CHEN1, D. BOSCO1, J. ZHENG1, M. XIE1, L.-J. WU1,2,3,4

Abstract

Microglia are known to be important for neuropathic pain, however, a causal relationship between microglia and development of neuropathic pain has yet to be directly tested in vivo. To address this question, we have developed CX3CR1CreER(LSL-HM4D) transgenic mice to enable selective expression of Gi DREADD and employed microglia-based chemogenetic techniques in a mouse model of neuropathic pain. We found that microglial Gi DREADD activation inhibited spinal nerve transection (SNT)-induced microglial activation, chronic pain initiation and maintenance. Gi DREADD activation downregulated the transcription factor interferon regulatory factor 8 (IRF8) and its downstream proinflammatory cytokines including interleukin 1 beta (IL-1β). These findings deepen our understanding the causal role of microglia in neuropathic pain pathogenesis and suggest the potential therapeutic approach of targeting microglial Gi DREADD for neuropathic pain treatment.

This work is supported by National Institute of Health (R01NS088627 and R21DE025689)

✿ Session 397 Pain: Thalamus, Cortex, and Amygdala Processing

1:00 PM - 5:00 PM

✿ Presentation 397.20 / M29 Inhibition of neuropathic pain by glial regulation in the insular cortex

*S. CHO1, K. KIM1,2, M. CHA1, S.-K. HONG1, M. XIE1,2,3

Abstract

The insular cortex (IC), one of the brain areas that process motivational and emotional aspect of pain information. Studies on the role of neuroglia have been carried out in various pain researches, but the majority of researches have been done at the spinal cord. We hypothesize that glial cells may mediate the neuronal alteration through regulating synaptic physiology of cortical neurons in the IC. The aim of this study was to reveal the associations between neuroglia and neurons in the IC on neuropathic pain (NP) condition. Fluorocitrate (FC) and minocycline (MC) were bilaterally administered into the IC at different injection time points. We conducted two experiments, one is injection of FC (1 nM) and MC (20 μM) into the IC for 7 days (NP 0-7 days) and the other is application of drugs in the chronic pain stage (NP 8-14 days) for 7 days. The behavioral tests were performed before and after drug application. Western blot analysis was performed to evaluate expression changes of glial cells performed. Especially, MC-treated group which belongs to early inhibition model showed a significant pain alleviation effect despite the drug withdrawal. The chronic pain stage inhibition model showed significant analgesic effect which was confirmed by behavioral tests during the period that FC and MC were applied. Interestingly, GFAP increased as much as vehicle in the MC-treated group of the early inhibition model. These data suggest that glial cell regulation in the IC has a pain relieving effects during the development of chronic pain. Suppression of glial cells just after the nerve injury could delay the neuronal changes associated with chronic pain development. This study was supported by the Basic Research Program through the National Research Foundation (NRF) funded by the Ministry of Science and ICT (NRF-2015R1C1A1A01053484 and 2017R1A2B3005753)

✿ Session 398 Central Nervous System Mechanisms in Pain

1:00 PM - 5:00 PM

✿ Presentation 398.17 / N6 Alleviation of neuropathic pain by the inhibition of mTOR complex in the insular cortex

* Presentation 397 / A. BHUSAL1, J.-H. KIM1, M. K. JHA2, Y. GO3, I.-S. JANG1,2, I.-K. LEE4, K. SUK1,4

Abstract

Chronic inflammation in the hypothalamus has been proposed as a key pathological factor that alters feeding behaviors and energy homeostasis associated with obesity and diabetes. Emerging evidence suggests that metabolic shift from oxidative phosphorylation to glycolysis contributes to neuroinflammatory responses and pathophysiology of diverse neurological disorders. We report that streptozotocin- or high fat diet-induced diabetes enhanced hypothalamic expression and activity of pyruvate dehydrogenase kinase (PDK), a key regulatory enzyme in mitochondria, that caused glycolytic metabolic shift along with substantial inflammatory activation in the hypothalamus. Genetic ablation or inhibition of hypothalamic PDK attenuated diabetes/obesity-induced neuroinflammatory hallmark in the hypothalamus and food/calorie intake. Moreover, dysregulation of hypothalamic neuropeptidergic circuitry involved in the regulation of feeding behavior was improved by deficiency or inhibition of hypothalamic PDK. Studies using primary astrocytes revealed that PDK plays a critical role in altered glycolytic metabolism and inflammatory activation of glial cells, which favor hypothalamic inflammation in vivo. Collectively, these findings unveil a novel role of PDK in regulating metabolic and inflammatory pathways that contribute to hypothalamic manifestations of diabetes and obesity.
Abstract

In the pain matrix, the insular cortex (IC) is mainly involved in discriminative sensory and motivational emotion. Recent studies have shown that the mTOR kinase is major regulator of protein synthesis and it could be involved in the regulation of synaptic plasticity and memory formation in the central nervous system. This study was conducted to determine the changes in pain behavior and downstream effectors by mTOR inhibition. In addition, the dynamic changes in the spatiotemporal patterns of the IC activities were analyzed and compared before and after inhibition of mTOR complex in the IC after nerve injury. Under isoflurane anesthesia, the neuropathic surgery was conducted to Sprague-Dawley rats and the rats were anesthetized with isoflurane. The behavioral tests were performed before and after microinjection of mTOR inhibitors (Torin1 and XL388) and vehicle. To assess the spatiotemporal patterns of the IC activities, the optical imaging was conducted. The response of neuronal activities was recorded and these signals were analyzed. Western blot was carried out in order to ascertain the expression changes in mTOR and its downstream effectors. As a result, mTOR inhibitors showed the pain-relieving effect four hours after microinjection of mTOR inhibitors in behavioral test. In optical imaging, the Torin1- and XL388-injected groups showed decreased signals and reduced activation area contrary to the vehicle group. The phosphorylation of downstream effectors of mTOR complex, such as P70S6K and 4EBP, were significantly increased in the vehicle-treated group. However, they were decreased in the Torin1- and XL388-treated groups. The other phosphorylated downstream effectors of mTOR complex, Akt and PKCα, also increased in the vehicle-treated group while significantly reduced in the mTOR inhibitor-treated groups. In addition, the expression level of phosphorylated mTOR significantly increased in the vehicle-treated group but, it was decreased in the Torin1- and XL388-treated groups. These findings suggested that the pain-relieving effect of Torin1 and XL388 was manifested by modulation of mTOR complex. This study was supported by the Basic Research Program through the National Research Foundation (NRF) funded by the Ministry of Science and ICT. (NRF-2015R1C1A1053484 and 2017R1A2B3005753)

Abstract

Oxytocin (OXT) is the evolutionarily conserved neuropeptide in mammals, which is produced by neurons of the paraventricular hypothalamic (PVH) and the supraoptic (SO) nucleus. Many studies have been conducted to show that OXT neurons projected to broad brain regions and the spinal cord, and revealed underlying mechanisms of OXT to the circuit-specific behaviors. However, it is unclear how OXT neurons within the hypothalamic nuclei are topographically organized with regard to input and output throughout the whole brain. Here, we employed viral vector-based techniques, which combined with adeno-associated virus (AAV) and monosynaptic rabies tracing techniques, to label axonal output and pre-synaptic input of OXT neurons in mice.
We imaged the whole mouse brains at cellular resolution using serial two-photon tomography and used whole-brain data processing pipeline to achieve quantitative input-output mapping of hypothalamic OXT neurons. The OXT neurons of PVH projected dorsally to the lateral zone of hypothalamic and continued into the medulla through the midbrain and the pons. This pathway provides dense input to the substantia nigra, the ventral tegmental area, the periaqueductal gray (PAG), and the parabrachial nucleus. The OXT neurons also projected to the forebrain regions: the nucleus accumbens (ACB), the lateral septal nucleus (LS), and olfactory cortex areas. Both of the OXT neurons in PVH and SO were ventrally projected into the tuberal nucleus (Tu), then reached to the median eminence. Rabies-virus-based input mapping indicated that OXT neurons of the PVH received synaptic input from the hypothalamus, the thalamus, and the striatum, while inputs in the SO were mainly from the hypothalamic area. Interestingly, the brain regions previously associated with social behavior, learning, and memory were reciprocally connected, including the ventromedial hypothalamic nucleus, the parasubthalamic nucleus, the lateral hypothalamic area, the central amygdalar nucleus, the bed nuclei of the stria terminals, the PAG, the LS, and the ACB. In summary, our data established the anatomical organization of OXT neurons in order to understand the neural circuit mechanisms of OXT neurons in regulating different circuit specific behaviors.

**Session 411 Fear and Aversive Learning and Memory: Circuits I**

**Presentation 411.20 / V44 The role of hippocampus to amygdala projection in two way active avoidance**

*K. SUNG*¹, J. YU², J. PYO², J.-H. KIM²;
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**Abstract**

Fear and defensive behavior triggered by fear are critical for survival of animal. For a decade, studies about neural circuit of fear are based on pavlovian fear conditioning paradigm whereas avoidance related fear circuit is overlooked. In prior studies, it is revealed that amygdala, medial prefrontal cortex, and nucleus accumbens are involved in avoidance learning & performance. But it is not well known about hippocampus in active avoidance. There were some reports that hippocampus involve in active avoidance performance. But it is not known how hippocampus contribute in avoidance learning and performance in our study, we found that hippocampal neurons are activated during active avoidance training & test by c-fos staining. And we found that hippocampal amygdala projection is necessary for active avoidance learning by optogenetically inhibiting hippocampal amygdala projection during avoidance learning.

**Session 414 Neural Circuits Underlying Alcohol Dependence**

**Presentation 414.20 / X10 Dopamine D2 receptor in ethanol induce behavioral sensitization**

*N. M. DELGADO*, C. M. SIERRA, P. R. SABANDAL, K. A. HAN;
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**Abstract**

Males rarely court other males in *Drosophila melanogaster*. However, ethanol experience causes disinhibited inter-male courtship that is augmented with repeated ethanol exposures. Our previous work uncovered the requirement of dopamine signaling and the D1-like Dopamine/Ecdysone receptor, but not D1 or D5 receptors, for this type of ethanol-induced behavioral sensitization. The role of the D2-like DA D2 receptor (dD2R), however, remains uncharacterized and this study addresses this knowledge gap. To do this, we exposed the wild-type Canton-S (CS) and D2 receptor mutant (d2r) males to ethanol till sedation every day and monitored the behavioral responses including initial sensitivity, tolerance development, locomotor response and disinhibited courtship. Compared to CS, d2r flies exhibited normal initial sensitivity to the sedative effect of ethanol but displayed reduced tolerance, blunted locomotor response as well as substantially dampened behavioral sensitization to the disinhibition effect of ethanol. These findings reveal multiple roles of dD2R in ethanol-induced behaviors. We found that re-expression of either of the three major D2 receptor isofoms differing in the third intracellular loop in either at or mushroom body neurons fully rescued the d2rs sensitization phenotype, indicating that the functional site of dD2R for sensitization is the mushroom body neurons. We are in the process of mapping the neural sites for the dD2R role in locomotor response. Our research may provide novel insights into the mechanisms that dD2R mediates multiple effects of ethanol.

