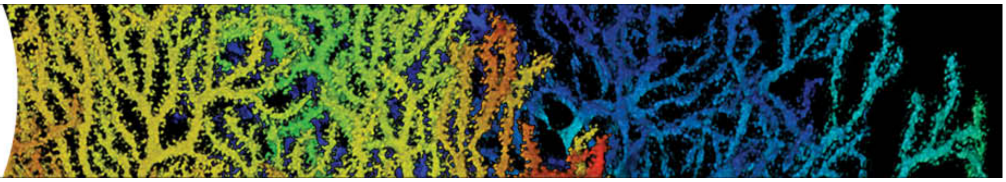
Neuroscience
2022



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SATURDAY, NOV. 12, 2022

☆ Session 028 Synapse Formation

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 028.05 / A5 Minimal molecular code for synaptic specificity in the fly visual system

1:00 PM - 5:00 PM

J. YOO[1], P. MIRSHAHIDI[1], A. NERN[2], S. A. LOCASCIO[1], S. L. ZIPURSKY[1], Y. Z. KURMANGALIYEV[1];
[1]UCLA, Los Angeles, CA; [2]Janelia Res. Campus, HHMI, Ashburn, VA

Abstract

Big data provides a broadly applicable approach to uncovering the molecular basis of synaptic specificity. First, EM level connectomes provide cell type specific connectivity. Second, single cell sequencing provides a detailed description of cell-type specific transcriptomes during development. Third, maps of cell surface protein interactions provide maps of potential molecular interactions between axons and dendrites of identified neuron types during development. And finally, genetic approaches provide ways for assessing function of these interactions regulating circuit formation. Here we show how these multiple types of big data can be utilized to elucidate the mechanisms of synaptic specificity in the Drosophila visual system. This provides a general strategy for uncovering synaptic specificity across species. T4/T5 neurons are direction-selective neurons. There are eight subtypes with discrete differences in synaptic specificity between them. Based on single cell sequencing we proposed that connectivity of each subtype is specified by gene modules, one dendritic and two axonal programs. These modules comprise a small number of differentially expressed genes encoding cell surface proteins as possible candidates for differences in synaptic specificity. Here we focused on cell surface proteins regulating the synaptic specificity of a discrete subclass of these neurons. To narrow down candidates for proteins uncovering synaptic specificity, we determined the developmental transcriptome of closely related neuron types post-synaptic to different T4/T5 neurons. Here we report the differential expression of different Beat and Side protein combinations expressed in different pre and postsynaptic cells and demonstrate through genetic analysis that these proteins regulate synaptic specificity. Together these studies and others from our lab and other groups established that three large families of immunoglobulin-containing cell recognition molecules(Dscams, DIPs/Dprs and Beats/Sides) regulate synaptic specificity in Drosophila.
References:Schmucker et al. (2000) PMID: 10892653;
Ozkan et al.(2013) PMID: 23827685***; Tan et al. (2015)*** PMID: 26687360***; Carillo et al. (2015)*** PMID: 23827685***; Xu et al. (2018)*** PMID: 30467079***; Li et al.(2017)*** PMID: 28829740; ***Sanes and Zipursky(2020)*** PMID: 32359437

☆ Session 031 Comparative Cellular and Molecular Mechanisms

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 031.08 / B28 Identifying cell-type specific actions of psychedelic drugs psilocybin and psilocin on mouse and human neocortical neurons

1:00 PM - 5:00 PM

***L. NG**[1], D.-W. KIM[1], M. KIM[1], B. E. KALMBACH[1], S. F. OWEN[2], D. KEENE[3], M. FERRERIA[4], A. KO[4], J. G. OJEMANN[4], J. HAUPTMAN[5], C. COBBS[6], H. ZENG[1], E. LEIN[1], J. T. TING[1], C. KOCH[1];
[1]Allen Inst. For Brain Sci., Seattle, WA; [2]Stanford Univ., Palo Alto, CA; [3]Pathology, [4]Neurolog. Surgery, Univ. of Washington, Seattle, WA; [5]Neurosurg., Seattle Children's Hosp., Seattle, WA; [6]Swedish Neurosci. Inst., Seattle, WA

Abstract

Psilocybin and other serotonergic hallucinogenic drugs can profoundly alter consciousness and have recently come to the forefront in brain research regarding their therapeutic potential for treating a range of debilitating psychiatric conditions. Although it is known that psilocybin and its psychoactive metabolite psilocin bind to and activate specific serotonin receptors, relatively little is known in the rodent and virtually nothing in human about cell type specific actions of these drugs in the brain. Furthermore, analysis of Allen mouse and human single cell RNA-seq datasets revealed marked species divergence in genes for serotonergic signaling pathways. These findings underscore the importance of testing drug action on human brain cell types directly rather than assuming conservation. To establish potency of our psilocin and psilocybin we performed *in vivo* drug administration in mice and analyzed the frequency of head-twitch response (HTR)—an established behavioral response to serotonergic hallucinogenic drugs dependent on 5-HT_{2A} receptor activation. Robust, dose dependent HTR was observed with both drugs but not saline control. We then performed Patch-seq in acute brain slices to measure electrophysiology, morphology, and transcriptomes of single mouse and human neurons in layers 2/3 and 5 following bath or focal application of psilocin or psilocybin (50 µM). We utilized RNA-seq data from the Patch-seq recorded neurons to map against our Allen Institute mouse and human cortical cell type taxonomies, respectively, to determine the transcriptomic cell types that responded to drug application. As a complementary approach, we monitored neuronal firing with the genetically encoded calcium indicator GCaMP8s during drug application to mark responding cells for sequential targeted Patch-seq recording. We find that ~20% of neocortical pyramidal neurons respond with a modest hyperpolarization for 10s of seconds while less than 10% of pyramidal neurons respond with strong depolarization leading to action potential firing lasting roughly equally long. These findings, together with Patch-seq mapping results, are strongly suggestive of cell type specific actions of psilocybin and psilocin. Additionally, we are now conducting scRNA-seq profiling and analysis of immediate early gene expression after psilocybin administration in mice to map the cell type and brain region-specific response profiles. Continued data generation and analysis will confirm the transcriptomic cell types most involved in psychedelic drug actions and the extent to which cell type specific mechanisms in the neocortex are conserved (or not) from mouse to human.

☆ Presentation 031.09 / B29 Characterization of AAV-based genetic tools for marking somatostatin and chandelier cells across species

1:00 PM - 5:00 PM

***D. MACHEN**[1], J. MICH[1], M. LEYTZE[1], B. KALMBACH[1], M. KIM[1], N. WEED[1], C. RADELII[1], L. NG[1], V. OMSTEAD[1], N. TASKIN[1], A. HUNKER[1], R. MARTINEZ[1], L. GRAYBUCK[1], K. SMITH[1], R. CANFIELD[2], Y. KOJIMA[2], G. D. HORWITZ[2], H. ZENG[1], T. DAIGLE[1], B. TASIC[1], E. LEIN[1], J. TING[1], B. LEVI[1];
[1]Allen Inst. for Brain Sci., Seattle, WA; [2]Washington Natl. Primate Res. Center, Univ. of Washington, Seattle, WA

Abstract

Viral genetic tools that label cell populations with high specificity across species will enable researchers to study cell type function and treat circuit dysfunction. In this study, we developed a collection of new enhancers that selectively drive gene expression in populations of Somatostatin+ (SST) and Chandelier cell (ChC) GABAergic interneurons in mouse, rat, and macaque cortex. We identified subclass-specific regulatory elements with mouse and human snATAC-seq data to construct reporter enhancer-adeno-associated viruses (AAVs). We established the specificity of reporter expression after systemic delivery of these enhancer-AAVs in the mouse using a combination of molecular approaches including multiplexed fluorescent in situ hybridization (mFISH), immunohistochemistry (IHC), and scRNA-seq. Enhancers that showed selective expression in mouse were then tested by intraparenchymal injection in macaque cortex. Cell selectivity was determined through a combined IHC and mFISH method. We report several enhancer-AAVs that drive gene expression in the SST cell subclass and the transcriptionally-defined ChC population with similar specificity across species. Lastly, we characterized the physiological properties and molecular identity of virus-labeled neurons using the Patch-seq technique and mapping to the Allen Institute human temporal cortex cell type taxonomy. Ultimately, this collection of tools will be key to the functional characterization of SST and ChC interneurons across species.

☆ Presentation 031.13 / B33 Cross species comparison of short-term synaptic dynamics in mammalian cortex

1:00 PM - 5:00 PM

***M. KIM**[1], C. RADAELLI[1], T. CHARTRAND[2], B. E. KALMBACH[3], L. CAMPAGNOLA[1], S. C. SEEMAN[1], N. DEE[1], N. TASKIN[1], N. J. WEED[2], T. CASPER[1], M. CLARK[1], J. GLOE[1], W. HO[1], A. KO[4], J. G. OJEMANN[5], D. L. SILBERGELD[7], R. P. GWINN[8], C. COBBS[8], C. D. KEENE[6], T. JARSKY[2], H. ZENG[2], J. T. TING[3], E. LEIN[3];
[1]Allen Inst. for Brain Sci., Seattle, WA; [3]Human Cell Types, [2]Allen Inst. For Brain Sci., Seattle, WA; [5]Dept Neurosurg., [6]Pathology, [4]Univ. of Washington, Seattle, WA; [7]Dept Neurosurg., Univ. Washington, Seattle, WA; [8]Swedish Neurosci. Inst., Seattle, WA

Abstract

Properties of cortical neuron short-term synaptic dynamics are essential for shaping functional cortical microcircuit motifs such as recurrent excitation and feedback inhibition. However, it is not well understood yet whether these circuit dynamics within a cortical column are conserved from mouse to non-human primate and human. To understand primate conservation and specialization of short-term synaptic dynamics, we extended prior studies of mouse V1 (VISp) and human temporal cortex (Seeman, Campagnola et al 2018; Campagnola, Seeman et al., 2021) to temporal cortex of mouse (TEa) and inferior temporal cortex of Southern pig-tailed macaque (Macaca nemestrina), and Rhesus macaque (Macaca mulatta). To access cell type-selective analysis we utilized multiple patch-clamp recordings in monkey organotypic slice cultures with a parvalbumin (PVALB) neuron specific enhancer adeno-associated virus (AAV) vector that allowed efficient targeting of fast spiking interneurons in addition to some neighboring pyramidal neurons (Mich et al., 2021). Here, we analyzed short-term synaptic dynamics between excitatory neurons, and from excitatory to fast-spiking inhibitory interneurons in layer 2/3 and 5 of human cortex compared to mouse (TEa and VISp) and non-human primate (inferior temporal gyrus) cortices. We find evidence for both conserved and species specialized features of short-term synaptic dynamics that vary by cell type. This direct cross-species comparative study of short-term synaptic dynamics and their recovery time courses will contribute to a better understanding of the functional properties of cortical column computations in each mammalian species.

☆ Session 032 Cellular Studies of Dopamine Neurons

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 032.09 / B58 Histone Deacetylase 6 (HDAC6) inhibitor restores the cellular functions in Parkinson Disease (PD) model

1:00 PM - 5:00 PM

***Y. PARK**, S. SUN, H. SEO;
Hanyang Univ., Ansan, Korea, Republic of

Abstract

Histone deacetylase (HDAC) has critical roles to regulate gene expression and various cellular functions adjusting the acetylation level of histone or non-histone proteins. HDAC6, one of the Class IIb deacetylases, can catalyze both histone and non-histone proteins due to its structure. HDAC6 inhibition has been reported as a potential therapeutic target in several neurodegenerative diseases. Although the function of HDAC6 in PD is not clearly defined yet, HDAC6-specific inhibition has been reported as a therapeutic target of PD. In this study, we used HDAC6 specific inhibitor, tubacin, to find out the neuroprotective mechanisms of HDAC6 inhibition in PD. We determined that tubacin improved the motor coordination in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) PD mice, and increased the number of tyrosine hydroxylase (TH)-positive dopaminergic neurons. In the primary cortical neuron culture, tubacin increased the length and number of neurites. Tubacin increased the survival of microglia and neurons in PD cell model. These results suggest the potential therapeutic application of tubacin for PD.

☆ Presentation 032.15 / B62 Senolytics treatment reduces senescent astrocytes and protects nigrostriatal neurons from alpha-synuclein preformed fibrils-induced damage in mice

1:00 PM - 5:00 PM

***A. GHOSH**[1], K. OFORI[1], D. VERMA[1], G. CABRERA[2], D. WHEELER[1], Y. KIM[1];
[1]Delaware State Univ. (Neuroscience), Dover, DE; [2]Delaware State Univ. (Biology), Dover, DE

Abstract

Parkinson's disease (PD) is well associated with protein aggregation and misfolding of a-synuclein, which results in progressive dopaminergic neuronal death. Although microglia and astrocytes are known to mediate neuronal death when the toxic milieu is not resolved within a reasonable timeframe, the impact of cellular senescence in damaged glial cells in PD pathology remains to be elucidated. Recently, the use of senolytics to eliminate toxic senescent cells in brains has revealed the potential application of senolytics for preventing neurodegenerative diseases. However, the clinical translation for senolytics application still has a major challenge due to the extent of non-specific cell death induction and off-target effects. This study aims to identify an optimal time window when senolytics application can be efficacious in rescuing damaged dopaminergic neurons in PFF-injected brains. Using 12 months old C57Bl/6 male and female mice (n=7-8/group), pre-formed fibrils (PFF) of mouse alpha-synuclein were stereotaxically injected into the dorsal striatum bilaterally. Then, the PFF-injected mice were gavaged with a potent senolytics (ABT-263) with 50 mg/kg for 7 consecutive days at 1.5, 2.5- and 3.5-months post PFF-injection or only vehicle treatments: positive control (no PFF) and negative control (PFF only). At the end of 5 months post-PFF injection, senolytics-treated groups, especially 2.5 months post-PFF injection showed significant improvement from motor deficits in various behavioral analyses, such as rotarod, nesting, hindlimb clasping, grooming, and pole test. In the following immunohistochemical analyses, our results demonstrated that oral senolytic treatment prevented or rescued dopaminergic neuronal loss in the SNc and enhanced the intensity of TH+ staining in the striatum in a blinded analysis. Further staining for reactive astrocytes or senescent astrocytes showed a substantial decrease in the number of non-proliferative p21+ senescent astrocytes when the senolytic treatment started at 2.5 months post PFF injection. In conclusion, our ABT-263 treated ***in vivo*** results suggest that a senolytic induced the cell death of senescent astrocytes prematurely, which mitigates the 2nd damage by toxic glial cells for neuronal loss in PD pathology.

☆ Session 033 Postsynaptic Organization and Structure

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 033.07 / C13 Unique versus shared functions of MDGAs in regulating synapse properties

1:00 PM - 5:00 PM

***S. KIM**, G. JANG, H. KIM, D. LIM, J. EUN, J. UM, J. KO;
DGIST, DGIST, Daegu, Korea, Republic of

Abstract

MDGAs (MAM domain-containing glycosylphosphatidylinositol anchors) are immunoglobulin superfamily of adhesion molecules composed of six immunoglobulin domains, a fibronectin III repeat, a MAM domain, and a GPI anchor. MDGA1 and MDGA2 were reported as suppressive factors for inhibitory and excitatory synapse development, respectively. However, various genetic manipulation studies have raised fundamental questions about the overall physiological role of MDGAs. Here, we have systematically analyzed the effects of conditional genetic deletions of MDGA paralogs, either individually or both, in cultured mouse hippocampal cultured neurons. We found that conditional genetic deletions of MDGA1 increased inhibitory synapse density without altering excitatory synapse density, whereas conditional genetic deletion of MDGA2 specifically increased excitatory synapse density. Strikingly, no synaptic alterations were found upon simultaneous deletion of both MDGA1 and MDGA2. These observations were consistently found in cultured neurons deleted sparsely and globally with individual MDGA paralog, suggesting cell-autonomous MDGA loss-of-function effects. These anatomical phenotypes were further corroborated by whole cell patch clamp recordings, revealing the specific effect of each MDGA deletion on miniature postsynaptic currents. Furthermore, MDGA gain-of-function experiments consistently supported specific action of each MDGA paralog on specific synapse types. Lastly, Sholl analysis showed that each MDGA paralog is required for dendritic branching and neuronal development. We are currently doing extensive structure-function analyses using various MDGA variants to elucidate the mechanistic basis underlying MDGA-regulated synapse and neuron development.

☆ Session 035 Synaptic Plasticity

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 035.02 / C53 MDGA1 negatively regulates amyloid precursor protein-mediated synapse inhibition in the hippocampus

1:00 PM - 5:00 PM

***J. KIM**[1], S. KIM[1], H. KIM[1], I.-W. HWANG[2], S. BAE[1], S. KARKI[3], D. KIM[1], R. OGELMAN[2], G. BANG[4], J. KIM[4], T. KAJANDER[3], J. UM[1], W. OH[2], J. KO[1];
[1]Dept. of Brain Sci., Daegu Gyeongbuk Inst. of Sci. and Technol., Daegu, Korea, Republic of; [2]Univ. of Colorado Sch. of Med., Max Planck Florida Inst. for Neurosci., Aurora, CO; [3]Univ. of Helsinki,, Helsinki, Finland; [4]Korea Basic Sci. Inst., Ochang, Korea, Republic of

Abstract

Balanced synaptic inhibition, controlled by multiple synaptic adhesion proteins, is critical for proper brain function. MDGA1 (meprin, A-5 protein, and receptor protein-tyrosine phosphatase mu [MAM] domain-containing glycosylphosphatidylinositol anchor protein 1) suppresses synaptic inhibition in mammalian neurons, yet the molecular mechanisms underlying MDGA1-mediated negative regulation of GABAergic synapses remain unresolved. Here, we show that the MDGA1 MAM domain directly interacts with the extension domain of amyloid precursor protein (APP). Strikingly, MDGA1-mediated synaptic disinhibition requires the MDGA1 MAM domain and is prominent at distal dendrites of hippocampal CA1 pyramidal neurons. Down-regulation of APP in presynaptic GABAergic interneurons specifically suppressed GABAergic, but not glutamatergic, synaptic transmission strength and inputs onto both the somatic and dendritic compartments of hippocampal CA1 pyramidal neurons. Moreover, APP deletion manifested differential effects in somatostatin- and parvalbumin-positive interneurons in the hippocampal CA1, resulting in distinct alterations in inhibitory synapse numbers, transmission, and excitability. The infusion of MDGA1 MAM protein mimicked postsynaptic MDGA1 gain-of function phenotypes that involve the presence of presynaptic APP. The overexpression of MDGA1 wild type or MAM, but not MAM deleted MDGA1, in the hippocampal CA1 impaired novel object recognition memory in mice. Thus, our results establish unique roles of APP-MDGA1 complexes in hippocampal neural circuits, providing unprecedented insight into trans-synaptic mechanisms underlying differential tuning of neuronal compartment-specific synaptic inhibition.

☆ Session 040 Preclinical Strategies and Alzheimer's Disease

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 040.07 / E13 Mutant KRAS in endothelial cells drive inflammatory responses in a mouse model of brain arteriovenous malformation

1:00 PM - 5:00 PM

M. LEE[1], S. M. WILFUR[1], S. HUANG[2], J. KÖRBELIN[4], J. P. J. SAVARRAJ[1], H. A. CHOI[1], S. P. MARRELLI[3], J. A. ARONOWSKI[3], P. R. CHEN[1], E. KIM[1], ***E. S. PARK**[1];
[1]Dept. of Neurosurg., [2]Dept. of Diagnos. and Interventional Imaging, [3]Dept. of Neurol., McGovern Med. School, The Univ. of Texas Hlth. Sci. Ctr. at Houston, Houston, TX; [4]II. Dept. of Intrnl. Med., Ctr. of Oncology, Univ. Med. Ctr. Hamburg-Eppendorf, Hamburg, Germany

Abstract

Brain arteriovenous malformations (bAVMs) are tangled blood vessels formed by direct connection of arteries and veins. Although bAVMs cause intracerebral hemorrhage (ICH), the inciting pathophysiology leading to ICH is unknown. Studies have shown that the presence of a bAVM is highly correlated with local inflammation of intranidal and surrounding brain parenchyma. Immunohistochemistry studies have identified dense concentrations of brain resident microglia and infiltrated macrophages surrounding bAVMs, suggesting microglia/macrophages (MΦ) are the prime drivers of bAVM-related inflammation. However, the underlying mechanism of MΦ-mediated inflammation in bAVM has not been studied. To interrogate the mechanisms of bAVM-associated inflammation, we established a pre-clinical bAVM mouse model based on the clinical observation of somatic ***KRAS*** mutations in human bAVM. We overexpressed the ***KRAS*** mutant (p.Gly12Val, ***KRAS***^{G12V}) in brain endothelial cells (ECs) (KRAS$^{G12V/bEC}$ mice) using an EC-specific adeno-associated virus (AAV-BR1, Retro-orbital venus sinus injection). Our mouse model recapitulates key human bAVM pathology, including tangled/snarled vasculature and the occurrence of spontaneous ICH whereas AAV-BR1-eGFP shows no bAVM/ICH. Using this model, we have observed that inflammation underlies mechanisms of bAVM-associated ICH. First, brain regions around unruptured bAVMs show a high number of Iba1+ MΦ compared to the intact (non-bAVM) in KRAS$^{G12V/bEC}$ mice at 4 and 8 weeks after AAV-BR1-KRAS^{G12V} and unruptured human bAVMs. Second, in the resected bAVMs from KRAS$^{G12V/bEC}$ mice and in cultured EC carrying mutant KRAS, mRNA levels of pro-inflammatory IL-6/IL-1β/TNF-α and proteolytic enzymes (MMP-2/9) are robustly increased. Moreover, ***in vitro*** studies show that normal microglia cultured with conditioned medium from KRAS^{G12V}-transfected ECs enhance the expression of markers for microglial activation states (IL-6, IL-1β, MMP-9, and Csf1r). Subsequently, normal ECs cultured with conditioned medium from activated microglia show decreased mRNA levels of adherens junction (Cdh5), a marker of blood-brain barrier integrity. Therefore, ***in vivo*** and ***in vitro*** studies suggest that mutant KRAS in ECs attracts the MΦ around bAVMs in the KRAS$^{G12V/bEC}$ mouse and substantiate the influence of MΦ in local inflammation that promotes bAVM rupture and ICH. The study will impact the development of new targeted pharmacological therapies to prevent inflammation-associated bAVM rupture in bAVM patients.

☆ Presentation 040.30 / E35 Dysfunction of striatal MeCP2 is associated with cognitive decline in a mouse model of Alzheimer's disease

1:00 PM - 5:00 PM

S. LEE, ***H.-I. IM**;
Korea Inst. of Sci. & Technol., Seoul, Korea, Republic of

Abstract

Cerebral Methyl-CpG binding Protein 2 (MeCP2) is involved in several psychiatric disorders that are concomitant with cognitive dysfunction. However, the regulatory function of striatal MeCP2 and its association with Alzheimer's disease (AD) has been largely neglected due to the absence of amyloid plaque accumulation in the striatal region until the later stages of AD progression. Considerable evidence indicates that neuropsychiatric symptoms related to cognitive decline are involved with striatal dysfunction. To this respect, we investigated the epigenetic function of striatal MeCP2 paralleling the pathogenesis of AD. We investigated the brain from amyloid precursor protein (APP)/presenilin1 (PS1) transgenic mice and postmortem brain samples from normal subjects and AD patients. The molecular changes in the brain, particularly in the striatal regions, were analyzed with thioflavin S staining, immunohistochemistry, immunoblotting, and MeCP2 chromatin immunoprecipitation sequencing (ChIP-seq). The cognitive function of APP/PS1 mice was assessed via three behavioral tests: 3-chamber test (3CT), Y-maze test (YMT), and passive avoidance test (PA). A multi-electrode array (MEA) was performed to analyze the neuronal activity of the striatum in APP/PS1 mice. Striatal MeCP2 expression was increased in the younger (6 months) and older (10 months) ages of APP/PS1 mice, and the genome-wide occupancy of MeCP2 in the younger APP/PS1 showed dysregulated binding patterns in the striatum. Additionally, we confirmed that APP/PS1 mice showed behavioral deficits in multiple cognitive behaviors. Notably, defective cognitive phenotypes and abnormal neuronal activity in old APP/PS1 mice were rescued through the knock-down of striatal MeCP2. We found that the MeCP2-mediated dysregulation of the epigenome in the striatum is linked to the defects in cognitive behavior and neuronal activity in the AD animal model, and that this alteration is initiated even in the very early stages of AD pathogenesis. Together, our data indicates that MeCP2 may be a potential target for the diagnosis and treatment of AD at asymptomatic and symptomatic stages.

☆ Session 041 Parkinson's Disease: Dopamine and Non-Dopamine Pathways

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 041.10 / E40 The progression of bradykinesia in people with Parkinson's disease with and without REM sleep without atonia

1:00 PM - 5:00 PM

***S. L. AMUNDSEN-HUFFMASTER**[1], J. CHUNG[1], R. SUMMERS[1], A. GROTHE[1], A. VIDENOVIC[2], M. HOWELL[1], P. J. TUITE[1], C. D. MACKINNON[1];
[1]Univ. of Minnesota, Minneapolis, MN; [2]Massachusettes Gen. Hospital, Harvard Med. Sch., Boston, MA

Abstract

The co-morbidity of rapid eye movement (REM) sleep without atonia (RSWA) and Parkinson’s disease (PD) may influence PD symptom progression due to involvement of brainstem areas contributing to movement control. We hypothesized that the slowing of arm movement (bradykinesia) would progress faster in PD with RSWA (PD+RSWA) compared to people with PD without RSWA (PD-RSWA) and healthy older adults.

Fifty-four people (PD: 18 PD+RSWA, 18 PD-RSWA, mean time since diagnosis = 2.4 ± 1.8 years; Controls: 18, age- and sex-matched to PD) completed an overnight polysomnography test and a ballistic elbow flexion task (72 deg. ROM) at baseline and 36 ± 7 months. The primary outcomes measures were the percentage of REM sleep with phasic and tonic chin electromyography and elbow flexion peak velocity and movement distance. Linear mixed effects models (RStudio) were used to investigate the effects of group, visit, arm (more vs. less affected, MA vs. LA), and their interactions. Significance was set to $p < 0.05$.

Peak velocity showed a significant visit x arm x group interaction effect, with sex, age, and movement distance as significant covariates. At baseline, both arms of the PD+RSWA participants were significantly slower (mean MA = 309 deg/s, LA = 298 deg/s) than controls (388 deg/s), but not in the PD-RSWA group. Instead, the PD-RSWA showed significant asymmetry between arms (MA =341 deg/s, LA = 364 deg/s) at baseline. At 3 years, both arms in the PD-RSWA group slowed significantly, but the rate of progression was greater in the LA arm, such that at follow-up, both arms were significantly slower than controls and asymmetry between sides was no longer present. Both arms of the PD+RSWA group remained significantly slower than controls, but there was no significant progression over 3 years. Movement distance also showed a significant group x visit interaction reflecting alterations in the overshoot of the target over time. At baseline, the PD+RSWA group moved a shorter distance (mean 76.7 deg) than the PD-RSWA (80.7 deg) and control (82.6 deg) groups, but at 3 years, PD-RSWA group now moved a shorter distance (77.5 deg) than controls (81.0 deg) while the PD+RSWA group marginally increased movement distance at follow-up (78.4 deg).

The course of progression of bradykinesia was different between PD+RSWA and PD-RSWA over 3 years. Contrary to our hypothesis, PD-RSWA progressed more rapidly and transitioned from a predominantly asymmetric to a symmetric presentation of bradykinesia, such that the two PD groups were similar at follow-up. The increased rate of progression in PD-RSWA group, particularly on the LA side, may reflect accelerated nigrostriatal dopamine depletion over the 3-year period.

☆ Session 042 Mouse Models of Parkinson's Disease

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 042.15 / E58 A new Parkinson’s disease model - Intracolonic rotenone causes alterations of gut microbiota and induces α-synuclein aggregation in the brain

1:00 PM - 5:00 PM

***M. SONG**, Y.-S. KIM;
Rutgers-Robert Wood Johnson Med. Sch., Piscataway, NJ

Abstract

Parkinson’s disease (PD) is a progressive neurodegenerative disease characterized by the loss of dopaminergic neurons in the substantia nigra (SN) and is linked to α-synuclein (α-Syn) misfolding and aggregation. The Braak hypothesis states that abnormal α-Syn can spread from the gut to the brain. Rotenone, a mitochondrial complex I inhibitor, has been used to model PD in animals by oral gavage or intraperitoneal injection. Based on this, we hypothesize that intracolonic gavage of rotenone could induce α-Syn pathology in the gut, which propagates to the SN and cause PD pathology. We developed a PD model by rotenone administration into the proximal colon for 6 weeks in C57BL6J mice. 28 weeks after treatment, we investigated α-Syn pathology in the gut led to dopaminergic neuronal death in the SN. Rotenone-treated mice showed increased α-Syn expression in the gut mucosal layer and increased pS129 expression in the myenteric plexus. Proteinase K-resistant staining in the colon

showed increased aggregate staining patterns in the submucosal plexus area. In the brain, pS129 expression was increased in the SN of rotenone-treated mice, similar to the findings in the colon. Tyrosine Hydroxylase (TH)-positive dopaminergic neurons in the SN were significantly reduced in rotenone-treated mice compared to vehicle-treated mice. We assessed motor dysfunction with the rotarod test, and the fall latency time was significantly reduced in rotenone-treated mice. Next, we investigated changes in gut microbiomes by 16S rRNA sequence analysis. Intriguingly, changes in microbiome persist even 22 weeks after rotenone administration. Firmicutes/Bacteroidetes ratio was significantly increased in the rotenone treatment group, and we found a strong negative correlation between ***Lactobacillus*** abundance and the number of dopaminergic neurons. Our study indicate that abnormal α-Syn may originate in the colon and propagate to the brain, leading to dopaminergic neuronal loss, and gut microbiota might contribute to this process.

☆ Session 051 Auditory Processing: Perception and Cognition 1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 051.08 / L1 CEDA: A Cost-Effective, Open-Source Device for Online Auditory Attention Detection with EEG 1:00 PM - 5:00 PM

***J. HA**[1], S.-C. BAEK[2], T. CHUNG[1], H. BYUN[1], Y. LIM[3], J. CHUNG[1];
[1]Hanyang Univ., Seoul, Korea, Republic of; [2]Max Planck Inst. for Empirical Aesthetics, Grüneburgweg, Germany; [3]Korea Inst. of Sci. and Technol., Seoul, Korea, Republic of

Abstract

Auditory attention detection (AAD) is used to identify an attended speaker in a multi-speaker environment based on brain activity. As AAD research grows considerably, the expectation for the applicability of AAD in daily life is increasing. To this end, this study developed a cost-effective device for AAD based on electroencephalography (EEG) and evaluated the usefulness of the device by implementing an online AAD outside the laboratory. The present study devised a Cost-Effective, open-source Device for online Auditory attention detection (CEDA), which provides a sound stimulus by a conventional earphone and allows the acquisition of EEG data synchronized to the sound stimuli to complete dichotic listening tasks with AAD. To test the feasibility of online AAD performance with CEDA in an everyday environment, nine candidates completed the dichotic listening paradigm tasks in a meeting room without soundproofing. In addition, to improve the accuracy of the AAD decoder, exponential moving average (EMA) was applied. The online AAD task was successfully demonstrated using the CEDA. It achieved an average decoder accuracy of up to 72% with nine participants. After applying an exponential moving average (EMA), the average decoder accuracy increased by up to 78%. Significance. This device allows for online AAD implementation with significant decoder performance outside the laboratory, as well as easy accessibility. These results would help expand the applicability of AAD in a daily life.

☆ Presentation 051.19 / L13 Flexible and stable representation of the auditory information in the cortico-cortical and cortico-collicular circuits 1:00 PM - 5:00 PM

***E. JUNG**, J.-H. KIM, S.-H. LEE;
Biol. sciences, Korea Advanced Inst. in Sci. and Technol., Daejeon, Korea, Republic of

Abstract

Reversal learning task requires animals to learn to reverse the association between sensory stimuli and motor actions. It is a highly cognitive process, involving multiple regions and circuits in the brain. However, it is still unclear which brain circuits reverse the sensorimotor transformation by updating reward contingencies in association with sensory stimuli. Here, we identified that the posterior parietal cortex (PPC), the auditory cortex (AC), and the inferior colliculus (IC) mutually interact with each other and play distinct roles in auditory reversal learning in mice. By performing ***in vivo*** single-unit recordings and muscimol-induced local inactivation, we found that the PPC and the AC are necessary for inverting their action after changing the stimulus-reward contingency. On the other hand, the IC is critical for gating sensory information to motor actions ***via*** representing stimulus and choice stably regardless of the reward contingency. Circuit-specific optogenetic inactivation revealed that the PPC-to-AC top-down projection mainly contributes to reversing the behavioral responses during the task, while the AC-to-IC projection is important for mice to transform auditory information into motor action. Taken together, our results demonstrate that the cortico-cortical and the cortico-collicular circuits exert distinct roles in updating auditory information according to the reward contingencies in animals flexibly adjusting their responses to the auditory stimuli. These two parallel circuits must be well-balanced for animals to take optimal action decisions.

☆ Session 055 Basal Ganglia: Physiology and Function I 1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 055.13 / Q5 Investigation of basal ganglia output pathways using optogenetic fMRI 1:00 PM - 5:00 PM

***B.-M. GU**[1], G. O. CRON[1], J. LEE[1,2,3,4];
[1]Dept. Neurol. and Neurolog. Sci., [2]Dept. of Bioengineering, [3]Dept. of Neurosurg., [4]Dept. of Electrical Engin., Stanford Univ., Stanford, CA

Abstract

Basal ganglia are critical in multiple behavioral controls, including movement, decision making and reward processing. Dysfunctions of this circuit have been known to be associated with multiple neurological and psychiatric diseases. Multiple information signals converge at the basal ganglia output nucleus, substantia nigra reticulata (SNr), and then the SNr sends

diverging outputs to multiple brain areas including thalamus, superior/inferior colliculus, and pontine reticular formation. Recent anatomical studies are starting to show cell-type-specific downstream targets of SNr. In particular, glutamic acid decarboxylase 2 (GAD2) and parvalbumin (PV) expressing cells in the SNr are reported to anatomically target different brain areas and are known to differentially modulate sleep. However, the downstream functions associated with these differential anatomical connections are unknown. In this study, using optogenetic functional MRI (ofMRI) and electrophysiology methods in mice, we showed the cell-type-specific effects of SNr on downstream targets. Using GAD2-cre and PV-cre mice, Cre-dependent ChR2 virus was expressed in the SNr and 10 Hz laser stimulations were applied repeatedly with 20s on and 40s off cycles. The optogenetic stimulation of specific cell types of SNr produced different whole brain activity patterns measured using BOLD signal. The findings reveal the common and distinct SNr downstream targets in a cell-type-specific manner.

☆ Session 065 Sleep Behaviors and Mechanisms

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 065.01 / CC3 Control of sleep by the preoptic area of the hypothalamus

1:00 PM - 5:00 PM

***J. SMITH**, A. HONIG-FRAND, H. ANTILA, F. WEBER, S. CHUNG;
Univ. of Pennsylvania, Philadelphia, PA

Abstract

The preoptic area (POA) is crucial for sleep regulation. Lesions in the POA lead to profound sleep impairment in humans and other mammalian species. The POA contains neurons that can promote sleep when activated and can be labeled with specific molecular markers. While these sleep-promoting neurons have been identified within the POA, it is not known how various subtypes of neurons change their activity throughout the sleep-wake cycle, and how they influence brain state transitions. Using fiber photometry combined with electroencephalogram (EEG) and electromyogram (EMG) recordings, we examined calcium activity in GABAergic and glutamatergic neurons within the POA throughout the sleep-wake cycle. Specifically, we found that GABAergic neurons are most active during REM sleep whereas glutamatergic neurons are least active during REMs while being most active during wakefulness. Furthermore, we used inhibitory optogenetic techniques to discover that inhibiting GABAergic neurons promotes wakefulness and suppresses NREM and REM sleep whereas inhibiting glutamatergic neurons decreases time spent in wakefulness. When performing closed loop inhibition of GABAergic neurons during REM, we found a significant decrease in the duration of REM episodes. We then conducted retrograde tracing experiments to determine if inputs of GABAergic and glutamatergic neurons in the POA originate from different regions throughout the brain. Our study will enhance our understanding of how POA neurons perform differing roles to control sleep.

☆ Presentation 065.10 / CC13 Neural circuit mechanisms underlying sleep disturbances in 16p11.2 deletion mouse model of autism

1:00 PM - 5:00 PM

***A. CHOI**, I. AN, H. ANTILA, A. SCHOTT, F. WEBER, S. CHUNG;
Univ. of Pennsylvania, Philadelphia, PA

Abstract

Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder, and its prevalence has markedly increased in the past 30 years. Many children with ASD suffer from insomnia, and sleep problems are positively correlated with the severity of ASD core symptoms such as communication deficits, withdrawal, and repetitive or stereotyped behaviors. In particular, the 16p11.2 hemideletion mouse model has been shown to sleep less and exhibit hyperactivity. However, neural circuit mechanisms underlying their sleep disturbances have not been well characterized. Using electroencephalogram (EEG) and electromyogram (EMG) recordings, we examined baseline sleep in 16p11.2 deletion and wild type mice and found that 16p11.2 deletion mice have increased microarousals resulting in fragmented sleep. To investigate the activity of the arousal promoting locus coeruleus (LC) noradrenergic neurons during sleep, we performed fiber photometry recordings and found that 16p11.2 deletion mice have an increased number of calcium peaks that largely overlap with microarousals during NREM sleep. Our study will contribute to understanding of circuit mechanisms underlying sleep fragmentation in 16p11.2 deletion mice, which may provide insight to neural mechanisms that promote disturbances in ASD.

☆ Session 067 Animal Models of Relevance to Psychiatric Illness and Treatment I

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 067.27 / HH3 Sociality regulation by cortico-habenula pathway in an animal model of depression

1:00 PM - 5:00 PM

***H. PARK**, C. CHUNG;
Konkuk Univ., Seoul, Korea, Republic of

Abstract

Impaired sociality is one of the behavioral symptoms oftenaccompanied with depression. The medial prefrontal cortex (mPFC) is known to beinvolved in social behaviors as well as physiological responses to stress andprojects to the lateral habenula (LHb). Given abnormal hyperactivity of the LHbin depressed patients and animal models, it has been suggested that themPFC-LHb pathway modulates depression-like behaviors. Previous studies mostlyfocused on animal models of depression caused by social defeat stress, however,the underlying mechanisms of sociality impairment in depression animal modelsinduced by non-social stress remain largely uninvestigated. In the presentstudy, we employed acute learned helplessness (aLH) mice and investigated anystructural and functional alterations in mPFC neurons projecting to the LHb byemploying electrophysiology, optogenetics and in vivo fiber-photometry. Usingretrograde tracing, we observed mPFC neurons project to the LHb, and theseneurons also project to the laterodorsal thalamus (LP) and paraventricularthalamus (PVT). We found that LHb-projecting mPFC neurons exhibited increasedneuronal excitability in aLH mice. Moreover, specific synaptic transmissiononto LHb neurons was potentiated. We also tested functional alteration of themPFC-LHb pathway during social interaction behaviors. The Ca2+ transient signalfrom soma and axon terminal of LHb-projecting mPFC neurons were facilitated inaLH mice. Finally, optogenetic suppression of the mPFC-LHb pathway restoresimpaired sociality of aLH mice. Our observations provide a highly valuableneural circuit to investigate mechanisms underlying the impaired sociality indepressive disorders.

☆ Session 072 Neural Mechanisms of Attention: Electrophysiology and Circuit Approaches

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 072.16 / LL4 Connectome-based predictions of individual performance improve when a task is more attentionally demanding

1:00 PM - 5:00 PM

***K. R. YOO**[1], Y. KWON[1], M. D. ROSENBERG[2], M. M. CHUN[1];
[1]Psychology, Yale Univ., New Haven, CT; [2]Psychology, Univ. of Chicago, Chicago, IL

Abstract

In connectome-based predictive modeling (Finn et al., 2015, ***Nat Neurosci***), functional brain connectivity can predict individual differences in behavior, and the predictions are more accurate from connectomes measured while participants perform cognitive tasks than from connectomes measured at rest (Greene et al., 2018, ***Nat Comms***). However, what makes task connectomes more predictive of behavior is still unknown. Here, we asked if the level of attentional demand within the same task influences the accuracy of behavioral predictions. We examined two possibilities: the same-network hypothesis vs. the different-network hypothesis. According to the same-network hypothesis, high and low levels of attention induce similar mental and brain states. Random mind-wandering is unavoidable at rest, and goal-directed attention in tasks may lessen inter-individual variation in ingoing cognition and connectomes, resulting in a similar degree of prediction improvement over rest. In the different-network hypothesis, high attentional demands engage different brain networks that can further improve predictions over both the easier condition or rest. We analyzed fMRI data from 92 subjects who completed multiple object tracking (MOT) and visual short-term memory (VSTM) tasks during fMRI scanning (Yoo et al., 2022, ***Nat Hum Behav***). Each task varied task difficulty, requiring higher and lower degrees of attention, and we calculated behavioral performance and the underlying brain connectomes separately for higher and lower attention trials. We used a generalized psychophysiological interaction-like general linear model to estimate attention level-specific connectivity while controlling for task activation. We employed connectome-based predictive modeling to predict behavior. Individual task performance was significantly lower in higher attention trials in both tasks ($p<0.001$; paired t test). The spatial similarity of the rest connectome to the high-attention connectome was significantly lower than that to the low-attention connectome in both tasks ($p<0.05$; paired t test). The high- and low-attention connectomes predicted individual task performance significantly better than the rest connectome, and they exhibited distinct patterns of predictive anatomy from each other. Compared to the low-attention connectome, the high-attention connectome predicted individual behavior significantly better (for all trials, $p<0.05$ from 1,000 permutations). Overall, in support of the different-network hypothesis, these results show that higher attentional task demands improve behavioral predictions over easier versions of the same task or rest.

☆ Session 073 Attention: Neural Mechanisms and Neural Circuits

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 073.04 / LL8 Dissociating motivation- from information-based neural salience drivers of attention

1:00 PM - 5:00 PM

***J.-C. KIM**, L. HELLRUNG, M. GRUESCHOW, S. NEBE, Z. NAGY, P. N. TOBLER;
Dept. of Econ., Univ. of Zurich, Zurich, Switzerland

Abstract

Salience optimizes behavior through attentional mechanisms. Traditionally, salience is thought to arise from the uncertainty and probability of motivationally charged (appetitive or aversive) outcomes. However, it remains unclear whether salience can also be bestowed by motivationally neutral outcomes, in line with an informational account of salience. To fill this important gap, we use human neuroimaging and a Pavlovian task where different cues predict appetitive, aversive or neutral liquids with different probabilities. We show that cue-elicited responses accelerate, and pupil sizes increase primarily for cues that predict motivationally charged outcomes with higher probability. With regard to neutral outcomes, particularly uncertainty (rather than probability) accelerates cue-induced responding and decreases pupil size. At the neural level, distinct regions of medial prefrontal cortex and occipital cortex separately process motivational or generic (i.e., motivation-related AND motivation-unrelated) salience signals. Moreover, the medial prefrontal, orbitofrontal, insular and occipital cortices dissociate probability-based motivational salience from uncertainty-based motivational salience. Thus, salience signals appear to be neurally distributed, in that purely informational forms of salience are coded separately from motivation-based forms. More generally, this dissociation suggests that for the brain not every bit of information is created equal and that there is traction in formalizing distinct forms of salience.

☆ Session 080 Human Memory Dynamics

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 080.04 / TT9 Solving the narrative puzzle: Memory retrieval in the hippocampus during ongoing narrative perception

1:00 PM - 5:00 PM

***J. PARK**[1,2,3], H. SONG[5], J. CHOI[1,4], W. SHIM[1,2,3];
[1]Ctr. for Neurosci. Imaging Research, IBS, Suwon, Korea, Republic of; [2]Dept. of Biomed. Engin., [3]Dept. of Intelligent Precision Healthcare Convergence, [4]Sungkyunkwan Univ., Suwon, Korea, Republic of; [5]Psychology, Univ. of Chicago, Chicago, IL

Abstract

Humans understand the story by constructing a coherent narrative structure from the perceived events according to their temporal and causal relationships. Previous computational work demonstrated that constructing the narrative structures when perceiving uncertain events entails retrieving past events from memory to piece together with the ongoing event (Qihong et al., 2022). In this study, we examined the neural signatures of narrative memory retrieval during the ongoing narrative perception. We conducted an fMRI experiment in which participants (N=65) watched a 10-min movie consisting of temporally scrambled events and recounted the story in its original sequence. From the scrambled structure of the events, we identified the moments at which the memory retrieval would occur to reconstruct the unscrambled narrative structure of the story. Around the event boundaries that correspond to those moments, we found selective responses for narrative memory retrieval in the hippocampus: Hippocampal activity patterns of the currently perceived event match the pattern representation of the event that immediately follows or precedes the current event in the original sequence of the movie. We further hypothesized that the memory retrieval in the hippocampus would be related to the participant's ability to reconstruct the story. To examine this question, we computed participants' story understanding ability from the amount of recalled information (content score) and the accuracy of reordering the temporal sequence of recalled events (ordering score) by comparing the similarity in the semantic content between the original movie annotations and each subject's recall using a topic modeling method (Heusser et al., 2021). We found that the ordering score was positively correlated with the narrative retrieval response in the hippocampus, whereas the content score was not. Furthermore, to investigate the characteristics of the narrative memory being retrieved, we estimated the coherence of each event in the narrative using the pre-trained deep language model. We found significant narrative coherence between the current and associated past events that evoke retrieval while controlling for the semantic similarities between events. These results suggest that the hippocampus plays a critical role in retrieving past memories during ongoing narrative perception. It also implies that the hippocampal memory retrieval can lead to individual differences in their cognitive abilities to construct the narrative structure in story comprehension.

☆ Presentation 080.05 / TT10 Spontaneous memory recall in the dynamic flow of thoughts

1:00 PM - 5:00 PM

***H. LEE**, S. BORN, C. J. HONEY, J. CHEN;
Psychological and Brain Sci., Johns Hopkins Univ., Baltimore, MD

Abstract

When our minds wander, memories of past events arise amidst other thoughts. What are the cognitive and neural states that trigger episodic memory recall within the flow of spontaneous thoughts? To explore this question, we performed an fMRI experiment in which subjects were asked to verbally describe any thoughts that entered their consciousness for 10 minutes. Subjects' verbal responses were manually segmented into individual "thoughts" based on changes in either the topic or the category of their speech. Five major thought categories were identified: episodic memory, autobiographical semantic memory, non-autobiographical semantic memory, future thinking, and current sensations and feelings. Episodic recall on average accounted for 16% of thoughts, sporadically distributed over the 10-minute session. To test whether episodic recall was triggered more by some categories of thoughts than others, we computed transition probabilities between different categories of thoughts. We found that episodic recall was not triggered by any specific thought category more than expected by chance, including episodic recall itself. We next computed semantic similarity between thoughts using a natural language processing model. Semantic similarity was higher between an episodic memory and its immediately preceding and following thoughts compared to more distant ones, suggesting that episodic memory was triggered by related thought content. This semantic similarity autocorrelation effect was also observed in other categories of thoughts. Finally, we examined brain activation patterns at transitions between different thought categories or topics, focusing on the posterior medial cortex (PMC). PMC previously exhibited an activation pattern specific to major mental context transitions, and the pattern was consistent across different tasks and stimuli (Lee & Chen, 2022, eLife). We found that PMC patterns at topic transitions were positively correlated with the major context transition pattern observed in the prior study more so than category-transition patterns were, implying that topic transitions were experienced as more prominent changes in mental contexts. Non-boundary patterns in the middle of thoughts were not correlated with the major context transition pattern. Together, these results demonstrate that episodic memories are naturally retrieved by shared meanings without any task demands, and suggest that semantic connections may be a major organizing principle of the flow of spontaneous thoughts.

☆ Session 083 Single Cell Profiling Techniques in Health and Disease

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 083.12 / VV26 Single-nuclei paired multiomic analysis of young, aged, and Parkinson's disease human midbrain reveals age- and disease-associated glial changes and their contribution to Parkinson's disease

1:00 PM - 5:00 PM

M. SONG[1], L. ADAMS[1], Y. TANAKA[2], ***Y.-S. KIM**[1];
[1]Rutgers-Robert Wood Johnson Med. Sch., Piscataway, NJ; [2]Maisonneuve-Rosemont Hosp. Res. Ctr., Montreal, QC, Canada

Abstract
Age is the primary risk factor for Parkinson's disease (PD), but how aging changes the expression and regulatory landscape of the brain remains unclear. Here, we present a single-nuclei multiomic study profiling shared gene expression and chromatin accessibility of young, aged, and PD post-mortem midbrain samples. We profiled 69,289 high-quality nuclei from 31 individuals (9 young donors, 8 aged donors, 14 PD patients). To investigate how aging process affects PD pathogenesis, we combined the snRNA and snATAC sequencing datasets and established a combined pseudopathogenesis (cPP) trajectory. cPP trajectory reveals all glial cell types are affected by age, but microglia and oligodendrocytes are further altered in PD. Using this analytical strategy, we identified three distinct subsets of oligodendrocytes in the human substantia nigra. Most cells exhibited a low cPP score and had a transcriptome signature characteristic of healthy, canonical oligodendrocyte function. All donors, regardless of age or disease status, had a large population of healthy cells. We present evidence for a novel disease-associated oligodendrocyte subtype characterized by a high cPP score and identify genes lost over the aging and disease process, including CARNS1 and RBFOX1, which may predispose healthy cells to develop a disease-associated phenotype. We also identified genes such as QDPR and SELENOP altered during PD. We confirmed our bioinformatics findings with RNA-FISH on FFPE human substantia nigra sections. Peak-gene association analysis from paired data identifies 89 PD-associated SNP loci, including five in MAPT, that show differential association with gene expression in disease-associated oligodendrocytes. Our study suggests a previously undescribed role for oligodendrocytes in aging and PD pathogenesis.

☆ Presentation 083.21 / VV35 Characterization of Cocaine-induced Neural Activation and Gene Expression Change in Transcriptomic Cell Types of Mouse Mesocorticolimbic Areas

1:00 PM - 5:00 PM

***D.-W. KIM**, C. LEE, T. CASPER, J. GLOE, M. CLARK, T. PHAM, A. TORKELSON, J. GOLDY, R. FERRER, J. GUZMAN, K. SMITH, N. DEE, Z. YAO, H. ZENG;
Allen Inst. for Brain Sci., Seattle, WA

Abstract
Drug addiction is one of major debilitating diseases but its underlying molecular and cellular mechanisms are not yet fully understood. Recent advances of single-cell RNA-sequencing (scRNA-seq) technology have allowed us to capture co-varying gene expression patterns in individual cells in a high-throughput and unbiased manner, and thereby enabling classification of distinct transcriptomic cell types (T-types) in regions of interest. Furthermore, a variant version of scRNA-seq (called "Act-seq") was introduced to identify active neuronal T-types during a particular behavior/manipulation by measuring endogenously induced expression of immediate early genes (IEGs), while unwanted further IEG activation during sample preparation was suppressed. Here we aim for characterizing activated T-types and gene expression changes after systemic injections of cocaine in major mesocorticolimbic areas in mice. We have collected ~858k cells (containing ~330k neurons) dissected from 7 areas (including prefrontal cortex (PFC), ventral striatum (STRv), anterior and medial thalamus (TH:Ant-MM), cortical subplate and amygdalar, midbrain, and hindbrain) using Act-seq (10x Genomics) in 6 different conditions of cocaine administration. Upon mapping QC-passed cells onto our existing whole-brain scRNA-seq taxonomy, we first observe strong IEG activations especially in T-types from PFC, TH:Ant-MM, and STRv in a graded manner (acute cocaine < chronic cocaine + short-term withdrawal < chronic cocaine + long-term withdrawal). Interestingly, some T-types from PL-ILA-ORB (L2/3 IT, L4/5 IT, L6 CT, and Sst GABAergic), TH:Ant-MM (Rxfp1_Epb4), and STRv (MSN D1) are persistently activated only in the chronic cocaine + long-term withdrawal condition. Consistent with previous literatures, we also find differentially expressed (DE) genes relating to epigenetics (e.g. Gadd45b, Kdm6b, Ehmt2) in some neuronal subclasses of PFC and STRv from chronic cocaine conditions. Overall, we have successfully generated large-scale and high-quality scRNA-seq datasets to profile cocaine-induced neural activations and transcriptomic changes at a T-type level. Ongoing work focuses on the following directions: i) how much these cocaine-induced T-type activation patterns are similar to those from other drugs of abuse like morphine, ii) where these activated T-types are spatially located (by mapping it onto our whole-brain multiplexed error-robust fluorescence in situ hybridization (MERFISH) data), and iii) what other interesting DE genes are induced by chronic exposure to cocaine in non-neuronal T-types.

☆ Session 084 Methods for Gene and Protein Expression in the Brain

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 084.18 / WW10 Mapping endogenous neurotransmitter receptors in the Drosophila brain at single cell and single synapse resolution

1:00 PM - 5:00 PM

***P. SANFILIPPO**[1], J. YOO[1], A. KIM[1], H. BEVIR[1], A. YUEN[1], P. MIRSHAHIDI[1], A. BHUKEL[2], Y. ASO[2], S. L. ZIPURSKY[1];
[1]UCLA, Los Angeles, CA; [2]Aso Lab., Janelia Res. Campus, Ashburn, VA

Abstract
The connectome of the ***Drosophila*** brain has revealed extraordinary complexity of brain wiring, with each neuron receiving hundreds to thousands of inputs from diverse neuron types. Synapses are molecularly diverse, in part, by the neurotransmitter receptors localized to them. The ***Drosophila*** genome encodes over 50 neurotransmitter receptor subunits. To map receptors to the connectome, we have modified endogenous receptor gene loci to simultaneously introduce tags and sparsely label processes of identified cell-types. Here we report the generation of conditional knock-in alleles of 11 cys-loop ionotropic receptor subunits belonging to a large family of structurally related proteins, including nAChRβ1, Rdl, and GluClα receptors for acetylcholine, GABA and glutamate, respectively.
We characterize diverse patterns of receptor localization and the spatiotemporal dynamics of localization during development in multiple optic lobe neurons. Of particular interest, we observe differential localization of Rdl and GluClα to respectively the base and the tip of motion sensitive T4 dendrites. This pattern of receptor distribution agrees with the select wiring of GABA and glutamate inputs at either the base or the tips of T4 dendrites as defined from EM connectome data. Strikingly, mapping of nicotinic acetylcholine receptor subunits in T4 dendrites shows differential distribution of nAChRα5 subunits to the middle of

the dendritic arbor and distal localization of nAChRβ1 subunits to the tips of the dendrites. The middle of T4 dendrites is innervated by two major cholinergic inputs while the dendritic tips receive inputs from adjacent cholinergic T4 neurons. This data raises the possibility that different cholinergic inputs wire into T4 dendrites by using distinct acetylcholine receptors. In addition, differential neurotransmitter receptor type distribution could play a role in the dendritic computation of motion detection in T4 dendrites.
These reagents provide tools for studying synapse development, the role of specific receptors in circuit function and behavior, and uncovering mechanisms of protein localization in an array of morphologically diverse neuron types.

SUNDAY, NOV. 13, 2022

Session 119 Alzheimer's Disease Clinical and Preclinical Studies

8:00 AM - 12:00 PM

SDCC Halls B-H

Presentation 119.02 / E21 Relationships between Neuropsychological Language Test Performance and Cortical Thickness in the Language-Relevant Brain Regions in Mild Cognitive Impairment and Alzheimer’s Disease Related Dementia

8:00 AM - 12:00 PM

R. SEO[1], C. M. PARSEY[2,3], D. J. PETERSON[1], T. J. GRABOWSKI[1,3];
[1]Univ. of Washington Dept. of Radiology, Seattle, WA; [2]Univ. of Washington Dept. of Neurol., Seattle, WA; [3]Univ. of Washington Alzheimer’s Dis. Res. Ctr., Seattle, WA

Abstract

ABSTRACTIn neurodegenerative disorders, such as Alzheimer’s disease dementia (AD) or frontotemporal dementia (FTD), patterns of neuropsychological test (NPT) performance can predict structural changes identified on neuroimaging (e.g., memory impairment and hippocampal atrophy; language impairment and temporal lobe degeneration). Advances in neuroimaging have produced regional and network-based metrics to better understand relationships between structural neuroanatomical change and cognitive symptoms. Here, we relate NPT performance and network level organization for language function. Three language-domain tests [measuring phonemic fluency (COWAT), category fluency (Animal naming) and naming (BNT)] were correlated with cortical thickness in language-related and domain-general networks (i.e., in the frontal and temporal lobes, and using Yeo et al. 2011 7-network model). Participants were selected from a memory clinic data repository, which included 3D MPRAGE MRI imaging and NPT. MPRAGE images were processed using FreeSurfer, and cortical thickness was averaged within the regions and networks of interest. Pearson correlations between the anatomical measures and the language test scores were examined in three participant groups: AD (n = 64), mild cognitive impairment (MCI; n = 202), and healthy cognition (HC; n = 72). In the AD group, correlations were significant between phonemic fluency and ventral attention network ($r = 0.326$, $p = 0.021$) and somato-motor network ($r = 0.286$, $p = 0.044$) cortical thickness, as well as frontal lobe volumes (L: $r = 0.363$, $p = 0.010$; R: $r = 0.386$, $p = 0.006$). Semantic fluency correlated significantly with frontal-parietal network ($r = 0.294$, $p = 0.040$) and default mode network ($r = 0.380$, $p = 0.007$). BNT correlated significantly with Yeo’s limbic network ($r = 0.355$, $p = 019$) and left temporal volume ($r = 0.408$, $p = 0.007$). For the MCI group, BNT scores correlated with cortical volumes in bilateral temporal lobes (L: $r = 0.601$, $p < 0.001$; R: $r = 0.318$, $p < 0.001$). No significant correlations in the HC group were found. Our findings revealed expected relationships of lower performances on language-specific NPTs with cortical thinning and volume loss in language-associated neural regions, in particular reduced semantic fluency with frontoparietal and temporal regions, and confrontation naming with anterior temporal lobe cortical thinning. However, other relationships between neuroimaging findings and NPT language performance were less clear and warrant further evaluation, including in atypical neurodegenerative presentations where language networks may be disproportionately affected.

Session 127 Human Chronic Pain Including Post-Injury

8:00 AM - 12:00 PM

SDCC Halls B-H

Presentation 127.03 / I14 Precision neuroimaging of chronic pain and personal narratives in fibromyalgia

8:00 AM - 12:00 PM

***J.-J. LEE**, C.-W. WOO;
Sungkyunkwan Univ., Sungkyunkwan Univ., Suwon-si, Gyeonggi-do, Korea, Republic of

Abstract

The experience of chronic pain is individually unique and multidimensional. However, it remains elusive how the human brain represents the idiographic experience of chronic pain. In this study, we used functional magnetic resonance imaging to investigate the brain representation of pain perception and self-narratives of individual patients with fibromyalgia. Two participants clinically diagnosed with fibromyalgia were recruited, who completed 11 (participant #1) and 9 (participant #2) out of 30 planned visits of Magnetic Resonance Imaging (MRI) scanning. For every visit, we collected functional MRI data from participants while they were continuously rating their subjective pain intensity, with or without performing a physical activity that exacerbated the ongoing pain before the scan. We also collected functional MRI data while participants were resting, answering questions designed to elicit personal narratives of pain, and listening to their recorded answers. Preliminary behavioral results showed that both participants reported an increase of pain intensity after the physical activity, though only the participant #2 showed statistically significant increase (participant #1, $t_{10} = 1.35$, $p = 0.21$; participant #2, $t_8 = 2.66$, $p = 0.029$). We further characterized personalized structural and functional brain architecture, and the relationships between the brain representations of pain and self-narratives. This study proposes a deeply-sampled and task-extensive imaging of individual patients as a new approach to understanding the neural mechanisms of chronic pain and to advancing the clinical utility of neuroimaging.

☆ Session 135 Basal Ganglia: Physiology and Function II

8:00 AM - 12:00 PM

SDCC Halls B-H

☆ Presentation 135.19 / S13 Neural correlates of impaired interlimb coordination in Parkinson’s disease

8:00 AM - 12:00 PM

***J. CHUNG**[1], I. MALIK[2], A. E. BOWER[1], C. A. KNIGHT[1,3], J. J. JEKA[1,3], J. P. MARTELLO[4], R. G. BURCIU[1,3];
[1]Dept. of Kinesiology and Applied Physiol., [2]Ctr. for Biol. & Brain Imaging, [3]Interdisciplinary Neurosci. Grad. Program, Univ. of Delaware, Newark, DE; [4]Dept. of Neurosciences, Christiana Care Hlth. Syst., Newark, DE

Abstract

Numerous functional MRI studies of Parkinson’s disease (PD) have used single-limb movements as a testing paradigm to gain insight into the brain mechanisms underlying some of the main motor symptoms in PD such as bradykinesia and rest tremor. While the effect of PD on the performance of single-limb movements and associated brain activity is well documented, little is known about the neural correlates of impaired coordination in PD. Coordinated control of multi-limb movements is essential to many activities of daily living, and is impaired in PD compared to healthy, older adults. Here we present preliminary results from a study that employs a force control paradigm to study brain changes in PD during an interlimb coordination task involving non-homologous limbs (i.e., hand and foot). Study participants included 18 PD and 17 controls that were age- and gender-matched. PD patients were tested following a 12-h withdrawal from antiparkinsonian medication and on the more affected side. Motor symptoms were assessed with the motor section of the MDS-sponsored revision of the Unified Parkinson’s Disease Rating Scale (MDS-UPDRS-III). The tested side for controls was randomized. Inside the MRI scanner, participants performed a visually cued force production task that involved using the hand and foot to produce force simultaneously. Force demands were set at 15% of maximum voluntary contraction (MVC). While both groups were able to produce 15% of MVC, PD had a slower rate of force development and force relaxation than controls. The fMRI analysis revealed that compared to controls, PD had reduced brain activity during the interlimb coordination task in the contralateral M1 foot area and globus pallidus, and increased brain activity in the contralateral superior frontal gyrus as well as ipsilateral cerebellar lobules Crus II and VIIb. Our preliminary findings suggest that force control deficits during interlimb coordination in PD are associated with extensive functional changes that span both the basal ganglia- and cerebellar-cortical motor loops. In the context of a complex task that presents participants with an increased motor and cognitive load, it is possible that the increased prefrontal and cerebellar activity in PD may reflect a compensatory effect facilitating task performance.

☆ Session 139 Neuroendocrine Anatomy and Physiology

8:00 AM - 12:00 PM

SDCC Halls B-H

☆ Presentation 139.22 / X14 Top-down brain circuit for slow breathing drives relief-like anxiolysis

8:00 AM - 12:00 PM

***J. JHANG**, S. LIU, S. HAN;
Salk Inst. for Biol. Studies, La Jolla, CA

Abstract

Breathing is more than simply the respiratory response to maintain gas homeostasis. Breathing rhythms are entrained by various purposeful and emotional behaviors that require orofacial and pharyngeal activity. Moreover, breathing rhythms can be controlled by conscious effort in humans - volitional breathing. Despite cumulating evidence indicating the presence of top-down circuits that control breathing, however, precise circuits and neurons that relay high-order cortical inputs to brainstem breathing centers remain unknown. Here, we identify a subset of neurons in the dorsal anterior cingulate cortex (ACCd) which projects to the pontine reticular nucleus (PnC) as a key modulator of slow breathing. Optogenetic activation of ACCd→PnC neurons reduces breathing rate and specifically alleviates anxiety-like behaviors without altering valence in mice. Calcium response of ACCd→PnC neurons was correlated with behaviorally entrained breathing cycles, as well as relief-like slow breathing patterns observed in anxiety tests. Our tracing experiments show that ACCd neurons are targeting inhibitory neurons in the PnC area, which in turn project to the pontomedullary breathing centers. Moreover, axon collaterals of the ACCd→PnC neurons are projecting to anxiety-related structures in the forebrain, thus comprising a neural network that synchronously modulates the breathing and the internal state of fear and anxiety. Together, our study expands the understanding of brain circuits for central breathing control and provides useful knowledge for treating breathing- and anxiety-related psychiatric illnesses.

☆ Presentation 139.07 / W15 Role of serotonin 2C receptors expressed by CRH neurons

8:00 AM - 12:00 PM

***E.-S. YOO**[1], M. SA[2], C. J. LEE[2], J.-W. SOHN[1];
[1]Biol. Sci., Korea Advanced Inst. of Sci. and Technol., Daejeon, Korea, Republic of; [2]Ctr. for Cognition and Sociality, Inst. For Basic Sci. (IBS), Daejeon, Korea, Republic of

Abstract

The anorexigenic (appetite-suppressing) effects of serotonin 2C receptor (*Htr2c*) agonists have been largely attributed to *Htr2c* expressed by the pro-opiomelanocortin (POMC) neurons in the arcuate nucleus of the hypothalamus. However, *Htr2c* is widely expressed in various brain regions, and it is possible that other neuronal populations that express *Htr2c*s may also contribute to *Htr2c*-induced anorexigenic effects. Here, we show the role of *Htr2c* expressed by the corticotropin-releasing hormone (CRH) neurons through the generation of conditional knock-out (KO) mice. We found that energy balance and glucose homeostasis of the conditional KO mice are not significantly changed, but the anorexigenic effects of the *Htr2c* agonist are significantly attenuated. We performed additional experiments to delineate the mechanisms involved in this phenotype. Taken together, we suggest that *Htr2c*s expressed by the CRH neurons are responsible for the anorexia induced by *Htr2c* agonists.

☆ Session 144 Neurobiology of Fear

8:00 AM - 12:00 PM

SDCC Halls B-H

☆ Presentation 144.12 / EE9 Extinction engram silences an original fear engram in the lateral amygdala.

8:00 AM - 12:00 PM

***S. PARK**[1], J. JUNG[2], P. W. FRANKLAND[2], S. A. JOSSELYN[2];
[1]The hospital for sick children, [2]The Hosp. For Sick Children, The Hosp. For Sick Children, Toronto, ON, Canada

Abstract

Memories for events are thought to be represented in sparse, distributed neuronal ensembles (or engrams). During an event, neurons that are more excitable or active are recruited or allocated to an engram. Our previous works have presented that fear memory engram is strongly correlated with the neuronal excitability of the randomly selected neurons in the lateral amygdala (S. Park et al., 2016; Rashid et al., 2016). Recent studies suggested that extinction training can recruit neuronal populations unlike fear neurons (Lacagnina et al., 2019). However, relatively little is known about how extinction engram is related to fear engram. Here we examined how extinctoin engram works in the lateral amygdala (LA). To manipulate the excitability of neurons, we used a strategy that allowed us to either activate (via ChR2) or inhibit (via NpHR3) the same neurons at different points in our experiment. First, we showed that after behavioral extinction (16 CS tones, no foot-shock), optogenetic activation of the original fear engram induces memory recall without any change in fear extinction memory. We allocated fear memory to randomly selected neurons, stimulating ChR2 (1mW, 20Hz, 473nm, 30s). Optogenetic stimulation on the neurons allocating fear memory induced fear responses in the extinction training context. This finding is consistent with previous results showing that behavioral extinction requires “new learning” rather than a modification of the original memory trace (Zhang et al., 2020). Second, we applied DREADD (hM4Di, an inhibitory receptor) to specifically silence extinction engram neurons and fiber photometry to observe the change of Ca^{2+} signals from fear engram neurons. To silence hM4Di-expressing neurons allocating extinction memory, the mice were systemically administered CNO or vehicle 1 hr before testing. Besides optogenetic memory allocation, we used a robust activity marking system (RAM) to label active neuronal ensembles (Sorensen, 2016). This approach enables fear and extinction engram to be tagged in the same animals. We found that the inhibition of extinction engram causes the mice to show increased freezing behavior, raising Ca^{2+} signals from fear engram neurons. Lastly, we tested if extinction engram is changeable to fear engram. For this experiment, we used the viruses having ‘Cre-off’ system. After extinction, we tried to allocate new fear memory to extinction engram neurons, optogenetically stimulating them. We found that extinction engram could be overwritten by another fear training, and the extinction engram becomes fear engram. Together, these findings begin to help us understand the fate of an engram (fear & extinction) once formed.

☆ Presentation 144.26 / FF9 Dopaminergic transmission and neuronal activity of the posterior basolateral amygdala are necessary for active avoidance learning

8:00 AM - 12:00 PM

***J. PYO**, S. LEE, S. CHOI, J. KIM;
POSTECH, Pohang-si, Korea, Republic of

Abstract

Over the decades, research has shown that the basolateral amygdala is necessary for threat memory and defensive behavior. Most studies focused on passive freezing behavior in an inescapable situation. However, in reality, animals also can actively avoid when they predict near harmfulness. To reveal neuronal circuits that switch two different defensive behavior, freezing and avoidance, we adopt the auditory two-way active avoidance paradigm with pharmacological treatment, fiber photometry, viral tracing and chemogenetics. Here we show the dopamine transient in the posterior basolateral amygdala (pBLA) and the activity of the $pBLA^{Ppp1r1b+}$ neuron are necessary for avoidance learning.