**Session 421 Human Learning: Feedback, Reinforcement, and Reward**

**Presentation 421.16 / AA11 Neural mechanisms underlying human reinforcement learning in a continuous choice space**

*J. LEE, S. KIM*;
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**Abstract**

Computational, behavioral and neural correlates of human reinforcement learning are well understood in decision making with discrete choices, however, little has been known about more generalized decision making with continuous action space. Here, we designed an fMRI experiment in which subjects search a hidden target in a 2-dimensional space given binary feedbacks. Subjects received a monetary reward each time they selected a point close enough to a hidden target which was randomly set after 12 searches. A “reward zone” centered around a hidden target continued to shrink only after each rewarded trial, guiding subjects to search a hidden target. We suggested two computational models accounting for individual subjects’ search behavior: (1) Maximum a posterior model assuming the Bayesian update of expected reward probability with greedy selection (full exploitation) and (2) maximum information gain model suggesting a choice maximizing the reduction of uncertainty of the expected reward probability (full exploration). For the preliminary fMRI results, we found model-based reward prediction error showing a distinct pattern that can be explained by the models we suggested.
Abstract
Meta-memory is the subjective judgement and monitoring of one's own memory. Although it has been associated with the prefrontal cortex (PFC), it is unclear whether meta-memory and actual memory accuracy can dissociate neural signatures. In this study, we began addressing this issue by identifying PFC activity related to meta-memory judgments using a portable, versatile high-density functional near infrared spectroscopy (fNIRS) system.

Healthy adults (n=8) watched various animations of objects moving one-by-one into baskets. After a delay, subjects were shown the target video or a lure video and were asked whether they recognized the video as one that they had seen before. To measure meta-memory, subjects were asked to rate the confidence of their recognition judgment and the amount of details that they remembered. To assess memory accuracy, subjects were prompted to recreate the original video by clicking with the mouse the objects and baskets in the correct sequence.

Overall, subjects had 81% accuracy in active recollection and 69% accuracy in recognition. Subjects reported higher confidence on correctly recognized trials than on incorrect trials (t(82)=-2.89, p=.005). Analysis of fNIRS activity showed that, consistent with previous studies, right lateral PFC activity was associated with subjective uncertainty of memory during recall (r=0.72, p=.067 for confidence of recognition, r=0.76, p=.048 for reported amount of detail) while left lateral PFC activity was associated with the higher meta-memory (p=0.71, p=.076). Moreover, different neural signals during encoding were predictive of subjective and objective recollection. Higher activation of the right PFC during encoding predicted later reporting of more details in subjective recollection. In contrast, higher frontopolar cortex activation during encoding predicted higher accuracy during recollection (right: r=0.70, p=.033; left: r=0.87, p=.010). Though it had been previously shown that the rPFC is associated with subjective recollection and that the frontopolar cortex is associated with episodic memory retrieval, their involvement in encoding has not been widely reported. One possible explanation is that the PFC's monitoring of new episodic information during encoding contributes to better performance during recollection.

In conclusion, we observed multiple signals from the PFC that correlate with subjective/objective memory and revealed that these predictive activations may be specific to the encoding or retrieval. Such measurements provided by a portable fNIRS system could have wide applications for assessing meta-memory in various clinical and educational settings.

...continued text...
Abstract

The cellular resolution via serial two-photon tomography on two different transgenic mouse lines (OTR-eGFP and OTR+/-) revealed the spatial and temporal patterns of OTR expression. This is particularly significant in the early postnatal brain, where the expression patterns of the oxytocin receptor (OTR) are critical for neurodevelopmental disorders such as autism spectrum disorder. Despite its significance to human health, knowledge of quantitative brain-wide spatial and temporal OTR expression patterns is limited, especially in the early postnatal period. Therefore, we imaged whole brain OTR expression patterns at discrete developmental stages with peak expression during early postnatal critical periods. Previous evidence suggests strong links between oxytocin receptor dysfunction and the pathogenesis of neurodevelopmental disorders such as autism spectrum disorder. Our study aims to provide quantitative and cellular-resolution information on OTR expression patterns, which will aid in understanding the developmental shifts with peak expression during early postnatal critical periods. This information will be crucial for the development of targeted therapies and interventions for neurodevelopmental disorders.


**Session 458** Autism: Physiology, Systems, and Behavior

8:00 AM - 12:00 PM

**Hall A**

**Presentation 458.11 / A34** Quantitative brain wide map of the oxytocin receptor in postnatally developing mouse brains

*K. T. NEWMASTER1, Z. NOLAN2, M. CHON2, M. TABBA3, S. HIDEMA2, K. NISHIMORI2, E. A. HAMMOCK2, Y. KIM2; 1Pennstate Col. of Med., Hershey, PA; 2Pennsylvania State Univ. Col. of Med., Hershey, PA; 3Psychology, Florida State Univ., Tallahassee, FL; 4Mol. Biol. Grad. Sch. of Agr. Sciences/Tohoku Un, Sendai-Shi, Japan; 5Grad Sch. of Agric Sci, Tohoku Univ., Sendai-Shi, Japan; 6Col. of Medicine, Penn State Univ., Hershey, PA

Abstract

Oxytocin is an endogenous neuropeptide that plays a critical role in the development and expression of social behavior. The primary postsynaptic mediator of oxytocin signaling is the oxytocin receptor (OTR). OTR expression undergoes dramatic developmental shifts with peak expression during early postnatal critical periods. Previous evidence suggests strong links between oxytocin receptor dysfunction and the pathogenesis of neurodevelopmental disorders such as autism spectrum disorder. Despite its significance to human health, knowledge of quantitative brain-wide spatial and temporal OTR expression patterns remains limited, particularly in the early postnatal brain. Therefore, we imaged whole brain OTR expression patterns at the cellular resolution via serial two-photon tomography on two different transgenic mouse lines (OTR-eGFP and OTR+/-).
Using newly generated 3D postnatal brain templates for early postnatal timepoints, we quantified OTR expressing cell density at postnatal days (P) P7, P14, P21, P28, and P35. These quantifications revealed that the heterozygote OTR<sup>hnuR<sup>ous</sup> line, but not the OTR<sup>eGFP</sup> line, faithfully reports OTR expression at the cellular level. We found that there is significant temporal and regional heterogeneity in OTR expression patterns across cortical and subcortical regions. We then used OTR-Cre:Al<sub>41</sub> cumulative labelling to identify expression downregulation and not cell death as the main mechanism driving developmental OTR patterns. Moreover, immunohistochemistry showed that majority of OTR-expressing neurons in the cortical layers except layer 6b are glutamatergic at P21. These results provide quantitative data that is essential to understanding the OTR development in the mouse brain.

**Session 471 Alzheimer's Disease: APP/Abeta Animal Models**
**Hall A**
**Presentation 471.12 / D29**

**Uregulation of MeCP2 level in red nucleus cause late-life depressive phenotypes**

*Y. CHOI<sup>1</sup>, J. RYU<sup>2</sup>, H.-S. KIM<sup>1</sup>, H.-I. IM<sup>1</sup>.

<sup>1</sup>School Natl. Univ. Col. Med., Seoul, Korea, Republic of; <sup>2</sup>Ctr. For Neurosci., Korea Inst. of Sci. & Technol., Seoul, Korea, Republic of

**Abstract**

Late-life depression affects 8 to 16% of older adults, and often co-occur with other neuropsychiatric disorders that many elderly people suffer from. To develop a protocol that selectively cause depression in old mice, we created a new stress schedule, and named our protocol the Social stress infused Unpredictable Chronic Mild Stress (SUCMS). Our study applied SUCMS to the C57BL<sub>6</sub>/J (B6) and C57BL<sub>6</sub> x C3H hybrid (B6/C3H) mice in young (2mo) and old age (7mo) to induce depressive-like state. The old B6 and B6/C3H mice, but not young B6 and B6/C3H mice, show increased lethargy when exposed to SUCMS. Interestingly, the old B6 and B6/C3H mice with SUCMS also exhibited cognition deficit. They also showed increased tendency of anxiety. For further study for other neuropsychiatric disorders related to late-life depression, we applied SUCMS in APP/P1 transgenic mice. SUCMS exposed APP/P1 transgenic mice showed increased tendency of lethargy, indicating that SUCMS can be also used for investigation of comorbidity study between depression and Alzheimer's disease (AD). Methyl CpG binding protein 2 (MeCP2) is a transcriptional regulator that involves in maintaining synapses and normal function of cells that reside in the brain. A previous study revealed that elevated MeCP2 in mice causes cognitive deficits and Tau dysregulation. Therefore, we would like to confirm the expression level of MeCP2 in SUCMS exposed brain. They showed increased expression of MeCP2 in the red nucleus (RN). The brain region that is not much studied so far except for having functions of motor integration. Previous studies about RN have shown that activity of RN is related to upper limb tremor, reach-to-grasp movements and the reflex response. Also, a recent human brain imaging study proved significant connectivity between RN and the cerebral cortex. Although it is well known that cerebral cortex plays a key role in memory and perception, how RN affects cognition function and depressive symptoms is not revealed. Our results indicate that induction of late-life depression results in overexpression of MeCP2 in RN, which eventually cause depressive behaviors, cognition decline and anxiety. We also expect that these pathological alterations in late-life depression affect the major symptoms of AD.

**Session 476 Neuroprotective Mechanisms**
**Hall A**
**Presentation 476.19 / G8**

**Gintonin, a ginseng-derived exogenous lysophosphatidic acid receptor ligand, attenuates mutant Huntingtin toxicity**

*B. CHEON<sup>1</sup>, M. JANG<sup>1</sup>, Y. CHANG<sup>2</sup>, S. LEE<sup>2</sup>, J. CHOI<sup>1</sup>, I.-H. CHO<sup>1</sup>.

<sup>1</sup>Kyung Hee Univ., Seoul, Korea, Republic of; <sup>2</sup>Korea Inst. of Sci. and Technol. (KIST), Seoul, Korea, Republic of

**Abstract**

Gintonin is a ginseng-derived exogenous G protein-coupled lysophosphatidic acid (LPA) receptor ligand. Although previous in vitro and in vivo studies demonstrated the therapeutic role of gintonin against Alzheimer's and Parkinson's diseases, the neuroprotective effects of gintonin in Huntington's disease (HD) are still unknown. In this study, we investigated whether gintonin could ameliorate the mutant huntingtin toxicity in cellular or animal model of HD. Gintonin reduced cell death and neuroprotective effects of gintonin in Huntington's disease (HD) are unknown. In this study, we investigated whether gintonin could ameliorate the mutant huntingtin toxicity in cellular or animal model of HD. Thus gintonin might be a therapeutic candidate to treat HD.

**Session 480 Traumatic Brain Injury: Mechanisms and Therapeutic Strategies**
**Hall A**
**Presentation 480.17 / I16**

**Growth differentiation factor 11 promotes survival of retinal ganglion cells in vitro and in vivo**

*H. YOO<sup>1</sup>, U. SHANMUGALINGAM<sup>2</sup>, D. CHAN<sup>2</sup>, M. LUI<sup>2</sup>, P. SMITH<sup>2</sup>.

Neurosci., Carleton Univ., Ottawa, ON, Canada

**Abstract**

The visual system is a well-established model system to study axon regeneration and cell survival in vitro and in vivo. The use of this model has resulted in the identification of a variety of factors that improve cell survival and axonal growth after axon injury. Growth differentiation factor 11 (GDF11), a transforming growth factor-β (TGF-β) family member, was previously identified as a rejuvenation factor that promoted neurogenesis in aging mice. Previous work has revealed that gdf11 mRNA is expressed in the developing retina, and that GDF11 protein can signal Xenopus retinal ganglion cell (RGC) growth in vitro. Previous work has revealed a striking decline in intrinsic RGC growth potential with age. The mechanisms mediating this dramatic loss of axonal
growth ability has fueled significant interest in defining the factors that could contribute to this limitation in growth ability. The potential regenerative effect of GDF11 on mammalian RGCs remain unclear. Experiments were designed to determine whether GDF11 treatment promotes RGC survival and axonal growth using in vitro RGC culture and in vivo optic nerve crush models. Our data revealed that GDF11 administration was sufficient in protecting RGCs both in vitro and in vivo, but did not promote axonal growth. Our data also suggest that GDF11 promotes its neuroprotective effects via activation of phospho-Smad2/3 in vitro.

**Session 486 Touch: Cortical Encoding and Plasticity**

**Presentation 486.05 / L13 Somatosensory brain mapping**

*S. LEE, M. LEE, J. KIM, S.-W. PARK, J.-H. AHN, S. YANG, S. YANG; 2Nano-Bioengineering, Incheon Natl. Univ., Incheon, Korea, Republic of; 3Yonsei Univ., Seoul, Korea, Republic of; 4City Univ. of Hong Kong, Kowloon, Hong Kong

Abstract
The shaping and responsiveness of brain map, an indicative of cognitive status, is drastically influenced by experience. Previous representative mapping tools such as penetrating electrodes and magnetic resonance methods have limitation to clinical use largely due to pervasiveness and low spatiotemporal resolution, respectively. Here, we recently develops graphene-based epipolar electronics are integrated into an electrocorticography (ECoG) array, therein having a large scale, real-time, and safe recording/stimulation with desirable resolution. This system is empirically tested for cortical representation of somatosensory maps. Also, electrical stimulation in a subset of graphene spots enables to enhance sensory responses, demonstrating activity-dependent plasticity in a large scale. We propose that this technology heralds a new generation of brain-machine interfaces for studying brain map, map plasticity, and map-related diseases.

**Session 502 Impacts of Sleep Disruption**

**Presentation 502.21 / V14 Voltage-gated potassium channel shaker promotes sleep via thermosensitive GABA transmission**

*J.-H. KIM, Y. KI, H. LEE, M. HUR, J.-H. HUR, C. LIM; UNIST, Ulsan, Korea, Republic of

Abstract
Genes and neural circuits coordinately regulate sleep homeostasis. However, it remains elusive how these endogenous factors shape animal sleep in response to environmental changes. Here, we found that Shaker (Sh) expressing GABAergic neurons projecting onto dorsal fan-shaped body (dFSB) constitute a neural pathway important for temperature-adaptive sleep behaviors in *Drosophila*. Loss of Sh function potently suppressed sleep at low temperature whereas light and high temperature cooperatively gated Sh effects on sleep. RNA interference-mediated depletion of Sh expression in GABAergic neurons partially phenocopied Sh mutants. Moreover, trans-heterozygous mutations that decrease GABA transmission rescued Sh mutant sleep. Transgenic mapping further revealed that the ionotropic GABA receptor, Resistant to dieldrin (Rdl), in dFSB neurons acts downstream of Sh and antagonizes the sleep-promoting effects of Sh. In fact, Rdl inhibited the intracellular cAMP signaling of constitutively active dopaminergic synapses on dFSB neurons at low temperature. On the other hand, high temperature silenced GABAergic synapses onto dFSB neurons, thereby potentiating the wake-promoting dopamine transmission. We propose that temperature-dependent switching between these two synaptic transmission modalities may adaptively tune the neural property of dFSB neurons to temperature shifts and reorganize sleep architecture for the benefit of animal fitness.

**Session 503 Sleep Regulation**

**Presentation 503.07 / V28 Scully in sleep regulation and dementia**

*A. ARZOLA, Jr, P. SABANDAL, K.-A. HAN; Biol. Sci., Univ. of Texas at El Paso, El Paso, TX

Abstract
Sleep is an important physiological process for memory, metabolic waste clearance in the brain, and other cognitive functions. The fruit fly *Drosophila melanogaster* and humans share aging-associated sleep features including reduced sleep time and fragmented sleep architecture. Sleep dysfunction is a common feature of Alzheimer's disease and related dementia; however, the mechanism by which sleep dysfunction contributes to dementia is not well understood. We found that the scully mutant flies have abnormal sleep. Scully is the fly homolog of 17-β-hydroxysteroid dehydrogenase 10 (HSD17B10), a versatile mitochondrial enzyme known to bind amyloid β-peptide and is overexpressed in the brain of Alzheimer's disease patients. Interestingly, scully mutant flies show the features of dementia that include dysfunctional inhibitory control and memory loss. To investigate whether abnormal sleep in scully is linked to dementia, we are investigating whether reinstatement of normal sleep in scully would rescue the dementia phenotypes and whether overexpressed scully causes sleep anomaly or dementia or both. The progress of the study will be presented. This study may provide novel insights in the role of scully in Alzheimer's disease and related dementia.
**Presentation 505.03 / W13** Dorsolateral periaqueductal gray activates antipredatory neural responses in the amygdala in foraging rats

**E. KIM**, M.-S. KONG, S. PARK1,2, J. ROMANI, S. KIM3, J. CHO4, J. J. KIM1,3;  
1Psychology, Univ. of Washington, Seattle, WA; 2Computer Sci. and Software Engin., Univ. of Washington, Bothell, WA; 3Program in Neurosci., Univ. of Washington, Seattle, WA; 4Catholic Kwandung Univ., Gangneung, Korea, Republic of; 5Catholic Kwandong Univ. Int'l. St. Mary's Hosp., Incheon, Korea, Republic of; 6Korea Univ. of Sci. and Technol., Daejeon, Korea, Republic of; 7Korea Inst. of Sci. and Technol., Seoul, Korea, Republic of

Abstract  
The dorsolateral division of the periaqueductal gray (dPAG) and the amygdala are known to direct defensive responses (Bandler & Shipley, 1994, Fanselow, 1994). We have previously reported that electrical stimulation of the dPAG caused rats foraging in food in an ecologically-relevant environment to escape to the safe nest (Kim et al., 2013). This fleeing response was blocked by amygdalar lesions and inactivation, suggesting that the dPAG-amygdala pathway is crucial to the brain's innate defensive system. Recently, we also found that dPAG neurons responded to a looming robotic predator and that optogenetic excitation of the dPAG neurons elicited neural activity in the amygdala. However, the specific function of the dPAG-amygdala neurotransmission when animals encounter predatory risks is unknown. To address this issue, we employed single unit recording and optogenetic techniques in our ‘approach food-avoid predator’ paradigm (Choi & Kim, 2010; Kim et al., 2018). Specifically, male Long-Evans rats were implanted with tetrode arrays into the BLA (basolateral amygdala) or CeA (central amygdala) and injected with AAV-CaMKIIa-hChR2-EYFP into the dPAG. After recovery, rats maintained on ~85% normal body weight underwent successive stages of habituation, baseline foraging, and optogenetic dPAG stimulation (473 nm; 10 ms pulses at 20 Hz; 2 s) and robot (Lego Mindstorms) testing, during which BLA and CeA units were collected. We found that optical dPAG stimulation increased neuronal activity in both BLA and CeA and caused naive rats approaching a food pellet to instantly flee to the nest. The dPAG photostimulation-responsive BLA neurons also exhibited rapid phasic spiking to the looming robot whereas the photostimulation-responsive CeA neurons showed delayed tonic spiking. Furthermore, higher proportions of photostimulation-responsive neurons in BLA and CeA also reacted to the robot compared to photostimulator-negative-responsive neurons. These results suggest that functional interaction between dPAG and amygdalar neurons subserve antipredatory defensive mechanisms.

**Session 524** Computational Tools for Brain and Behavioral Experiments  
Hall A

**Presentation 524.11 / DD27** Web-based integrated database platform for exploring and sharing omics datasets

**J. CHOI**, N. KIM, Y.-J. JANG, J. HEO, B. HA, *S.-J. JEONG;  
KBRRI, Daegu, Korea, Republic of

Abstract  
It has been recently increasing to demand the data base platform for analysis of big data such as brain images and omics including proteomics and transcriptomics data in neuroscience field. Many database open to be shared, but most of them just provide the data obtained from experiments on their own interests and purposes, not such a kind of the platform. In this study, we created a web-based database system for searching, sharing, and analyzing the multiple data integrated by the open resources which are already existed. This system includes proteomics data, especially secretomes from extracellular vesicles (EV) of either neurons or astrocytes. REST(Representational State Transfer) service were adapted in our system to integrate the open resource such as datasets of Allen Brain Atlas and STRING DB. It allows users to get the information and compare them with their own data as well as the information of protein interaction. We usually used the SDK library to store the data in a web service, but the server was slow and stopped because of the high traffic and memory usage. Web-based RESTful service was utilized to develop lightweight, fast, scalable, and easy to maintain, so we used it. In order to visualize integrated data on the web, we have parsed the resource represented in XML as a DOM(Document Object Model) method and obtained the objects and visualized them as PHP language. Consequently, we established fundamental database platform with the omics data integrated by open resources. It is expected to be useful for researchers who want to compare and analyze their own data and several open data.

**Session 535** Neurodevelopmental Disorders: New Molecular Mechanisms  
Room N427

**Presentation 535.01** Dissecting the molecular basis of MTOR somatic mutations in aberrant brain development and neural circuit formation

**S. PARK**, J. LIM1, S. RAMAKRISHNA2, S. KIM3, W. KIM4, J. LEE5, H.-C. KANG6, J. F. REITER7, D. KIM1, H. KIM1, J. LEE1;  
1KAIST, Daejeon, Korea, Republic of; 2Hanyang Univ., Seoul, Korea, Republic of; 3Yonsei Univ., Seoul, Korea, Republic of; 4KISTI, Daejeon, Korea, Republic of; 5Univ. of California, San Francisco, CA

Abstract  
Focal malformations of cortical development (FMCds), including focal cortical dysplasia (FCD) and hemimegalencephaly (HME), are major etiologies of pediatric intractable epilepsies exhibiting cortical dyslamination. Brain somatic mutations in MTOR have recently been identified as a major genetic cause of FMCds. However, the molecular basis of MTOR somatic mutations in aberrant brain development and neural circuit formation remains poorly understood. Especially, the molecular mechanism by which these mutations lead to cortical dyslamination is still elusive. Here, using patient tissue, genome-edited cells, and mouse models with brain somatic mutations in MTOR, we discovered that disruption of neuronal ciliogenesis by the mutations underlies cortical dyslamination in FMCds. We found that abnormal accumulation of OFD1 at centriolar satellites due to perturbed autophagy was responsible for the defective neuronal ciliogenesis. Additionally, we found that disrupted neuronal ciliogenesis accounted for cortical dyslamination in FMCds by compromising Wnt signals essential for neuronal polarization. Next, we are trying to dissect the molecular basis of MTOR somatic mutations in aberrant neural circuit formation causing epileptic neural network, with several techniques including virus injection for neuronal tracing, optogenetics, and single-unit recording. We observed aberrant neuronal projection and firing, both of which are attributable to MTOR somatic mutations. We
Session 555 Animal Models of Epilepsy II
Hall A

Presentation 555.11 / B67 Zebrafish model of post-traumatic epilepsy

S.-J. Cho1, E. Park2, A. Baker2, A. Reid1
1Univ. Hlth. Network, Toronto, ON, Canada; 2St. Michael's Hosp., Toronto, ON, Canada

Abstract
Background: Post-traumatic epilepsy (PTE) is a complication from traumatic brain injury (TBI). PTE is defined as recurrent and unprovoked seizures occurring more than one week after TBI. Animal studies of PTE are lengthy and expensive. Zebrafish are an emerging model organism for studying disease and development due to their ease of use and require less maintenance than rodents. In this study, we developed a cost-effective PTE model using zebrafish to bridge the gap between in vitro studies and low-throughput animal studies.