☆ Session 145 Neural Circuits and Encoding of Emotional Behaviors

8:00 AM - 12:00 PM

SDCC Halls B-H

☆ Presentation 145.14 / GG12 Gaze following in third-party observers of simulated social conflict shows few reflexive and many mentalizing features

8:00 AM - 12:00 PM

***T. CHAMP**, S. LEE, A. B. MARTIN, C. M. BOLLES, S. KIM, K. M. GOTHARD;
Physiol., Univ. of Arizona, Tucson, AZ

Abstract

Humans and non-human primates can point with their eyes, redirecting the visual attention of their social partner toward areas of high interest in their visual field. By following the gaze of interacting individuals, the observer obtains information about the emotions, mental states, and intentions of others. We presented three adult monkeys (*Macaca mulatta*) with videos of simulated social interactions and quantified their eye movements to determine which observed behaviors were conducive to joint-attention and gaze-following (JAGF) saccades. Social conflict was simulated by juxtaposing two videos depicting a threatening and an appeasing (or affiliative) individual facing each other, with the timing of the facial and bodily displays adjusted to mimic an exchange of facial signals. Histograms of JAGF saccade counts per frame were generated for each observer and individual movie monkey. Each histogram showed the clustering (or not) of JAGF saccades generated by an observer monkey in response to one video monkey. These clusters suggest that some videos contained signals that compelled a reflexive redirection of the observer's attention. Theoretically, viewers could produce 4-5 interactive, JAGF saccades per second. In our data, even in clusters with a high probability of JAGF, the frequency did not exceed 1.5 interactive saccades/s (viewer C: 1.03 ± 0.416 Hz, n=32 clusters; viewer D: 1.14 ± 0.37 Hz, n=37 clusters; and viewer P: 1.36 ± 0.43 Hz, n=17 clusters). Furthermore, the movie frames that elicited the JAGF saccades within significant clusters overlapped only 1.3% of the time across the three observers and 7.96% of the time across two of the three observers, therefore 90.7% of the time the clusters were unique to each observer. It is unlikely, therefore, that the videos contained "irresistible" signals that triggered automatic stereotypical behaviors. On the contrary, the distribution of the JAGF saccades suggest more complex processing. All three viewers showed sequences of joint-attention saccades by switching back and forth between the two video monkeys resulting in bi-directional gaze interactions or "check-backs". We found 36 cases of these "check-backs" between paired clusters (viewer D: n= 15, C: n= 14, P: n= 7). These observations argue for more socially elaborate, mentalizing processes that guide the eye movements of third-party observers.

☆ Presentation 145.17 / GG15 Saccade-related neural activity in the macaque amygdala and hippocampus is modulated by the social status of observed conspecifics

8:00 AM - 12:00 PM

***S. LEE**[1,2], A. B. MARTIN[1], U. RUTISHAUSER[3,4,5], K. M. GOTHARD[1];
[1]Dept. of Physiol., [2]Dept. of Electrical & Computer Engin., The Univ. of Arizona, Tucson, AZ; [3]Dept. of Neurosurg., [4]Ctr. for Neural Sci. and Med., Cedars-Sinai Med. Ctr., Los Angeles, CA; [5]Div. of Biol. and Biol. Engin., Caltech, Pasadena, CA

Abstract

The role of the primate amygdala in social behavior is demonstrated by selective neural responses to face identity, facial expressions, gaze direction, and social status. The amygdala is also involved in allocation of visual attention to stimuli of high socio-emotional salience. During natural social behaviors, high status individuals receive more attention than low status individuals. A recent phenomenon that has been identified in both humans and macaques is that ongoing theta oscillations in the hippocampus are phase reset by saccades. Further, in humans, these phase resets are particularly prominent for saccades that land on faces. The role of these phase resets in the processing of social information remains unknown. To examine this question, we tested the hypothesis that local field potentials in the non-human primate amygdala and hippocampus differentiate between saccades toward high status and low status individuals. We recorded eye movements and neural activity from the amygdala and hippocampus of a monkey while he watched one of three types of videos: (1) a video of a simulated hierarchical interaction between a high-status and low-status macaque, (2) a video of two moving objects, and (3) a video of natural scenes including macaques. The local field potentials elicited by saccades while scanning these three types of videos were compared to control saccades of similar length and duration produced while the viewer looked at a black screen. The eye-movement related component of the event-related potentials (ERPs) (recorded from 32 contacts spanning the distal 6-mm of two V-probes advanced each into the amygdala and hippocampus) was removed by subtracting from all channels the signal corresponding to the common average reference. The shapes of the resulting ERP's were nucleus- specific (amygdala) and layer-specific (hippocampus). In 49 of 59 contacts in the amygdala and 12 of 29 contacts in the hippocampus the magnitude of the saccade-onset aligned ERP's was higher for saccades originating from high-status compared to low-status individuals. Although this effect was relatively small (between 2-25 microvolts), it survived the additional control of removing the ERPs resulting from saccades while watching the black screen. These preliminary results suggest that looking at individuals of high-social status engages mesoscale neural populations in the non-human primate amygdala and hippocampus more so than when viewing low-social status individuals. Ongoing studies explore oscillatory and coupling effects between the amygdala and hippocampus during these viewing behaviors.

☆ Presentation 145.01 / FF13 The pontomesencephalic PACAPergic pathway mediates panic-like behavioral and somatic symptoms in mice

8:00 AM - 12:00 PM

***S. J. KANG**[1], J. KIM[2], D.-I. KIM[1], B. Z. ROBERTS[1,3], S. HAN[1];
[1]Salk Inst. for Biol. Studies, Salk Inst. for Biol. Studies, La Jolla, CA; [2]Ctr. For Cognition and Sociality/Ibs, Ctr. For Cognition and Sociality/Ibs, Daejeon, Korea, Republic of; [3]UCSD, La Jolla, CA

Abstract

Panic disorder (PD) is characterized by uncontrollable fear accompanied by somatic symptoms that distinguishes it from other anxiety disorders. Neural mechanisms underlying these unique symptoms are not completely understood. Here we report that the pituitary adenylate cyclase-activating polypeptide (PACAP)-expressing neurons in the lateral parabrachial nucleus projecting to the dorsal raphe (DR) are critical for panic-like behavioral and physiological alterations. These neurons are activated by panicogenic stimuli, but inhibited in conditioned fear and anxiogenic conditions. Activating these neurons elicits strong defensive behaviors and rapid cardiorespiratory increase without creating aversive memory, whereas inhibiting them attenuates panic-associated symptoms. Chemogenetic or pharmacological inhibition of downstream DR PACAP receptor-expressing neurons completely abolishes panic-like symptoms, demonstrating that the pontomesencephalic PACAPergic pathway mediates panicogenesis, and provides promising therapeutic target for treating PD.

☆ Session 146 Behavioral Phenotypes and Neural Mechanisms of Relevance to Psychiatric Illness

8:00 AM - 12:00 PM

SDCC Halls B-H

☆ Presentation 146.10 / II3 Stress resilient role of mGluR5 in BLA target neurons

8:00 AM - 12:00 PM

***J. KIM**[1], S. KANG[2], T.-Y. CHOI[3], K.-A. CHANG[4], J. KOO[1];
[1]Korea Brain Res. Inst., Korea Brain Res. Inst., Daegu, Korea, Republic of; [2]Gachon Univ., Gachon Univ., Incheon, Korea, Republic of; [3]Korea Brain Res. Inst. (KBRI), Korea Brain Res. Inst. (KBRI), Daegu, Korea, Republic of; [4]Gachon Univ, Colleage of Med., Gachon Univ, Colleage of Med., Incheon, Korea, Republic of

Abstract

The metabotropic glutamate receptor 5 (mGluR5) has been implicated in stress-related psychiatric disorders, particularly major depressive disorders. Although growing evidence supports the pro-resilient role of mGluR5 in corticolimbic circuitry in the depressive-like behaviors following chronic stress exposure, the underlying neural mechanisms, including circuits and molecules, remain unknown. We measured the c-fos+ expression and probability of neurotransmitter release in and from the basolateral amygdala (BLA) neurons projecting to the medial prefrontal cortex (BLA to PFC), and ventral hippocampus (BLA to HPC) after chronic social defeat stress (CSDS). The role of the BLA projections in depressive-like behaviors was assessed using optogenetic manipulations, and the underlying molecular mechanisms of mGluR5 and downstream signaling were investigated by Western blotting, viral-mediated gene transfer, and pharmacological manipulations. CSDS disrupted the neural activity and glutamatergic transmission in both BLA to PFC and BLA to HPC projections. Optogenetic activation of the BLA projections reversed the detrimental CSDS effects on depressive-like behaviors and mGluR5 expression in mPFC and vHPC. Conversely, inhibition of the BLA projections of mice undergoing subthreshold social defeat stress-induced a susceptible phenotype and mGluR5 reduction. These two BLA circuits appeared to act in an independent way. Importantly, we demonstrate that mGluR5 overexpression in mPFC or vHPC was pro-resilient, while the mGluR5 knockdown was pro-susceptible and that the pro-resilient effects of mGluR5 are mediated through distinctive downstream signaling pathways in the mPFC and vHPC. These findings identify mGluR5 in the mPFC and vHPC that receive BLA inputs as a critical mediator of stress-resilience, highlighting circuit-specific signaling for depressive-like behaviors.

☆ Session 147 Treatment and Drug Discovery for Mood Disorders

8:00 AM - 12:00 PM

SDCC Halls B-H

☆ Presentation 147.26 / KK7 Virtual screening of Tachykinin Receptor 1 Inhibitors using Machine-Learning

8:00 AM - 12:00 PM

***H. YOO**[1], C.-S. LEE[2], J.-I. HWANG[3], H. LEE[1], H. KIM[1];
[1]Dept. of Anat., [2]Med. Sci. Res. Ctr., [3]Dept. of Biomed. Sci., Korea Univ., Seoul, Korea, Republic of

Abstract

Substance P and Tachykinin receptor 1 (TACR1) have been one of the important antidepressant target molecules, and substance P is well-known to be elevated in major depressive disorder patients. However, no current TACR1 antagonist has a known effect on depressive symptoms after the phase 3 clinical trial failed. We used machine learning and in-silico docking to identify molecules that effectively antagonize TACR1. We collected the pChEMBL value (-$\log_{10}$IC50 or Ki) of 2499 ligands on TACR1 using the CHEMBL and NCBI databases and divided them into training (80%) and test set (20%). Using KNIME and Maestro (Schrodinger v2021-2), we compared six machine learning methods with 5-fold cross-validation and selected the model with the highest R^2 and lowest RMSE (root mean squared error) on average. Next, we used the best performing algorithm, Deepchem, to predict the pChEMBL value of 2.68 million ligands in the ENAMINE library. The prediction scores were binned into 20 categories, and ligands in the top 2 categories with high prediction scores were used for further analysis. The ligands were clustered using hierarchical clustering based on morgan fingerprint; we selected 15 ligands based on prediction score and clustering results. Each ligand and substance P was treated on TACR1-transfected HEK293 cells to measure the inhibitory effect of the ligand on TACR1. Using FLIPR Calcium 6-QF Assay, three ligands showed reduced F/F0 value in 50μM compared to 5μM, and dose-dependency was measured. This revealed the possibility of a noble structured TACR1 antagonist. For further study, we are trying to modify the structure of screened ligands and apply it to the depression animal model for in vivo study.

☆ Session 148 Stress, Depression, and Other Psychiatric Disorders

8:00 AM - 12:00 PM

SDCC Halls B-H

☆ Presentation 148.18 / LL8 Differential effects of sub-anesthetic dose of ketamine on spontaneous excitatory postsynaptic currents in GluN2D knock-out mice

8:00 AM - 12:00 PM

***D. HAN**[1], I. HONG[1], J. CHOI[1], P. PARK[1], J.-Y. BAEK[1], H. PARK[1,2], S. IDE[2], K. IKEDA[2,3], M. MISHINA[3], B.-K. KAANG[1];
[1]Seoul Natl. Univ., Seoul Natl. Univ., Seoul, Korea, Republic of; [2]Tokyo Metropolitan Inst. of Med. Sci., Tokyo, Japan; [3]Ritsumeikan Univ., Shiga, Japan

Abstract

There has been growing interest in the long-lasting antidepressant effects of ketamine which is well known as an antagonist of the N-methyl-D-aspartate receptor (NMDAR). However, sub-anesthetic dose of ketamine exerts side effects including hyperlocomotion, necessitating a further understanding of its working mechanism. Previous research pointed out GluN2D-containing NMDARs as the molecular mediator of ketamine-induced hyperlocomotion in rodents. Another line of research suggested that an increased synaptic transmission in the medial prefrontal cortex (mPFC) is a potential physiological mechanism through which ketamine triggers hyperlocomotion. Therefore, we examined the potential role of GluN2D-containing NMDARs in the ketamine-induced increase in the synaptic transmission in mPFC. Ketamine (25 mg/kg) administration increased the frequency of spontaneous excitatory postsynaptic currents (sEPSC) in wildtype mice, which effect was absent in GluN2D knock-out mice. Injection of the same dose of ketamine did not change the paired-pulse ratio and the amplitude of sEPSC in both of the genotypes. This study adds evidence to the perspective that GluN2D-containing NMDARs are involved in the ketamine-induced increase in the number of excitatory synapses and hyperlocomotion.

☆ Session 149 Addictive Substances and Memory Mechanisms

8:00 AM - 12:00 PM

SDCC Halls B-H

☆ Presentation 149.02 / MM3 Stimulation of parabrachial CGRP neurons extinguishes addictive-like behavior

8:00 AM - 12:00 PM

***G. PYEON**, J.-S. CHOI, Y. JO;
Sch. of Psychology, Korea Univ., Seoul, Korea, Republic of

Abstract

To extinguish unwanted, but addictive behavior, various types of punishment such as electric shocks or physical discipline have been used across cultures. Among these methods, electrical shocks produce the strongest effects on behavioral correction, but they could come with a considerable risk of harm. Recently, it has been shown that calcitonin gene-related peptide in the parabrachial nucleus (CGRP^{PBN}) provides affective pain signals and generates general alarm signals. Here we investigated whether stimulation of CGRP^{PBN} neurons can mimic electrical shock and able to suppress addictive-like behavior. To address this idea, we first genetically expressed channelrhodopsin-2 (ChR2) in midbrain dopamine neurons and CGRP^{PBN} neurons of DAT-cre::Calca-cre mice. To form addictive-like behavior, the mice were first trained to press a lever to receive a brief optical stimulation of dopamine cells (1s, 20Hz) until they reached the asymptotic level (more than 400 lever presses per hour). Then, they received optical stimulation into the CGRP^{PBN} (3s, 30Hz) instead of the stimulation of dopamine cells when they pressed the lever. Upon activation of CGRP^{PBN} neurons, the mice exhibited brief freezing responses, and their lever-pressing behavior was significantly reduced compared to the control animals without ChR2 expression in CGRP^{PBN} neurons. This also had an impact on long-term memory in which the suppression effect on addictive-like behavior remained even 10 days after the last stimulation of CGRP^{PBN}. Moreover, combined stimulation of CGRP^{PBN} neuron terminals with combinations of two among multiple downstream targets (central amygdala, substantia innominata, and ventroposteromedial thalamus) was able to suppress addictive-like behavior compared to the control group. We then investigated whether the inactivation of CGRP^{PBN} can abolish alarm signals in the brain even in the presence of an electrical footshock. CGRP^{PBN} was inactivated by tetanus toxin which blocked the release of neurotransmitters. The mice underwent the same procedure to elicit lever-pressing behavior, and then instead of activating CGRP^{PBN} when they press the lever, a footshock was delivered (1s, 0.3mA). Usually when the animals received a footshock, they learned to avoid and did not press the lever almost immediately. However, the mice with inactivated CGRP^{PBN} pressed the lever more than the control animals. Collectively, these results show that stimulation of CGRP^{PBN} generates alarm signals in the brain and able to extinguish addictive-like behaviors. Moreover, stimulation of CGRP^{PBN} mimics electric shock in behavioral correction but does not elicit physical pain or fear responses.

☆ Session 153 Decision Making Under Motivational Conflict: Neural Circuitry and Pharmacology

8:00 AM - 12:00 PM

SDCC Halls B-H

☆ Presentation 153.09 / SS6 Heterogenous encoding of spatial and non-spatial information by the medial prefrontal cortex in rats during naturalistic foraging

8:00 AM - 12:00 PM

***J. JEONG**, S. LIM, J.-S. CHOI;
Sch. of Psychology, Korea Univ., Seoul, Korea, Republic of

Abstract

The medial prefrontal cortex (mPFC) has been implicated in goal-directed spatial navigation tasks due to its role in working memory and planning. In this regard, several studies attempted to predict animals' location using neural activity within the mPFC. However, the accuracy of the spatial information decoded from mPFC ensemble activity varies across different studies. Here we subject food-deprived rats to a naturalistic foraging situation where an opportunity to acquire food resources and a threat posed by a predatory attack coexist. The foraging arena was composed of three distinct sections: Nest zone (N), Foraging zone (F), and Threat zone (T). Initially, the rats were free to explore and approach the sucrose solution dispenser within T. Next, they were trained to shuttle between N and T across F until they consistently acquired rewards. In the following days, they were faced with a striking attack by Lobsterbot, named after its fast-closing jaw, 3 or 6 s after the first lick while approaching for sucrose. The attack immediately evoked a withdrawal response. This paradigm continued to produce a mixture of approach and avoidance behavior during which neuronal activities were recorded using implanted tetrodes micro-drive. Single unit activities from 635 units were analyzed based on their firing rate. Among them, 56 % showed significant modulation of approach-related activity, 46 % avoidance, and 37% both. To further investigate the ensemble encoding of their behavioral relevance, we implemented a 4-layer artificial neural network (ANN) to predict the head position from simultaneously recorded neural activity. The results show a striking discrepancy in encoding accuracy depending on the zone. The L1 error of the ANN position predictor was 15.78 cm (distance from Lobsterbot), which was significantly lower than the predictor based on shuffled unit activity. On the other hand, the error rate of the ANN predictor significantly increased compared to F when animals were moving in N or facing the robot in T. Considering the modulation of approach and avoidance-related firing within T, these data suggest that neurons in mPFC encode goal-relevant spatial information only when the location is moderately distant and perhaps switch to a different encoding mode when the task demand changes.

☆ Session 155 Long-Term Memory: Consolidation and Reconsolidation: Behavior

8:00 AM - 12:00 PM

SDCC Halls B-H

☆ Presentation 155.08 / TT13 Differential effects of memory reconsolidation on episodic details versus subjective feelings.

8:00 AM - 12:00 PM

***G. SHIN**[1], S. DUBROW[2], V. P. MURTY[3];
[1]Psychology, [2]Dept. of Psychology, Univ. of Oregon, Eugene, OR; [3]Psychology, Temple Univ., Philadelphia, PA

Abstract

Memory becomes prone to reconstruction during restorage after retrieval. While mainly studied in rodent models, clinical neuroscience has begun to capture the role of reconsolidation in humans. Given that episodic memory and subjective feelings are represented in discrete neural substrates (i.e., hippocampus vs. striatum), this field often limits investigations to one form of emotional memory leaving open questions regarding their putative interactions. To provide a more comprehensive understanding of the downstream consequences of reconsolidation, it is essential to characterize their interactions. Here, we conducted a study that examines how both episodic details and feelings change with biased re-exposure during reconsolidation. Human participants (n=24) performed a reconsolidation experiment over three days. On Day 1, they learned positive and negative attributes of novel faces. On Day 2, within the reconsolidation window, faces were re-exposed with previous positive attribute (Update+), negative attribute (Update-), or were not updated (Control). On the last day, we characterized face recognition, face-attribute associative memory, and subjective valence ratings. Face recognition was greater in the Update+ and Update- versus Control condition (all $p < .001$), with no significant differences between Update+ and Update- ($p = .991$). While associative memory was above chance in all conditions (50%; all $p < .001$), there were no significant differences across conditions, suggesting that reconsolidation did not influence associative memory. However, faces in the Update- condition had lower subjective valence ratings compared to the Control condition ($p = .006$), and were marginally lower compared to the Update+ condition ($p = .059$). In general, these findings show that re-exposure during reconsolidation increases face recognition but surprisingly does not influence associative memory. Further, there were valence-specific effects where negative but not positive updates influenced later subjective feelings. These findings support a model in which episodic memory and subjective feelings may be independently influenced via reconsolidation. We hope to extend these findings by probing the underlying neural mechanisms to provide new insights into how to increase the effectiveness of targeting and editing unique traumatic memories during the reconsolidation window in the clinic.

☆ Session 157 Molecular Mechanisms of Memory

8:00 AM - 12:00 PM

SDCC Halls B-H

☆ Presentation 157.09 / VV21 Valproate-adjuvant cognitive behavioral therapy for bipolar disorder and comorbid panic disorder

8:00 AM - 12:00 PM

***M. JIN**[1,2,3], T. SUN[1], D. KIM[1,2], K.-Y. CHOI[1,4];
[1]Dept. of Med. Sci., Chungnam Natl. Univ., Daejeon, Korea, Republic of; [2]Dept. of Anat. and Cell Biol., Chungnam Natl. Univ. Col. of Medicine, Brain Res. Inst., Daejeon, Korea, Republic of; [3]Brain Korea 21 PLUS Project for Med. Sci., Chungnam Natl. Univ. Col. of Med., Daejeon, Korea, Republic of; [4]Dept. of Psychiatry, Chungnam Natl. Univ. Hosp., Daejeon, Korea, Republic of

Abstract

Anxiety disorders are the most common comorbid psychiatric disorders in patients with bipolar disorder. However, managing anxiety symptoms in comorbid conditions is challenging and has received little research interest. Studies of fear conditioning, an animal model of anxiety disorder, have suggested that memory reconsolidation-update (exposure-based therapy) combined with valproate might facilitate the amelioration of fear memory in preclinical research. To the best of our knowledge, this is the first attempt to combine cognitive-behavioral therapy with valproates in patients with panic disorder, agoraphobia, and comorbid bipolar disorder. We describe case series of successful amelioration of agoraphobia and panic symptoms in patients who failed to respond to 2-3 consecutive standard pharmacotherapy trials over the course of several years. Additionally, we summarize the background of this combination therapy based on the reconsolidation-updating mechanism, critical period reopening and valproate, clinically available histone deacetylase 2 (HDAC2) inhibitor, in preclinical research.

☆ Presentation 157.27 / Web Only Trametinib rescues neurodegeneration by enhancing TFEB-dependent autophagic lysosomal function in Alzheimer’s Disease model mice

8:00 AM - 12:00 PM

***Y. CHUN**[1], M.-Y. KIM[1], S.-Y. LEE[1], M. KIM[1], H. KIM[1], T.-I. KAM[2,3], S. HAN[1];
[1]Genuv Inc., Seoul, Korea, Republic of; [2]Neuroregeneration and Stem Cell Programs, Inst. for Cell Engineering, Johns Hopkins Univ. Sch. of Med., Baltimore, MD; [3]Dept. of Neurology, Johns Hopkins Univ. Sch. of Med., Baltimore, MD

Abstract

Alzheimer’s Disease (AD) is a progressive neurodegenerative disorder, characterized by cognitive deficit due to synaptic loss and neuronal death. Extracellular amyloid β plaques and intracellular tau tangles are pathological hallmarks of AD, and their enhanced clearance by exploiting cellular intrinsic homeostatic systems has been an attractive therapeutic approach for this devastating disease. We observed that a MEK1/2 inhibitor, trametinib (GSK1120212, SNR1611), reduced Aβ deposition in the 5XFAD mice (2.5 month-oral administration to 5-month-old) and thus protected against Aβ-mediated apoptotic neuronal death. In addition, trametinib also showed an effect on the recovery of impaired neuronal structures and cognitive deficits in 5XFAD mice. To elucidate the underlying mechanisms of these results, we performed RNAseq from the whole brain of wild-type C57BL/6 mice and found that trametinib induces the expression of genes regulating the autophagic-lysosomal pathway, which is essential for maintaining cellular homeostasis by driving clearance of aberrant protein aggregates and is known to be dysfunctional in AD. In addition, lysosomal inhibitors prevented the protective effect of trametinib on Aβ42-induced-dendritic spine loss in primary hippocampal neurons. We further demonstrated that trametinib inhibited the phosphorylation of transcription factor EB (TFEB) at Ser142 by ERK, promoting its nuclear translocation, which in turn induced the expression of autophagic lysosomal-related genes. Knockdown of TFEB eliminated the effect of trametinib on the increase of mature cathepsin B, degradation of p62, and prevention of apoptosis in primary cortical neurons treated with Aβ42 oligomers. Finally, we showed that the level of pTFEB is higher in AD patient brains than in age-matched normal brains, indicating the relevance of our studies in human disease. Altogether, we have demonstrated that MEK inhibition by trametinib provides neuronal protection from Aβ burden through increased autophagic lysosomal activity and present it as a potential therapeutic strategy for AD.

☆ Session 162 Bioinformatics and Systems Biology 8:00 AM - 12:00 PM

SDCC Halls B-H

☆ Presentation 162.03 / WW59 Resolving clustering bias during animal behavior mapping and kinematic profiling 8:00 AM - 12:00 PM

***J. KWON**, S. KIM, J. JOO, S. KIM, C. J. LEE;
Ctr. for Cognition and Sociality, Inst. for Basic Sci., Daejeon, Korea, Republic of

Abstract

In behavior science, deep-learning-based pose estimation systems allow us to easily collect large-scale motion datasets from freely moving animals. For behavior mapping and kinematic profiling of animal movements, a common computational practice pipeline includes clustering and differential analysis. However, during this process, if the same dataset is used for both clustering and differential analysis, a clustering bias, so-called 'P-hacking', can emerge, leading to false discoveries. Here, we introduce an alternative clustering approach to resolve this bias while retaining the clustering performance. We hypothesized that extracting the independent features for clustering can prevent the cross-contamination of datasets, which is a primary cause of clustering bias. To test this hypothesis, we used spectrograms as extra features for clustering, as they confer time-frequency information and are expected to be independent of kinematic features. Using both simulated and experimental animal behavior data, we found that the alternative clustering approach based on spectrograms effectively remove the clustering bias, approaching near the P-values of the ground truth. Moreover, we found that the clustering bias can occur regardless of the statistical tests, clustering algorithms, or embedding methods. Our empirical results show that the scalar angle differences of clustering-hyperplane and ground-truth-hyperplane projecting to the feature axis are highly correlated with false discoveries, providing clues for the origin of the clustering bias. In summary, we propose the clustering approach based on spectrograms as a practical solution for the clustering bias problem, providing a foundation for the universally applicable guideline for animal behavior mapping and kinematic profiling with minimal false discoveries.

☆ Presentation 162.08 / XX5 Exploring exercise-induced myokines directly transmitted to the brain 8:00 AM - 12:00 PM

***H. KIM**[1,2], H.-W. RHEE[3], H. PARK[1,2];
[1]Korea Brain Res. Inst., Korea Brain Res. Inst. (KBRI), Daegu, Korea, Republic of; [2]Daegu Kyeongbuk Inst. of science & technology, Daegu, Korea, Republic of; [3]Seoul university, Seoul, Korea, Republic of

Abstract

Cognitive functions such as learning and memory is enhanced after physical exercise, and such cognitive enhancement is known to be regulated by exercise-induced peripheral organ-brain communication that is partly mediated by peripheral organ-originated hormonal proteins. Skeletal muscles are the endocrine organ secreting cytokines called as “myokine” during exercise. Among exercise-induced myokines, some of them may be directly transmitted to the brain and are involved in memory enhancements after exercise. However, due to the insufficient methods for detecting in vivo secretory proteins, molecular identities directly transmitted to the brain and mediating exercise-induced cognitive enhancements are not fully understood. To detect myokines released from skeletal muscle by exercise and transmitted to the brain over the blood brain barrier (BBB), we here adopted a proximity labeling tool by employing the promiscuous biotin ligase, TurboID. we directed TurboID expression in the endoplasmic reticulum (ER) lumen through introducing KDEL sequence in the TurboID (TurboID-ER) and generating Cre-dependent TurboID-ER knock-in mouse (LSL-TurboID-ER mouse). The LSL-TurboID-ER mouse were crossed with the skeletal muscle-specific Cre driver mouse (Acta1-Cre) resulting in the ACTuR (Acta1-Cre:: TurboID-ER) model mouse, to label myokines released from skeletal muscles. Using this mouse tool, we could validate exercise-induced secretion of biotinylated myokines and detect increases in biotinylated myokines in blood plasma after the aerobic exercise using activity wheel for 4 weeks. Furthermore, we show that biotinylated myokines could directly localize to the several brain areas, and such direct transmission of the myokines to the brain was significantly enhanced after the 4-week exercise. Our study provides evidence for exercise-induced myokine directly transmitted to the brain and modulation of cognitive function by these muscle-derived factors.

☆ Session 176 Autism: Genetics to Phenotypes 1:00 PM - 4:00 PM

SDCC 1

☆ Presentation 176.03 Modulation of cerebello-neocortical structural covariation in neurotypical development and autism spectrum disorder 1:30 PM - 1:45 PM

***F. D'OLEIRE UQUILLAS**[1], B. LI[1], M. A. TROTTER[1], R. GESUE[1], M. LATIF[1], K. STEELE[1], E. BUEICHEKÚ[2], J. SEIDLITZ[3], V. ZHANG[1], T. FASULO[1], P. M. HOYOS[1], E. DANIEL HERTZ[1], E. SEFIK[1], S. R. GUARIGLIA[1], S. JANARTHANAN[1], J. LEE[1], G. J. BROUSSARD[1], J. L. VERPEUT[4], M. KISLIN[1], H.-J. BOELE[1], J. SEPULCRE[2], S. S.-H. WANG[1], J. GOMEZ[1];
[1]Princeton Univ., Princeton, NJ; [2]Gordon Ctr. for Med. Imaging, Massachusetts Gen. Hospital, Harvard Med. Sch., Boston, MA; [3]Lifespan Brain Institute, Children's Hosp. of Philadelphia, Univ. of Pennsylvania, Philadelphia, PA; [4]Arizona State Univ., Tempe, AZ

Abstract

Using structural covariance analysis, here we investigate relationships between cerebellar and cerebral brain volumes in neurotypical and individuals with autism spectrum disorder (ASD) given that cerebellar injury at birth carries the largest non-genetic risk ratio in ASD. We computed individualized MRI volumes in all regions found in the HCP-multimodal brain parcellation and SUIT cerebellar atlas for 993 participants of the ABIDE consortium database (6-30 years old, 28% female). In typically developing (TD) children and young adults (n=512), cerebellar cortex volumes related inversely to deep cerebellar nuclei (DCN) (spearman correlations; $p<0.05$), and DCN volumes related positively to sensorimotor cerebral cortex (SMC) ($p<0.0001$). These results are consistent with the idea that net excitatory drive from cerebellar nuclei plays a positive role in neocortical growth and/or survival, and that inhibitory output of the cerebellar cortex has a negative influence. The magnitude of correlations did not significantly differ in ASD (n=481). Given the focal position of the thalamus in cerebello-neocortical pathways, we next analyzed the influence of sensorimotor thalamic volumes. Volumes of deep cerebellar nuclei were positively related to contralateral thalamic nuclei [$p<0.05$: deep dentate nucleus x thalamic ventromedial (VM), laterodorsal (LD), and lateral posterior (LP) nuclei], except for an inverse correlation between right interpositus deep nucleus and left ventral posterolateral (VPL) thalamic nucleus ($p<0.01$). Thalamic and ipsilateral SMC volumes were similarly positively correlated ($p<0.05$: SMC vs. VM, LD, LP), again with the exception of an inverse relationship with bilateral VPL thalamic nuclei ($p<0.05$). Interaction models testing whether thalamic nuclei modulate the relationship between DCN and SMC revealed that greater thalamic size was associated with a stronger link between DCN and SMC size (dentate nucleus vs. VPL, VM, VLp, LD, and LP models: $p<0.05$; interpositus vs. LD model: $p<0.05$). The role of the thalamus as a moderator differed in ASD in a three-way interaction model ($p=0.02$). Overall, the thalamus seems to play a key role in the anatomical development of cerebello-neocortical regions. We are now further investigating how these effects change with age and in ASD.

☆ Session 189 Other Ion Channels

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 189.03 / B57 Hcn1 channelopathy in the mouse model of social avoidance

1:00 PM - 5:00 PM

J. KIM, ***C. KIM**;
Neurosci. and Regenerative Med., Augusta Univ., Augusta, GA

Abstract

The CA1 pyramidal neurons have a non-uniform distribution of voltage-gated ion channels. They control how incoming information is processed and how synaptic plasticity is induced. Hyperpolarization-activated cyclic nucleotide gated nonselective cation 1 (HCN1) channels are highly expressed in the hippocampus. A gradient of increasing HCN1 channel density along the somatodendritic region of CA1 is an essential feature. An increasing amount of evidence suggests that HCN1 channel mislocalization in CA1 neurons is linked to the abnormal cellular and behavioral properties. While chronic stress increases hyperpolarization-activated current (I_h) in dorsal hippocampal CA1 neurons, the underlying molecular mechanisms are entirely unknown. Following chronic social defeat stress (CSDS), susceptible mice displayed social avoidance and impaired spatial working memory, which were linked to decreased neuronal excitability, increased perisomatic HCN1 protein expression, and elevated I_h in dorsal but not ventral CA1 neurons. In control mice, bath application of corticosterone (CORT) reduced neuronal excitability, increased tetratricopeptide repeat-containing Rab8b-interacting protein and HCN1 protein expression, and elevated I_h in dorsal but not ventral CA1 region/neurons. CORT-induced upregulation of functional I_h was mediated by the glucocorticoid receptor, HCN channels, and the protein kinase A but not the calcium/calmodulin-dependent protein kinase II pathway. Three months after the end of CSDS, susceptible mice displayed persistent social avoidance when exposed to a novel aggressor (i.e., a trigger). The sustained behavioral deficit was associated with lower neuronal excitability and higher functional I_h in dorsal CA1 neurons, both of which were unaffected by CORT treatment. Our findings show that CORT treatment mimics the pathophysiological effects of dorsal CA1 neurons/region found in susceptible mice. The aberrant expression of HCN1 protein along the somatodendritic axis of the dorsal hippocampal CA1 region might be the molecular mechanism driving susceptibility to social avoidance.