Methods: Severe closed-head TBI was induced in AB strain wild-type zebrafish (6-12 months old) using pulsed high-intensity focused ultrasound, with naïve zebrafish as controls. We used an automated behavioral tracking system to evaluate locomotor/psychological deficits, and spontaneous behavioral seizure activity was manually scored for 21 days post-injury (DPI).

A behavioral seizure susceptibility test was also performed using a sub-convulsive dose of 2.5 mM pentylenetetrazole (PTZ) on day 7, 14, and 21. In addition, we recorded forebrain electrophysiological signals to confirm seizure activity.

Results: The severe closed-head TBI model resulted in mortality in 25% of the injured zebrafish. Locomotor activity was disrupted post-injury and never fully recovered by 21 DPI. Also, the TBI group had heightened anxiety for 21 days. 100% of the TBI group showed spontaneous myoclonic-like jerking behavior for 21 days. 44% of the TBI group developed clonic-like prolonged jerking behavior at 3 DPI (n=15), which increased to 80% at 21 DPI (n=15). Such activities were not detected in the naïve group (n=10). After the administration of 2.5 mM PTZ, 90% of injured zebrafish had clonic-like seizures at 7 DPI (n=10), increasing to 100% at 14 DPI and 21 DPI (n=10), versus 30% of the naïve group. Of those progressing to clonic seizures, the average seizure onset time was significantly longer in the naïve group at 750±50s versus 258±46.5s in the TBI group at 7 DPI, 217±41.2s at 14 DPI and 298±45.2s at 21 DPI. Lastly, we demonstrated interictal epileptiform discharges and electrophysiological seizure activity in the TBI group, which were not detected in the naïve controls.

Conclusion: We have demonstrated increased PTZ-induced seizure susceptibility as well as spontaneous behavioral and electrophysiological seizure activity, after TBI in zebrafish. These changes endured for at least 21 DPI, suggesting this may be a useful model that can accelerate research in PTE.

Session 558 Alzheimer's Disease: Neuroinflammation and Immune Actions
Hall A

Presentation 558.17 / C44 Expression of miRNA146 and regulation of neutrophil proinflammatory functions sheds new light on the pathogenesis of Alzheimer's disease

S. Kim1, S. Kim2

Abstract
For more than two centuries now, Alzheimer disease (AD) is under research intending to develop various treatment and diagnostic approaches. Despite decades of scientific advances, AD is still representing a challenge for contemporary medicine. Current drug therapies may provide a little relief about the quality of life of AD patients; however, they are still insufficient to reverse tissue injury and are often generating side-effects. The difficulty arises from the considerable fluctuation of the clinical course of AD among patients, making the predictive prognosis difficult. Resolution of inflammation needs effective and timely removal of dead cells and other toxic products of neutrophils, monocytes, and macrophages in AD mouse model. In this study, we evaluated the role of monocytes in the clearance of neutrophil extracellular trap (NET) and apoptotic neutrophils in the inflammation site of early stage AD mice. For this study, immune cells were observed microscopically after exposing them with NETs and/or apoptotic bodies. A subset of immune cells exposed to NETs ejected extracellular traps and this was shown to be mediated by proteins like elastase and citrullinated histones present in NET supernatant. More and more studies underline the profound influence of the neutrophil and immune cells multifaceted functions in the pathogenesis of AD. In this study, we aim to update the recent results on the multiple facets of neutrophils in AD, in particular their impact in promoting the inflammation-based AD through the release of the cytokine-like HMGB2 and S100A8/A9 protein complex, as well as the importance of NETosis in the disease progression and development. Furthermore, we delve into the complex question of neutrophil heterogeneity and plasticity and determine the emerging role of miRNA-146 and PTM (post-translational modification) markers influencing the inflammatory response of neutrophils in AD. Acknowledgments This research was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number: H17C1260).
Abstract

The contribution of sensory feedback from the leg for walking has been well established with the two-level half-center central pattern generator (CPG) model. Several gait therapies have also been introduced to evaluate the efficacy of motion-dependent sensory feedback from the leg on gait rehabilitation after spinal cord injury (SCI). For example, robotic devices or motorized belts move paralyzed lower limbs, in turn generating motion-dependent feedback. These body-weight supported treadmill training (BWSTT) interventions show positive effects on gait rehabilitation in both rats and humans after SCI. However, the efficacy of BWSTT on human gait rehabilitation is limited. Recent studies suggest that this may be due to insufficient peripheral sensory feedback. The fact that gait rehabilitation with BWSTT becomes more effective with sensory augmentation, produced with epidural stimulation or vibration on leg muscles, supports the notion. Indeed, the reduced loading of the legs with body-weight support reduces the force-dependent feedback. To compensate for this reduced leg loading, which might be the clearest sensory deficit for BWSTT, the current study aimed to augment tactile feedback from the foot sole, by stimulating the distal-tibial nerve as seen in human and cat studies, and ultimately to test whether the plantar cutaneous augmentation could compensate for reduced leg loading and promote gait rehabilitation. First, we developed a fully-implantable stance detection and plantar cutaneous augmentation system. As a proof of concept, we conducted experiments with two intact rats. We tested that the implantable system could record electromyography from the Soleus muscle, which was used for stance phase detection. Second, we measured compound action potentials from the proximal-tibial nerve while applying electrical stimulation to the distal-tibial nerve. Based on the propagation speed of the measured action potential and the plantar innervation of distal-tibial nerve, we believe that the electrical stimulation on distal-tibial nerve could augment plantar cutaneous feedback.

**Session 574 Auditory Processing: Neural Coding**

1:00 PM - 5:00 PM

**Presentation 574.14 / I25 Neural decoding model of auditory attention in a dichotic listening condition**

J. PARK1, J.-S. KYONG2, J. CHO4, M.-W. SUH4, S. KIM2, Y. LIM4;

Abstract

Human can successfully parse different sound streams and focus on a specific target sound in a cocktail party condition. Recently, several studies have shown that estimating attended sound is feasible with linearly trained neural decoders. In this study, we took the similar approach to build an auditory attention decoder based on human EEG signal recorded during dichotic listening experiment (64 channels, Neuroscan SynAmps RT). Nineteen participants are instructed to attend a speech on the one side of the ear and ignore another speech presented to the opposite side of the ear (order of stimuli presentation is randomly selected). Length of the stimuli was 1 min long and excerpted from a Korean listening comprehension audio samples for college entrance test (Female voice only). Since it has been reported that low-frequency of speech envelope is linearly related to the low-band of EEG, a 2-8 Hz band-pass filter was applied to extract low-frequency component of EEG data and 8 Hz low-pass filter was used for extracting speech envelope after applying Hilbert transform. Auditory attention decoder was trained using linear regression method and was validated by leave-one-out validation method. Attended sound stream was selected based on the correlation between envelope of reconstructed speech and that of the original speech. First, we tried to build a subject-specific attention decoder with EEG recordings of all channels. However, most of the trained decoder shows lower performance on auditory attention decoding (mean accuracy of attended decoder: 54.4%, mean accuracy of unattended decoder: 51.4%, 5% of significance level: 67.9%). To increase the accuracy of the trained decoder, we tried forward feature selection method which incrementally searches the feature space and adds effective channels that could give better performance. As a result, we were able to successfully decode auditory attention of each subject (mean best accuracy of attended and unattended decoder: 86.3%). Also, for attended decoder model, channels around temporal region are mostly selected, which could reflect the auditory processing of current auditory attention task. In summary, we have shown that auditory attention can be successfully decoded with neural signals from selected EEG channels. In the future, we are going to try building single decoder model that could be generally applied to different participants without user specific optimization process and also try real-time decoding for applications such as human-robot interaction and hearing aid technology.

**Session 584 Brain-Computer Interface: Rehabilitation**

1:00 PM - 5:00 PM

**Presentation 584.18 / N20 Magnification of visual feedback alters modulation of motor neuron pool in older adults**

*S. PARK*, M. KOWN3, E. A. CHRISTOU1;
1Applied Physiol. & Kinesiology, Univ. of Florida, Gainesville, FL; 2Physical Therapy, Marquette Univ., Milwaukee, WI

Abstract

Magnification of visual feedback impairs control in older adults by increasing the power in low-frequency oscillations in force. However, it is unclear how the impaired visual information processing in older adults alters the modulation of the motor neuron pool that increases the low-frequency oscillations in the force output with magnified visual feedback. To address this, eleven healthy young adults (21.82 ± 3.52 years, 6 females) and 11 healthy older adults (78.27 ± 5.59 years, 7 females) performed an isometric ankle dorsiflexion task at 15% maximal voluntary contraction with magnified visual feedback (1.2x). We recorded the force output and multiple motor unit activity from the tibialis anterior muscle and quantified the following outcomes: 1) force variability using the standard deviation (SD) and coefficient variation (CV) of force and 2) power spectrum of force and multiple motor unit activity. Older adults exhibited greater force variability compared with young adults (SD: P = 0.045; CV: P = 0.01). The greater force variability was associated with greater power in the <0.3 Hz oscillations in force (SD: R² = 0.30; CV: R² = 0.36). The power in the <0.3 Hz oscillations in force were positively related to power <0.3 Hz in multiple motor unit activity (R² = 0.42). These results provide novel evidence that magnification of visual feedback alters the modulation of the motor neuron pool with detrimental consequences to force control in older adults.
**Presentation 594.06 / U35** An ecologically-relevant paradigm to study fear and foraging strategies in mice

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**Abstract**

Laboratory models used to investigate fear have consistently relied upon Pavlovian fear conditioning (pairing a neutral cue with an aversive stimulus, and later measuring the fear response to the cue) to understand the neural mechanisms underlying adaptive and maladaptive fear behavior. However, in nature, it is disputed that Pavlovian fear conditioning is the primary mechanism by which animals come to fear stimuli; animals are typically not afforded multiple conditioning trials to learn that a particular stimulus (e.g., a predator) is dangerous and therefore should be avoided. In contrast, ecological studies from multiple labs investigating innate, unlearned fear responses to artificial predator stimuli have shown that rodents display reliable fear and avoidance behaviors to such stimuli with no prior experiences necessary. Our lab has previously developed a naturalistic, “approach–food avoid–predator” paradigm in rats used to study innate fear and risky-decision making behaviors and their underlying neurocircuitry (Choi and Kim, 2010). Briefly, hungry animals foraging for food pellets encounter a robotic “terrestrial predator”, which is programmed to surge at the animal as it approaches a food pellet. Fear responses are measured over multiple predator testing days. In light of the rapidly increasing use of mice in neuroscience research—largely due to the availability and feasibility of transgenic animals—we have adapted our approach-avoid-predator paradigm for use in mice. Additionally, we made the predator stimulus more realistic than our rat version by replacing the robotic threat with a taxidermy weasel. We demonstrate that mice naturally forage for food pellets in an open arena as well as flee from a surging predator. Likewise, mice required multiple days of predator testing for fear responses to habituate to the consistent looming threat, as seen in rats. Finally, we show that the presence of stationary but realistic predator does not deter mice from attempting to procure food, suggesting that the looming motion is evolutionarily reliable signal of danger. This paradigm would be useful for researchers seeking to harness the powerful capabilities of transgenic animals to study naturalistic fear behavior and neurocircuitry.
Hydrocephalus is a condition in which the intracerebral ventricles are engorged because cerebrospinal fluid (CSF) is obstructed, overproduced, or inadequately reabsorbed. Among the most common neurodevelopmental disorders, it can be caused by genetic mutation, infection, or brain injury. Without timely surgical intervention, it produces devastating intellectual and motor disability. However, the cellular and molecular mechanisms of hydrocephalus pathogenesis are not well understood.

Developing an effective and reliable therapeutic approach to treat spinal cord injury (SCI) is a difficult challenge for several reasons. First, the acute primary insult and secondary injury to the spinal cord cause central hemorrhagic necrosis and disruption of ascending and descending spinal tracts which communicate sensory and motor information to and from the brain. Second, subsequent gliosis at the injury site repairs the blood-brain barrier (BBB) can obstruct axon growth/regeneration. Moreover, the central nervous system (CNS) and the complex inhibitory SCI environment, there is a critical need for effective strategies to stimulate robust axon regeneration and neurite outgrowth to re-establish the damaged neural circuitry. To this end, we have developed a nanoparticle-based artificial transcription factor (NanoScript) capable of efficiently and selectively regulating the well-reported PTEN/mTOR pathway in a non-viral transient manner to promote axon growth and regeneration. We rationally designed the NanoScript platform to repress PTEN expression (NanoScript-PTEN) and evaluated the therapeutic effect of NanoScript-PTEN on SCI rehabilitation. We hypothesized that the efficient repression of PTEN expression would lead to upregulation of mTOR and therefore promoted regeneration of axons at the spinal injury site. The NanoScript platform replicates the multi-domain structure of natural TF proteins and emulates the gene-regulating function of TFs. Most importantly, we believe NanoScript can provide a safe and efficient gene manipulation method that will accelerate efforts for axonal regeneration and ultimately functional recovery of spinal cord injury.
Abstract

AMPAR-type glutamate receptors (AMPARs) mediate most of the fast excitatory synaptic transmission in the brain. AMPARs are composed of four subunits (GluA1-4) and GluA1/A2 and GluA2/A3 are prevalent in the brain (W. Lu et al., 2009). Their abundance at postsynaptic sites determines synaptic strength. Surface expression and phosphorylation of AMPARs increase during the long term potentiation (LTP) of synaptic transmission. AMPARs are inserted to the membrane in a retromer dependent manner. β2 Adrenergic Receptor (β2AR) forms supramolecular signaling complexes with AMPARs and regulates phosphorylation of AMPARs through Gs protein, adenylyl cyclase (AC), and PKA signaling, which are also associated with the AMPARs (Joner et al., 2010). Phosphorylation of S845 by PKA augments AMPAR surface expression and postsynaptic targeting. Norepinephrine (NE) is the endogenous ligand of β2AR and is crucial for arousal and learning in novel and emotionally-charged situations inducing LTPs in hippocampus. The voltage-gated calcium channel (VGCC) CaV1.2 mediates calcium influx, which governs neuronal excitability, LTP, and learning. Importantly, it stabilizes surface insertion of AMPARs, which otherwise undergoes only short-lived insertions (10-30 sec) (Hiester et al., 2017). We investigated how trafficking of AMPARs to surface is mediated by stimulation of β2AR by NE. Hippocampal neuron culture from rats were treated with NE and stained with antibodies against surface GluA1 and total PSD95, which define postsynaptic sites. Colocalization of sGluA1 and PSD95 puncta was quantified. In parallel, mouse brain slices were incubated with NE to examine the change in phosphorylation of AMPAR GluA1 subunit at S845. After immunoprecipitation of GluA1 from brain slice lysates, phosphorylation of GluA1 was analyzed by immunoblotting. Interaction of AMPARs with their accessory proteins and retromer proteins was investigated by co-immunoprecipitation from brain slice lysates with or without NE treatment. The results of immunostaining with hippocampal neuron culture show that stimulation of β2AR by NE enhances insertion of AMPARs into the plasma membrane. The effect of NE on surface insertion of GluA1 is blocked by L-type calcium channel inhibitor. Also, phosphorylation of S845 was increased by NE. These results represent that stimulation of β2AR by NE promotes trafficking of AMPARs to the cell surface in an L-type channel dependent manner. Electrophysiological analysis suggests that this mechanism is important for certain forms of LTP.
**Abstract**

Alzheimer's disease (AD) is the most common neurodegenerative disease, but there are still no drugs available to treat or prevent AD dramatically. However, efforts to develop early diagnostic ways should also be made along with the development of treatment of AD for appropriate medical intervention from the early stage of the disease. Here, we have examined the change in the level of selected proteins implicated in the pathogenesis of AD using the plasma of control subjects and patients with cognitive impairment. To precisely categorize the diseases, all the patients were examined by amyloid PET scan and the white matter hyperintensity was scored by magnetic resonance imaging. By analyzing quantitative immunoblot and ELISA, we found the plasma level of cathepsin D which is a major lysosomal protease significantly decreased in the group with amyloid plaque deposition at the brain compared to the control group. These results suggest that the plasma cathepsin D level could be a candidate to be developed as a diagnostic biomarker of AD. This study also suggests that lysosomal degradation activity could be associated with the onset or the progression of AD.

**Presentation 660.04 / H9**

**Modulation of integrin signaling in the hydrogel-induced extracellular matrix to facilitate axonal ingrowth following spinal cord injury**

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**Abstract**

Axon regeneration failure beyond lesion site following central nervous system (CNS) injuries is hampered by fluid-filled cystic cavities formed at the lesion epicenter. Previously, we demonstrated that injection of imidazole-poly (organophosphazene) (I-5), a hydrogel with thermosensitive sol-gel transition behavior, prevented cystic cavity formation by promoting extracellular matrix (ECM) remodeling. However, the extent of axonal ingrowth into the hydrogel-induced ECM was limited. We hypothesized that inhospitable microenvironment in newly deposited ECM provides inhibitory influence to regenerating axons and that modifying the ECM environment can facilitate axonal growth into the ECM. I-5 injection results in the formation of fibrotic matrix filled with type I collagen surrounded by highly reactive astrocytes, reminiscent of the fibrotic scar. It has been reported that interaction between collagen in the ECM and integrin expressed in reactive astrocytes drives formation of glial scars, a potent inhibitory factor for axon regeneration. The present study aimed to modify microenvironment of I-5-induced ECM by modulating integrin signaling. Activated integrin beta 1 immunoreactivity was observed in migrating astrocytes intermingled with ECM 1 week after I-5 injection. By 4 weeks, integrin immunoreactivity was diminished but still found at the border between reactive astrocytes and collagen-rich ECM. To suppress integrin activation, I-5 hydrogel mixed with integrin beta 1 functional blocking antibody was injected 1 week after spinal cord injury in rats. Our data showed that I-5 mixed with integrin beta 1 functional blocking antibody increased the extent of 5-HT (serotonin) axonal growth into fibrotic matrix. This study suggests that integrin signaling can be targeted to facilitate axonal growth in the hydrogel-induced matrix following spinal cord injury.

**Presentation 666.04 / J44**

**Distinct light dependent human magnetoreception in geomagnetic food orientation**

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**Abstract**

It is well established that dozens of magnetoreceptive animals, from worms to mammals, use the Earth's magnetic field (geomagnetic field, GMF) to navigate short- or long-distance and modulate body alignment to fulfill biological needs, depending on species. For humans, it is largely thought that GMF cannot be sensed, even though some previous studies suggested that human may sense magnetic fields including the GMF. Very recently, using a self-rotatory chair experiment, we reported that human males can sense the GMF and use it to search for food direction in a blue light-dependent manner under starved condition. Here, we provide additional behavioral mechanistic evidence for human magnetoreception of the GMF. In a two-alternative forced choice paradigm, starved men showed a distinct light wavelength-dependent magnetic orientation, which may not be consistent with conventional role of light in magnetoreception. The exact reversal of the GMF resulted in orientation toward the magnetic north, indicating that orientation is mediated by axial direction but not polarity of magnetic field. The results confirm that human can sense the GMF and use it for magnetic food orientation in a light- and inclination compass-dependent manner. Further, the results suggest that magnetite may not be involved in the observed human magnetoreception.

**Presentation 667.19 / L3**

**Topological diversity of cell types in the subthalamic nucleus using single-molecule fluorescence in situ hybridization (smFISH)**

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**Abstract**

The subthalamic nucleus (STN) which relays extensive inputs from a variety of cortical and subcortical structures serves as a convergence hub and a successful target for deep brain stimulation. However, there is little systematic investigation into fundamental characteristics including cellular and synaptic profiles as well as the functional anatomy. Indeed, the complexity of
The lateral hypothalamus (LHA) regulates various motivated behaviors including food intake. Among those subpopulations, LHA may have competing roles during sleep-dependent memory processing. We found that high amplitude slow-waves (SW; <4 Hz) and delta-waves (δ) subsequent sleep. Strikingly, we found that high amplitude slow-waves (SW; <4 Hz) and delta-waves (δ) have dissociable roles in memory consolidation during sleep. By modulating cortical spiking linked exclusively to SW or δ, we could respectively weaken or strengthen memory reactivations and thereby strengthening versus forgetting of the "motor memory" of novel skills gained through practice. We specifically examined how neural reactivations during NREM sleep are causally linked to two likely competing processes. We specifically recorded ten trials of MEP at a TMS intensity of 120% of active motor threshold. Both averages of H-max and MEP responses were normalized to the M-max average to allow for between-group comparisons. We performed two independent t-tests with the alpha level was set at <0.05. There were no significant group differences for Hmax/Mmax ratio (LAS: 0.11±0.07 and healthy control: 0.14±0.09, p=0.39). These preliminary results indicate that spiral and corticospinal excitability may not change following LAS, and suggest that other neurophysiological mechanisms may contribute to single-limb balance deficits following LAS.

Sleep has been implicated in both selective memory consolidation as well as forgetting of memories after prolonged awake periods. However, it is unclear what physiological process governs the fundamental balance between memory strengthening and weakening. Here we specifically tested how activity-dependent processing during sleep might differentially regulate these two likely competing processes. We specifically examined how neural reactivations during NREM sleep are causally linked to strengthening versus forgetting of the “motor memory” of novel skills gained through practice. We specifically recorded populations of neurons in the primary motor cortex of rats while they were trained on a brain machine interface (BMI) task and subsequent sleep. Strikingly, we found that high amplitude slow-waves (SW; <4 Hz) and delta-waves (δ; 1-4 Hz) have dissociable roles in memory consolidation during sleep. By modulating cortical spiking linked exclusively to SW or δ using closed-loop optogenetic methods, we could respectively weaken or strengthen memory reactivations and thereby bidirectionally modulate sleep-dependent performance gains. We further found that changes in the precise temporal coupling of spindles (10-14 Hz) to SW could account for such effects. Thus, our results indicate that neural activity driven by SW and δ may have competing roles during sleep-dependent memory processing.