☆ Session 197 Alzheimer's Disease: Preclinical Insights

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 197.27 / Web Only Identification of new drug that reduces BACE1 expression with cell-based screening system

1:00 PM - 5:00 PM

***Y. LEE**, J. PARK, H.-G. BAE, D.-G. JO;
Sch. of Pharm., Sungkyunkwan Univ., Suwon, Korea, Republic of

Abstract

Alzheimer's disease (AD) is a chronic neurodegenerative disease. AD exerts an enormous burden on managing costs though the cause of AD is still unclear. Amyloid hypothesis postulated that exceeding extracellular amyloid-beta (Aβ) deposits are the fundamental cause of the disease. Aβ is made by sequential proteolysis to amyloid-beta precursor protein (APP) by β-secretase (BACE1) and γ-secretase. Another important phenomenon in AD patients is increased BACE1 expression. However, direct and complete blocking of enzymatic activity of BACE1 can cause unpredictable side effects because of numerous physiological substrates of BACE1. Therefore, we tried to find specific drugs reducing BACE1 expression rather than direct inhibition of BACE1. Using USA FDA-approved drug library (Prestwick Chemical Library), we could discover putative therapeutic chemicals by cell-based assay. Using Bace1 promoter-reporter screening, we found an effective drug for reducing BACE1 gene expression. This compound effectively reduced the levels of BACE1 protein and mRNA in SH-SY5Y cells. In primary cultured neurons, BACE1 decreased with this compound treatment in a dose-dependent manner. We also confirmed that the BACE1 lowering compound could improve the cognitive functions of 3xTg-AD mice. In Morris water maze test, this compound treated 3xTg-AD mice showed restored performance compared to vehicle-treated 3xTg-AD mice. The compound-treated 3xTg-AD mice also exhibited similar latency of chamber entering in passive avoidance test compared to WT. The drug-treated AD mice showed a decreased level of Aβ deposition and BACE1 expression. Together, we suggest that the BACE1 expression lowering agent could be a novel drug that modulates the expression of the BACE1 level, providing a new direction for AD therapy.

☆ Session 200 Spinocerebellar Ataxias

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 200.08 / F28 Beneficial effects by administration of human mesenchymal stem cells in a mouse model of spinocerebellar ataxia type 2

1:00 PM - 5:00 PM

***C. SHARMA**[1], U. JUNG[3], S. KIM, PHD[2];
[1]Kyungpook Natl. Univ., [2]Sch. of Life Sci. & Biotech., Kyungpook Natl. Univ., Daegu, Korea, Republic of; [3]Pukyong Natl. Univ., Busan, Korea, Republic of

Abstract

We have investigated the therapeutic potential of human mesenchymal stem cells (hMSCs), transplanted intrathecally (IT), in a transgenic mice model bearing a polyQ mutation in the ataxin-2 gene. Our results showed that IT transplantation of hMSCs at 26 weeks old could induce a significant improvement of abnormal motor function, measured by the ataxic scoring system, shown in spinocerebellar ataxia type 2 (SCA2) mice until 24 weeks after hMSCs administration. In addition, we observed that hMSCs administration protected the loss of purkinje cells through production of neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF), and inhibition of cerebellar inflammatory responses by production of anti-inflammatory molecules such as tumor necrosis factor stimulated gene-6 (TSG-6) and Follistatin-like 1 (FSTL1), respectively. Altogether, the administration of hMSCs improved motor behavior and ataxia-pathology alleviation by stimulating endogenous regeneration and suppressing inflammatory responses. Notably, the results of this study strongly support further exploration of the feasibility to design new clinical approaches for SCA2 patients.

☆ Presentation 200.13 / F32 Effects of human mesenchymal stem cells in Ara-C-induced animal model of cerebellar ataxia

1:00 PM - 5:00 PM

***P. NARAE**[1], S. KIM, PHD[2];
[1]kyungpook national university, kyungbook national university, daegu, Korea, Republic of; [2]Sch. of Life Sci. & Biotech., Kyungpook Natl. Univ., Daegu, Korea, Republic of

Abstract

This study investigated the therapeutic effects of transplanting human mesenchymal stem cells (hMSCs) into wild-type (WT) mice intraperitoneally administered with cytosine arabinoside (Ara-C) to develop cerebellar ataxia (CA) during the first 3 postnatal days. hMSCs were injected intrathecally into 10-week-old mice one or three times at 4-week intervals. The hMSC administered mice showed improved motor and balance coordination compared to non-treated mice as measured using the Rota-rod, open field, and ataxic scoring assessments. Additionally, an increase in protein levels of neuronal nuclear protein (NeuN) and doublecortin (DCX), responsible for neurogenesis was observed in hMSC-treated mice compared with non-treated mice. Furthermore, hMSCs implantation significantly elevated neurotrophic factors including brain-derived neurotrophic factor (BDNF), and glial cell line-derived neurotrophic factor (GDNF), and suppressed TNF-α and IL-1β mediated pro-inflammatory responses. Collectively, our results demonstrated that hMSCs exhibit therapeutic potential for Ara-C -induced CA by protecting neurons by stimulating neurotrophic factors and inhibiting cerebellar inflammatory responses which improved motor behavior and ataxia-pathology alleviation. In summary, this study suggests that hMSCs are effective for treating ataxia-related symptoms.

☆ Session 201 Neuroprotection I

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 201.06 / F38 Gamma entrainment using sensory stimuli alleviate cognitive deficits and demyelination induced by chemotherapy agents

1:00 PM - 5:00 PM

***T. KIM**, B. T. JAMES, M. C. KAHN, C. BLANCO-DUQUE, F. ABDURROB, M. ISLAM, N. S. LAVOIE, L.-H. TSAI;
MIT, MIT, Cambridge, MA

Abstract

Cancer patients undergoing chemotherapy treatments suffer from a neurological condition called chemotherapy induced cognitive impairment (CICI), or chemo brain, which may last for the rest of their life. Despite the increasing number of chemo brain patients, neither the mechanism nor treatment is well explored. Recent findings indicate that chemo brain shares multiple features with neurodegenerative diseases such as chronic neuroinflammation, DNA damage and synaptic loss. We tested if Gamma Entrainment Using Sensory stimuli (GENUS), which has been shown to be effective against Alzheimer's disease pathophysiology, can be utilized as a tool to treat chemo brain. Here we show GENUS alleviates cisplatin-induced symptoms such as neuroinflammation and neurodegenration. Also, we found that GENUS promotes oligodendrocyte survival during chemotherapy and preventes demyelination, which is tightly associated with cognitive impariment in cisplatin-induced chemo brain. These alterations indeed led to significant improvement of cognitive functions in the mouse model. Furthermore, we show the effect of GENUS is not limited to cisplatin-induced chemo brain, but also applies to methotrexate (MTX)-induced symptomology, demonstrating that GENUS can be a versatile treatment approach for a wide range of chemo brain patients.

☆ Session 202 Neuroinflammation: Pain, TBI, and Nerve Injury

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 202.20 / G3 Mirna-146a-5p nanoparticles reduce mia-induced pain behaviors and sensory peripheral innervation

1:00 PM - 5:00 PM

***H. PARK**[1,3], J. SHIN[1,3], D. KIM[4], N. SHIN[1,3], H. SHIN[3], J. BEOM[5], J. KIM[2], D. KIM[1,3,4];
[1]Dept. of Med. Sci., [2]Dept. of Intrnl. Med., Chungnam Natl. Univ. Col. of Med., Daejeon, Korea, Republic of; [3]Dept. of Anat. and Cell Biology, Brain Res. Inst., Chungnam Natl. Univ., Daejeon, Korea, Republic of; [4]Nanoglia company, Daejeon, Korea, Republic of; [5]Dept. of Rehabil. Med., Seoul Natl. Univ. Bundang Hosp., Seongnam, Korea, Republic of

Abstract

Osteoarthritis (OA) is a degenerative disease that worsens over time, often resulting in chronic pain. Following the progression of OA, a calcitonin gene-related peptide (CGRP)-positive sensory nerves innervate the synovial membrane, meniscus, and subchondral bone of the knee joint in rodents, deteriorating OA pain. Recent studies have suggested that sensory innervation for OA pain between cartilage and subchondral bone is considered as a key factor for disease progression. However, the understanding of the mechanism poorly remains. In this study, we performed to reduce OA pain by regulating the distribution of differentiated sensory nerves in the subchondral bone through miRNA-146a-5p encapsulated PLGA nanoparticles (miR146a-5p NPs) in a monoiodoacetate (MIA)-induced OA model. MIA induced OA pain behaviors were measured 10 days and confirmed that the CGRP+ sensory nerves are increased in subchondral bone with the upregulation of neuroninflammatory cytokines, including (TNF)-α and MMP13. Appling miR146a-5p NPs into the knee joint of the MIA model showed the significant reduction of OA pain relate mRNA genes, distribution of CGRP+ sensory nerves, and pain behavior. As joint nociceptors terminated in the dorsal horn of the spinal cord, we also found that the decrease of microglia activation in miR146a-5p NPs group compared to MIA-induced rats. Taken together, injection of miR-146a-5p NPs can effectively down-regulate sensory nerve innervation in subchondral bone by reducing OA pain. Therefore, it is suggested that modulation of sensory innervation may be a new target in OA pain.

☆ Session 206 Itch Mechanisms and Non-Neuronal Cells and Pain

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 206.02 / I14 A novel spinoparabrachial pathway for mechanical itch

1:00 PM - 5:00 PM

***X. REN**[1,3], S. LIU[2,3], A. VIRLOGEUX[1], J. BRUSCH[1], S. J. KANG[2], S. HAN[2], M. GOULDING[1], D. ACTON[1];
[1]Mol. Neurosci. Lab., Salk Inst. for Biol. Studies, San Diego, CA; [2]Peptide Biol. Labs., Salk Inst. for Biol. Studies, La Jolla, CA; [3]Biol. Grad. Program, UCSD, San Diego, CA

Abstract

Itch is an unpleasant sensation that generates scratching, a conditional protective reflex behavior. Whereas scratching can be elicited via a simple spinal reflex pathway, itch incorporates sensory-discriminative, affective-motivational, and cognitive components, consistent with growing evidence that, in vivo, scratching is generated and modulated by supraspinal areas in a context-dependent manner. Scratching can be triggered by a range of cutaneous stimuli including light touch (mechanical itch) and chemical irritants such as histamine and chloroquine (chemical itch). Recent studies have identified distinct molecular and circuit mechanisms for the transmission and gating of mechanical and chemical itch information in the periphery and spinal cord; however, the supraspinal regions that facilitate context-dependent responses to itch have not been described in detail. Here, we show that the parabrachial nucleus (PBN) receives mechanical itch information from the spinal cord and is essential for eliciting protective scratching in response to tactile stimuli. Additionally, we have identified and molecularly characterized the subsets of spinoparabrachial (SPB) projection neurons and PBN neurons that drive mechanical itch and alloknesis. We find that the ascending SPB neurons for the transmission of mechanical and chemical itch are segregated into discreet populations, which then converge in the PBN onto a common population of neurons that are required for scratching. Our results argue that the PBN plays an important role in the generation of protective scratching in response to light touch stimuli in awake behaving mice.

☆ Session 213 Cerebellum: Climbing Fibers and Learning

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 213.05 / R4 Plasticity mechanisms for bidirectional oculomotor learning

1:00 PM - 5:00 PM

***H. SHIM**, A. FANNING, J. RAYMOND;
Neurobio., Stanford Univ., Stanford, CA

Abstract

Activity-dependent neural plasticity has long been thought to be a cellular substrate for experience-driven behavioral changes. A fundamental unanswered question is the direction of plasticity (long-term potentiation, LTP vs. long-term depression, LTD) at each synaptic site within a given circuit during learning. In the cerebellum, LTD at the parallel fiber-to-Purkinje cell synapses (PF-PC LTD) is well established as a cellular mechanism supporting learning. Yet accumulating evidence suggests that PF-PC LTD contributes selectively to certain cerebellum-dependent learning tasks, and not others, raising the question of how other plasticity mechanisms in the cerebellum contribute to learning. Here, we identify a role of LTP at the PF-PC synapses in bidirectional vestibulo-ocular reflex (VOR) learning. Published results reported PF-PC LTD in slices of the cerebellar flocculus prepared from mice that had learned to increase the amplitude of their VOR (VOR-increase learning; Jang et al., 2020). Here, we performed slice electrophysiology following learning to decrease the amplitude of the VOR, induced by vestibular-visual pairing (VOR-decrease learning) and following habituation of the VOR, induced by vestibular stimulation alone. We observed PF-PC LTP following both VOR-decrease learning and VOR habituation. In addition, 100 Hz optogenetic stimulation of granule cells, whose axons form the PFs, to induce PF-PC LTP occluded subsequent VOR-decrease or habituation learning. To gain insight about which subset of PF-PC synapses may undergo LTP, we measured the generalization of VOR learning to the optokinetic reflex (OKR), the reflexive eye movement driven by motion of a visual field. During VOR-decrease learning, the population of PF-PC synapses in the flocculus carries visual as well as vestibular signals, whereas during VOR habituation only the PF-PC synapses carrying vestibular signals would be activated. The OKR was increased after VOR-decrease learning, consistent with previous work, but not after habituation. Hence, during VOR-decrease learning, LTP may occur selectively in PF synapses carrying vestibular signals, while PF synapses carrying visual signals may undergo LTD, which has been implicated in increasing the OKR. Together, the results indicate that bidirectional oculomotor learning is supported by bidirectional changes at the PF-PC synapses, and highlight the necessity for additional work to integrate analyses of coding of sensory and motor signals as well as plasticity at these synapses.

☆ Presentation 213.02 / R1 Rim4 deficiency in purkinje cells disrupts neuronal signals in cerebellar circuit and therefore causes a motor dysfunction in mice

1:00 PM - 5:00 PM

***H. KIM**, N. MELLITI, E. SCHÖNHENSE, K. MICHEL, S. SCHOCH, D. DIETRICH;
Univ. of Bonn, Univ. of Bonn, Bonn, Germany

Abstract

Signal transmission from a neuron to its target cell is tightly controlled by synaptic proteins. Rab3-interacting molecules (RIMs) are key proteins in regulating neurotransmitter release at the presynaptic active zone. Among four members of the RIM family, the function of the short RIM isoforms, RIM3 and RIM4, has not been fully resolved yet. In this study, we investigated the functional role of RIM4, using RIM4 lacking mice. We generated constitutive RIM4 KO mice (RIM4 KO_{const}) that develop an episodic motor phenotype that strongly impairs their hindlimbs. Unlike the large RIM isoforms, we find that RIM4 has no critical role in the regulation of presynaptic neurotransmitter release. In accordance with its previously described role in the regulation of neurite outgrowth dendritic arborization of Purkinje cells is decreased in RIM4 KO_{const} mice. ***In vitro*** recordings of spontaneous spikes of Purkinje cells show that RIM4 KO_{const} mice display a disturbed pace-making activity and strongly altered spikes upon caffeine application. The functional alteration in spontaneous activity induced by RIM4 deficiency but not the effect on dendritic growth is reversible in neonatal and adult cerebellar Purkinje cells at the cellular level by re-expression of RIM4 after via rAAV transduction. We further examined the functional role of RIM4 in mediating calcium signaling in cerebellar network by performing calcium imaging in slices and ***in vivo***. Climbing fiber-mediated calcium transients in Purkinje cells are strongly reduced in RIM4 KO_{const} mice. ***In vivo*** calcium imaging also showed a reduced synchronicity of the spontaneous calcium events in neighboring Purkinje cells in RIM4 KO_{const} mice. Our slice recordings suggest that Purkinje cells without RIM4 show a deficit in the integration of synaptic input from the inferior olive.Taken together, our data shows that RIM4 deficiency unexpectedly shows a much more severe phenotype than the RIM1/2 KO even though synaptic transmission is not altered.

☆ Session 223 Sleep Regulation and Mechanisms

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 223.24 / EE5 Rhythmic Transcriptome Network and a Significant Connection between the Rhythmic Transcriptome and Autism Spectrum Disorder

1:00 PM - 5:00 PM

***C. LEE**[1], J. S. TAKAHASHI[2];
[1]The Univ. of Texas Southwestern Med. Ctr., Dallas, TX; [2]Chair, Dept. of Neurosci., Univ. of Texas Southwestern Med. Center, Howard Hughes Med. Inst., Dallas, TX

Abstract

Autism spectrum disorder (ASD) has had significant impacts on medical and social care world-wide with approximately 1 case in every 68 people. ASD is known to be driven by changes in the transcriptome and is also associated with impacts on circadian rhythms which are controlled by the internal, biological clock. One such impact is that well over 80% of ASD patients have been documented to suffer from sleep disorders. However, the connection between the disruption of sleep rhythms and ASD has not yet been clearly identified at the transcriptomic level. Here, rhythmic transcriptome studies in nine wild-type mouse brain regions and liver tissues have identified differences in phase and amplitude. Results from the SCN and liver tissues showed a distinct phase advance in their transcriptomes as compared to those of other brain regions. Within the other brain regions, we were also able to identify rhythmic transcriptome networks many of which still showed strong connections to the main network despite the differential phase and amplitude. The exception being the transcriptomes of the olfactory bulb (OB) and cerebellum (CB) which exhibited weak connections to the rhythmic transcriptome network and thus generated unique expression patterns. Both the OB and CB exhibited genes with phase shifts between day and night of which they were enriched with fear response genes in neuronal synapses. Additionally, the rhythmic genes peaking in the evening within the SCN were significantly enriched for ASD-risk genes similar to the rhythmic genes with peak phases in the other brain regions at

night. These genes are strongly enriched for sleep deprivation genes suggesting a connection to the ASD sleep phenotype. Since the frontal cortex is the most disrupted brain region in ASD patients, I further studied its particular transcriptome using single nucleus RNA-seq. The identified cell numbers were from high to low in the following the order: neuron, astrocyte, oligodendrocyte, microglia, and endothelial. Among them, neurons were the only cell type driving this rhythmic gene expression in brain and that this unique rhythmic expression has exceptionally strong enrichment with ASD-risk genes. Taken together, genome-wide transcriptome analyses have shown a significant connection between the rhythmic transcriptome and ASD in neuronal cells.

☆ Session 236 Social Cognition and Motivation

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 236.08 / UU3 Ventral tegmental area to nucleus accumbens dopaminergic circuit is responsible for effort-based social decision making behavior

1:00 PM - 5:00 PM

***T.-E. KIM**, J. KIM, J. KOO;
Emotion, Cognition & Behavior Res. Group, Korea Brain Res. Inst. (KBRI), Daegu, Korea, Republic of

Abstract

Motivation is an essential part of an animal's goal-oriented behaviors, making animals overcome many adversities. For highly social animals like humans and some rodents, social interaction per se is a powerful driving force to endure effortful conditions. However, the underlying mechanism of motivation for social rewards has not yet been well studied. Effort-based social decision-making (ESDM) task was designed for this study and it was suitable for evaluating the social motivation levels. With this behavior paradigm, we analyzed the effort-based choice behaviors of male mice to meet female. When the interaction time with the female was given as a freely accessible social reward, the male mice chose to meet the female (EFBX). Interestingly, we observed that the male mice chose to meet female even if they had to climb the barrier (EFBO) more frequently than the EFBX group on the last day of the task. To explain these phenomena, we first investigated gene expression levels of dopamine receptor D1 gene (***Drd1a***) and D2 gene (***Drd2***) in the nucleus accumbens (NAc), the key brain region that mainly receives dopaminergic projections, by quantitative PCR. As a result, ***Drd1a*** gene expression, but not ***Drd2***, was significantly higher in the EFBO group than in other groups. To confirm the role of the D1 receptor in triggering social motivation, we infused D1R antagonist SCH-23390 directly into the NAc and found that effort-related choice level was decreased in the EFBO group. Since the ventral tegmental area (VTA) is the principal region for releasing dopamine, we manipulated the VTA-to-NAc circuit during the decision-making. Optogenetic inhibition reduced the effort-related choice level in the EFBO group. Conversely, activation on the second training day increased the level. Taken together, these data suggest that NAc D1-cells receiving signals from VTA are possibly involved in effort-based decision-making for the social reward.

☆ Presentation 236.20 / UU15 Neurogranin regulates blood-brain barrier permeability and accumbal reward response

1:00 PM - 5:00 PM

***A. AKANDE**, H. W. NAM;
LSU Hlth. Shreveport, Shreveport, LA

Abstract

Disruption of the BBB in the NAc has been linked to susceptibility to social defeat-induced stress and depression; however, its molecular mechanism remains unclear. Neurogranin (Ng), a calcium-calmodulin regulating protein, is highly expressed in the neuron and regulates reward response in rodents. In humans, Ng dysregulation has been associated with neurological diseases such as autism spectrum disorder, Alzheimer's disease, addiction, and schizophrenia. Interestingly, we identified that Ng is also expressed in the BBB. Therefore, we hypothesize that Ng expression in the BBB of NAc contributes to reward response. First, we assessed BBB permeability using Evans blue extravasation assay and found increased apical-basolateral permeability from blood to brain tissue in Ng null mice. Then, fluorescein-labeled dextran dye was injected bilaterally into the ventricles to measure basolateral-apical permeability. Ng null mice showed significantly increased levels of blood dextran dye compared to their wild-type littermates. We found that Ng null mice show considerably decreased claudin-5 and occludin expression in the NAc of Ng knockout mice which may contribute to increased BBB permeability. Finally, label-free proteomic analysis of NAc and endothelial-specific Ng null mice identified Akt-mediated gene expression change consistent with conventional Ng null mice. We found that depletion of Ng expression in the NAc decreases the sociability in mice. In conclusion, Ng depletion in the neurovascular unit leads to a loss of BBB integrity, as evidenced by increased BBB permeability and a decrease in the expression of crucial tight junctional proteins in the NAc. This may contribute to neurological disease phenotypes of altered reward response against natural reward and hedonic stimuli.

☆ Session 238 Hippocampus Physiology

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 238.05 / VV26 Inactivation of the intermediate hippocampus impairs value-based navigation in a virtual environment more severely compared to the dorsal hippocampal inactivation

1:00 PM - 5:00 PM

***H. HWANG**, S.-W. JIN, I. LEE;
Seoul Natl. Univ., Seoul Natl. Univ., Seoul, Korea, Republic of

Abstract

During goal-directed navigation, the hippocampus may process value information of the goal location along with its spatial information. However, the neural mechanisms underlying the hippocampal integration of place and value representations are poorly understood. To dissociate the dorsal and intermediate regions of the hippocampus, we inactivated the dorsal hippocampus (dHP) and the intermediate hippocampus (iHP) in a place-preference task by using a VR navigation system. Body-fixed rats (n=7) were trained to run on a ball-shaped treadmill to find two unmarked reward zones, each associated with a different amount of honey water at a six-to-one ratio in a circular VR arena. Once trained, rats showed a significant preference for the high-reward zone. Inactivation of either dHP or iHP bilaterally in the same rats increased the travel distance to the goal zone significantly compared to control conditions ($p<0.01$ for dHP, $p<0.0001$ for iHP; one-way ANOVA). However, only iHP-inactivated rats were significantly impaired in finding the high-value zone by showing decreased place preference ($p<0.0001$). The accuracy and effectiveness of wayfinding behavior, measured by both the departing angle at the start location and the arriving angle at the arena boundary in a given trial, were more severely disrupted with the iHP inactivation than with the dHP inactivation compared to control conditions. Specifically, dHP-inactivated rats showed less accurate wayfinding by showing less optimal orientations when departing the start point and also when arriving at the boundary of the arena ($p<0.01$ at departure, $p<0.0001$ at arrival; Watson-Williams test). However, the dHP-inactivated rats still demonstrated effective wayfinding behavior on average (***n.s.*** when comparing the mean vector lengths for the angular deviations measured at both departure and arrival; one-way repeated measures ANOVA). In contrast, iHP-inactivated rats were severely disrupted in both measures (p's<0.0001 for angular deviation at both departure and arrival; $p<0.01$ and $p<0.0001$ for the mean vector lengths for the angular deviations measured at departure and arrival, respectively). Direct comparisons between the inactivation conditions for the dHP and iHP also showed that the iHP inactivation caused more severe impairment than dHP inactivation (p's<0.05 for departure and p's<0.01 for arrival for both angular deviation and mean vector length). Overall, our findings suggest that the iHP is essential for accurate and effective goal-directed navigation, whereas the dHP is more important for precise spatial targeting during navigation.

☆ Session 239 Hippocampal Physiology I

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 239.09 / VV42 Value-dependent reactivation of place cells in the intermediate, but not in the dorsal hippocampus

1:00 PM - 5:00 PM

***S.-W. JIN**, I. LEE;
Seoul Natl. Univ., Seoul Natl. Univ., Seoul, Korea, Republic of

Abstract

It is widely held that the hippocampus is important for episodic memory, which is composed of autobiographical events that occurred at specific times and places. One of the neural mechanisms of memory consolidation is the reactivation of hippocampal cells during sharp-wave ripples (SWR). It is postulated that events acquired during active behavior are reactivated during sleep and transferred to the neocortex, where it becomes permanently stored. Because high-value events tend to be remembered more easily than low-value events, the reactivation may also be affected by the event's value information. we tested the hypothesis that value information influences the reactivation strength of place cells in the iHP. We used a place-preference task in the T-maze while simultaneously recording single units from the dorsal hippocampus (dHP) and iHP using 24-tetrodes in rats (n=6). In block 1, they tended to choose the sunflower seed-baited arm over the cheerios-baited arm through trial and error. In block 2, the starting position was moved to the opposite arm to make the hippocampal-dependent learning. In block 3, the starting position was the same as in block 1, but the arms associated with sunflower seeds and cheerios were reversed. Our preliminary results show that the amounts of ripples in the dHP and iHP decreased transiently after the spatial values were swapped, but overall ripple rates associated with high- and low-value rewards were similar both in dHP and iHP. Meanwhile, the high-value-coding place cells (HVC-PCs) in the iHP was reactivated more frequently during SWR than other cell types during the task. Furthermore, the reactivation probability of HVC-PCs was higher than other cell types during the post-sleep session compared to the pre-sleep session, and the higher probability of firing of HVC-PCs during post-sleep compared to pre-sleep was positively correlated with the learning speed on the next day. These findings were not observed in dHP. Our findings suggest that reactivation of HVC-PCs in the iHP during sleep may underlie the strong consolidation of high-value places.

☆ Presentation 239.06 / VV40 Is the rat prefrontal cortex crucial for cognitive control during spatial cognition?

1:00 PM - 5:00 PM

***E. PARK**[1], G. GRUBBS[1], K. NICHOLAS[1], D. TABORGA[1], A. S. AHMED[1], K. C. O'REILLY[2], A. A. FENTON[1];
[1]New York Univ., New York, NY; [2]Child and Adolescent Psychiatry, New York State Psychiatric Inst., New York, NY

Abstract

Cognitive control tasks require using one class of information while ignoring another, competing class of information. The central role of the medial prefrontal cortex (mPFC) in cognitive control is well established because mPFC damage impairs tasks that may require cognitive control, as inferred, typically from the task design. We have previously established that cognitive control is required to perform an active place avoidance task on a rotating arena that requires rodents to avoid shock by using information about their location in the stationary room and ignoring information about their location on the rotating floor. Here we test whether rat mPFC lesion impairs cognitive control in the active place avoidance task to test the "central-computation" hypothesis that mPFC is essential for the computations required for cognitive control. Adult rats received either bilateral ibotenic acid or sham lesions of mPFC. Dorsal CA1 ensembles were recorded from lesion (n=3) and sham (n=2) rats during active place avoidance training. CA1 discharge alternates judiciously between representing stationary and rotating locations according to the proximity of shock (p's<0.005), demonstrating cognitive control in hippocampal discharge of both sham and lesion rats**.** Both lesion (n=10) and sham (n=8) rats learned to reduced errors of entering the shock zone across the initial 16 10-min trials (8 trials/day; Group: $F_{1,16} = 0.002$, $p = 0.9$; Day: $F_{1,16} = 26.34$, $p = 10^{-4}$; Trials: $F_{3.22,\,51.50} = 36.76$, $p = 10^{-13}$). The time to first enter the shock zone on each trial increased in both groups as trials progressed (Group: $F_{1,16} = 0.1$, $p = 0.76$; Day: $F_{1,16} = 69.61$, $p = 10^{-7}$, Trials: $F_{5.33,\,85.33} = 12.15$, $p = 10^{-9}$). Memory retention on day 3 was indistinguishable in the lesion and sham times to first enter the shock zone ($t_{16} = 1.01$, $p = 0.3$) and errors ($t_{16}= 0.95$, $p = 0.4$). The shock was relocated by 180° to additionally assess the impact of mPFC lesion on cognitive flexibility. The groups did not differ (errors: $F_{1,16} = 0.21$, p =

0.65). Cytochrome oxidase (CO) activity in the brains of a subset of the lesion (n = 8) and sham (n = 8) rats shows the lesion decreased coupling amongst multiple brain areas. Although the mPFC lesion was effective and altered the coordination of metabolic activity within the dorsal hippocampus, mPFC lesion did not impair cognitive control assessed by neural representations and active place avoidance. These findings support the alternative “local computation” hypothesis: the computations required for cognitive control can occur locally in brain networks independently of the mPFC as a central computational locus for cognitive control.

☆ Session 244 Gene, Protein, and Cell Based Techniques

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 244.14 / XX33 A Novel approach for Glioblastoma Cell line-derived Xenograft Model in Mice by Intracerebroventricular Injection Using 3D-Printed Mouse Head Fixation Holder

1:00 PM - 5:00 PM

***J. KIM**[1], J.-H. NOH[2], J.-H. SONG[3], J. LEE[4], H. KIM[1], S. PARK[1], K.-H. HAN[5];
[1]Plasbio Inc., Jeonju, Korea, Republic of; [2]Keyprime Researh, Cheongju, Korea, Republic of; [3]Dept. of pharmacy, Kangwon national university, Chuncheon, Korea, Republic of; [4]Korea zoonosis research institute, Iksan, Korea, Republic of; [5]Korea institute of toxicology, Deajeon, Korea, Republic of

Abstract

Glioblastoma is the most aggressive of all brain tumors and difficult to treat. Since the animal Cell line-derived xenograft (CDX) model of glioblastoma represents the physiological specificity of cancer, it can be used as a tool to study tumor biology and therapeutic effects. In glioblastoma xenograft disease models, it is mainly used as a method of transplanting cells by intracerebroventricular (I.C.V.) or intrathecal as the route of administration. However, there are many problems to be solved, such as lack of speed, technical difficulties, and expensive equipment. In response to these troubles, we have designed a novel mouse head fixation holder (MFH) via 3D scanning and 3D printing technology. 3D scanning technology that provides accurate head measurement data and 3D printing technology that can produce various shapes through CAD were applied to this study. We describe a simple, exact, inexpensive and rapid method for I.C.V. injection without stereotaxic surgery in mice. First of all, the MFH was designed based on the mouse head 3D scanning data and all the components were coordinated in CAD file using Fusion 360 (AUTODESK). The G-code was generated using the slicing software Preform (Formlabs). 3D printing was fabricated with stereolithography (SLA) of FORM2 3D printer and photosensitive polymer (resin). To evaluate the effectiveness of the MFH, trypan blue and Cy 5.5 were directly injected into the SCID mouse’s lateral ventricle. Compared with hands on and MFH significantly increased the probability these dye solutions were administered into the brain ventricle. Hematoxylin & Eosin and Immunohistochemistry-DAB staining images of brain sections after human glioblastoma likely cell line U87MG injection showed that MFH had the same injection accuracy and CDX model generation ability as stereotaxic apparatus. These results indicate that a novel MFH can make it very effective, easy and economical for researchers to generate CDX model of glioblastoma. Furthermore, 3D printing technique provides a reproducible, flexible, simple and cost-effective method for researchers to produce the equipment needed to quickly adopt neurological experiments.

☆ Session 169 Industrial Insights and Perspectives Into Translational Neuroscience - Baihan Lin

2:00 PM - 4:30 PM

SDCC 6CF

☆ Session 174 Peter and Patricia Gruber Lecture: Expanding Horizons in Theoretical and Computational Neuroscience: Larry Abbott, Emery N. Brown, Terrence Sejnowski, Haim Sompolinsky

3:00 PM - 4:30 PM

SDCC Ballroom 20

MONDAY, NOV. 14, 2022

☆ Session 259 Tau Seeding and Pathology *In Vivo* Models

8:00 AM - 11:30 AM

SDCC 1

☆ Presentation 259.05 Big tau isoform resists pathological changes

9:00 AM - 9:15 AM

D. C. CHUNG[1,3], J.-P. REVELLI[1,3], R. RICHMAN[1,3], A. HAN[1,3,4], B. TADROS[1,3], M. DIAS[1,3], H. YALAMANCHILI[2,3], H. Y. ZOGHBI[1,3,5];
[1]Dept. of Mol. & Human Genet., [2]Dept. of Pediatrics, Baylor Col. of Med., Houston, TX; [3]Jan and Dan Duncan Neurolog. Res. Inst., Houston, TX; [4]Rice Univ., Houston, TX; [5]Howard Hughes Med. Inst., Houston, TX

Abstract

In Alzheimer’s disease (AD), hyperphosphorylated tau aggregates in selective brain regions such as the cortex and hippocampus. However, the cerebellum remains largely intact even at the most advanced stage of AD. Given this observation of regional brain vulnerability, we questioned whether the various tau isoforms are differentially expressed in the cerebellum and the forebrain. We found that the protein level of the “big tau” isoform is highly elevated in the mouse cerebellum compared to other brain regions using both total tau antibody and our newly developed big tau-specific antibody. Similarly, the transcript level of big tau was also found to be significantly elevated in the mouse cerebellum. Moreover, from the human brain

RNA sequencing database analysis, we confirmed that the level of big tau transcript is significantly higher in the human cerebellum than the cortex. These findings were particularly intriguing as previous studies have described big tau mostly in the context of the peripheral nervous system. Of note, big tau has an extremely elongated N-terminal region due to inclusion of exons 4a and 6 of the MAPT gene. Given its unique structure, we speculated that big tau possesses properties distinct from those of other tau isoforms. To assess aggregation propensity of big tau, we performed detergent fractionation using cells expressing mutant big tau or tau441 (the longest one of six major tau isoforms). This cellular experiment revealed that big tau protein is significantly less likely to aggregate compared to tau441. To further test this in an animal model, we injected neonatal wild-type mice with adeno-associated viruses (AAVs) that express either mutant big tau or tau441. After aging these mice for 6 to 9 months, we examined their brains to analyze pathological changes associated with either of these two tau isoforms. Consistent with results from the cellular model, big tau did not become aggregated or phosphorylated unlike tau441 in the brains of AAV-injected mice at 6 months of age. Big tau remains to be not pathologically altered even after aging these mice for 9 months. Taken together, our data from multiple models suggest that big tau has a significantly lower tendency to undergo pathological changes compared to tau441. The higher level of big tau in the cerebellum may potentially protect this brain region from developing tau pathology in AD.