The symptom of eating disorders that is difficult to treat is a dissociation between food-seeking behavior and metabolic needs. The lateral hypothalamus (LHA) regulates various motivated behaviors including food intake. Among those subpopulations, LHA...
GABAergic neurons are known to be involved in modulation of food reward and consumption. Previous studies showed that activation of LHA GABAergic neurons enhance food intake and compulsive behaviors in mice. However, specified behavioral phenotypes and functions of the subset of LHA GABAergic neurons are unclear. Thus, our research aimed to identify the food-related behavioral phenotypes that are regulated by leptin receptor-expressing neurons in LHA. We performed food-seeking test, operant chamber test, overall chow and palatable food intake test and marble burying test. Interestingly, through behavior assays, we found that chemogenetic activation/inhibition of LHA leptin receptor neurons only modulate “food-seeking” behavior. However, activation of LHA GABAergic neurons increased both food intake and compulsive behaviors without affecting food-seeking. These results suggest that food-seeking is independent from food intake, and LHA leptin receptor expressing neurons are specifically involved in food-seeking behavior that can be targeted to treat eating disorders.

**Session 684** Depression: Physiology, Pharmacology, and Treatment

**Presentation 684.07 / V19** Neural prediction of anxiety and depression when processing negative emotion

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Abstract

Aberrant neural activation, when processing negative emotion, is a major feature of Major Depressive Disorder (MDD) and Anxiety Disorder (AD). While existing literature suggests that there exist both common and distinct patterns of fMRI responses in MDD and AD, it is a limitation that most studies used univariate analysis (general linear modeling), and multivariate patterns among brain regions are often neglected. Here, we aimed to identify multivariate patterns of fMRI response when processing emotional stimuli that will predict individuals’ level of depression and anxiety. To achieve the goal, we applied a machine learning approach (elastic net) to fMRI data from clinical populations with multiple diagnoses. Participants included 99 patients with primary diagnoses of MDD, social anxiety disorder, or generalized anxiety disorder, and additional 37 healthy controls. They completed the emotional facial matching task inside the MRI scanner. The participants’ levels of depression and anxiety were measured with the Hamilton Depression Scale (HAM-D) and Hamilton Anxiety Scale (HAM-A), respectively. Preliminary results suggest that angry faces generate neural responses that are predictive of both HAM-D and HAM-A, and we found common regions predicting both HAM-D and HAM-A in the insula, the anterior cingulate cortex, and the middle temporal gyrus. These results highlight the importance of transdiagnostic and quantitative approaches in characterizing the neural underpinnings of psychiatric disorders.

**Session 686** Psychiatric Disorder: Rodent Models

**Presentation 686.07 / W18** Cocaine drives schizophrenia-like behaviors via reduced neuronal activity in the nucleus accumbens

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Abstract

Schizophrenia (SCZ) is a complicated disorder with abnormal symptoms in various categories: positive, negative, and cognitive symptoms. Although specific cause of SCZ has been not elucidated until now, many researchers have believed that genetic factors are involved in these symptoms based on numerous genomic studies. However, development of SCZ-like behaviors also can be provoked by a number of environmental factors at adulthood. As one of environmental stimuli, some drugs such as cocaine can induce schizophrenic behaviors. Despite of obvious SCZ-like symptoms by these drugs, drug-induced SCZ models have been mainly studied about reliability and validity as an animal model of SCZ. The purpose of this study is to make a cocaine-induced schizophrenia (CIS) model with reliability and validity, and to explore important genes of CIS. First, we used cocaine to induce schizophrenic symptoms into young adult C57BL/6 male mice, which is a dopamine reuptake inhibitor. We successfully established CIS mouse model with three categories of symptoms. Subsequently we checked whole brain changes with immunostaining of neuronal activity related protein, ribosomal protein S6. Interestingly we found that reduced intensity of that through whole brain, and we observed that most altered region was nucleus accumbens, where neurons receive major inputs from ventral tegmental area. In addition, we observed decreased number of spike in nucleus accumbens with microelectrode array. Finally, to study the effects of the environmental factor on schizophrenia, by performing RNA sequencing, we found that expression changes of several genes in the nucleus accumbens of the CIS model. These findings suggest that SCZ-like behaviors induced by cocaine may be mediated via reduced neuronal activity of neurons within nucleus accumbens. This brain dysfunction maybe resulted from changes of genes such as miR-5126, miR-3473g, LCAM2, and ZAR1L. As a result, this new model is reliable and valid as a SCZ model, and the neurological change could be used in the study of SCZ in the future.

**Session 687** Other Psychiatric Disorders

**Presentation 687.06 / W32** Transcranial direct current stimulation reduced food craving and nucleus accumbens response to high calorie food cues among individuals with obesity

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Abstract

Underpinnings of psychiatric disorders and their comorbidity is a major area of research. While mood disorders and anxiety disorders are well-studied and there are established interconnections between these psychiatric disorders, less is known about other psychiatric disorders. There are many different psychiatric disorders, and it is important to understand their brain underpinnings. In this study, we aimed to identify the brain regions involved in craving and food reward in obese individuals. We also tested whether these brain regions are associated with food craving and food consumption in obese individuals. We used transcranial direct current stimulation (tDCS) to reduce food craving and nucleus accumbens response to high calorie food cues. Our results suggest that tDCS can reduce food craving and nucleus accumbens response to high calorie food cues among individuals with obesity.
Previous studies have reported that individuals with obesity tend to be more sensitive to reward stimuli such as high calories foods. Obese people also show greater reward-related circuit response to food pictures because they may be more rewarded by food cues. Transcranial direct current stimulation (tDCS) is a neuromodulation technique that shown to be effective to reduce food craving and consumption. The present study aimed to investigate the tDCS effects on neural and behavioral response involved in eating. Method: Fourteen obese adults participated in this study (4 female, BMI=29.63±1.16, age=29.53±12.65). This study employed a single-blind sham-controlled within subjects crossover design in which all participants received real and sham tDCS. An intersequence interval was at least two weeks for avoiding any carryover effects due to stimulation. Visual analogue scales (1-10 score) related to food craving were measured before and after tDCS session, respectively. All participants were scanned while they were viewing 100(50 high-calories food/50 low-calories food) picture stimuli during an fMRI assessment. ROI analysis was conducted using a pre-determined region of interest (ROI), especially the nucleus accumbens(NAcc) implicated in reward and motivation processing. Parameter estimates of the high vs. low contrast image were extracted from the NAcc ROI. Paired t-tests on behavioral ratings (e.g., fullness) and neural activation (i.e., NAcc response to high-calories vs low-calories food pictures) were used to compare the real vs. sham tDCS sessions. Results: There were statistically significant differences in the fullness score (t(10)=2.246, p<0.05) between real and sham stimulation. Food preference score for high-calorie food that acquired in scanner was not different between real and sham tDCS condition (t(13)=1.309, p=0.213). ROI analysis revealed that left accumbens area activity for high-calories food is greater after the sham tDCS session than real session (t(12)=2.555, p<0.05). However, there was no statistical correlation with right NAcc activation and food preference rating for each of food cues (r=0.592, p<.05). Conclusion: Brain stimulation with tDCS modulated eating behaviors and NAcc activation. Our study implies that the brain stimulation with tDCS represents a promising option for treating obesity in humans by modulation of neural circuits associated with reward and motivation in response to food cues.
Experimental evidence to support this hypothesis has not been addressed. Physical exercise has beneficial effects on the regeneration capacity and neuronal growth. Epigenetic changes are widely considered to play an important role, but reported that epigenetic changes induced by SCI might modulate regeneration-associated genes (RAGs) which control the regeneration capacity and neuronal growth. Spinal cord injury (SCI) is a major devastating lesion which causes various pathophysiological mechanisms.

**Abstract**

Many genes and environmental factors contribute to the development of autism spectrum disorder. But we do not know if there is a common mechanism causing social deficit in many ASDs and if there exist specific neural circuit for a specific social behavior. Excitation and inhibition imbalance of mPFC is a leading mechanism of social deficit. In the medial prefrontal cortex (mPFC) of Shank2 mice, synaptic E/I balance is skewed to excitation but not all optogenetic recovery of E/I imbalance of mPFC rescued social deficit in three chamber test and direct interaction. Only strong pulsatile optogenetic 10Hz stimulation of parvalbumin (PV) interneuron with Chi2 is effective.

**Session 743 Parkinson's Disease: Therapeutics**

**Presentation 743.06 / C86** Astrocyte elevated gene-1 as an endogenous anti-apoptotic factor in nigral dopaminergic neurons *in vivo*

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**Abstract**

We recently reported the protective role of astrocyte elevated gene-1 (AEG-1) in nigral dopaminergic (DA) neurons *in vivo*. Similar to decrease in the level of AEG-1 in the postmortem substantia nigra (SN) tissues from patients with Parkinson's disease (PD), the reduction of AEG-1 in nigral DA neurons was also observed in the 6-hydroxydopamine (6-OHDA)-treated mouse model of PD. In addition, AEG-1 upregulation using adeno-associated virus serotype 1 (AAV1) attenuated the 6-OHDA-triggered apoptotic death of nigral DA neurons in the SN of mouse brain. Furthermore, although the post-administration of AAV-AEG-1 alone after disruption of nigrostriatal DA system showed no neurorestorative effect, we observed that the maintenance of neuronal AEG-1 using AAV1 contributed to the intensification of neurorestoration such as behavioral recovery by post-treatment with a constitutively active form of ras homolog enriched in brain (Rheb[S16H]), which could induce axonal regeneration from damaged DA neurons in the 6-OHDA-treated animal model of PD. Collectively, these results demonstrated that the sustained level of AEG-1 as an important anti-apoptotic factor could potentiate the therapeutic effects of treatments, such as Rheb(S16H) administration, on the degeneration of the DA pathway that characterizes PD.

**Session 747 Spinal Cord Injury and Repair**

**Presentation 747.15 / F23** Exercise accelerates epigenetic changes after spinal cord injury

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**Abstract**

Spinal cord injury (SCI) is a major devastating lesion which causes various pathophysiological mechanisms. Recent studies reported that epigenetic changes induced by SCI might modulate regeneration-associated genes (RAGs) which control the regeneration capacity and neuronal growth. Epigenetic changes are widely considered to play an important role, but experimental evidence to support this hypothesis has not been addressed. Physical exercise has beneficial effects on the
modulation of neuronal plasticity and promoting intrinsic growth capacity through epigenetic modulation in the brain. This study was carried out to investigate whether treadmill exercise affects epigenetic change and functional recovery after SCI. We made contusion models at thoracic spinal cord using adult Sprague-Dawley rats, and performed dot blotting of 5-methylcytosine (5mc) and 5-hydroxymethylcytosine (5hmC), and real-time PCR to analyze the expression level of Ten-eleven translocation (Tet) family, RAGs, and pro-inflammatory cytokines as well as histological and functional assessments. Rats which were placed in the treadmill without running were considered as controls. Within the motor cortex of the brain of rats which received treadmill exercise for 12 weeks, the staining intensity and the expression level of 5hmC of cortical neurons were significantly increased. The mRNA levels of Tet family (TET1, TET2, and TET3) of brain tissues were also increased more in the exercise group than in control at 12 weeks after SCI. Pro-inflammatory genes including interleukin-1 beta, interleukin-6 and tumor necrosis factor alpha were decreased, and RAGs were increased more in the exercise group. Therefore, we concluded that the 12-week treadmill exercise promotes the epigenetic changes and improves functional recovery after SCI.

**Session 748** Somatosensation: Treatments for Persistent Pain

**Presentation 748.11 / F42** p66shc-PLGA nanoparticles alleviate mitochondrial dysfunction mediated pain behaviors

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**Abstract**

**AIMS:** Reactive oxygen species has been suggested as a key player in neuropathic pain, causing central sensitization by glial activation and loss of GABAergic interneuron in spinal dorsal horn. However, it remains unclear as to what type of reactive oxygen species changes what aspect of glial activation and GABAergic interneuron for central sensitization in neuropathic pain conditions. In this study, we investigated whether mitochondrial superoxide affects both excitatory in spinal dorsal horn neurons after peripheral nerve injury.

**RESULTS:** Downregulation of mitochondrial superoxide level by p66shc-PLGA nanoparticles alleviated neuropathic mechanical hypersensitivity caused by L5 spinal nerve ligation. In SNL model, superoxide product DHE and mitochondrial ROS signal was highest at 9 days postoperatively. In SNL condition, the DHE and Mitochondrial ROS signal, pain behavior and inflammatory cytokine and decreased after p66shc-PLGA nanoparticles in spinal dorsal horn. In addition, Mitophagy regulatory factor and inflammatory cytokine level were attenuated in microglia and neuronal cell line by p66shc-PLGA nanoparticle co-treatment after H2O2 treatment.

**CONCLUSION:** These results suggest that, high levels of mitochondrial superoxide through p66shc in spinal dorsal horn neurons and microglia increase sensory threshold after peripheral nerve injury and contribute to neuropathic mechanical hypersensitivity.

**KEY WORDS:** Neuropathic pain, Spinal cord ligation, p66shc, Nanoparticle, ROS

**Session 749** Role of Inflammatory and Immune Responses in Chronic Pain

**Presentation 749.06 / G18** Spinal cytochrome p450c17-induced astrocyte activation is mediated by p38 mitogen-activated protein kinase phosphorylation in a mouse model of neuropathic pain


**Abstract**

It has been suggested that peripheral nerve injury induces spinal astrocyte activation and leads to the development of neuropathic pain. We have recently demonstrated that cytochrome P450c17 is increased in spinal astrocytes and plays a critical role in the development of neuropathic pain following peripheral nerve injury. However, whether or how spinal P450c17 modulates pathological changes in astrocytes remain unclear. Here we investigated whether cytochrome P450c17 modulates astrocyte activation and whether this process is mediated by p38 mitogen-activated protein kinase (MAPK) and leads to the development of mechanical allodynia in a mouse model of neuropathic pain. Chronic constriction injury (CCI) of the sciatic nerve induced a significant mechanical allodynia in the superficial dorsal horn (GDH, laminae I-II) and nucleus proprius (NP, laminae III-IV) regions of the spinal cord. Repeated daily (from days 0-3 post-surgery) intrathecal (i.t.) administration of the P450c17 inhibitor, ketoconazole significantly inhibited the CCI-induced pathological activation of astrocytes. In addition, i.t. administration of ketoconazole significantly inhibited the CCI-induced increase in p38 MAPK phosphorylation, which is expressed in GFAP-positive astrocytes in the SDH and NP regions. I.t. administration of a sub-effective dose of the p38 MAPK inhibitor, SB203580 potentiated the pharmacological effect of ketoconazole on the development of mechanical allodynia as well as astrocyte activation in the spinal cord of CCI mice. Collectively these results suggest that spinal cytochrome P450c17 activates astrocyte via p38 MAPK phosphorylation, ultimately leading to the development of mechanical allodynia induced by peripheral nerve injury.

**Key Words:** MAP kinase; Astrocyte; Neuropathic pain.

**Presentation 749.07 / G19** Amitriptyline and duloxetine loaded PLGA nanoparticles prolong the analgesic duration through enhanced targeting to microglia


**Abstract**

Neuropathic pain caused by functional disorders or pathological changes of the nervous system and various mechanisms has
been revealed in previous study but still no treatment has been developed.Both amitriptyline (AMI) and duloxetine (DLX) are potent analgesic agents and are currently used as analgesics in clinical practice. Although AMI and DLX are known as a reuptake inhibitor of serotonin (S-HT) and noradrenaline (NA) from synapse cleft to primary neuron, these drugs have recently been reported to also act on microglia activation. Since microglia activation control is known to be capable of sustaining analgesic action, PLGA nanoparticles were introduced to enhance microbial cell targeting of AMI and duloxetine DLX. Despite AMI and DLX injected group showed analgesic effect on neuropathic pain by spinal nerve ligation (SNL) in rats, the duration time of mitigation was 4 h. We confirmed that AMI and DLX-encapsulated PLGA nanoparticles significantly alleviated mechanical allodynia for 5 days compared to AMI and DLX treatment. Both microglial activation and proinflammatory mediators were notably reduced in spinal dorsal horn with histological and cytokine analysis. Taken together, these data suggest that AMI and DLX encapsulating PLGA nanoparticles can improve for therapeutic duration for neuropathic pain.

**Presentation 749.16 / G28 Arginase II attenuates neuroinflammation & pain behaviors after nerve injury in mice**

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Abstract

Microglia phenotypes have been divided into two groups: M1 & M2 microglia based upon their promotion to inflammatory pathogenesis. Arginase-II (Arg-II) is an enzyme involved in arginine metabolism & expressed in microglia in central nervous system. In this study, we attempted to determine whether Arg-II is in M1 or M2 microglia phenotype & its regulation on neuroinflammatory process. Finally we investigated loss of Arg-II exaggerates microglia activation & pain behaviors after nerve injury-induced neuropathic pain. Spinal nerve transection (SNT) experimental model was used in this study to induce neuropathic pain in mice. As a result of peripheral nerve injury, SNT induced microgliosis, astrogliosis in spinal cord, & upregulation of inflammatory signals in both WT & Arg-II KO mice. Notably, these inflammatory implications were significantly increased in Arg-II KO group compared to WT group. We also observed the more robust microgliosis, & lower pain threshold in Arg-II KO group than those in WT group. Furthermore, our data revealed the higher upregulations of M1 pro-inflammatory cytokines, such as IL-1β, IL-6, NO & the lower downregulations of M2 anti-inflammatory cytokines, including Arginase-I, IL-10, IL-4, in Arg-II KO mice. Additionally, the stronger expression of iNOS, ROS, & the decrease in the expression of CD206, YM1, Foxp3 in Arg-II KO Group were found compared to WT group. These results suggested that Arg-II promote contribution to inflammatory resolution. The reduction or loss of Arg-II results in the stronger development of neuroinflammation in spinal dorsal horn, & then pain behaviors after nerve injury-induced neuropathic pain.

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**Session 755 Visual Systems: Functional Architecture and Circuits**

Hall A

**Presentation 755.02 / J10 Distinct functional networks of peripheral and central visual representations in primary visual cortex during rest and task**

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Abstract

The central and peripheral visual fields, which correspond to the posterior and anterior portions of the primary visual cortex (V1), respectively, are known to play distinct functional roles: The central visual field of V1 is specialized in processing fine-grained visual information whereas the peripheral visual field is involved in monitoring changes in the environment by integrating multisensory information. Although previous work reported distinct patterns of functional connectivity between subregions of V1 and other visual areas, associations of each V1 subregion with functional networks beyond visual areas remain to be known. In the current study, we examine the intrinsic patterns of functional connectivity between subregions of V1 and the whole brain during rest and their modulations during a task. fMRI data during resting state, a visual working memory task, and an auditorily presented language task were obtained from the Human Connectome Project database. Using the connectivity-based parcellation approach, V1 was parcellated into the anterior and posterior portions and the whole brain seed-based connectivity was performed between each subregion of V1 and the rest of the brain. The results showed distinct patterns of functional connectivity between each V1 subregion and auditory, somatosensory, extrastriate visual, and frontoparietal areas, as well as their differential modulation by task. During the resting state, strong functional associations between the anterior V1 and auditory and somatosensory cortex were found. The functional associations of the anterior V1 and other sensory cortex were largely reduced during both tasks whereas the functional connectivity between the anterior V1 and frontoparietal areas increased. On the other hand, the posterior V1 increased its functional connectivity with the extrastriate visual areas when a visual working memory task was performed while the anterior V1 decreased its functional connectivity with other visual areas. Our findings support that distinct functional roles of peripheral and central visual field representations in V1 are supported by different functional networks in which each subregion of V1 is embedded: The posterior V1 forms the primary visual network with the extrastriate visual areas supporting the processing of focal visual information whereas the anterior V1 may form long-range functional connections with other sensory cortices for environmental monitoring via multisensory integration during rest but may be reconfigured to participate in the frontoparietal control network when cognitive task demand is high.

**Presentation 755.03 / J11 Principles of columnar and salt-and-pepper organizations of orientation tuning in visual cortex**

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Abstract

In the mammalian visual cortex, spatial organization of orientation tuning in the primary visual cortex (V1) is arranged in different forms across species. For instance, columnar orientation maps are observed in primates while noisy salt-and-pepper organizations are found in rodents. However, it is unknown whether these disparate organizations indeed reflect species-specific patterns of functional connectivity between subregions of V1 and other visual areas, associations of each V1 subregion with functional networks beyond visual areas.
specific developmental mechanisms of cortical circuits in evolution (Kaschube, 2014), or if any biological parameters (such as cortex size) determine it. To address this issue, we first analyzed neural parameter data in eight mammalian species, and found that the retina-to-cortex feedforward sampling ratio is a key factor that predicts the V1 organization of orientation tuning. We show that whether a species would have columnar maps or with salt-and-pepper organization, can be predicted solely by the retinocortical sampling ratio, as estimated from the size of the retina and V1 in each species. In particular, we show that the cortical organization of four species with V1 of similar size (columnar map in ferrets and tree shrews; salt-and-pepper organization in rabbits and gray squirrels) could be readily predicted by the ratio between the sizes of the retina and V1. This was impossible when considering only a single parameter such as V1 size. We confirmed that the sampling ratio between retinal and cortical neurons successfully predicts V1 organization of all eight species examined so far. Interestingly, we found that the results are mathematically consistent with a prediction by the Nyquist theorem in the Paik-Ringach model (Paik, 2011). Our results suggest a simple but fundamental principle of cortical organization: physical constraints in the periphery can initially contribute to the circuit design of the primary sensory cortex.

**Session 762** Posture and Gait II

**Session 768** Preclinical and Human Studies in Neurovascular Coupling Mechanisms

**Session 771** Biological Rhythms: Entrainment and Phase Shifts
**Presentation 771.20 / T7** Indoleamines related to melatonin are secreted from the pineal gland at night and act on melatonin receptors

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**Abstract**

In darkness, melatonin is produced by the pineal gland, a neuroendocrine organ in the brain. Night signals from the retina pass through the suprachiasmatic nucleus (SCN), the master biological clock, and eventually to the superior cervical ganglia, which send postsynaptic sympathtic fibers to the pineal that release norepinephrine (NE). Sympathetic NE upregulates the rate-limiting pineal enzyme arylalkylamine N-acetyltransferase (AANAT), which synthesizes N-acetylserotonin (NAS) from serotonin. This precursor is converted to melatonin in one more step. AANAT also converts tryptamine to N-acetyltryptamine (NAT), a structural analog of melatonin. The literature suggests that NAT and NAS are secreted from the pineal gland at night together with melatonin. Do NAT and NAS have similar roles as melatonin? To answer this question, we first tested whether NAT and NAS activate melatonin receptors (1 ME) and 2 ME) using dynamic mass redistribution (DMR), a real-time optical assay. The receptors overexpressed in HEK293 cells were activated by melatonin, NAT, and NAS, but melatonin was more potent than NAT and NAS for both receptors. All effects were blocked by melatonin receptor antagonists. Thus, NAT and NAS are weak partial agonists. We next investigated secretion of the three agonist indoleamines from isolated rat pineal glands with ultra-performance liquid chromatography-mass spectrometry (UPLC/MS). NE treatment for 6 hours increased pineal secretion of melatonin, NAT, and NAS by 12, 38, and 41 fold, respectively. Finally, we measured serum levels of the three agonist indoleamines to examine whether NAT and NAS are also right hormones. Serum melatonin increased 32 fold at night, an increase completely abolished after pinealectomy. For NAT and NAS, the basal serum concentrations were already elevated and showed no or weaker circadian rhythms, respectively. The night serum levels of NAT and NAS were several orders of magnitude lower than the EC50 for melatonin receptor activation. Taken together, three agonist indoleamines secreted by the pineal gland can activate melatonin receptors, but in circulating blood only the melatonin concentration is high enough to activate peripheral melatonin receptors. NAT and NAS may still act in a circadian paracrine manner on receptors in or near the pineal gland where they are at higher concentration, or there may be other more sensitive peripheral receptors for them.