☆ Session 271 Short-Term Synaptic Plasticity

8:00 AM - 12:00 PM

SDCC Halls B-H

☆ Presentation 271.11 / C9 Altered short-term synaptic plasticity in the PVN of the FKBP5-deficient mice

8:00 AM - 12:00 PM

***S. ZHANG**, C. CHUNG;
Dept. of Biol. sciences, Konkuk Univ., Seoul, Korea, Republic of

Abstract

FKBP5 is one of negative modulators of glucocorticoid receptors (GR) and certain FKBP5 SNPs are clinically known to be highly related with psychiatric disorders, including anxiety disorders and depression. FKBP5 overexpressing mice are reported to show increased anxiety and depression-like behaviors whereas FKBP5-deficient mice exhibit stress-resilient phenotypes such as faster stress copying behavior and anxiolytic behavior. Moreover, the paraventricular nucleus of the hypothalamus (PVN)-specific deletion of FKBP5 mice showed increased GR activity. PVN is the key modulator of the HPA axis, governing stress responses in the body through a well-known short-term plasticity (STP) mediated by the inhibition of NMDARs. We investigated the impact of FKBP5 loss on STP of the PVN and found that stress did not induce STP in the PVN of FKBP5-deficient mice, leaving NMDAR-mediated spontaneous transmission intact. Additional blockade of TrkB signaling allows stress-induced STP in FKBP5 lacking PVN neurons. Our observations suggest that BDNF-TrkB signaling may contribute to the stress resilience of FKBP5-deficient PVN, thereby providing a useful coping strategy against stress with clinical relevance.

☆ Session 277 Alzheimer's Disease: Roles of the Cerebrovasculature

8:00 AM - 12:00 PM

SDCC Halls B-H

☆ Presentation 277.09 / D50 Neurogranin regulates blood-brain barrier integrity and amyloid-β clearance

8:00 AM - 12:00 PM

J. PARK[1], S. ALEXANDER[2], K. STOKES[2], *H. NAM[1];
[1]Pharmacology, Toxicology, and Neurosci., [2]Mol. Cell. Physiol., LSU Hlth. Sci. Center-Shreveport, Shreveport, LA

Abstract

Blood-brain barrier (BBB) disruption promotes amyloid-β (Aβ) accumulation in the neurovasculature that contributes to the pathophysiology of Alzheimer's disease (AD). Clinical researchers discovered a reduction of neurogranin (Ng) expression in postmortem brains of AD patients. Although Ng is predominantly expressed in the neuron, we previously reported that Ng is also expressed in the endothelial cells that contribute to the endothelial activation process. Thus, we hypothesize that Ng is expressed in human cortical microvessel endothelial cells (hCMEC/D3) and that depletion of Ng impacts BBB breakdown by inducing endothelial activation. To test this hypothesis, we generated Ng knockdown in hCMEC/D3 and analyzed Ng-mediated molecular signaling and cellular permeability change. In this study, we found that Ng is expressed in the hCMEC/D3 and that Ng knockdown decreased AKT and mTOR activity and increased VCAM-1 expression indicating endothelial dysfunction. Then, we measured how the lack of Ng alters physiological responses in the BBB. Ng knockdown cells show a decreased transendothelial electrical resistance (TEER) response, indicating that lack of Ng disrupts BBB integrity. Moreover, we observed increased Aβ permeability in Ng knockdown cells compared to mock control cells. Overall, we are the first study to explore how Ng expression in the BBB plays an essential role in neurovasculature and BBB integrity. Our future in vivo study will support the role of Ng in BBB integrity and the Aβ clearance mechanism related to AD. Our study on the Ng mechanism will provide a better understanding of the vascular hypothesis of AD pathophysiology.

☆ Session 286 Microglia, Neuroinflammation, and Immune Function: Animal Models

8:00 AM - 12:00 PM

SDCC Halls B-H

☆ Presentation 286.09 / G18 Role of PARP-1 in microglia-mediate neuroinflammation

8:00 AM - 12:00 PM

***Y. CHOI**[1], V. L. DAWSON[1,2,3], T. M. DAWSON[1,2,3], T.-I. KAM[1];
[1]Inst. for Cell Engineering/ Dept. of Neurol., Johns Hopkins Med. Institutions, Baltimore, MD; [2]Dept. of Pharmacol. and Mol. Sci., Johns Hopkins Univ. Sch. of Medicine,, Baltimore, MD; [3]Diana Helis Henry Med. Res. Fndn., New Orleans, LA

Abstract

Neuroinflammation is a common pathway in neurodegenerative disease. We recently revealed that PARP-1 [Poly (ADP-ribose) polymerase-1) activation in neurons has a crucial role in α-synuclein (α-syn) neurodegeneration of Parkinson's disease (PD). However, less effort has been spent on understanding the contribution of microglial PARP-1 activation to neurodegeneration. We found that activation of microglia can convert the neurotoxic reactive astrocyte in models of Alzheimer's disease and PD. Genetic depletion and pharmacological inhibition of PARP-1 in primary microglia prevented the pathologic α-syn-induced microglial activation, which result in the suppression of neurotoxic reactive astrocyte formation. As an action mechanism, we further found that PARP-1 is required for α-syn PFF-induced inflammasome activation in microglia. Consistently, intrastriatal injection of α-syn preformed fibril (PFF) as a model of sporadic PD increased microglial and astrocyte activation in WT mice, while PARP-1 KO mice injected with α-syn PFF failed to show the microglial and astrocyte activation. Taken together, PARP-1 is required for pathologic α-syn-induced microglia activation and neurotoxic reactive astrocytes formation via regulating inflammasome activation in microglia, which contributes to non-cell autonomous neurodegeneration in a model of PD.

☆ Session 290 Dorsal Root Ganglia and Afferents: Ion Channels and Receptors

8:00 AM - 12:00 PM

SDCC Halls B-H

☆ Presentation 290.17 / M11 Activation of TRPV1 by PN (Plumula nelumbinis) and UR (Uncaria Rhyncophylla)

8:00 AM - 12:00 PM

T. HA, G. HONG, *B. KANG;
Korea Inst. of Sci. and Technol., Korea Inst. of Sci. and Technol., Seoul, Korea, Republic of

Abstract

This study investigated the activation of ion channels by Plumula Nelumbinis (PN) extract and Uncaria rhynchophylla(UR) extract at the cell level. Activation of TRPV1 was analyzed through a calcium imaging assay and through patch clamp experiments. The ion channels were overexpressed in HEK/293T cells using FuGENE ® HD Transfection Reagent. NNG Extract and UR extract activate Transient receptor potential vanilloid member 1(TRPV1) but not Transient receptor potential ankyrin 1(TRPA1) and TRPV2, TRPV3, TRPV4. TRPV1 was activated by several chemicals originating from extracts. Extracts activate TRPV1 of Dorsal Root ganglion(DRG) neurons. The extracts did not inhibit TRPV1. In conclusion, our study showed that several chemicals originating from herb extracts act as agonists of TRPV1. The findings of this study indicate the discovery of a new modulator of TRPV1, and further confirm their potential in pain therapy.

☆ Session 298 Sensorimotor Behavior

8:00 AM - 12:00 PM

SDCC Halls B-H

☆ Presentation 298.01 / W7 An insect vision-inspired flight control algorithm with an auto-tuned efference copy

8:00 AM - 12:00 PM

***A. CANELO**[1], A. J. KIM[2];
[1]Electronic Engin., [2]Biomed. Engin., Hanyang Univ., Seoul, Korea, Republic of

Abstract

Flying insects can process multiple visual features in parallel neural circuits and generate an appropriate action. Neural processing of singly presented visual patterns has been studied intensively in ***Drosophila*** for the past few decades. How do parallel visual circuits responding to different features presented concurrently are integrated to control a shared motor circuit? An influential theory proposed for combining multiple sensorimotor circuits is an efference copy mechanism, in which an intended action offsets other sensory circuits to prevent them from responding to reafferent sensory inputs caused by the action. Recent studies in ***Drosophila*** have identified efference copy-like signals in an array of motion-sensitive visual neurons that mediate visual stability reflexes. We used a classical approach to model visually guided flight control in ***Drosophila*** and captured its behavioral responses to elementary visual patterns. Through these responses and using a dynamical systems approach, we implemented two computational models that combine the stability reflex with spontaneous or other visually evoked flight controls such as object tracking and avoidance. The models combine the two neural pathways, one additively, and the other by the modulation of an efference copy, respectively. Furthermore, we included in the second model a simple multi-layered perceptron (MLP) that is used to auto-tune its efference copy enabling the modulation even in changing visual environments. The model demonstrates that the visual stability reflex dampens spontaneous as well as visual object-induced flight turns when combined additively and that the modulation of the stability reflex by an efference copy permits undamped, concurrent operation of multiple visual behaviors. Finally, the inclusion of the MLP auto-tunes the efference copy to match variations in sensory feedback associated with changes in internal or environmental variables. Our study provides an integrative model of vision-based flight control when multiple visual features are presented simultaneously in changing visual environments and may be extended to an adaptive flight control mechanism for artificial flying agents such as drones.

☆ Session 301 Premotor and Motor Cortex Dynamics During Movement Planning and Execution

8:00 AM - 12:00 PM

SDCC Halls B-H

☆ Presentation 301.05 / Z12 Stable neural dynamics in premotor cortex during motor planning

8:00 AM - 12:00 PM

***J.-H. KIM**, N. LI;
Dept. of Neurosci., Baylor Col. of Med., Houston, TX

Abstract

Motor planning is a fundamental brain function that give rise to volitional movements. However, it remains unclear whether the underlying neural dynamics that produce the same movement are stably maintained or flexibly reorganized over long time periods. Neurons in mouse anterior lateral motor cortex (ALM) exhibit preparatory activity that instructs future movements. Using longitudinal two-photon calcium imaging, we measured activity from the same ALM populations for over one month in mice performing a tactile-based delayed response task. Mice discriminated object location using their whiskers and reported choice using directional licking after a delay epoch. Mice were well-trained in the task with high performance before the imaging commenced. We found that task-related activities of ALM neurons were remarkably stable (Pearson's correlations (r) for task-aligned activity across sessions, 0.66 ± 0.07, mean ± SD across sessions). To assess the stability of preparatory activity at the population level, we trained a linear decoder to read out future lick directions from ALM delay activity. A decoder trained in one session can reliably predict movement direction when applied to other sessions regardless of the time interval between sessions (decoding accuracy, 81.18 ± 10.00%, mean ± SD across sessions). Taken together, these results suggest that preparatory activity under the same task context is conserved over at least one month.

☆ Session 310 Integrative Physiology and Behavior: Sleep Systems I

8:00 AM - 12:00 PM

SDCC Halls B-H

☆ Presentation 310.04 / LL6 Prefrontal cortical regulation of REM sleep

8:00 AM - 12:00 PM

***J. HONG**[1], K. T. BEIER[2], S. CHUNG[1], F. WEBER[1];
[1]Univ. of Pennsylvania, Univ. of Pennsylvania, Philadelphia, PA; [2]Univ. of California Irvine, Irvine, CA

Abstract

Rapid-eye-movement (REM) sleep is characterized by intense cortical activity underlying its wake-like electroencephalogram (EEG). The neural activity inducing REM sleep is thought to originate from subcortical circuits in the brainstem and hypothalamus. However, despite the functional importance of REM sleep in cortical synaptic plasticity and memory processing, whether cortical neurons also possess the capability to regulate REM sleep has remained overlooked. Here, we show that the medial prefrontal cortex (mPFC) strongly promotes REM sleep. Bidirectional optogenetic manipulations demonstrate that excitatory mPFC neurons or their projections to the lateral hypothalamus (LH) induce REM sleep and regulate phasic events, reflected in intensified theta oscillations in the EEG during REM sleep. Calcium imaging reveals that the majority of LH-projecting mPFC neurons are maximally activated during REM sleep and a subpopulation of these neurons is recruited during phasic events. Our results delineate a cortico-hypothalamic circuit for the top-down control of REM sleep and thus demonstrate that cortical neurons are directly involved in the regulation of REM sleep.

☆ Session 312 Neural Basis of Reward I

8:00 AM - 12:00 PM

SDCC Halls B-H

☆ Presentation 312.06 / NN14 Mesolimbic dopamine release conveys causal associations

8:00 AM - 12:00 PM

***H. JEONG**, M. ZHOU, B. WU, D. A. BURKE, V. K. NAMBOODIRI;
Neurol., Univ. of California San Francisco, San Francisco, CA

Abstract

Learning to predict rewards based on environmental cues is essential for survival. It is widely believed that animals learn to predict rewards by updating predictions whenever the outcome deviates from expectations. Such violations of predictions are called reward prediction errors (RPEs) and thought to facilitate learning. RPEs are the critical teaching signal in the most widely accepted model for cue-reward associative learning—temporal difference reinforcement learning (TDRL). TDRL RPE has been successful at explaining the activity dynamics of dopaminergic cell bodies and release in the nucleus accumbens. Hence, TDRL RPE has become the dominant theory of dopamine's role as the critical regulator of behavioral learning. An alternative approach to learn cue-reward associations is to infer the cause of meaningful outcomes such as rewards. Since causes must precede outcomes, a viable approach to infer whether a cue causes reward is to learn whether the cue consistently ***precedes*** reward. This approach is advantageous as predicting the future is highly demanding in a cue-rich environment but inferring the cause of a rarer meaningful outcome simply requires a memory of previous experience. In other words, if an animal knows that a stimulus it just received is meaningful (e.g., a reward), it can look back in memory to infer its cause. Using this intuition, here we propose a causal inference algorithm that infers whether a cue is a cause of reward. Based on this algorithm, we denote stimuli (cues or rewards) whose cause should be learned by the animal as "meaningful causal targets" and propose that mesolimbic dopamine signals whether a current event is a meaningful causal target using an adjusted net contingency for causal relations (ANCCR) of that event in relation to other meaningful causal targets. We found that ANCCR makes similar predictions as RPE under commonly studied experimental settings. Hence, to distinguish between the two hypotheses (RPE or ANCCR signaling by mesolimbic dopamine release), we performed eight experimental tests by measuring dopamine release in nucleus accumbens core. We found that mesolimbic dopamine conveys causal associations but not RPE in every case, thereby challenging the dominant theory of reward learning in the brain. Our results provide a new conceptual and biological framework for associative learning.

☆ Session 313 Positive and Negative Affect: Neuroanatomy and Neuromodulation

8:00 AM - 12:00 PM

SDCC Halls B-H

☆ Presentation 313.03 / PP15 Optogenetic inhibition of the central amygdala at discrete time points modulates approach against dynamic threat in rats

8:00 AM - 12:00 PM

***J. LEE**, J.-S. CHOI;
Sch. of Psychology, Korea Univ., Seoul, Korea, Republic of

Abstract

The central amygdala (CeA) is involved in processing both aversive and appetitive stimuli, yet how CeA is recruited to guide optimal choices in a conflict situation is not well-understood. Here we investigated the role of CeA in a conflict situation where both threat and reward exist. Taking advantage of the high temporal resolution of optogenetic stimulation, CeA was inhibited at specific time points during risky foraging against a predator-like robot or the Lobsterbot named after its striking claws, programmed to generate a threat motion against approaching rats seeking sucrose solution. We bilaterally injected a viral vector carrying red-shifted inhibitory rhodopsin and implanted optic fibers over CeA of male Sprague-Dawley rats. During the baseline sessions (5-6 days), rats were trained to approach the sucrose port located near the Lobsterbot, which remained stationary. In the following conflict sessions (3 days), the Lobsterbot initiated striking attacks 6 s after the first lick, disrupting the rats' foraging behavior. Within the conflict session, optogenetic stimulation was delivered at three different time points depending on the group: Pre-attack period (PRE), Attack period (ATTACK), or Both (BOTH). The PRE group received laser stimulation for 6 s from the start of the first lick until the Lobsterbot initiated an attack. The ATTACK group received stimulation for the same amount of time as the PRE group, but the stimulation started simultaneously with the attack. The BOTH group received stimulation from 6 s before the striking attack to 6 s after the attack (total of 12 s). Rats with bilateral optic fibers implanted without a viral vector were used as the control group (CONT). The number of approaches and the number of licks during the conflict session were significantly decreased compared to the baseline sessions. During the conflict session, BOTH showed significantly more approaches than either CONT or ATTACK. Moreover, PRE also showed more approaches than either CONT or ATTACK. Collectively, approach-oriented behavior increased most effectively when inhibitory stimulation was applied during the pre-attack period in which rats anticipate an upcoming threat, suggesting that depending on discrete-time points when the CeA inhibition is applied the approach-oriented responses vary in a conflict situation.

☆ Session 318 Neural Mechanisms of Value Based Decision Making in Non-Human Primates and Humans

8:00 AM - 12:00 PM

SDCC Halls B-H

☆ Presentation 318.15 / VV17 Supplementary Eye Field encodes temptation-modulated monitoring and evaluative signals to guide behavior during intertemporal choice

8:00 AM - 12:00 PM

***K. LEE**[1], J. HWANG[3], V. STUPHORN[2];
[1]Psychological and Brain Sci., [2]Mind/Brain Inst., Johns Hopkins Univ., Baltimore, MD; [3]Section on Neurobio. of Learning and Memory, Lab. of Neuropsychology, NIMH/NIH, Bethesda, MD

Abstract

In real-life situations a choice may not lead to an immediate reward, instead requiring a wait before reward delivery. In these situations with temporally separated choice and reward, information must be retained after choice to successfully evaluate its outcome. Moreover, there must be continuous monitoring for relevant environmental changes that can occur during the delay and change the value of the upcoming reward. How an individual evaluates and monitors in the context of delayed rewards are therefore integral to understanding how we pursue and achieve long-term goals. However, it remains unclear how neuronal activity supports these processes. The Supplementary Eye Field (SEF) is known to carry context-dependent action value signals (i.e., the subjective value of selecting an option) and also monitoring and evaluative signals, making the SEF a potential candidate for this role. Here, we examined how the SEF represents sustained task-related signals throughout the delay, and whether they are used to inform behavior in the context of delayed rewards. We recorded the activity of 201 single neurons from the SEF of two monkeys performing a self-control task, a modified intertemporal choice task in which for a small proportion of trials, the monkey is presented with the temptation to switch from his initial choice to the other option. First, we found that SEF neurons continue to represent task-related value information throughout the delay and reward delivery periods. In particular, SEF activity after reward delivery predicted choice in the subsequent trial, suggesting that the SEF retains value information for evaluation and for modulating future choice. Second, we found that the sustained value representation in the SEF reflects the unexpected appearance of temptation. Finally, we found that SEF activity predicts for how long the monkey remains at his initial choice of the larger delayed reward before ultimately giving into the temptation to switch to the more immediate smaller reward. Together, this work demonstrates that the SEF continues to encode task-related variables after choice to support monitoring and evaluative roles in the context of delayed rewards.

☆ Session 324 Hippocampal/Entorhinal Physiology I

8:00 AM - 12:00 PM

SDCC Halls B-H

☆ Presentation 324.04 / XX18 Inhibition of theta oscillations reveals that a single and reliable time cell sequence is not needed for working memory

8:00 AM - 12:00 PM

***H. YONG**[1], H. CHANG[3], M. P. BRANDON[2];
[1]McGill Univ., Verdun, QC, Canada; [2]Psychiatry, McGill Univ., Montreal, QC, Canada; [3]Neurosci., Canadian Ctr. For Behavioural Neurosci., Lethbridge, AB, Canada

Abstract

Recent work has shown that neurons in the hippocampus are sequentially activated during the delay period of a delayed spatial alternation task. Experimental data and a model proposed in Wang et al. (2015) suggest that the readout of this sequential activity required hippocampal theta oscillations. Further, the readout of this sequence has been proposed to be necessary for successful performance in the delayed spatial alternation task. However, this prior study used a long-acting GABA receptor agonist to inhibit the activity of all medial septum neurons for the entire testing session, raising the possibilities that 1) septal contributions other than theta generation may support delay encoding, and 2) that memory deficits could be the result of septal inactivation outside of the delay period. To assess these possibilities, we applied an optogenetic strategy to selectively silence the theta-generating GABAergic population in the medial septum (MS) specifically during the delay period as mice performed the delayed spatial alternation task. Mice were trained to run on a treadmill for 10 seconds between each alternation lap on the Tmaze, and were deemed to have learned the task after reaching 80% correct or better for two consecutive days. Once they reached the criteria, septal GABAergic neurons were pseudo-randomly inhibited in 50% of the trials, for the entire 10 second duration of the delay period. We show that inhibition of these neurons significantly reduced the amplitude of hippocampal theta oscillation (mean theta reduction: 73%), and induced remapping in many of hippocampal neurons that encoded the delay period. Thus, we observed a new delay sequence only on trials when the septal GABAergic input to the hippocampus was suppressed. This phenomenon was not observed in laser-on GFP-only expressing control experiments. This result suggests the possibility that region CA1 of the hippocampus receives competing delay sequences from CA3 and the medial entorhinal cortex (MEC), both of which are known to contain delay cells. We suggest the possibility that MS inactivation disrupts the MEC delay sequence (similar to the effect of MS inactivation on MEC grid cells), which then gives the CA3 input more influence over CA1 sequences. Finally, we observed that remapping of the delay sequence had no impact on behavioral performance on the T-maze delayed alternation task. Our data suggests that this is driven by the preserved trajectory-dependent information.

☆ Session 330 Computational Models at the Cellular Level

8:00 AM - 12:00 PM

SDCC Halls B-H

☆ Presentation 330.17 / Web Only Construction of Physiological Cerebral Environment Augmented with a Brain Decellularized Extracellular Matrix - Matrigel Hybrid

8:00 AM - 12:00 PM

***H. NGO**[1], M. BAE[2], Y. KANG[1], J. JANG[2], D.-W. CHO[2], H. CHO[1];
[1]Dept. of Biophysics, Sungkyunkwan Univ., Suwon, Korea, Republic of; [2]Dept. of Mechanical Engin., POSTECH, Pohang, Korea, Republic of

Abstract

The brain extracellular matrix (ECM) anchors cellular components and helps maintain brain homeostasis from development to adulthood. However, specific biochemical components participating in regulation of cellular behaviors in both healthy and diseased conditions are yet to be elucidated due to the lack of ex vivo models that can faithfully recapitulate the combinatorial biophysical and biochemical components of the brain ECM. Here, we used the porcine brain decellularized ECM (P-BdECM) supplemented with Matrigel (MTG) (P-BdECM - MTG or Hybrid) to create a human brain-mimicking microenvironment ex vivo, with human brain cell cultures, enabling the discovery of biochemical factors regulating brain physiology and pathology. We encapitulated human brain cells, including neural progenitor cells (NPCs), astrocytes (ACs) and microglia (MG), into P-BdECM, Matrigel (MTG) or Hybrid. The results showed that Hybrid promoted the neural stemness characteristic of NPC, evidenced by the increase in Pax6 marker (2-fold). Hybrid condition also enhanced the differentiation of NPC into Neuron (Tuj1, 2.3-fold) and Astrocyte (Aldh1l1, 3-fold). We also characterized ACs phenotypes in Hybrid, which showed that Hybrid maintained ACs in their homeostatic state, with increased homeostatic marker Aldh1l1 (1.2-fold) and reduced basal reactivity level compared to MTG (GFAP 0.7-fold vs MTG). We found that Hybrid maintained ACs in resting state (A0) via BdECM-derived ANNEXIN A1 protein (ANXA1). Supplementing MTG with the same amount of ANXA1 contained in Hybrid (0.74μg/ml) showed the increase in homeostatic marker Aldh1l1 (1.2-fold) and the reduction in reactivity (GFAP) to the same level of Hybrid (Aldhl11 1.2-fold vs MTG, GFAP 0.7-fold vs MTG). In the presence of LPS, Hybrid dramatically shifted ACs into an inflammatory state with greater increase in GFAP level (2.7-fold vs 1.3-fold of MTG) and ROS level (5.3-fold vs 2.7-fold of MTG). Hybrid also kept MGs in resting state with low reactivity level, including CD86 (0.5-fold vs MTG), ROS (0.4-fold vs MTG), iNOS (0.8-fold vs MTG) and NO (0.3-fold vs MTG). Similar to AC, MG in Hybrid also dramatically responded to LPS, with greater increase in proinflammatory MG (M1) marker, including CD86 (3.8-fold vs 1.6-fold of MTG), ROS (8.3-fold vs 3.3-fold of MTG), iNOS (1.9-fold vs 1.3-fold of MTG) and NO (3.9-fold vs 1.5-fold of MTG). Taken together, our study showed that P-BdECM - MTG Hybrid have provided a very useful tool in ex vivo brain modeling that can be applied to neuroscience research, material-based neuroregeneration and translational medicine.

Keywords—Brain decellularized extracellular matrix, Neurogenesis, Neuroinflammation

★ Session 333 Special Lecture: Understanding Brain Cell Type Diversity - Hongkui Zeng

12:00 PM - 1:00 PM

SDCC Ballroom 20

★ Session 370 Alzheimer's Disease: Ion Channels and Excitability

1:00 PM - 5:00 PM

SDCC Halls B-H

★ Session 372 Cellular Mechanisms of Parkinson's Disease

1:00 PM - 5:00 PM

SDCC Halls B-H

★ Session 380 Understanding Traumatic Brain Injury (TBI)

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Session 345 Itch and Pain Mechanisms in Rodents and Humans

1:00 PM - 4:30 PM

SDCC 33

☆ Presentation 345.05 Subtype specificity of collateral sprouting mediated skin reinnervation after peripheral nerve injury

2:00 PM - 2:15 PM

***S. JEON**[1], A. PRADEEP[1], L. MCDONOUGH[1], A. LATREMOLIERE[1], L. K. CRAWFORD[2], M. J. CATERINA[1];
[1]The Johns Hopkins Univ. Sch. of Med., Baltimore, MD; [2]2University of Wisconsin - Madison Sch. of Vet. Med., Madison, WI

Abstract

Partial denervation, as a result of partial sciatic nerve transection, in skin results in collateral sprouting of spared sensory nerves into neighboring denervated territory. Collateral sprouting provides a potential means of restoring sensory function without surgery, but it occurs concomitantly with unwanted events such as neuropathic pain. A better understanding of collateral sprouting mechanisms and consequences is therefore needed. In this study, we performed whole-mount immunofluorescence staining of hind paw skin in the mouse spared nerve injury (SNI) model, in which the tibial and peroneal branches of the sciatic nerves are ligated and transected, leaving the sural nerve intact. Seven days after SNI, we observed a large reduction in immunoreactivity (IR) for peptidergic (CGRP) and myelinated (NF-H) nerve fibers in the middle of the ipsilateral hind paw skin formerly supplied by the tibial nerve. However, at 28 and 56 days after injury, progressive reinnervation by CGRP$^+$ and NF-H$^+$ nerve fibers into denervated, apparently from saphenous and sural territories, was observed. We next asked whether low-threshold mechanoreceptors (LTMRs) participate in collateral sprouting after nerve injury, by performing SNI surgery on labeled LTMR mouse lines. Seven days after injury, we observed an obvious reduction in nerve terminal structures for Aβ RA-LTMRs, Aδ RA-LTMRs, Aβ SAI-LTMRs, Aβ Field-LTMRs, and C-LTMRs in the ipsilateral hind paw. Even 56 days after SNI, no collateral sprouting of any LTMR populations into the denervated region was evident. However, sympathetic nerve fibers had begun to sprout into the denervated skin by day 28 and increased until day 56, and these sympathetic neurons formed LTMR-like nerve circumferential endings on hair follicles. To define the functional recovery of collateral sprouts in denervated skin after nerve injury, we performed optogenetic experiments in Pirt^{Cre};Rosa26$^{LSL\text{-}ChR2\text{-}EYFP}$ and Calca^{Cre};Rosa26$^{LSL\text{-}ChR2\text{-}EYFP}$ mice, which express the light-gated ion channel channelrhodopsin-2 in all sensory neurons and in peptidergic nociceptors, respectively. Light-induced paw withdrawal frequency on the ipsilateral hind paw of both mouse lines dropped dramatically by 3 days after SNI, but returned gradually to near basal level over 28 days. Mechanical sensitivity, assayed utilizing von Frey monofilaments and an Austerlitz pin applied to the midline of the hind paw, also showed a marked decrease 3 days after SNI, but returned gradually to basal level by 28 days, without evidence of hyperalgesic overshoot. These results suggest that collateral sprouting contributes to functional recovery of sensory nerves in denervated skin.

☆ Session 346 Visual Processing During Behavior

1:00 PM - 2:45 PM

SDCC 5

☆ Presentation 346.07 Visually evoked activity of the SST-expressing interneurons and the SST release in the V1 of mice discriminating visual stimuli in a freely moving state

2:30 PM - 2:45 PM

***J. YOON**, S.-H. LEE;
Korea Advanced Inst. of Sci. and Technol., Daejeon, Korea, Republic of

Abstract

The activity of interneurons in the visual cortex is critical for visual processing and perceptual behaviors. Among the interneurons, somatostatin-expressing interneurons (SST$^+$ INs) are important for sensory gating via inhibition of the pyramidal neurons or other interneurons. Moreover, a recent study showed that the exogenous application of somatostatin (SST), a neuropeptide potentially released from the SST$^+$ INs, enhanced the visual gain of primary visual cortex (V1) neurons and the visual discriminability of mice. However, it is still unclear when the SST$^+$ INs release the SST peptides and modulate V1 processing in animals performing visual tasks. Here, we present an experimental setup that enables ***in vivo*** calcium imaging of V1 neurons in mice discriminating visual stimuli in the T-maze. In this setup, mice learn to discriminate the two different static grating orientation stimuli for left or right choices. In the well-trained mice, we measured the activity of SST$^+$ INs in the V1 using a miniaturized 1-photon fluorescence microscope. Interestingly, we found that their activity increased after the stimulus onset but decreased when mice entered the reward zones. This opposite responsiveness was not observed in the excitatory neurons during the task. We next measured the SST release via GRAB$_{SST}$ sensor imaging in the V1 of task-performing mice using fiber

photometry. We found that the SST release increased after the stimulus onset, in correlation with the activity increase of SST$^+$ INs during the task. Our data suggest that the activity of SST$^+$ INs increases and the SST is released in the V1 when animals process visual information for their behavioral choices.

☆ Session 351 Cell Lineage, Fate, and Migration

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 351.07 / A16 Ano1 regulates neural stem cell fate and underlying physiological evidences in forebrain development

1:00 PM - 5:00 PM

K. KIM[1], B. KANG[1], P. LEE[1], M.-S. KIM[1], H.-Y. KIM[1], *U. OH[2], G. HONG[3];
[1]Korea Inst. of Sci. and Technol., Seoul, Korea, Republic of; [2]Korea Inst. of Sci. and Technol. (KIST), [3]Neurosci., Korea Inst. of Sci. and Technol. (KIST), Seoul, Korea, Republic of

Abstract

The mammalian forebrain is associated with motor function, emotion and cognition by processing high-level thinking. Malformation of the forebrain incurs disruption of neural circuits correlated with psychiatric and developmental disorders including anxiety, depression, schizophrenia, epilepsy, autism spectrum disorder and Timothy syndrome. The fine regulation of neurogenesis by neural stem cells (NSCs) are mediated by neurotrophic factors and genes including sonic hedgehog, Wnt proteins, glutamate, ATP, gamma-aminobutyric acid (GABA), epidermal growth factor (EGF) and fibroblast growth factor (FGF). Here, we report new findings of the molecular mechanism of anoctamin 1 (ANO1), a Ca^{2+}-activated Cl^- channel including activation mechanism of ANO1 and underlying other ion channel activity in specialized NSCs of the mouse embryonic ventricular zone. Further results of cell biological and physiological evidences from Ano1 knock-out mouse will be presented.

☆ Session 354 Autism: Synaptic Mechanisms

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 354.15 / B47 Early postnatal synaptic correction leads to long-lasting correction of synaptic and behavioral phenotypes in Arid1b-haploinsufficient mice

1:00 PM - 5:00 PM

***H. KIM**[1], D. KIM[2], Y. CHO[3], K. KIM[2], J. D. ROH[2], Y. KIM[4], E. YANG[5], S. KIM[6], S. AHN[6], H. KIM[5], H. KANG[7], Y. BAE[3], E. KIM[2];
[1]Dept. of Biol. Sci., Korea Advanced Inst. for Sci. and Technol. (KAIST), Yuseong-gu, Korea, Republic of; [2]IBS, Daejeon, Korea, Republic of; [3]Sch. of Dentistry, Kyungpook Natl. Univ., Daegu, Korea, Republic of; [4]Grad. Sch. of Biomed. Engin., KAIST, Daejeon, Korea, Republic of; [5]Korea Univ. Col. Med., Seoul, Korea, Republic of; [6]KRICT, Daejeon, Korea, Republic of; [7]KISTI, Daejeon, Korea, Republic of

Abstract

ARID1B, also known as BAF250B, is a subunit of the SWI/SNF chromatin remodeling complex and has been implicated in intellectual disability, autism spectrum disorders (ASD), and Coffin-Siris syndrome. We characterized Arid1b-haploinsufficient mice and found that these mice display autistic-like behaviors, including social impairments and repetitive behaviors. Electrophysiological analyses indicate that mutant cortical neurons display synaptic deficits at juvenile and adult stages, which accompanies transcriptional changes in synapse-associated genes. Pharmacological corrections of these synaptic deficits at early postnatal stages prevent both synaptic and behavioral deficits in adult mice, highlighting the importance of early postnatal corrections of mechanistic deviations for long-lasting effects.