**Session 773** Dopamine, Reward, and Reinforcement

1:00 PM - 5:00 PM

**Presentation 773.01 / U9** Temporally specific dopaminergic control of reward-conditioned movements


**Abstract**

Midbrain dopamine (DA) neurons encode both reward and movement-related events, and are implicated in disorders of reward processing as well as movement. However, disentangling the contribution of DA neurons in reinforcing versus generating movements is challenging and has lasting controversy. We dissociated these functions in mice trained on a Pavlovian trace conditioning task, in which presentation of an olfactory cue frequently elicited a conditioned response in the form of anticipatory licking that began prior to reward delivery. In this task, movement generation and reinforcement signals occur at distinct time periods (pre- and post-reward, respectively), and can thus be disentangled with temporarily precise optogenetic manipulations. To test the contribution of DA neurons to these processes we virally expressed eNpHR3.0 in lateral ventral tegmental area (VTA) DA neurons (n = 14 eNpHR3.0 and 14 YFP DAT-Cre mice, including medial regions of substantia nigra pars compacta, SNc). We examined behavioral performance across multiple test sessions representing different time periods of optogenetic stimulation. Each session was comprised of three blocks of 40 trials, with the laser activated in the second block. Continuously inhibiting DA neurons for 2 s immediately after reward delivery significantly reduced the probability of anticipatory licking, and this deficit was reversed when the optical stimulation was removed. However, inhibiting neurons for 4 s prior to reward (i.e., in the time period coinciding with cue presentation and the onset of anticipatory licking) had a comparatively smaller effect on licking. A similar bias toward the post-reward period was found for DA neurons in the lateral SNc (n = 9 eNpHR3.0 DAT-Cre mice). In contrast, inhibiting the secondary motor cortex (n = 9 eNpHR3.0 mice) produced a significantly greater effect on behavior in the pre-reward as opposed to the post-reward period. To further deconstruct the behavioral role of post-reward DA signals, we parametrically delayed the timing (0, 0.25, 0.5, 1 s) of inhibitory optical stimuli relative to the reward (n = 10 eNpHR3.0 and 11 YFP mice). Additionally we performed optogenetic activation of DA neurons during an extinction test (n = 10 Chrimson and 8 YFP DAT-Cre mice). We found that DA activity within about one second of the expected reward time is both necessary and sufficient to sustain conditioned responses on future trials. Together, the results indicate a temporally restricted role of DA neurons primarily related to reinforcing stimulus-reward associations, and suggest that directly generating movements is a comparatively less important function.

**Session 778** Depression and Bipolar Disorders: Treatment Strategies in Animal Studies

1:00 PM - 5:00 PM

**Presentation 778.26 / X20** Valeriana fauriei exerts antidepressant-like effects through anti-inflammatory and anti-oxidant activities by inhibiting brain-derived neurotrophic factor associated in chronic restrained stress

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**Abstract**

**Background:** Depression is the most common psychiatric disorder, but its pharmacological properties are not well-known. Although *Valeriana fauriei* (VF) extract has been reported to exert beneficial effects in several neurological studies, little information is available regarding its antidepressant activity.

**Methods:** In present study, we demonstrated the antidepressant activity and its underlying mechanism of VF extract in a chronic restraint stress (CRS)-induced depression model in mice.

**Results:** Oral treatment ofVF extract for 14 days significantly ameliorated depression-like behaviors (immobility time) in tail
suspended and forced swim tests following CRS induction, in accordance with decrease of the levels of serum corticosterone. Vf extract ameliorated c-Fos expression, microglial activation and phosphorylated p38 expression, and inflammatory response (the level of protein expression of cyclooxygenase-2 and inducible nitric oxide) in the hippocampus and amygdala of mice after CRS induction. However, Vf extract enhanced the stimulation of the nuclear factor erythroid 2 related factor 2 pathways, which correspond with protein expression of brain-derived neurotrophic factor (BDNF).

**Conclusion:** Collectively, our findings provide that Vf extract has antidepressant-like activity against CRS-induced depression through anti-inflammatory and antioxidant effects via inhibiting BDNF expression. Further studies are warranted to investigate the possibility of Vf extracts fraction and components as future antidepressant.

**Presentation 780.13 / Y10** Sex differences in intravenous ketamine infusion on stress and fear in rats

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**Abstract**

The U.S. Department of Defense has recently opened combat roles to women that were previously restricted to men. As a result of this policy change, military health care providers can anticipate an increased frequency of combat-related injuries in female service members in the future. Ketamine, an NMDA receptor antagonist, is a preferred battlefield analgesic due to its hemodynamic stability and a lack of respiratory suppression in wounded service members. However, ketamine administration in the peri-trauma period may produce dissociation and hallucination which may worsen traumatic memory consolidation. We previously reported that subanesthetic intravenous (IV) ketamine infusion dose-dependently increased stress hormone corticosterone (CORT) levels and fear memory in male rats. Here, we investigated the effects of IV ketamine infusion on CORT and fear memory in female rats. Adult female Sprague-Dawley rats received a 2-hour IV ketamine infusion (0 and 10 mg/kg) after auditory fear conditioning (3 times of tone and footshock pairing). Spontaneous locomotor activity was monitored during the infusion and plasma CORT levels were measured after the infusion. Fear memory retrieval, fear extinction, and fear recall were tested between 2 and 4 days after the fear conditioning/ketamine infusion. The IV ketamine infusion suppressed locomotor activity and elevated plasma CORT levels in female rats. The IV ketamine infusion following enhanced fear memory retrieval and delayed fear extinction in rats. These results indicate that subanesthetic dose of IV ketamine infusion stimulates stress hormone pathway and enhances fear memory in intact female rats.

**Presentation 780.2 / BB19** Learning to learn persistently modifies a neocortical-hippocampal inhibitory microcircuit

***A. CHUNG, A. A. FENTON; Ctr. for Neural Sci., New York Univ., New York, NY**

**Abstract**

The brain can learn to learn. Although cognitive behavior therapy (CBT) takes advantage of cognitive control training to improve cognitive abilities, the critical neurobiological evidence of 1) CBT-induced 2) long-lasting, and 3) memory-independent changes in synaptic function is lacking. Here, we test predictions of "the neuroplasticity hypothesis" by investigating the entorhinal cortex (EC) to dentate gyrus (DG) perforant path circuit changes after cognitive control training (CCT). Adult mice received either CCT in the active place avoidance task, or place learning (PL) to avoid the same location in a task variant with lower cognitive control demand, or unconditioned spatial exploration (SE) in the same environment with no cognitive demand. Upon subsequent testing to learn a new CCT task in a novel environment, only the CCT-trained mice showed learning to learn. Some mice had been implanted with stimulating electrodes in the perforant path and 32-site recording electrodes spanning the somatodendritic axis of dorsal hippocampus. DG evoked potential responses were measured in response to test stimulation before and 2h after each training session. Initial training in CCT mice but not PL or SE mice, reduced the EPSP slope localized to the inner molecular layer of the supra-pyramidal blade of DG (supDG); changes were minimal in the population spike and at the infra-pyramidal blade (inDG). This circuit change persisted 60 days without further training. Subsequent learning in a novel environment did not cause further changes. Optogenetic manipulations with evoked potential recording in urethane-anesthetized Gad2-Cre-ChR2-eYFP mice, showed that DG interneuron activation mimics the CCT-induced changes without training, and CCT training occludes the changes, indicating that CCT modifies inhibitory interneuron circuit function. Paired pulse ratio results showed that CCT causes faster activity dependent release from inhibition. Optogenetic manipulations of DG interneurons in ex vivo hippocampus slice showed that CCT increases feedforward disinhibition in supDG. Immunofluorescence for PKMzeta, which is necessary and sufficient for maintaining LTP, confirmed that CCT persists increases PKMzeta expression, specifically in somatostatin expressing GABAergic interneurons in DG hilus. These findings confirm predictions of the neuroplasticity hypothesis, demonstrating that cognitive training causes persistent changes to an entorhinal-hippocampal disinhibitory microcircuit independent of the sparse excitatory-excitatory synaptic changes that are assumed to encode specific memories.

**Presentation 785.22 / DD1** Individually tailored segmentation method for distorted hypothalamus in craniopharyngioma patient

**M. LEE1, A. HONG1, J. LEE1, J. KIM3, Y. KIM2, H. CHOI1**

Abstract

Introduction:
Segmentation of specific brain region contour is an essential process for neuroimaging study. Auto-segmentation and semi-auto-segmentation methods are developed for some brain regions. However, certain brain regions, such as hypothalamus, are difficult for segmentation due to low signal contrast. Another problem related to brain region segmentation is a distortion due to surgery or tumor. Therefore, segmentation of low signal contrast structure in distorted brain is a challenging process. The present study aimed to investigate the optimal methods for hypothalamus segmentation of craniopharyngioma patients who have undergone surgical removal.

Methods:
Seventy seven (43 male and 34 female) adult craniopharyngioma patients who underwent tumor removal surgery in Seoul National University Hospital between 2012 and 2017 were analyzed. Manual segmentation of hypothalamus in 3 tesla MRI images was carried out by two independent raters, well trained neuroimaging analyst and expert neurosurgeon. Segmentation was carried out in T1-weighted and T2-weighted MR images of 3mm thickness acquired at 3 Tesla. Sixty one patients’ data was analyzed for method 1 and 77 patients analyzed in methods 2. Method 1: segmentation on T1-weighted images in order to established boundaries of hypothalamus. Method 2: segmentation was carried out based on T2-weighted images. Lateral borderline was individually tailored in order to adjust for their distortion level. And thalamus area was excluded.

Results:
Median of age and post-operative duration were 46 years (range: 18-76 years) and 37 months (range: 3-95 months). Pre-operative tumor size was 8142mm3, sd=11804. Hypothalamic volume of 61 segmented by method 1(m=631.73mm3, sd=227.36) is larger than those by method 2(m= 507mm3, sd=112.31), t=4.730, p<.001, but positively correlated, r=.412, p=.001.
In method 2, hypothalamic volumes in 77 patients were 496.mm3, sd=114.83 in first rater, 497mm3, sd= 128 in second rater. Inter-rater correlation was excellent, r=.852, p<.001. Association between post-operative hypothalamus volume and clinical parameters, such as metabolic phenotype and surgical complications, are analyzed.

Conclusions:
In patients with severe damage, hypothalamic volume could be biased by outwardly displaced location of optic nerve. We have attempted to find an optimized method for hypothalamic volume segmentation by performing quantitative analysis on a large number of cohorts of various degrees of damage. We suggest that an individually tailored assessment is required depending on the degree of hypothalamic damage.