☆ Presentation 354.11 / B43 Adult re-expresssion of BBB-penetrant IRSp53 rescues NMDA receptor function and social behavior in IRSp53-mutant mice

1:00 PM - 5:00 PM

***Y. NOH**[1], C. YOOK[2], J. KANG[2], S. LEE[1], Y. KIM[1], E. YANG[3], H. KIM[3], E. KIM[1];
[1]Korea Advanced Inst. of Sci. and Technol., Korea Advanced Inst. of Sci. and Technol., Daejeon, Korea, Republic of; [2]Ctr. for Synaptic Brain Dysfunctions, Inst. for Basic Sci. (IBS), Daejeon, Korea, Republic of; [3]Dept. of Anat. and BK21 Grad. Program, Biomed. Sciences, Col. of Medicine, Korea Univ., Seoul, Korea, Republic of

Abstract

IRSp53 (or BAIAP2) is an abundant excitatory postsynaptic scaffolding/adaptor protein that is involved in actin regulation and has been implicated in autism spectrum disorders, schizophrenia, and attention-deficit/hyperactivity disorder. IRSp53 deletion in mice leads to enhanced NMDA receptor (NMDAR) function and social deficits that are responsive to NMDAR inhibition. However, it remains unclear whether IRSp53 re-expression in the adult IRSp53-mutant mouse brain after the completion of brain development could reverse these synaptic and behavioral dysfunctions. Here we employed a brain-blood barrier (BBB)-penetrant adeno-associated virus (AAV) known as PHP.eB to drive adult IRSp53 re-expression in IRSp53-mutant mice. The adult IRSp53 re-expression normalized social deficits without affecting hyperactivity or anxiety-like behavior. In addition, adult IRSp53 re-expression normalized NMDAR-mediated excitatory synaptic transmission in the medial prefrontal cortex. Our results suggest that adult IRSp53 re-expression can normalize synaptic and behavioral deficits in IRSp53-mutant mice and that BBB-penetrant adult gene re-expression has therapeutic potential.

☆ Session 355 Developmental Disorders: Genetic Models II

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 355.02 / B57 Glutamatergic and GABAergic neurons mediate distinct neurodevelopmental phenotypes of STXBP1 encephalopathy

1:00 PM - 5:00 PM

***J. KIM**, W. CHEN, E. S. CHAO, H. CHEN, A. RIVERA, M. XUE;
Baylor Col. of Med., Houston, TX

Abstract

Heterozygous pathogenic variants in syntaxin-binding protein 1 (STXBP1, also known as MUNC18-1) cause ***STXBP1*** encephalopathy and are among the most frequent causes of developmental and epileptic encephalopathies and intellectual disabilities. STXBP1 is an essential protein for presynaptic neurotransmitter release, and its haploinsufficiency impairs glutamatergic and GABAergic neurotransmission. However, the cellular origin of the broad spectrum of neurological phenotypes is poorly understood. Here we show that glutamatergic and GABAergic neurons-specific ***Stxbp1*** haploinsufficient mice exhibit different subsets of the cognitive and seizure phenotypes observed in the constitutive ***Stxbp1*** haploinsufficient mice. Developmental delay and most of the motor and psychiatric phenotypes are only recapitulated by GABAergic ***Stxbp1*** haploinsufficiency. Thus, glutamatergic and GABAergic neurons mediate distinct disease features with few overlaps. The contrasting roles of excitatory and inhibitory signaling in ***STXBP1*** encephalopathy identify GABAergic dysfunction as a main disease mechanism and reveal the possibility to selectively modulate disease phenotypes by targeting specific neurotransmitter systems.

☆ Presentation 355.03 / B58 Reactivating paternal Ube3a alleviates the disturbance of brain rhythms and sleep in juvenile and adult Angelman syndrome mouse models

1:00 PM - 5:00 PM

***D. LEE**[1,3,4], W. CHEN[1,3,4], H. KAKU[1,3,4], X. ZHUO[2], E. S. CHAO[1,3,4], A. SORIANO[5], A. KUNCHERIA[1], S. FLORES[1], J. KIM[1,3,4], F. RIGO[5], P. JAFAR-NEJAD[5], A. L. BEAUDET[2], M. S. CAUDILL[1], M. XUE[1,3,4,2];
[1]Neurosci., [2]Mol. and Human Genet., Baylor Col. of Med., Houston, TX; [3]The Cain Fndn. Labs., Houston, TX; [4]Jan and Dan Duncan Neurolog. Res. Inst., Texas Children's Hosp., Houston, TX; [5]Ionis Pharmaceuticals, Carlsbad, CA

Abstract

UBE3A encodes ubiquitin protein ligase E3A and is paternally imprinted in neurons because the ***UBE3A*** antisense transcript ***(UBE3A-ATS)*** represses paternal ***UBE3A***. Maternal ***UBE3A*** deficiency causes Angelman syndrome, a severe neurodevelopmental disorder. A promising therapeutic approach to treating Angelman syndrome is to reactivate the intact paternal ***UBE3A*** by suppressing ***UBE3A-ATS***. Prior studies show that many neurological phenotypes of maternal ***Ube3a*** knockout mice can only be rescued by reinstating ***Ube3a*** expression in early development, indicating a restricted therapeutic window for Angelman syndrome. Here we report that reducing ***Ube3a-ATS*** by antisense oligonucleotides in juvenile or adult maternal ***Ube3a*** knockout mice alleviates the abnormal electroencephalogram rhythms and sleep disturbance, two prominent clinical features of Angelman syndrome. The degree of phenotypic improvement correlates with the increase of Ube3a protein levels. These results indicate that the therapeutic window of genetic therapies for Angelman syndrome is broader than previously thought, and electroencephalogram power spectrum and sleep architecture should be used to evaluate the clinical efficacies of therapies.

☆ Session 358 Autism Mechanisms: Mouse Models

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 358.08 / C51 Characterization of a novel mouse model for autism spectrum disorder

1:00 PM - 5:00 PM

***C. A. BRADLEY**[1], S. Y. KO[1], L. D'ABATE[1], J. LEE[2], J. WANG[2], X. FANG[1], A. RUTHERFORD[1], G. L. COLLINGRIDGE[2], P. W. FRANKLAND[1], S. W. SCHERER[1];
[1]The Hosp. For Sick Children, Toronto, ON, Canada; [2]Lunenfeld-Tananbaum Res. Inst., Toronto, ON, Canada

Abstract

Autism Spectrum Disorder (ASD) is a prevalent neurodevelopmental disorder characterized by social communication deficits and the display of restrictive, repetitive behaviors. Our genomic studies have implicated the ***PTCHD1 / PTCHD1-AS*** locus on chromosome X as a penetrant susceptibility locus in males, contributing to ASD and intellectual disability in ~ 1% of cases. Genes at this locus include protein-coding genes ***PTCHD1, DDX53*** and a long non-coding RNA (lncRNA) ***PTCHD1-AS.*** Males with deletions in ***PTCHD1-AS*** strongly correlate with an ASD outcome**.** We, therefore, generated two mouse lines removing the conserved exon 3 of ***Ptchd1-as,*** the first line termed ***Ptchd1-as*** $^{Ex3-}$, and in the second line, inserting a 2x polyA termination signal to truncate the transcript after the third exon referred to as ***Ptchd1-as*** ^{PolyA}. Guided closely by the human phenotype data, we have characterized the behavioral and cellular effects in ***Ptchd1-as*** mutant mice to look at the transcriptional consequences of a deletion within the critical region associated with high functioning autism. Both mutant mice lines recapitulate the human phenotype with mild to moderate impact on ASD-relevant tasks (repetitive grooming, social interaction; N = 10-12, $p < 0.05$ for all tasks) with no deficits in a learning task (Touchscreen pairwise discrimination; ***Ptchd1-as*** ^{PolyA} N = 10, 13, $p > 0.05$). Furthermore, hippocampal synaptic function was normal; altogether a phenotype indicative of a pure, high-functioning ASD. Droplet digital PCR and deep sequencing of brain mouse ***Ptchd1-as*** demonstrate both age and region-specific expression patterns as well as enrichment in GABAergic cell types of both interneurons (N= 3, 4, $p < 0.01$) and striatal tissues (N = 6, $p < 0.01$). Transcriptome analysis of ***Ptchd1-as*** ^{PolyA} mutants show modest effects in whole-brain tissues with more differentially expressed genes observed in young mice relative to adults (N=6 per genotype and age). Quantitative PCR showed ***Ptchd1-as*** ^{PolyA} mutants exhibited alterations in NMDA and AMPA receptor genes in young, which were down-regulated in a subunit-dependent manner (N=6, $p < 0.05$). Further cellular and synaptic investigation aim to identify the critical molecular changes that alter social function in an otherwise overtly normal mouse.

☆ Session 365 Epilepsy: Networks and Oscillations 1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 365.17 / F11 Neuromodulatory Effects on Hippocampal Subnetwork by High Frequency Electrical Stimulation during Seizure-like Events in Entorhinal-Hippocampal Slice Recording 1:00 PM - 5:00 PM

***Y. CHOI**[1,2], S. KIM[1,2,3], Y. KIM[1], S. AN[4], S. JUN[4,5,6], H. LEE[1,2,3];
[1]Med. Science, Sch. of Med. and Ewha Med. Res. Inst., [2]Neurol., [3]Grad. Program in Syst. Hlth. Sci. and Engin., [4]Electronic and Electrical Engineering, Sch. of Engin., [5]Grad. Program in Smart Factory, [6]Dept. of Brain and Cognitive Sci., Ewha Womans Univ., Seoul, Korea, Republic of

Abstract

Hippocampus plays an important role for seizure generation in temporal lobe epilepsy (TLE), but network interaction inside the hippocampal subnetwork is not fully understood. In this study, we investigated the causal relationship of spatiotemporal dynamics during seizure-like events (SLEs) and the effects of high frequency electrical stimulation (HFS) to abort SLEs in hippocampal subnetworks.

We recorded neuronal activities from entorhinal-hippocampal slices including the dentate gyrus (DG), CA3, CA1, subiculum, medial entorhinal cortex (MEC) and lateral EC (LEC) in 14-day-old male Sprague-Dawley rats' brain using microelectrode array (MEA) recording system. When SLEs induced by 4-aminopyridine (4-AP) administration were clearly identified, we applied 130Hz HFS to layer III of the MEC through an external electrode-connected stimulator. Integrated net causal outflows (iOF) based on Granger Causality (GC) was calculated to identify the location and time of seizure onset. The directional network interaction was analyzed by iOF and GC values between all the electrode pairs, to investigate the strength and directional changes of in 7 different frequencies; delta (1-4Hz), theta (4-8Hz), alpha (8-13Hz), beta (13-25Hz), gamma (25-55Hz), ripple (65-200Hz), and fast ripple (250-500Hz).

The onset time of SLEs, which was identified by the maximum iOF values at the time of iOF increase greater than 3 standard deviations of baseline values, were observed 5.03 ± 3.72 sec earlier compared with the visual analysis. The iOF value was increased first in the area of seizure-onset electrodes, which was propagated into other channels along with the epileptic hippocampal subnetworks. After applied HFS on the MEC during SLEs, the mean duration of SLEs was significantly reduced in the stimulation group compared to the non-stimulation group (59.02 ± 34.95 sec vs 237.65 ± 269.82 sec, respectively). Also, GC values were significantly different in SLEs before and after HFS (0.14 ± 0.08 vs 0.06 ± 0.03, respectively).

The present study showed that HFS on the MEC significantly reduced seizure durations. Also, GC values were altered by HFS, which could contribute disrupting the propagation of epileptic activities from seizure-onset zones to other hippocampal subregions. Insights into the directional network interaction of hippocampal subnetwork during seizure generation could provide more efficient therapeutic strategies to suppress seizures as well as in-depth understandings of the spatiotemporal dynamic mechanisms involving ictogenesis.

☆ Session 366 Microglia and Neurodegeneration 1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 366.03 / F26 The mTOR expression in microglia and astrocyte of temporal lobe epilepsy model 1:00 PM - 5:00 PM

***M. KIM**[1], H. PARK[1], Y. YI[3], J. KANG[2,4], D. KIM[1];
[2]Chungnam Natl. Univ., [1]Chungnam Natl. Univ., Daejeon, Korea, Republic of; [3]Dept. of Pediatrics, Col. of Med., Hallym Univ. and Gangdong Sacred Heart Hosp., Seoul, Korea, Republic of; [4]Chungnam Natl. Hosp., Daejeon, Korea, Republic of

Abstract

Epilepsy is a chronic disease that causes repetitive seizures by generating excessive electrical discharge due to functional and structural abnormalities of neuronal cells. Recent studies have implicated those reactive astrocytes and microglia play a key role in epilepsy. When extensive pathological activation in astrocytes and microglia at the injury core, it contributes to epileptic seizures and causes neuronal hyperexcitability. The mTOR signaling pathway, which is involved in brain development, neuronal morphology, and plasticity, is important for understanding the mechanism of epilepsy, following that a consistent activation of the mTOR pathway in astrocytes and microglia have been reported. In this study, we used Kainic acid-induced status epilepticus model and recorded behavioral SE induction rates. After 7 days, we confirmed that mTOR expression was increased not only reactive astrocyte but also microglia in the CA3 regions of hippocampus, accompanied by mossy fiber sprouting. For therapeutic applications targeting mTOR, we applied mTOR targeting siRNA-encapsulated PLGA nanoparticles and confirmed the suppression of seizure activities and inflammatory responses. Taken together, our data suggests that down-regulation of mTOR with nanoparticle applications significantly ameliorated reactive astrocytes and microglia activation, and neuroinflammation in the hippocampus, resulting the alleviation the epileptic seizures.

☆ Session 368 Alzheimer Disease and Immune Mechanisms 1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 368.07 / Web Only Ifng-driven nrf2 downregulation in microglia exacerbates alzheimer's disease 1:00 PM - 5:00 PM

***Y. KANG**[1,2], S. HYEON[5], A. MCQUADE[6], J. LIM[7,8], S. BAEK[3], D.-G. JO[3], C. LEE[8], M. BLURTON-JONES[9,10,11], H. RYU[5], H. CHO[1,2,4];
[1]Inst. of Quantum Biophysics, [2]Dept. of Biophysics, [3]Sch. of Pharm., [4]Dept. of Intelligent Precision Healthcare Convergence, Sungkyunkwan Univ., Suwon-si, Korea, Republic of; [5]Korea Inst. of Sci. and Technol., Seoul, Korea, Republic of; [6]Inst. for

Neurodegenerative Dis., Univ. of California, San Francisco, CA; [7]IBS Sch., Univ. of Sci. and Technol., Daejeon, Korea, Republic of; [8]Ctr. for Cognition and Sociality, Inst. for Basic Sci., Daejeon, Korea, Republic of; [9]Neurobio. & Behavior, [10]Sue and Bill Gross Stem Cell Res. Ctr., [11]Inst. for Memory Impairments and Neurolog. Disorders, Univ. of California Irvine, Irvine, CA

Abstract

Recent reports reveal that microglia interacting with beta-amyloid plaques appears to be neuroprotective yet retaining proinflammatory phenotype often precedes neurodegeneration in AD. However, it remains unclear how microglial activity transits to the neurotoxic state in response to AD-associated environments, in part due to the lack of pathophysiological and accessible models of human AD brains. Here, we investigate the underlying mechanism of detrimental innate immunity in AD, particularly focusing on microglia, by employing our 3D human APP-mutated mini-brains including human induced pluripotent stem cells (iPSC)-derived microglia. We observe that reactive astrocytes initiate neuroinflammation by releasing interferon-gamma (IFNγ) and excessive oxidative stress (H_2O_2) under amyloid-beta (Abeta)-rich environments. Our results show that the astrocytic IFNγ downregulates microglial nuclear factor erythroid-2-related factor 2 (Nrf2) ***via*** Kelch-like ECH-associated Protein 1 (Keap1) upregulation. Interestingly, the downregulation of Nrf2 sensitizes microglia to the oxidative stress and induces the transition into the neurotoxic phenotype in AD. These proinflammatory microglia in turn produce neurotoxic nitric oxide and inflammatory mediators resulting in synaptic impairment, phosphorylated-tau accumulation, and discernable neuronal loss. We validate the reduction of Nrf2 in neurodegenerative microglia adjacent to aggregated phosphorylated-tau in IFNγ-expressing brain tissues of late-staged human AD patients and 5XFAD mice. Overall, our study concludes that IFNγ-driven Nrf2 downregulation in microglia as a key mediator of AD pathogenesis.

☆ Session 369 Metabolism Alterations in Alzheimer's Disease

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 369.11 / G9 Brain-pancreas connectivity study of habenular cholinergic neurons with transsynaptic retrograde tracer in AD and WT mice

1:00 PM - 5:00 PM

S. CHUNG[1,3], S. LEE[1,3], M. SUH[1,4,2,3], *J. JEONG[4,2];
[1]Biomed. Engin., [2]Biomed. Inst. for Convergence at SKKU (BICS), Sungkyunkwan Univ., Suwon, Korea, Republic of; [3]Ctr. for Neurosci. Imaging Res. (CNIR), Inst. for Basic Sci. (IBS), SKKU, Suwon, Korea, Republic of; [4]IMNEWRUN Inc., Suwon, Korea, Republic of

Abstract

Degeneration of cholinergic circuit contributes to memory loss in Alzheimer's disease (AD) and disruption of glucose homeostasis mediated by an imbalance between energy intake and energy expenditure. Recent studies have shown that medial habenula (mHb) cholinergic neurons are connected to brain-pancreatic axis to regulate circulating glucagon and insulin levels (Duncan, A., Heyer, M.P., Ishikawa, M. ***et al. Nature*** **574,** 372-377 (2019). However, how mHb cholinergic neurons affect the cognitive function and learning and memory function has not yet fully understood. Here, single cell RNA sequencing data shows that the cholinergic neuronal circuit is impaired in AD mice compared with WT mice. Also, we observed impaired glucose homeostasis using oral glucose tolerance test (OGTT) in AD mice compared with WT mice. To investigate the role of cholinergic neurons on brain-pancreatic axis, we utilized transsynaptic retrograde tracer in WT and AD mice and studied the detailed brain connectivity of cholinergic neurons. As a result, we observed retrograde tracer labelled cholinergic neurons in the hippocampus, medial habenula and hypothalamus area. The fact that retrograde tracer labelled cholinergic neuron found in the hippocampus, indicates a possible link between cholinergic neurons and memory function. In addition, we found that glucagon-like peptide receptor 1 (GLP1R) positive neurons in the subiculum of hippocampus directly project to mHb cholinergic neurons. This suggests that GLP1R agonist, such as dulaglutide, may be involved in regulating not only overall glucose homeostasis but also the activity of cholinergic neurons in the brain. Based on these results, we suggest that modulating mHb cholinergic neurons may be effective in the treatment of AD, especially AD with hyperglycemia, insulin resistance and/or metabolic disorders.

★ Session 370 Alzheimer's Disease: Ion Channels and Excitability

1:00 PM - 5:00 PM

SDCC Halls B-H

★ Presentation 370.08 / G26 Development of small-molecule Tau-SH3 interaction inhibitors that prevent amyloid-β toxicity and network hyperexcitability

1:00 PM - 5:00 PM

***J. R. ROTH**[1], T. RUSH[1], S. J. THOMPSON[1], A. R. ALDAHER[1], T. B. DUNN[1], J. S. MESINA[1], J. N. COCHRAN[1], N. R. BOYLE[1], H. B. DEAN[1], Z. YANG[2], V. PATHAK[4], P. RUIZ[4], J. J. DAY[3], J. R. BOSTWICK[4], M. J. SUTO[4], C. E. AUGELLIA-SZAFRAN[4], E. D. ROBERSON[1];
[1]Neurol., [2]Biochem. and Mol. Genet., [3]Neurobio., Univ. of Alabama at Birmingham, Birmingham, AL; [4]Chem. Dept., Southern Res., Birmingham, AL

Abstract

Alzheimer's disease (AD) is the leading cause of dementia and lacks highly effective treatments. Tau-based therapies are attractive and Tau reduction prevents amyloid-β (Aβ)-induced dysfunction in preclinical AD models. Tau reduction also prevents amyloid-independent dysfunction in diverse disease contexts, suggesting that strategies exploiting the mechanisms underlying Tau reduction may extend beyond AD. Tau binds several SH3 domain-containing proteins implicated in AD via its central proline-rich domain. We previously used a peptide inhibitor to demonstrate that blocking Tau interactions with SH3 domain-containing proteins ameliorates Aβ-induced dysfunction. Here, we describe a high-throughput screen for small molecules that inhibit Tau-FynSH3 interactions and optimization of a top hit with medicinal chemistry. The resulting lead compound is a potent cell-permeable Tau-SH3 interaction inhibitor that binds Tau and prevents Aβ-induced dysfunction, including network hyperexcitability. These data support the potential of using small molecule Tau-SH3 interaction inhibitors as a novel therapeutic approach to AD.

★ Session 372 Cellular Mechanisms of Parkinson's Disease

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 372.07 / I9 Dysregulated phosphorylation of Rab GTPases induces axon degeneration

1:00 PM - 5:00 PM

***E.-H. JANG**[1,2], G. JEONG[5], Y. YAMAMOTO[6], K. TANAKA-YAMAMOTO[6], B. LEE[5], E.-M. HUR[1,3,4,2];
[1]Res. Inst. for Vet. Science, Col. of Vet. Med., [2]Lab. of Neuroscience, Col. of Vet. Med., [3]BK21 Four Future Vet. Med. Leading E&R Center, Col. of Vet. Med., [4]Interdisciplinary Program in Neuroscience, Col. of Natural Sci., Seoul Natl. Univ., Seoul, Korea, Republic of; [5]Kyung Hee Univ., Seoul, Korea, Republic of; [6]Korea Inst. of Sci. and Technol., Seoul, Korea, Republic of

Abstract

Mutations in the ***LRRK2*** (leucine-rich repeat kinase 2) gene are the most common genetic cause of Parkinson’s disease (PD), and LRRK2 has been associated with both familial and sporadic PD. A subset of Rab GTPases has been identified as authentic substrates of LRRK2, providing a link between intracellular trafficking and LRRK2 kinase activity. Previously, we have shown that dysregulation of Rab phosphorylation in the LRRK2 site induces neurodegeneration, and this study aims at investigating the mechanism by which dysregulation of Rab GTPases induces neurotoxicity. Here we show that dysregulated phosphorylation of Rab GTPases in the LRRK2 site causes defects in organelle trafficking and further support the notion that defects in intracellular trafficking can cause neurodegeneration.

☆ Session 374 CMT and Other Degenerative Diseases

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 374.12 / M16 Functional characterization of KY021 genetic variant in a rare neurological disorder using zebrafish disease model

1:00 PM - 5:00 PM

***S. KI**, S. PARK, B. HWANG, Y. KEE;
Kangwon Natl. Univ., Chuncheon, Korea, Republic of

Abstract

Tens of millions of people suffer from rare diseases worldwide. Model organism research is essential to investigate the pathophysiology of rare diseases. The genetic variants of the patients with global developmental delay, no acquisition of independent walking, and Rett symptoms were clinically detected by the ***Trio***-Based Whole-Genome Sequencing study. This study aims to validate the function of an undiagnosed genetic variant and investigate the mechanism underlying the pathophysiology of the rare neurodevelopmental disorder that affects the way the brain develops. Here, we obtained the zebrafish knockout animal (KO) for the KY021 gene and analyzed the anatomical and behavioral phenotypes in early zebrafish development. The results show the early development phenotypes of the homozygous mutants recapitulate the patient symptoms: the abnormal motility of the homozygous mutants and the cell death in the developing brain. We performed rescue experiments for the phenotypes by injecting the mRNA of the genetic variants into 1-cell zebrafish embryos. mRNA of the patient variant was not efficient in rescuing the KO abnormalities compared to wild-type mRNA. The present study implicates that the KY021 de novo variant is a loss-of-function mutation causing the patient's developmental and neurological symptoms. The further analysis explores the mechanism underlying the neurodevelopmental pathology of the variant in the undiagnosed disease.

☆ Session 378 Neuroinflammation and Mechanisms of Neurodegeneration

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 378.04 / Web Only Helicobacter pylori's cell-free supernatant ($_{\text{HP}}$CFS) induces neurodegenerative neuroinflammation in human mini-brain

1:00 PM - 5:00 PM

***V. TRAN**, H. CHO;
Sungkwunkwan Univ., Sungkwunkwan Univ., Suwon-si, Korea, Republic of

Abstract

Several epidemiological studies show the correlation between chronic ***Helicobacter pylori*** infection and neurological disorders. However, cellular interaction has not been validated yet, partly due to the lack of model systems that reflect the physiologically relevant innate immunity in the human brain. Here, we utilized the human brain platform reconstituting key aspects of neuroinflammation and neurodegeneration to study multicellular interaction under the ***Helicobacter pylori***'s cell-free supernatant ($_{\text{HP}}$CFS) stimulation. Firstly, the $_{\text{HP}}$CFS were collected during their proliferation, followed by centrifuging and 0.2-um membrane filtering to remove bacterial pellets and collect toxic factors. We discovered that the $_{\text{HP}}$CFS-containing both VacA toxin/LPS induced inflammatory responses in microglia and astrocytes, producing neurotoxic factors (NO, H_2O_2) with 3-folds and pro-inflammatory cytokines (Il-8 and IL-18) with 4-folds compared to unstimulated microglia and astrocytes. We next

observed that the $_{\mathrm{HP}}$CFS elevated neuroinflammation (3-folds, CD86, microglia; 4.5-folds, GFAP, astrocytes) compared to non-stimulated cells. We also found that the combination of $_{\mathrm{HP}}$CFS and soluble factors from stimulated astrocytes induced microglial autophagy (2-folds, LC3b), and migration (3-folds) compared to a single treatment. In addition, we explored that direct treatment with the $_{\mathrm{HP}}$CFS exacerbates phosphoric tau (p-Tau) accumulation with 4-folds greater than control, respectively. Finally, neuroinflammation and neurodegeneration were partially reduced by inhibiting the LRP1 and TLR4 on the cell membrane for VacA and LPS inhibition, respectively. This study envisioned that ***Helicobacter pylori*** can be a potential infectious risk factor for neuroinflammation and neurodegeneration through the gut-brain axis.
Keywords: ***Helicobacter pylori,*** cell-free supernatant, cytotoxicity, brain inflammation, neurodegeneration.

☆ Presentation 378.11 / Web Only Resistin and glucose stimulation promotes proinflammatory astro-microgliosis in human obesity hyperglycemia

1:00 PM - 5:00 PM

***H. CHO**;
Biophysics, Sungkwunkwan Univ., Suwon, Korea, Republic of

Abstract

Obesity is a major cause of hyperglycemia; the exact mechanism between obesity and degenerative brain diseases still needs further research. In obese people, this is important because there are high concentrations of adipokine resistin and glucose in the bloodstream, which may be the basis for astrocyte-derived neuroinflammation. Here, we applied the simultaneous stimulation of resistin (200 ng/mL) and high concentration of glucose (15 mM) to human astrocyte and microglia, respectively, to investigate the effects of proinflammatory astrogliosis and microgliosis. Resistin and glucose simultaneous stimulation increased expression of reactive astrocyte marker such as GFAP, iNOS, and NO expression by 2.13-fold, 2.67-fold, and 1.92-fold, respectively ($p < 0.001$), and inflammatory soluble factors such as IFN-γ, TNF-α, IL-1β, CXCL12, CCL1, and MIP-1 by 2.06-fold, 1.85-fold, 2.50-fold, 3.03-fold, 4.51-fold, and 4.26-fold, respectively ($p < 0.05$), compared to normal astrocyte. Resistin induces mild microglial activation with CD86 expression by 1.54-fold, compared to normal. However, resistance/glucose-stimulating astrocyte conditioned medium (ACM) recruited microglia by 2.61-fold ($p <0.001$) and increases CD86 expression by 2.13-fold ($p < 0.01$) and inflammatory soluble factors such as serpins, IL-16, IL-2, and TNF-a by 2.25-fold, 3.33-fold, 1.92-fold, and 4.77-fold, respectively ($p < 0.05$). Astro-microgliosis CM (AMCM) induced neuronal cytotoxicity by 2.18-fold ($p < 0.001$) confirmed with LDH assay. Our study suggests the obesity hyperglycemia could be a risk factor for neurodegeneration through inter-glial inflammation.
Acknowledgment: This work was supported by the National Research Foundation (nos. 2020R1A2C2010285, I21SS7606036) and the Ministry of Health & Welfare and Ministry of Science and ICT (no. HU22C0115) through the Korea Health Industry Development Institute (KHIDI) and Korea Dementia Research Center (KDRC) to H.C.
Keywords: obesity, adipokine resistin, glucose, proinflammation, astrogliosis, microgliosis

☆ Session 383 Thalamic and Cortical Processing in the Somatosensory System

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 383.01 / X11 Measuring tactile discrimination performance using closed loop whisker stimulation system

1:00 PM - 5:00 PM

***H. JEONG**[1], H. KWAK[1], C. PARK[1], E. CHEONG[1], E. LEE[2];
[1]biotechnology, yonsei university, Seoul, Korea, Republic of; [2]Anat., Col. Of Medicine, Yonsei Univ., Seoul, Korea, Republic of

Abstract

Mice use active whisking combined with free movement in order to discriminate objects. In sensory discrimination, the level of motivation strongly influences sensorimotor strategy and sensory acuity. The classical head fixed, go/no-go task enables the evaluation of sensory discrimination performances of mice. However, the task does not consider the trial-by-trial variations in motivation levels. To evaluate discriminative abilities while regarding both motivation and locomotion, we developed a closed loop tactile discrimination task for head fixed mice to analyze discrimination performances and neuronal encodings only in motivated trials— meaning the subjects are involved in discrimination trials only when they intently move forward (i.e. motivated to move). Using textures with various roughness levels, we found that the closed loop task showed discriminatory performance levels comparable to those of passive stimulation discrimination tasks. These results indicate that our discrimination task system is a more comprehensive method for measuring the level of discrimination that reflects motivation and locomotion.

☆ Session 386 Subcortical Visual Processing, Including Feedforward and Feedback Pathways

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 386.21 / CC13 Modeling feature-specific inhibition with convergent input from local interneurons in mouse visual thalamus

1:00 PM - 5:00 PM

***Y. MIAO**[1], A. GORIN[1], S. AHN[1], F. T. SOMMER[3], J. A. HIRSCH[2];
[1]Neurosci. Grad. Program, [2]Neurobio., USC, Los Angeles, CA; [3]Univ. California, Helen Wills Neurosci Inst., Helen Wills Neurosci. Inst., Berkeley, CA

Abstract

Before reaching the visual cortex, retinal information is processed by intrinsic circuits in the visual thalamus. Specifically, relay cells in the dorsal lateral geniculate nucleus (dLGN) receive powerful feedforward inhibition from local interneurons. In carnivore and primate, the arrangement of inhibition and excitation in the relay cell's receptive field has a stereotyped, center-surround structure with a push-pull profile (i.e., in subregions where a bright stimulus excites, a dark stimulus inhibits and vice versa); interneurons have receptive fields with similar structures. The situation in rodent differs. While 40-50% of murine relay cells have center-surround receptive fields, others have single On or Off regions, or overlapping On and Off responses with varied arrangements of inhibition. We thus asked how local interneurons might contribute to diverse forms of inhibition in murine relay cells and tested competing hypotheses about whether interneurons provide a one-size-fits-all form of inhibition (as is primarily the case in mouse cortex) or if the inhibition they provide is feature-specific. Our approach combined physiological and computational methods. First, we made multielectrode recordings from optogenetically labeled local interneurons in dLGN and mapped their receptive fields with sparse-noise stimuli (bright and dark squares of various sizes flashed separately at randomized positions in the stimulus grid). We found that interneurons had diverse receptive-fields, similar to relay cells, including center-surround, On, Off, and On-Off varieties. To quantify these receptive field structures and overcome the empirical constraint of limited data, we used a linear-nonlinear Poisson model (with two linear components in the case of On-Off cells). We then used these models to explore how input from different types of local interneurons might generate patterns of visually-evoked inhibitory currents recorded from relay cells. Towards this end, we separated net suppressive currents from the raw recordings from relay cells by subtracting EPSCs (sorted using a support vector machine and fitted by a linear-rise-exponential-decay function) and spikes, followed by rectification to remove any uncaptured excitation. Then we utilized metaheuristic methods to find an ensemble of interneuron models that best resembled the relay cell's suppressive field. This method gives a lower bound for ensemble performance. Our models provide proof of concept that diverse types of interneurons can provide feature-specific inhibition to relay cells.

☆ Presentation 386.22 / CC14 Interneurons in the lateral geniculate nucleus of the thalamus form dense and complex dendrodendritic networks

1:00 PM - 5:00 PM

***S. AHN**[1,2], R. MELTZER[2], A. KUMAR[2], A. GORIN[1,2], D. ALSTON[3], V. SURESH[2], M. A. FOX[4], J. A. HIRSCH[1,2], M. E. BICKFORD[3];
[1]Neurosci., [2]Biol. Sci., USC, Los Angeles, CA; [3]Anatom. Sci. & Neurobio., Univ. of Louisville, Louisville, KY; [4]Neurosci., Virginia Tech., Blacksburg, VA

Abstract

Comparative perspectives reveal strategies brains use to process information. We applied this approach to explore inhibitory circuits in the dorsal lateral geniculate nucleus. Previously, we showed that recordings from relay cells in carnivore are dominated by serial EPSCs while those from interneurons comprise trains of IPSCs, each preceded by a depolarizing notch (this profile suggested involvement of dendrodendritic synapses between interneurons). By contrast, recordings from both cell types in mouse feature trains of EPSCs, consistent with a dominance of retinal vs intrinsic inhibitory input. Thus, we were motivated to use serial block-face electron microscopy to study inhibitory networks across species. We first explored glomeruli--synaptic clusters in which dendrodendritic synapses are often embedded and participate in triads. Classical triads involve one retinal bouton that synapses on a dendritic appendage of a relay cell and another of an interneuron that contacts the relay cell in turn. In principle, the feedforward inhibition triads generate could explain the notch+IPSC recorded from carnivore, should triads with two interneurons exist. We observed that glomeruli in carnivore comprised a large retinal bouton encircled by dendritic appendages of interneurons and relay cells and a few other inputs. The pattern in mouse was almost the inverse; glomeruli included many retinal boutons, consistent with reports of far greater retinal convergence in mouse than carnivore. Triads involving two interneurons were present in both species but situated in different synaptic milieux. In carnivore, triads involved only one (rarely two) retinal bouton(s). In mouse, by contrast, interneuron appendages received input from more retinal boutons than the one driving the triad, potentially diluting triadic impact. Further, we found that one interneuron often synapsed on the shaft of another; this finding was more common in carnivore, where we also observed lengths of dendrite that lacked retinal input but synapsed onto **≤** ten other interneuron dendrites. Moreover, dendrodendritic inputs usually targeted thicker dendrites for carnivore vs mouse interneurons, suggesting a longer-range influence. Thus, our findings are consistent with the idea that the notch+IPSC profile arises from triadic connections between interneurons as these appear to have a stronger impact in carnivore than mouse, and/or with schemes in which one retinal afferent forms dispersed contacts with two interneurons connected via shafts. All told, interneurons in the geniculate are richly interconnected and their mutual influence is particularly powerful in highly visual animals.

☆ Session 388 Sensorimotor Transformations: Neural Circuits

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 388.02 / FF2 A visuomotor circuit for evasive flight turns in Drosophila

1:00 PM - 5:00 PM

***H. KIM**[1], A. J. KIM[2];
[1]Artificial Intelligence, [2]Artificial Intelligence;Electronic Engineering;Electrical and Biomed. Engin., Hanyang Univ., Seoul, Korea, Republic of

Abstract

Visual systems extract multiple features from a scene using parallel neural circuits. Ultimately, the separate neural signals must come together to coherently influence action. In this study, we delineate a neural circuit underlying evasive flight turns in flying *Drosophila*. Using an optogenetic activation technique, we first screened various types of visual projection neurons (VPNs) and descending neurons (DNs) by unilaterally activating their dendrites. We found five types of VPNs and one type of DN that caused flies to turn away from the activated side. To test whether these neurons are indeed required for the small object avoidance, we reversibly blocked synaptic transmission of these neurons using thermogenetics while presenting a translating or looming visual object pattern. We found that the amplitude of wing responses reduced significantly when LPLC2 and DNp06 neurons were silenced, for both visual patterns. From the hemibrain connectome, we found that LPLC2 and DNp06 form

strong synaptic connections, likely to mediate the small object avoidance. To further corroborate the role of these neurons in the visual avoidance behavior, we measured physiological responses of LPLC2 neurons with calcium imaging and DNp06 with electrophysiological means. We found that both neurons respond to both visual patterns (i.e., translating or looming objects). How does the LPLC2-DNp06 pathway attain visual selectivity to a looming disc as well as to laterally moving spots? We noted that LPLC2 neurons have two dendritic ramifications, one in the lobula and the other in the lobula plate. When we blocked the majority of visual inputs to the lobula plate by silencing elementary motion detectors (T4/T5), calcium responses of LPLC2 neurons decreased selectively for a looming visual object and fast-moving spot. Furthermore, direction-selective visual responses to a laterally moving spot almost completely disappeared when T4/T5 neurons were silenced. Combining these results, we concluded that LPLC2 neurons' visual properties emerge by integrating multiple visual features - speed, size, direction, and shape - that are represented in two separate, early visual structures, and DNp06 neurons inherit most of these visual properties. This study highlights a clear example of how distinct visual signals converge on a single class of premotor neurons to drive action, revealing a concise pathway for evasive flight maneuvers in ***Drosophila.***

☆ Presentation 388.13 / FF11 Projection-specific roles of the anterior cingulate cortex in sensory-to-motor transformation

1:00 PM - 5:00 PM

***H.-Y. PARK**, D.-H. MA, S.-H. LEE;
Biol. Sci., KAIST, Daejeon, Korea, Republic of

Abstract

The anterior cingulate cortex (ACC) is implicated in transforming sensory information into motor actions in mice performing perceptual tasks. However, it is still poorly understood how the ACC neurons projecting to different brain areas contribute to the sensory-to-motor transformation in animals performing goal-directed actions. Here, we examined the anatomical features of the V1-projecting ACC (ACC→V1) and the DMS-projecting ACC (ACC→DMS) neurons by dual-retrograde tracing and found that these two populations of neurons are segregated in the ACC at different layers. To figure out their functions, we labeled the ACC→V1 and the ACC→DMS neurons with GCaMP6 by injecting retrograde AAV-Cre in the V1 or the DMS of Ai148 mice. We then trained the mice to perform the visual detection task and measured task-related activities of the labeled neurons before and after the learning. We found that the ratio of the sensory(visual)-responsive neurons increased in both populations after learning. Interestingly, the ACC→DMS neurons showed a higher sensory response in hit trials compared to miss trials. In contrast, the ACC→V1 neurons showed consistent visual responses to the visual stimuli regardless of learning or licking after the stimuli. In both populations of neurons, the ratio of motor(lick)-responsive neurons decreased, but their activity increased after learning. To clarify how the task-relevant activities of the ACC neurons are modulated across the learning, we measured the release of dopamine (DA) and acetylcholine (ACh), well-known neuromodulators in the cortex, using the fiber photometry and imaging GRAB sensors in the ACC. The DA release was higher in hit trials than in miss trials, and the ACh release significantly increased during licking. Together, these results demonstrate that the ACC→V1 and the ACC→DMS neurons show distinct modulation properties during the task, which might be caused by the neuromodulators, such as the DA and ACh, released in the ACC.

☆ Session 389 Neurophysiology: Decoding and Neural Processing I

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 389.05 / GG6 Enhancing EEG-based hand movement trajectory decoding by using an ECoG-informed EEG feature extraction strategy

1:00 PM - 5:00 PM

***S. JANG**[1], J. JEONG[2];
[1]Korea Advanced Inst. in Sci. and Technol., Daejeon, Korea, Republic of; [2]KAIST, Daejeon, Korea, Republic of

Abstract

Hand movement trajectory decoding using human neural signals is one of the key issues in brain-machine interface (BMI). The performance of BMIs largely depends on the choice of neural recording techniques, which include invasive methods such as the electrocorticogram (ECoG), and non-invasive methods such as the electroencephalogram (EEG). The relatively poor spatial resolution of EEG is often pointed out as the culprit of lower decoding accuracies in trajectory decoding compared to when using ECoG. Considering the similar representation of temporal neural dynamics in EEG and ECoG however, we sought to understand the degree of spatiotemporal congruence between EEG and ECoG feature distribution obtained during hand movement. We hypothesized that the lead field model of the head tissue layer behaves as a linear operator to map a set of local ECoG activities to a composite signal that manifests in the form of EEG. To this end, we conducted an EEG experiment which was designed identical to a preceding ECoG experiment that instructed subjects to perform both real and imagined hand movement trajectories in three-dimensional space. We found that spatial distribution of movement-related neural features was different between the EEG and ECoG. More than half (≈53.3%) of the significant features for real movement originated from the sensorimotor cortex in ECoG, whereas for the EEG the proportion was lower (≈44%). A substantial proportion of movement-related neural features also originated from the superior temporal gyrus (≈32%) for the EEG, whereas a lower involvement of the same area was observed in ECoG (≈13.3%). Average amount of movement-related information was also significantly different between the two signal types (EEG: 0.1794±0.0011, ECoG: 0.1877±0.0014; student's t-test $p<1e-5$). In addition, these features were used for trajectory decoding, which resulted in correlation coefficients of ≈0.3855 and ≈0.4996 for the EEG- and ECoG-based decoding respectively. Finally, we selected features that were highly preserved across the two techniques for developing an EEG-based BMI for robotic arm end-point velocity control. Quadrant hit success rates ranged from 30 to 40%, which was significantly above both the chance level (≈25%) and when feature selection was not informed by cross-comparing EEG features to those of ECoG. These findings suggest that non-invasive trajectory decoding can be enhanced by extending feature extraction strategy to select for neural features that are consistent across recording techniques rather than just extracting only those that are specific to non-invasive recording.

☆ Session 392 Motor Unit Recordings, Kinematics, and EMG

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 392.23 / LL15 New tools to interpret the role of spinal interneurons in motor modularity

1:00 PM - 5:00 PM

***T. S. SMITH**[1], T. KIM[1], T. D. SANGER[2], S. F. GISZTER[1];
[1]Neurobio. & Anat., Drexel Univ. Col. of Med., Philadelphia, PA; [2]Electrical Engin., CHOC, Redondo Beach, CA

Abstract

Motor behaviors operate through the spinal cord to controls the musculature quickly and efficiently. In the motor modularity model of movement, dynamic ‘building blocks’ are combined to construct most routine motor commands. We define a motor ‘module’ as a neural element evoking stereotyped motor activity, extracted from kinetic or biological features (e.g. muscle EMG). In the spinal frog, free of the influence of higher centers, spinal modularity has been studied in various contexts. The protective inter-hindlimb wiping reflex is an inducible behavior composed of three motor modules. Alternatively, focal stimulation to the intermediate spinal gray, such as via intraspinal microstimulation (ISMS), directly evokes multi-muscle motor behavior with dual-site stimulation usually summing independently (i.e. behaving modularly). Because such ISMS recruits motoneurons in a naturalistic recruitment order, its use has been proposed for neuroprostheses. During wiping, the spinal cord must control when modules are recruited and how modules coordinate the motor pools to evoke muscle synergies, while also retaining flexiblity to permit corrections to external perturbations. Previous research has suggested that such corrections are gated by spinal state. Integration of ISMS-evoked responses into spinal motor plans remains an area of active research. If ISMS responses are independent throughout wipe, ISMS-based manipulations may be implemented as a simple linear sum of existing motor components, while phase dependence may reveal intrinsic motor constraints and clarify granularity of motor recruitment. Beyond evaluating the linearity of the evoked force and muscles responses, one method of elucidating this relationship is to investigate patterns of motoneuron recruitment within and across motor pools. We can record activity from both single motor units and interneurons with our fine-wire braided electrodes, and have found that single motor units may be strongly tuned to activity of a synergist muscle, suggesting fixed patterns of muscle coactivations. Because the role of individual spiking units in the motor pattern may be small and spinal-state dependent, we utilize the stochastic dynamic operator (SDO) framework to evaluate relationships between spike times and continuous signals (e.g. EMG). We demonstrate here that the SDO improves upon the classical spike-triggered average for predicting post-spike signal behavior. As we continue to explore interpret this data, we expect to further elucidate the neural underpinnings of spinal modularity. Furthermore, we anticipate our innovations to be broadly applicable to other realms of neuroscience.

☆ Presentation 392.18 / LL10 Enhancing Force Control and Motor Unit Behavior with Contralateral Tendon Vibration in Parkinson’s Disease

1:00 PM - 5:00 PM

***C. KIM**, K. A. LAROCQUE, J. M. JAKOBI;
Univ. of British Columbia, Kelowna, BC, Canada

Abstract

Unilateral functional electrical stimulation (FES) improves contralateral motor performance in persons with Parkinson’s Disease (PD)(Popa et al., 2012, 2013). Force steadiness is impaired in persons with PD, and there is evidence to suggest that the fluctuation in force output arises from alterations in motor unit activity. Tendon vibration is an effective way of enhancing motor performance by altering Ia afferent feedback (DeForest et al., 2020). In this study, we aim to determine the effects of acute contralateral tendon vibration of the distal biceps brachii tendon on force steadiness and motor unit activity in persons with PD.Six males and four females with mild to moderate PD severity performed a ramp, hold and deramp isometric elbow flexion at 5% of maximum voluntary contraction (MVC) with the more-affected arm while vibration (100Hz, ± 3.5-4.0mm) was applied to the distal biceps brachii tendon on the contralateral, less-affected arm. Using intramuscular fine wire electrodes, 35 MUs in the short and long head of the biceps brachii on the more-affected arm were recorded and tracked across three vibration conditions (pre-vibration, vibration, and post-vibration). Motor unit recruitment threshold, derecruitment threshold, discharge rates (MUDR), discharge rate variability (MUDRV), and elbow flexion force steadiness were compared across the three vibration conditions. CV of force and MUDRV decreased in the post-vibration compared with pre-vibration and vibration conditions, and MUDR did not differ between these conditions. MU recruitment thresholds were higher than derecruitment thresholds regardless of vibration; however, the total number of MUs that were recorded during the de-ramp were fewer in the post-vibration condition. These results suggest that contralateral tendon vibration could be an important neurophysiological path in improving force control in PD; characterized by a decrease in MUDRV and enhancement in force steadiness.

☆ Presentation 392.05 / KK16 Braided Multi-Electrode Intramuscular EMG probes for Single Motor Unit Recordings

1:00 PM - 5:00 PM

***T. KIM**[1], T. S. SMITH[1], A. BORISYUK[1], B. BINDER-MARKEY[2], S. F. GISZTER[1];
[1]Neurobio. & Anat., Drexel Univ. Col. of Med., Philadelphia, PA; [2]Physical Therapy & Rehabil., Drexel Univ. Col. of Nursing & Hlth. Professions, Philadelphia, PA

Abstract

The braided multi-electrode probe (BMEP) is an ultrafine microwire bundle in a tubular micro braid form, which was initially designed as a novel neural probe to chronically record neural signals for neural interfaces in brain, spinal cord, and peripheral nerves. The main advantages of BMEPs are that the BMEP provides not only high mechanical flexibility to follow tissue motions and deformation, but also 6 ~ 24 channels for recording/stimulation within a 200um or smaller diameter footprint. Long (~10cm) probes are possible, and, combined with flexibility and individual 9.6um microwires, BMEPs are easily applied to Electromyography (EMG) and especially single unit applications. The volume of muscle fibers is bigger than neural axons and the amplitude of EMG signals is thus relatively bigger than neural signals. We have explored several ways to use BMEPs in single unit and aggregate EMG applications. Laser ablation techniques allow us to expose a controlled impedance recording sites on the body of microwires, not only the tips of microwires, by ablating plastic insulation material with a precision laser, adjust the area size and shape of recording sites on braided microwires and systematically allocate the recording sites on various positions of microwires. Using laser ablation, we made tested recording sites of ~150um length on each of the 9.6um Nichrome braid wires, removing the 3um thickness of polyimide insulation, and successfully recorded good SNR single motor units with the BMEPs. The BMEPs designed for EMG are currently built in two different primary forms: braided microwires on a needle for acute recording and braided microwires designed like a suture thread for chronic recording in frogs and rats. We demonstrate features and relations between single motor units recorded from BMEPs and aggregated EMG signals recorded from classic stainless-steel wire electrodes. We discuss further new designs and applications of the BMEP EMG probes and coupling with neural recordings.

☆ Session 395 Integrative Physiology and Behavior: Sleep Systems II

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 395.11 / QQ7 Neuronal and homeostatic regulation of sleep by the preoptic area and tuberomammillary nucleus

1:00 PM - 5:00 PM

***J. MAURER**, S. CHUNG;
Neurosci., Univ. of Pennsylvania, Philadelphia, PA

Abstract

While sleep is evolutionarily conserved across all animals studied, the precise function of sleep remains unknown. It is vital that organisms receive an adequate amount of sleep, as sleep deprivation has profound physiological effects. The preoptic area (POA) of the hypothalamus contains sleep-active GABAergic neurons and activation of their axons innervating the wake-active tuberomammillary nucleus histamine (TMN^{HIS}) neurons are critical for sleep regulation. However, it is not yet understood exactly how the activity of POA GABAergic axonal projections to the TMN (POA^{GABA}→TMN) changes in response to increased sleep need and whether they are necessary to integrate homeostatic pressure. Using fiber photometry in mice, we have found that TMN^{HIS} neurons are most active at wake onset, but as mice transition from wake to NREM sleep the activity gradually decreases and continues to decrease until they reach their lowest activity during REM sleep. Conversely, fiber photometry also revealed that POA^{GABA}→TMN neurons are sleep active, with most mice displaying the highest population activity during REM sleep. Following sleep deprivation, the sleep-active POA^{GABA}→TMN neurons display elevated activity during sleep rebound across all sleep states, suggesting an important role of these neurons in regulating sleep homeostasis. Using optogenetics, we found that inhibition of TMN^{HIS} neurons during sleep rebound produces a deeper quality of sleep, suggesting the inhibition of these neurons is a critical component of regulating sleep in response to sleep need. Future experiments aim to address whether inhibition of POA^{GABA}→TMN neurons is necessary for sleep rebound and how individual POA^{GABA}→TMN neurons respond to sleep loss. Together, these studies will identify novel circuit mechanisms by which the POA and TMN coordinate their activity during sleep/wake and periods of homeostatic sleep pressure.

☆ Presentation 395.18 / QQ11 Neural population dynamics in midbrain and pons during sleep

1:00 PM - 5:00 PM

***D. LOZANO**, J. STUCYNSKI, F. WEBER;
Univ. of Pennsylvania, Philadelphia, PA

Abstract

Rapid eye movement (REM) sleep is characterized by a desynchronized electroencephalogram (EEG), muscle atonia, and vivid dreaming. The core circuits generating REM sleep are distributed throughout the brainstem and are composed of REM sleep-promoting (REM-on) and REM sleep-suppressing (REM-off) neurons. While much progress has been made in identifying specific neuronal populations that promote or suppress REM sleep, the neural dynamics that arise from the interactions between these REM regulatory populations and the dynamical mechanisms which gate transitions into REM sleep are largely unknown. We have previously demonstrated using optogenetic manipulations in mice that GABAergic neurons in the dorsomedial medulla (dmM) promote the induction of REM sleep via their projections to the dorsal and median raphe nuclei. To identify the neural dynamics within these downstream areas underlying NREM-to-REM sleep transitions, we employed Neuropixels probes to record the population activity in the dorsal and medial raphe, as well as neighboring midbrain and pontine brain areas, during spontaneous sleep in mice. We applied principal component analysis (PCA) to describe the population dynamics across the recorded brain regions. We found that the population activity during NREM and REM sleep is captured within low-dimensional subspaces. Furthermore we found that wakefulness, NREM, and REM sleep correspond to distinct areas along the trajectories traversed by the population activity within the PCA space. The REM sleep-promoting effect of dmM stimulation largely resulted from an activation of REM-on and inactivation of REM-off neurons, effectively forcing the population activity towards REM sleep. Overall, these results demonstrate that the population activity during sleep in midbrain and pons areas are low-dimensional and provide a geometric description of how inputs from the REM-promoting dmM neurons affect the population dynamics within these areas to induce NREM-to-REM sleep transitions.

☆ Session 399 Fear, Anxiety, and Pain

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 399.11 / UU7 Subspace alignment as a computational mechanism of the integration between cue and stimulus intensity in pain perception

1:00 PM - 5:00 PM

***J.-W. KIM**[1,2,3], S. GIM[1,2], S. M. YOO[1,2], C.-W. WOO[1,2,3];
[1]Ctr. for Neurosci. Imaging Research, Inst. for Basic Sci., Suwon, Korea, Republic of; [2]Dept. of Biomed. Engin., [3]Dept. of Intelligent Precision Healthcare Convergence, Sungkyunkwan Univ., Suwon, Korea, Republic of

Abstract

Pain is a multidimensional experience that comprises external sensory inputs and internal processes such as prior expectations. Previous studies have examined which brain regions engage in or mediate the different components of pain. However, these brain mapping studies cannot provide the computational mechanisms of how the brain integrates information from multiple internal and external sources. Here, we adopted the dynamical systems perspective in the analysis of human functional Magnetic Resonance Imaging (fMRI) data to understand how different brain regions integrate information of pain-predictive cues and nociceptive inputs. We hypothesized an alignment of the subspaces encoding cue and stimulus effects as the integration of the cue and stimulus information and the extent to which the two subspaces are aligned changes along the cortical hierarchy. We implemented a cue-induced expectation pain experiment ($N = 56$), in which we delivered pain predictive cues and noxious stimuli to participants. When we analyzed an alignment index, a ratio of the degree to which cue and stimulus are explained by both subspaces, respectively, we found that the limbic network shows the most, and the visual network shows the least alignment. Note that each network is at the top and bottom of the cortical hierarchy, respectively. Then, we measured the amount of cue and stimulus information in each subspace using the decodability and examined the population dynamics for different experimental conditions in the visual, limbic, and somatomotor networks. We hypothesized that the limbic network would contain both cue and stimuli information in population dynamics at the low-dimensional manifold. In the visual network, the cue information was dominant which was encoded with a form of a rotational dynamics occupying distinct location of the subspace. In the somatomotor network, the stimulus intensity information was dominant. Interestingly, the intensity of the stimulus generated dynamics with different curvature - i.e., the higher stimulus intensity exhibits higher curvature. In the limbic network, population dynamics at cue and stimuli subspace encoded each information in a way similar to that of the visual and somatomotor networks, respectively. This result implies the integration of cue and stimulus information is most prominent at the top of the cortical hierarchy, which was also consistent with the degree of the alignment of subspaces. These findings provide the computation-level understanding of how cue and stimulus information is integrated, going beyond the “box-and-arrow” explanation of cognitive and pain processes.

☆ Presentation 399.26 / VV1 Know pain, know gain: Shared brain representations of sensory pleasure and pain

1:00 PM - 5:00 PM

***S. LEE**[1,3], J.-J. LEE[1,3], J. HAN[4], M. CHOI[5,3], C.-W. WOO[1,2,3];
[1]Dept. of Biomed. Engin., [2]Dept. of Intelligent Precision Healthcare Convergence, Sungkyunkwan Univ., Suwon-si, Korea, Republic of; [3]Ctr. for Neurosci. Imaging Research, Inst. for Basic Sci. (IBS), Suwon-si, Korea, Republic of; [4]Korea Brain Res. Inst., Daegu, Korea, Republic of; [5]Dept. of Biol. Sci., Seoul Natl. Univ., Seoul, Korea, Republic of

Abstract

Pain and pleasure are often considered to be the opposite ends of a continuum. They are known to influence each other even though they engage distinct peripheral and spinal-level processes. However, it remains unclear how these two opposite-valenced affective experiences are connected at brain systems level. Here, we aimed to identify the brain regions important for both pain and pleasure experiences induced by capsaicin and chocolate. First, we selected 48 ***a priori*** regions-of-interest (ROIs) known to be responsive to either pain or pleasure based on the previous studies. We conducted an fMRI experiment (Study 1: $n = 58$, 27 females, mean of age = 22.81, SD of age = 2.83) and trained a multivariate predictive model for each ROI to identify brain regions that showed significant predictions both for pain and pleasure. We found that the ventromedial and lateral prefrontal cortices, the orbitofrontal cortex, the anterior insula, and the amygdala encoded both pain and pleasure information among the 48 ROIs. Then, we hypothesized two-dimensional information that can be shared across pain and pleasure—affective intensity and affective valence and developed multivariate predictive models of the two dimensions. The predictive models of affective intensity and valence showed significant prediction performances across two datasets (Study 1 training dataset with leave-one-participant-out cross-validation, intensity prediction: $r = 0.25$, P << 2.22×10^{-16} and valence prediction: $r = 0.11$, $P = 0.0014$; Study 2 independent test dataset [$n = 62$], intensity prediction: $r = 0.17$, $P = 2.47 \times 10^{-10}$ and valence prediction: $r = 0.14$, $P = 3.55 \times 10^{-4}$). When we examined the patterns of predictive weights, we found that the predictive models of affective valence versus intensity involved distinct sub-populations of voxels within the common brain regions. In addition, these sub-populations showed distinct patterns of large-scale network connectivity—the valence model was largely associated with the limbic and default mode networks, whereas the intensity model was largely associated with the ventral attention network. In sum, this study provides new insights into the shared brain representations of pain and pleasure and their dimensional components, promoting the systems-level understanding of human affective experiences.

☆ Session 401 Auditory, Visual, Proprioceptive Perception

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 401.05 / VV31 Distinctive cortical networks underlying oddball and omission responses during sequential auditory perception

1:00 PM - 5:00 PM

***J. SHIN**[1], Y.-H. WU[2], L. FAES[3], Z. YU[4], M. A. CLOOS[5], S. DEVORE[1], W. K. DOYLE[6], P. DUGAN[1], D. FRIEDMAN[1], A. SEEDAT[1], O. DEVINSKY[1], E. S. YACOUB[7], F. DE MARTINO[3], L. MELLONI[8];
[1]Neurol. Dept., [2]Neurosci. Inst., New York Univ. Sch. of Med., New York, NY; [3]Dept. of Cognitive Neurosci., Maastricht Univ., Maastricht, Netherlands; [4]Dept. of Med., Univ. of Hawai'i, Honolulu, HI; [5]Ctr. for Advanced Imaging, Univ. of Queensland, Brisbane, Australia; [6]Dept. of Neurosurg., NYU, New York, NY; [7]Dept. of Radiology, Univ. of Minnesota, Minneapolis, MN; [8]Neural Circuits, Consciousness and Cognition Res. Group, Max Planck Inst. for Empirical Aesthetics, Frankfurt am Main, Germany

Abstract

There is substantial evidence that auditory processing is influenced by the prediction of upcoming sounds. Yet, there remain long-standing questions regarding the local circuit and network-level mechanisms that implement predictive processing including which specific cortical areas and layers reflect the active calculation of prediction errors vs automatic stimulus specific adaptation. In this study, we combine non-invasive high-resolution laminar fMRI at 7 Tesla with intracranial electrocorticography (ECoG) to investigate the laminar profile of responses to predicted and unpredicted auditory stimuli, as well as the circuit level responses. We adapted an auditory oddball paradigm where syllables were repeated four times in a sequence. In 25% of trials, we replaced the last repetition with either a deviant syllable (12.5%) or silence (12.5%) in order to examine oddball and omission responses, respectively. This paradigm enabled us to simultaneously investigate auditory predictions errors (i.e., unexpected syllables) as well as unexpected omissions. Using ECoG in treatment-resistant epilepsy patients, we found that electrodes in the superior temporal gyrus (STG) and frontal areas show distinctive oddball and omission responses. Consistent with previous reports, deviant syllables triggered stronger responses in these electrodes. Omission trials also induced responses; however, the omission responses did not always correlate with the oddball responses at the single electrode level. Importantly, neither prediction errors nor omission responses were caused by motor preparation as we also observed these responses in a no-report paradigm under passive listening conditions. We also performed laminar functional imaging in the STG using 7 Tesla MRI to elucidate the laminar origin of oddball and omission responses. Our results suggest that different types of auditory prediction signals are generated by distinct cortical networks.

☆ Session 405 Prefrontal Cortex Networks and Behavior 1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 405.06 / XX8 Role of VIP neurons and dopamine D1 receptors in working memory in the prefrontal cortex 1:00 PM - 5:00 PM

***J. BAE**[1], J. YI[2,3], S. CHOE[2], Y. YOON[1], M. JUNG[1];
[1]Dept. of Biol. Sci., Korea Advanced Inst. of Sci. and Technol. (KAIST), Inst. for Basic Sci. (IBS), Yuseong-gu, Daejeon, Korea, Republic of; [2]Ctr. for Synaptic Brain Dysfunctions (CSBD), Inst. for Basic Sci. (IBS), Yuseong-gu, Daejeon, Korea, Republic of; [3]These authors contributed equally, ., Korea, Republic of

Abstract

The prefrontal cortex (PFC) plays a critical role in working memory, and dopamine is known to modulate PFC neural processes including those supporting working memory. Of various types of neurons in the PFC, vasoactive intestinal polypeptide (VIP)-expressing neurons are thought to exert powerful influences on PFC circuit operations by modulating other inhibitory neuronal activity. Also, as the only inhibitory neurons expressing dopamine D1 receptors, they may also play a key role in mediating dopaminergic influences on the PFC. We investigated these issues in the medial PFC in mice performing a delayed match-to-sample task. The mice were trained to perform the task as the duration of delay was increased gradually from 0.5 to 4 s. Chemogenetic inactivation (n = 11) of VIP neurons or selective knockdown of VIP neuronal D1 receptors (KD = 7, CTR = 5) impaired behavioral performance when delay duration was increased to 3-4 s, but not before this phase. In well-trained mice, VIP neurons conveyed significant working-memory signals and their inactivation impaired trial-by-trial behavioral performance. In contrast, selective knockdown of VIP neuronal D1 receptors did not impair working-memory performance. These results indicate that PFC VIP neurons are critically involved in working memory, and that dopamine modulation of VIP neurons via D1 receptors is critical for learning to use, but not the maintenance of, working memory for guiding behavior.

☆ Presentation 405.15 / XX15 Task-specific neural firing patterns in the medial prefrontal cortex in a hippocampal-dependent scene-based working memory task. 1:00 PM - 5:00 PM

***E.-H. PARK**, I. LEE;
Dept. of Brain & Cognitive Sci., Seoul Natl. Univ., Seoul, Korea, Republic of

Abstract

It has been known that the medial prefrontal cortex (mPFC) plays a critical role in working memory (WM) to maintain task-related information during goal-directed behavior. Prior studies suggest that its function is not only to hold the information but also to temporally organize the relevant pieces of information. Taking advantage of the presence of the unilateral monosynaptic projections from the intermedial hippocampus (iHPC) to the mPFC, we tested the functional significance of the visual contextual information presumably transmitted from the iHPC to the mPFC in a scene-dependent memory task in which the temporal organization of information according to task phase is critical. We inactivated the iHPC with muscimol (MUS) and recorded single-unit spiking activities (n = 88 in control sessions; n = 73 in MUS sessions) in the mPFC by using the hyperdrive equipped with 24 tetrodes in rats (n=5). A body-fixed rat was trained in a VR environment to run on a cylindrical treadmill to sample one of four visual scenes (Forest, City, Playground, Room) during a sample phase, and, after a 3-s delay phase, the rat must lick either the left or right licking port in a choice phase to obtain honey water as reward (30μL) in association with the sampled visual scene. MUS injections into the iHPC resulted in a severe performance deficit ($t_{(9)}=5.67$, $p<0.001$). Our preliminary analysis suggests that the neural firing correlates of task variables in the mPFC appear to be associated with specific task phases (sample, delay, test) and changed their firing correlates across multiple task phases in a dynamic fashion seemingly to facilitate information processing in each task phase. The dynamic shifts of task phase-specific firing patterns were more prominent in the infralimbic cortex (IL) than in the prelimbic cortex within the mPFC ($Z=2.22$, $p<0.05$). MUS injections into the iHPC decreased the proportion of these task-specific cells in the mPFC ($X^2=26.96$, $p<0.0001$). In addition, when MUS was injected into the iHPC, the mPFC population did not exhibit such dynamic firing patterns across multiple task phases to match the the temporal structure of the WM task. Overall, our findings suggest that the visual contextual information from the iHPC to the IL is critical for the mPFC network to temporally organize task-relevant information according to WM task demands in a goal-directed fashion.

☆ Session 406 Learning and Memory: Hippocampal: Cortical Interactions I 1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 406.23 / XX44 Coordination of sleep slow oscillations and hippocampal sharp-wave ripples during manifold exploration in motor cortex

1:00 PM - 5:00 PM

***J. KIM**[1,3], A. JOSHI[2], L. FRANK[2], K. GANGULY[1,3];
[1]Neurol. department, [2]HHMI and Departments of Physiol. and Psychiatry, Univ. of California San Francisco, San Francisco, CA; [3]Neurol. and Rehabil. Service, San Francisco Veterans Affairs Med. Ctr., San Francisco, CA

Abstract

Systems consolidation - a process for long-term memory stabilization - has long been hypothesized to occur in two-stages. Whereas newly acquired memories require the hippocampus, they become integrated into cortical networks over time, making them increasingly independent of the hippocampus. How hippocampal-cortical dialogue precisely evolves during this process and what informs the transitions between stages are not clear. Moreover, how cortical representations precisely evolve during systems consolidation is unknown. Here, we use a skill learning task to monitor the temporal dynamics of cross-area coupling during NREM sleep along with changes in primary motor cortex (M1) representational stability during learning. Our results indicate that the precise temporal dynamics of cross-area coupling between hippocampus, prefrontal cortex (PFC) and M1 can demarcate two stages of cortical processing. We specifically find that each animal demonstrates a sharp increase in PFC and M1 sleep slow oscillation (SO) coupling that is linked to stabilization of task performance. This sharp increase then predicts a drop in hippocampal sharp-wave ripple (SWR)-M1 SO coupling - suggesting feedback to inform hippocampal disengagement and transition to a second stage. Notably, the first stage shows significant increases in hippocampal SWR-M1 SO coupling in the post-training sleep and is closely associated with rapid learning and variability of the M1 low-dimensional manifold. Strikingly, even after consolidation, inducing new manifold exploration by changing task parameters reengages hippocampal-M1 coupling. We thus find evidence for dynamic hippocampal-cortical dialogue that is associated with exploration of cortical representations during both motor learning and adaptation.

☆ Session 410 Novel Genetic Tools for Understanding Brain Function

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 410.08 / YY35 Imaging presynaptic release of neuropeptides in vivo

1:00 PM - 5:00 PM

***D. KIM**[1], S. HAN[2];
[1]PBL-H, The Salk Inst. for Biol. Studies, La Jolla, CA; [2]PBL-H, Salk Inst. For Biol. Studies, La Jolla, CA

Abstract

Imaging presynaptic release of neuropeptides *in vivo* Neuropeptides are one of core molecules for neuronal communication and they are involved in critical brain functions. However, attempts to study neuropeptides in circuit-level have been restricted, possibly due to lack of methods for detecting its release at presynaptic terminals in behaving animals. Here we genetically engineered the sensor that detects neuropeptide release using large dense core vesicle (LDCV) targeting protein and a superecliptic pHluorin as a fluorescence reporter. In the assays with cultured cell line and acute brain slices, our results show that the sensor is pH- and calcium-dependent and displays increased activity in response to varying intensities of electrical stimulation. We also tested the efficacy of the LDCV release sensor in awake behaving mice using fiber photometry technique in mice expressing it in the neuropeptidergic neurons. Our preliminary results show that the sensor reliably detect presynaptic release of neuropeptides in awake behaving mice in response to multiple sensory and emotional stimuli. We propose that the LDCV sensor as a readout of neuropeptide release is a useful tool for real-time measurement of presynaptic neuropeptide release and thus for understanding neuropeptidergic signaling.

☆ Session 411 Light and Electron Microscopy Techniques

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 411.10 / YY61 Investigation of oral-brain neuro-axis by development of the optimized tissue clearing protocol in jaw bones

1:00 PM - 5:00 PM

***Y. YUN**[1], S. KANG[2], J.-Y. PARK[2], H. CHOI[1];
[1]Dept. of Anat. and Cell Biol., Seoul Natl. Univ. Col. of Med., Seoul, Korea, Republic of; [2]Dept. of Oral and Maxillofacial Surgery, Seoul Natl. Univ. Sch. of Dent., Seoul, Korea, Republic of

Abstract

With the growing demand for dental work such as tooth extraction and implant surgery, trigeminal nerve injuries are increasingly common. Although conventional neurohistological analysis was attempted to provide microscopic images of the nerves in dental pulp, three-dimensional (3D) visualization of the whole maxilla and mandible in an intact tooth has remained a technically challenging task. In particular, the neural structure of the peripheral nerve branch that passes through the alveolar bone where the teeth are planted is not known. In this work, we established a simple and rapid method that combines decalcification, tissue clearing, immunohistochemistry, confocal microscopy, light-sheet fluorescence microscopy, and quantitative analysis of full-thickness bowel for 3D imaging at high resolutions of the maxilla and mandible in mice. Three-dimensional image reconstruction and statistical methods were used to describe the neuronal network and provide novel insights into neuronal morphology. The results in the present study confirmed the fact that the time required for the complete decalcification process was at least 40% EDTA for 2 weeks. The overall structure details, as well as staining characteristics, were optimal after electrophoretic tissue clearing mode for 16 hours and then further immersed in SDS buffer at 60℃ for 14 hours. We achieved 3D macroscale-level visualization of the mouse mandible and maxilla, and visualized peripheral nerve branch that passes through the alveolar bone in the whole dental pulp. Full-thickness mandible images, viewed with a 10x objective lens, were as large as 8 x 3 x 1 mm^3. Quantitative data for maxilla and mandible showed relatively different aspects. In conclusion, the established methods could provide a comprehensive 3D visualization of nerve fibers of soft tissues surrounded by hard tissues. This method could be used to enable diverse research methods on neural-immune interaction by providing 3D visualization of various immune cells in intact mouse maxilla and mandible.

TUESDAY, NOV. 15, 2022

☆ Session 430 Neurobiological Basis of Timing

8:00 AM - 11:30 AM

SDCC 33

☆ Presentation 430.03 The neural basis of an internally generated, temporally organized action sequence

8:30 AM - 8:45 AM

B. WU[1], M. ZHOU[1], H. JEONG[1], J. FLOEDER[1], V. LEE[2], A. TAYLOR[1], D. BURKE[1], A. MORSI[2], A. SANDERS[1], *V. NAMBOODIRI[1];
[1]Univ. of California San Francisco, San Francisco, CA; [2]Univ. of California Berkeley, Berkeley, CA

Abstract

Actions span a continuum along multiple dimensions. They may be either 1) entirely triggered by external sensory stimuli or internally generated; 2) performed at random moments or occur in sequences with exquisite temporal organization; and 3) frequently or sparsely reinforced. Actions in the real world are often internally generated, occur in sequences with a temporal structure and are sparsely reinforced (e.g., playing music, getting dressed, or playing sports). Though the neural basis of action generation has been a subject of key interest in neuroscience over many decades, internally generated, temporally organized action sequences that are only sparsely reinforced have not been studied in the laboratory. Here, we develop a new behavioral task in which head-fixed mice learn to develop an action strategy in which they lick metronomically at regular intervals (i.e., temporally organized) in the absence of any external sensory cue (i.e., internally generated) with each timed action having a <2% probability of reinforcement (i.e., sparsely reinforced). Mice (n=30, both sexes) show evidence of clear behavioral learning in this task within ~3 days and reliably produce periodic metronomic licks (with a period ranging from 1.5-3 s between individuals) for an entire behavioral session (except for consummatory bouts) lasting ~40 minutes. Overall, mice produce >1,000 timed licks within a single session, even though they obtain only ~20 sucrose reward drops (5 uL each) over this period. Hence, this task is highly valuable to study the basis of internally generated, temporally organized action sequences. Using this task, we studied the encoding of such actions by mesolimbic dopamine release in the nucleus accumbens. Surprisingly, we found that even though the metronomic licking is necessary for obtaining rewards (i.e., it is an operant action), mesolimbic dopamine dipped around these actions (n=3 animals, n=5 sessions each after stable behavior, $p<0.05$ in each animal). Interestingly, the magnitude of the dip in dopamine levels predicted the moment of the next lick, i.e., the next internally-generated timed action (mean $r = -0.20$, $p = 6.6E-6$, $t(14)=-7.0$; n=15 sessions from n=3 mice). Such a fast timescale correlation between dopamine and ongoing movement is rarely observed and hence, we hypothesize that the study of internally generated temporally organized action sequences may be critical to study the role of dopamine in movement. Overall, we developed a highly reliable task in mice to study internally generated, temporally organized actions with sparse reinforcement, and show that mesolimbic dopamine level predicts the upcoming movement time.

☆ Session 437 Animal Models of Autism: Behavior

8:00 AM - 12:00 PM

SDCC Halls B-H

☆ Presentation 437.15 / B41 Cell type-specific deletion of Shank3 exons 14-16 in mice differentially affects synaptic and behavioral phenotypes

8:00 AM - 12:00 PM

T. YOO[1], ***H. CHO**[1], J. LEE[1], H. PARK[1], Y.-E. YOO[1], E. YANG[2], J. KIM[2], H. KIM[2], E. KIM[1];
[1]IBS, Daejeon, Korea, Republic of; [2]Korea Univ., Seoul, Korea, Republic of

Abstract

Shank3 is an excitatory postsynaptic scaffolding protein, which has been implicated with multiple brain disorders, including autism spectrum disorders and Phelan-McDermid syndrome. Many ***Shank3***-mutant mice studies have been reported, but it remains largely unclear how cell type-specific ***Shank3*** deletion affects disease-related phenotypes in ***Shank3***-mutant mice. Here, we generated ***Shank3***-mutant mice with exon 14-16 deletion to validate cell type-specific roles of Shank3. Excitatory (glutamatergic) and inhibitory (GABAergic) cell type-specific ***Shank3***-mutant (exon 14-16) mice displayed distinct synaptic and behavioral phenotypes. Both glutamatergic and GABAergic ***Shank3***-mutant (exon 14-16) mice displayed increased social interaction and increased repetitive behaviors, similar to global ***Shank3***-mutant (exon 14-16) mice. However, in the case of social communication and movement, only GABAergic ***Shank3***-mutant mice recapitulated the phenotypes of global ***Shank3***-mutant; decreased social communication and hypoactivity. In addition, the decreased excitatory synaptic transmission in the dorsolateral striatum of global ***Shank3***-mutant mice was well recapitulated in GABAergic but not glutamatergic ***Shank3***-mutant mice. Our results suggest GABAergic neuron-specific Shank3 deletion has stronger impacts on phenotypes relative to glutamatergic neuron- specific Shank3 deletion.

8:00 AM - 12:00 PM

☆ Session 444 Neuroinflammation and Immune Actions: *In Vivo* Models

SDCC Halls B-H

☆ Presentation 444.01 / D33 Drug Repurposing for Alzheimer’s Disease by Modulating Tau Pathology

8:00 AM - 12:00 PM

***J. HAN**[1], J.-H. JEONG[1], K. SUH[1], H. KIM[2], I. MOOK-JUNG[1,2];
[1]Seoul Natl. Univ. Col. of Med., Seoul Natl. Univ., Seoul, Korea, Republic of; [2]Seoul Natl. Univ. Col. of Med., SNU Dementia Res. Ctr., Seoul, Korea, Republic of

Abstract

Alzheimer’s Disease (AD) is characterized by accumulation of amyloid beta plaques and neurofibrillary tangles, which ultimately lead to neuronal cell death. Millions of people are suffering from AD, yet clinical therapies targeting AD are still under development. Here we propose FDA-approved Drug A for its potential therapeutic effects on AD. In a mouse model of AD, oral administration of Drug A alleviated tau pathology and prevented neuronal cell death, resulting in improved cognitive functions. We also found that Drug A reduced total and hyperphosphorylated tau by modulating mTOR pathway, which is responsible for lysosomal degradation of abnormal tau proteins. These data reveal that FDA-approved Drug A is effective in ameliorating AD pathology, and suggest Drug A as a prospective therapy for AD.

☆ Presentation 444.03 / D35 Long-term excessive NE exposure to brain induces tau aggregation and behavioral disorders

8:00 AM - 12:00 PM

***J.-H. JEONG**, D. KIM, S. CHUNG, I. MOOK-JUNG;
Seoul Natl. Univ. Col. of Med., Seoul Natl. Univ., Seoul, Korea, Republic of

Abstract

The two neuropathological hallmarks of Alzheimer’s disease (AD) are the intracellular aggregation of hyperphosphorylated tau and the extracellular deposition of amyloid beta plaques. The locus coeruleus (LC), the major source providing norepinephrine (NE) to brain, is one of the earliest sites of neurofibrillary tau formation in AD. Although the LC-supplied NE plays a key role in a variety of brain functions, including cognition, emotion, locomotion, and the sleep-wake cycle, the contribution of NE to the tau aggregation remains elusive. To clarify the role of NE in the brain associated with tau, we injected intraperitoneally (IP) either N-(2-chloroethyl)-N-ethyl-bromo-benzylamine (DSP4), a selective neurotoxin for noradrenergic neurons, to make NE depletion or Reboxetine (RBX), a drug of the norepinephrine reuptake inhibitor (NRI), to augment the degree of NE in the three-month-old tau transgenic mice expressing mutant human P301L tau for two months. Because we began to inject these drugs into the young tau mice before the known onset of tau pathology, we were able to examine whether the changes of the NE level promote or delay the onset of taupathy. Interestingly, we observed that the only mice treated with RBX had cognitive deficits in Y-maze and novel object recognition test (NOR) as well as motor dysfunctions in rotarod test. In addition, we discovered that the mice with RBX gained more aggregation of hyperphosphorylated tau in both cortex and hippocampus than the other mice did by performing western blotting and immunohistochemistry. These results suggest that excessive NE in the brain may be related to the hyperphosphorylation of tau either directly or indirectly, which could be explained why the LC is the first region of the tau deposition in AD. Thus, the approach targeting the LC-NE system to regulate the NE level in the brain may be a pivotal therapy to AD.

☆ Presentation 444.07 / D39 Sting activation promotes brain inflammation and memory impairment in alzheimers disease model

8:00 AM - 12:00 PM

***S. CHUNG**, J.-H. JEONG, J.-C. PARK, H. CHOI, D. LEE, J. KIM, J. HAN, D. KIM, E. JUNG, I. MOOK-JUNG;
Seoul Natl. Univ. Col. of Med., Dept. of Biomed. Science, Seoul Natl. Univer, Seoul, Korea, Republic of

Abstract

Neuroinflammation accelerates neurodegeneration in Alzheimer’s disease (AD), the prominent cause of dementia. Here, we report that cyclic GMP-AMP synthase (cGAS) - Stimulator of interferon genes (STING) pathway is activated in AD and STING inhibition reduces neuroinflammation, Aβ burden, and tau phosphorylation in Alzheimer’s disease model mice.cGAS-STING pathway plays a central role in ectopic DNA recognition and following interferon-related pro-inflammatory responses. Interestingly, both protein levels were elevated in two independent AD model mice, especially enriched in Aβ plaque-associated microglia. Aβ activated cGAS-STING downstream signaling molecules and STING inhibition reduced these responses in microglia. In App$^{NL\text{-}G\text{-}F}$/MAPT double-KI mice, which manifest Aβ and tau pathology without artifact of protein overexpression, pharmacological STING inhibition reduced both pathologies and rescued memory impairment. Furthermore, microgliosis and brain inflammation were reduced by STING inhibition. These results indicate that microglial STING activation contributes to neuroinflammation and worsens Aβ and tau pathogenesis in AD mouse model. Thus, the modulation of microglial phenotype through the STING regulation may provide a therapeutic strategy to cure AD.

Acknowledgments: We sincerely appreciate Dr. Takaomi Saido at RIKEN Center for Brain Science for providing the App$^{NL\text{-}G\text{-}F}$ and MAPT knock-in mice.

☆ Session 447 Parkinson's Disease Animal and Cellular Models

8:00 AM - 12:00 PM

SDCC Halls B-H

★ Presentation 447.09 / E11 Evaluation of Anti-Parkinson’s activity of Trachyspermum ammi on Rotenone induced Parkinson’s

8:00 AM - 12:00 PM

disease in Drosophila melanogaster.

***A. SHANKAR**[1], V. DATE[2];
[1]Dept. of Pharmacol. & Therapeut., [2]Seth GS Med. Col. & KEM Hosp., Mumbai, India

Abstract

Evaluation of Anti-Parkinson's activity of *Trachyspermum ammi* on Rotenone induced Parkinson's disease in Drosophila melanogaster. Arun Shankar NairInstitute- Department of Pharmacology & Therapeutics, Seth GS Medical College & KEM Hospital, Parel, Mumbai- 400012.
Background and rationale: The study was designed to validate the claims in Ayurveda regarding the efficacy of Ayurvedic drugs in neurodegenerative disorders. It was decided to conduct an efficacy study using a herbal drug which has anti-oxidationve effect. The herbal plant selected was ***Trachyspermum ammi.*** Parkinson's disease has symptom descriptions in Ayurveda and modern medicine. The latter offers only the symptomatic therapy by replacing dopamine, the neurotransmitter involved, but does not slow down or reverse the loss of dopaminergic neurons.**Methods:** Rotenone, in a final concentration of 125 μM, was induced for inducing Parkinson's disease in Drosophila melanogaster. Table concentration of *Trachyspermum ammi* was selected on the basis of viability assays carried out in our lab. The group serving as negative control will not have the study drugs in the cornmeal medium and the flies from positive control will be fed with L-dopa dissolved in the medium in the concentration of 1 mM. The flies in the bottle will be maintained for a period of 7 days at 25^{O}C. On the 8th day, they will be subjected to climbing assay. Malondialdehyde and Glutathione estimation will be carried out to check for the anti-oxidative properties of the drug. The brain tissue of Drosophila melanogaster will be dissected and be subjected to immunohistochemistry against Tyrosine hydroxylase.**Results:** Climbing assays showed a significant reduction in the climbing/ motor ability between the control and disease control groups. There was an improvement in the levels of MDA and GSH in the study group as compared to the disease control group. There was a significant improvement in the climbing ability of flies fed with l-dopa and study drug. Immunohistochemistry showed a significant reduction of dopaminergic neurons in the disease control group and a significant reduction in the loss of dopaminergic neurons in the study group. **Conclusion:** *Trachyspermum ammi* was effective in reducing the rotenone induced dopaminergic loss of neurons.**Ethics statement:** NA.**Acknowledgement:** I would like to acknowledge SAIF dept., IIT Mumbai and our lab members for their support.

☆ Session 449 Parkinson's Disease Animal Models

8:00 AM - 12:00 PM

SDCC Halls B-H

☆ Presentation 449.01 / E42 A novel NOX inhibitor alleviates Parkinson's disease pathology in PFF-injected mice.

8:00 AM - 12:00 PM

***K. OFORI**[1], A. GHOSH[1], D. VERMA[1], G. CABRERA[1], D. WHEELER[1], S. MOON[2], S. LEE[2], Y. KIM[1];
[1]Delaware State Univ., Dover, DE; [2]AptaBio Therapeut. Inc, Heungdeok IT valley, Korea, Democratic People's Republic of

Abstract

Parkinson's disease (PD) is the most prevalent motor neurodegenerative disorder, resulting from the decline of dopaminergic neurons in the midbrain. Although numerous genetic mutations have been identified in PD pathology, a key pathological hallmark is mis-folded protein aggregation called Lewy body formation. Thus, it has been emphasized to develop therapeutics to halt the Lewy body formation to prevent dopaminergic neuronal loss in the nigrostriatal pathway. Despite the causes in up-stream, oxidative stress-mediated damage in down-stream often underlines PD pathology. Therefore, ultimately regulating oxidative stress can be an effective approach to prevent PD pathological progress. Here we assessed the efficacy of an exogenous reactive oxygen species (ROS) regulator, nicotinamide adenine phosphate (NADPH) oxidase (NOX) inhibitor, compound-11 which was synthesized by Aptabio Therapeutics. The compound is a safe and specific inhibitor for NOX-1, 2 and 4, based on our preliminary assessments. Using rat dopaminergic cells and alpha-synuclein preformed fibrils (PFF)-injected mouse model, we tested the novel NOX inhibitor as a potential therapeutic for PD. PFF is known to be a pathogenic form of alpha-synuclein leading to rapid protein aggregation for recapitulating PD pathology. In our ***in vitro*** assays, the novel compound enhanced cell viability and reduced cytotoxicity against PFF exposure at a wide range of concentrations (1 nM-10 μM), but we confirmed that 1 μM was an optimal concentration ***in vitro***. We also found a significant reduction in ROS and protein aggregation in Thioflavin-T stain with the compound treatment in N27 cells. After 7-8 weeks of oral treatment (5 or 25 mg/kg), starting 3 months post-PFF injection using 12-month-old mice, we found that both doses of the compound treated mice (n=7/group) showed a significant reduction in motor deficits assessed by behavioral assays, such as grooming, nesting, rotarod, hindlimb clasping and pole test, in a blinded assessment. Further, in immunohistochemistry, the treatment reduced the level of protein aggregation and prevented or reversed dopaminergic neuronal loss in the striatum and Substantia Nigra, suggesting that the inhibition of NOX can be a viable option for developing potential therapeutics for PD.

☆ Presentation 449.02 / E43 Restoring neuronal p38γ MAPK by p38αMAPK inhibition ameliorates synaptic degeneration in a mouse model of DLB/PD

8:00 AM - 12:00 PM

***M. IBA**[1], C. KIM[1], S. KWON[1], M. SZABO[1], C. PEER[3], X. REED[1], R. A. RISSMAN[4], M. R. COOKSON[1], C. OVERK[4], W. WRASIDLO[4], E. MASLIAH[1,2];
[1]Lab. of Neurogenetics, [2]Div. of Neurosci., Natl. Inst. on Aging, Natl. Inst. of Hlth., Bethesda, MD; [3]Clin. Pharmacol. Program, Natl. Cancer Institute, Natl. Inst. of Hlth., Bethesda, MD; [4]Dept. of Neurosciences, UCSD Sch. of Med., La Jolla, CA

Abstract

Aggregation of presynaptic protein, alpha-synuclein (α-syn) is a hallmark of neurodegenerative diseases such as Parkinson's disease (PD) or dementia with Lewy bodies (DLB). We previously reported that p38γ, one of mitogen activated protein kinases (MAPKs) are mis-localized in neuronal cell bodies in DLB patients and a DLB/PD mouse model although p38γ locates in peripheral dendritic regions of the cells in healthy control or non-transgenic littermates mice (Iba et al., 2020). Activation of p38α and mis-localization of p38γ are associated with neuroinflammation and synaptic degeneration in DLB/PD, respectively. We hypothesized that p38α might modulate the distribution of p38γ, and inducing synaptic degeneration in models of DLB/PD.

To investigate this hypothesis, we treated DLB/PD models in vivo and in vitro with SKF86002 which is a compound that attenuates inflammation by inhibiting p38α/β and investigated the effects on p38γ and neurodegenerative pathology. We found that inhibition of p38α reduced neuroinflammation, ameliorated synaptic function, protected neurodegeneration, and improved motor function in the α-syn transgenic (tg) mice. Moreover, this compound promoted the re-distribution of p38γ to the synapse and reduced the accumulation of α-syn in α-syn tg mice. Further, we found that in iPSC derived human neural cultures from familial PD (A53T α-syn), this compound reduced the accumulation of α-syn and promoted the re-distribution of p38γ in neurons. p38α inhibition ameliorated α-syn-induced neurodegeneration only when microglia were pre-treated with SKF86002, although direct treatment of SKF86002 to neurons did not affect to α-syn-induced neurotoxicity, which suggest SKF86002 treatment only inhibits microglial neurotoxicity. These results support that reducing neuroinflammation by targeting p38α is a promising therapeutic approach to DLB and PD because it's effects on p38γ MAPK and synaptic stability. We provide a novel pathogenic mechanism for initiation of synaptic degeneration in DLB and PD which includes the pathogenic crosstalk between microglial neuroinflammation and synaptic neurodegeneration via p38α/p38γ MAPK respectively.

☆ Presentation 449.10 / E51 Senp-1 inhibition ameliorates the pff induced toxicity and alleviates Parkinson's disease-related signs in mice

8:00 AM - 12:00 PM

***D. VERMA**[1], A. GHOSH[1], K. OFORI[1], B. SEO[2], G. CABRERA[1], D. B. WHEELER[1], H. KO[2], Y.-H. KIM[1];
[1]Dept. of Biol. Sci., Delaware State Univ., Dover, DE; [2]Inst. for Cell Engin., Johns Hopkins Univ. Sch. of Med., Baltimore, MD

Abstract

Small Ubiquitin-like modifier (SUMO) conjugation is a dynamic post-translational modification on lysine residues, catalyzed by SUMO-specific ligases and removed by SUMO-specific proteases (SENPs). The physiological consequences of (de)SUMOylation in Parkinson's disease (PD) pathology are not well understood. In this study, we characterized which isoform of SENPs is involved in detaching SUMOs from α-synuclein when 1-methyl-4-phenylpyridinium (MPP+) or pre-formed fibrils (PFF) of α-synuclein induces toxicity, in the scope of understanding the idiopathic mechanisms of PD pathology. After PFF or MPP^+ exposure to N27 rat dopaminergic cells, we found that SENP-1 expression was particularly elevated among other SENP family proteins, such as SENP-1, 3, 5, 6, 7 and 8. An increase in SENP-1 expression and a decline in SUMO-1 level were detected in PFF-treated primary cortical neuron culture, midbrain and striatum of PFF injected C57Bl/6 mice and the SNpc of human PD patient brains. The knock-down of SENP-1 by siRNA resulted in an increase of SUMO-1 level in PFF-treated N27 cells. Next, we assessed various commercially available SENP-1 inhibitors targeting SENP-1 suppression and found significant decreases in the levels of ROS and protein aggregates, derived from PFF toxicity. Since a SENP-1 inhibitor, Momordin Ic was more efficacious than others based on our ***in vitro*** assays, we have orally treated Momordin to PFF-injected >12-month-old mice at two doses (10 or 50 mg/kg) for 6-7 weeks. The SENP-1 inhibition alleviated motor deficits induced by PFF injection in behavioral tests, such as rotarod, nesting, grooming, hindlimb clasping and pole test. In the striatum and midbrain region of PFF injected mice, immunohistochemical analyses revealed the increased levels of protein aggregates in Thioflavin-T staining and phosphorylated alpha-synuclein, a pathological marker, were significantly reduced by Momordin treatment. These results were further verified by an increase in the number of TH+ neurons in the SNc and enhanced TH intensity in the striatum in a blinded analysis. Taken together, our results strongly suggest that SENP-1 inhibition can be applied to halt and further reverse the pathology of PD, due to the reduction of protein aggregation and oxidative stress.

☆ Presentation 449.15 / E56 Analysis of CNS-derived exosomes as biomarkers of Parkinson's Disease

8:00 AM - 12:00 PM

***K. K. ZAND**[1], T. T. NILLES-MELCHERT[1], S. H. WEE[1], H. KIM[1], M. S. BURNETT[2], J.-Y. HWANG[1];
[1]Dept. of Pharmacol. and Neurosci., [2]Dept. of Neurol., Creighton Univ. Sch. of Med., Omaha, NE

Abstract

Parkinson's Disease (PD) is the second most common neurodegenerative disease in the world. PD is caused by severe loss of nigrostriatal dopaminergic neurons and is characterized by increases in cytoplasmic inclusions of alpha-synuclein. A timely diagnosis of PD is critical to providing the proper treatment and advice regarding care to patients. However, presently a suitable diagnostic laboratory test for PD does not exist. Therefore, the identification of reliable biomarkers is clinically imperative. Exosomes are nanovesicles found throughout the body that carry various proteins, mRNAs, and microRNAs. Central nervous system (CNS)-derived exosomes can cross the blood-brain barrier and have been suggested as a potential source of neurodegenerative disease biomarkers in some pilot studies. Thus, research related to further validation and a large independent cohort study is needed for relevancy and accuracy. To examine the possibility of using CNS-derived exosomes as biomarkers and identify new candidates, we used an animal model of PD. We isolated CNS-derived exosomes from peripheral blood of rats with rotenone-induced PD, collecting samples at 2-week and 4-week time points. The results from Western blot analysis on the samples using antibodies against L1CAM and MAP2, proteins known to be present in CNS exosomes, showed that CNS-derived exosomes were successfully isolated from peripheral blood. Next, we examined whether PD-related pathogenic proteins were changed. We found that phosphorylated alpha-synuclein and DJ-1 were increased at four weeks post rotenone injection compared to sham, suggesting their potential use as biomarkers for diagnosing PD. To identify new candidates in CNS-derived exosomes, we are currently preparing samples for next-generation sequencing and anticipate our analysis may identify novel mRNA and/or miRNA biomarkers from CNS-derived exosomes.

☆ Session 452 Animal Models and Tau

8:00 AM - 12:00 PM

SDCC Halls B-H

★ Presentation 452.08 / F45 Impact of reduced gut bacteria on neurodegeneration in a Drosophila model of human tauopathy

8:00 AM - 12:00 PM

O. BAT-ERDENE, L. DIGGAN, J. R. FIGURA, L. GRAY, M. J. HIRST, V. R. WILSON, ***K. M. LOHR**;
Biol., Washington and Jefferson Col., Washington, PA

Abstract

Deposition of the microtubule-associated protein tau is a hallmark pathology of the family of neurodegenerative diseases known as tauopathies, including Alzheimer's disease, frontotemporal dementia, and chronic traumatic encephalopathy. Ongoing work on mechanisms of tau-mediated neurodegeneration suggest that genetic contributions interact with peripheral or environmental factors to contribute to disease onset and severity. Recently, the gut microbiota has emerged as a potential modifier of brain function in human, rodent, and invertebrate models via changes to neurotransmitter levels and systemic inflammation. We have previously shown that ***Drosophila*** expressing human tau in neurons show reduced gut motility and an increased bacterial load compared to control animals. Further, tau transgenic flies show activation of the innate immune system as shown by antimicrobial peptide expression. To expand upon these studies, we have grown control and tau transgenic flies in an environment with limited bacterial exposure and show enhanced neurodegenerative outcomes. Taken together, these data suggest that tau transgenic flies have an innate deficit in gut function and that manipulation of the gut microbiota is capable of altering neuronal health in this ***Drosophila*** model of human tauopathy.

☆ Session 453 Therapeutics: ALS and SMA

8:00 AM - 12:00 PM

SDCC Halls B-H

☆ Presentation 453.04 / F52 Fda-approved pde4 inhibitors reduce the dominant toxicity of als-ftd-associated chchd10^{s59l} in drosophila and human cells

8:00 AM - 12:00 PM

***N. KIM**, M. BAEK, Y.-J. CHOE;
Univ. of Minnesota, Univ. of Minnesota, Duluth, MN

Abstract

Mutations in coiled-coil-helix-coiled-coil-helix domain containing 10 (CHCHD10) are a genetic cause of amyotrophic lateral sclerosis and/or frontotemporal dementia (ALS-FTD). Using ***in vivo Drosophila*** models expressing C2C10H^{S81L}, and human cell models expressing CHCHD10^{S59L}, we have identified that the PINK1/Parkin pathway is activated and causes cellular toxicity. Furthermore, we demonstrated that pseudo-substrate inhibitors for PINK1 and mitofusin2 agonists mitigated the cellular toxicity of CHCHD10^{S59L}. Therefore, we have further evaluated various additional small molecule compounds that can modulate the PINK1/Parkin pathway and reduce CHCHD10^{S59L}-induced cytotoxicity. Among these compounds, FDA-approved PDE4 inhibitors successfully reduced CHCHD10^{S59L}-induced morphological and functional mitochondrial defects in human cells and an in vivo Drosophila model expressing C2C10H^{S81L}. Multiple PDE4 inhibitors decreased PINK1 accumulation and downstream mitophagy induced by CHCHD10^{S59L} via the cAMP-PKA pathway. These findings suggest that PDE4 inhibitors currently available in the market can be repositioned to treat CHCHD10^{S59L}-mediated ALS-FTD and possibly other related diseases.

☆ Session 454 Neuronal Injury and Death I

8:00 AM - 12:00 PM

SDCC Halls B-H

☆ Presentation 454.03 / G12 Role of CHFR in neuronal DNA damage responses

8:00 AM - 12:00 PM

***K. KIM**[1], J. SONG[2], E. LEE[3], J. SEOL[2], M. KIM[1];
[1]Korea Brain Res. Inst., Daegu, Korea, Republic of; [2]Seoul Natl. Univ., Seoul, Korea, Republic of; [3]Ajou Univ., Suwon, Korea, Republic of

Abstract

Neurodegenerative disorders are often associated with uncontrolled DNA damage responses and neuronal dysfunction, including abnormal neuronal apoptosis and neurite shrinkage. Neurons are known to re-enter the cell cycle upon DNA damage, leading to neuronal cell death. However, little is known about how neurons respond to DNA damage conditions. Here, we have identified that CHFR, also known as a cell-cycle checkpoint, is substantially expressed throughout the brain. Based on the high expression of CHFR in neurons, we have investigated whether the stability of CHFR is modulated under DNA damage conditions. We showed that neuronal cell death was augmented in a CHFR-dependent manner, and the expression of death-related genes was also increased under DNA damage conditions. Interestingly, neuronal senescence was elevated in the presence of both CHFR and DNA damage-inducing drug doxorubicin in a dose-dependent manner shown by SA-β-gal (senescence-associated beta-galactosidase) analyses. CHFR methylation levels were decreased by the DNA double-strand break-inducing decitabine treatment, analyzed by the Infinium MethylationEPIC array. We showed that the neurite length was shortened when CHFR was more introduced into mouse primary cortical neurons. Moreover, the neurite length was shorter when pan cyclin-dependent kinase (CDK) inhibitor roscovitine was treated in the presence of CHFR. Therefore, our results suggest that CHFR plays an important role in neuronal DNA damage responses to maintain neuronal integrity. This work was supported by Mid-career Research Program (NRF-2019R1A2C1011083, NRF-2022R1A2C1004326), KBRI basic research program (22-BR-02-02) funded by the Korea government (MSIT).

☆ Session 455 Neuroprotection II

8:00 AM - 12:00 PM

SDCC Halls B-H

☆ Presentation 455.19 / H8 TREM1-mediated neuroinflammation in global ischemia pathology

8:00 AM - 12:00 PM

***R. URQUHART**, H. KIM, G. P. JADHAV, J.-Y. HWANG;
Pharmacol. and Neurosci., Creighton Univ., Omaha, NE

Abstract

Comorbid with cardiac arrest, global ischemic stroke is caused by loss of cerebral blood flow, which induces hypoxia affecting the whole brain. Global ischemia promotes selective, delayed neurodegeneration of hippocampal CA1 pyramidal neurons, contributing to hippocampal-based learning and memory deficits. Understanding the molecular mechanisms driving global ischemia pathology is of urgent necessity for development of novel therapeutic strategies to address global ischemia-induced neurodegeneration and cognitive deficits. RNA-seq and Ingenuity Pathway analysis of rat CA1 subjected to global ischemia via 4-vessel occlusion revealed the triggering receptor expressed on myeloid cells-1 (TREM1) pathway is activated at 48 hr after ischemia. TREM1 is an innate immune receptor responsible for initiating and amplifying inflammation via synergism with immune-response related Toll-like receptors. TREM1 has an established proinflammatory role in myocardial ischemia, sepsis, and focal ischemia, but its role in global ischemia pathology is unclear. Thus, it was hypothesized that TREM1-mediated neuroinflammation promotes global ischemia-induced neurodegeneration, and TREM1 inhibition can rescue hippocampal integrity and function. In our validation experiments, RT-qPCR and Western blot analyses of rat CA1 reveals that TREM1 expression is significantly elevated within 3 hr of ischemic insult, and this increase is maintained for 48HR. Additional targets associated with TREM1 activation and signaling, including signaling partners (DAP12 (TYROBP), SYK), signal transduction targets (Nf-kB, STAT3), and downstream inflammatory cytokines (IL-1B, IL-18, IL-6) are differentially expressed within 3-48HR of ischemic insult. To examine a causal relationship between global ischemic insult and activation of TREM1 signaling, we tested if TREM1 inhibition can prevent global ischemia-induced neurodegeneration and cognitive deficit. LR12, a TREM1 inhibitory peptide, was stereotaxically administered directly into hippocampal CA1 in rats immediately after ischemic or sham surgery. Data is currently being collected to determine the neuroprotective effect of LR12. If LR12 administration can prevent TREM1 signaling and ameliorate loss of neurons and hippocampal-based learning and memory, this research will have established the importance of TREM1-mediated neuroinflammation and the therapeutic potential of TREM1 inhibition in global ischemia.

☆ Session 456 Mechanisms of Neurodegeneration: Molecular, Cellular, and Human Studies

8:00 AM - 12:00 PM

SDCC Halls B-H

☆ Presentation 456.27 / K8 Hyperammonemia-derived glutamine storm promoting MAO-A mediated tauopathy in human edema mini-brain

8:00 AM - 12:00 PM

***M. TRAN**, Y. KANG, H. CHO;
Sungkyunkwan Univ., Sungkwunkwan Univ., Suwon, Korea, Republic of

Abstract

Brain edema is a frequent manifestation of hepatic encephalopathy (HE)-induced neuronal disorder exhibits elevated levels of ammonia levels, characterized by liver failure. However, the significance of HE to the etiology of tauopathy remains uncertain due to the absence of models demonstrating the predominance of conversion among cell-cell interactions. Here, we introduce a 3D human mini-brain of hyperammonemia in microfluidic platform, which may recapitulate key features of native edema pathophysiology. First, we stated that ammonia-induced malfunctioning of microglia is accompanied by a decrease in migratory activity and in phagocytic activity, indicating that type II astrocytes play a crucial role in hyperammonemia. Second, we asserted that H_2O_2 and glutamine exert the most extraordinary dominance among the neurotoxic components efflux from astrocytes. The increase of glutamine levels efflux from astrocytes was associated with monoamine oxidase A (MAO-A) overactivation, results in hyperpolarization of the mitochondrial membrane leading to buildup of intracellular reactive oxygen species (ROS) in neurons causing synaptic dysfunction and accumulation of phosphorylated tau. Finally, we confirmed that the MAO-A inhibitor (clorgyline) is a promising therapeutic development option for their ability to restore neuronal function by demonstrating the recovery of mitochondrial membrane potential, reducing intracellular ROS by 2.25-fold, prevention of phosphorylated tau accumulation by 1.6-fold and the enhancement of neuronal cell population by 41.9%. We envision that our findings will provide light on the mechanisms behind tau phosphorylation in brain hypertrophy and, ultimately, on the robust indicators for medication development.

Keywords: *In vitro* model, hepatic encephalopathy, brain edema, glia-neuron interaction, mitochondria dysfunction, oxidative stress, tauopathy

☆ Session 457 Mechanisms and Biomarkers of Inflammation in Neurodegeneration

8:00 AM - 12:00 PM

SDCC Halls B-H

☆ Presentation 457.09 / L6 Microglia and Astrocyte-mediated Neurodegeneration in Parkinson’s Disease

8:00 AM - 12:00 PM

***T.-I. KAM**[1], V. DAWSON[2], T. M. DAWSON[3];
[1]Neurology/Institute for Cell Engin., [2]Johns Hopkins Univ., Baltimore, MD; [3]Johns Hopkins Univ. Inst. for Cell Engin., Johns Hopkins Univ. Inst. for Cell Engin., Baltimore, MD

Abstract

Parkinson’s disease (PD) is the second most common neurodegenerative disorder. During the pathogenesis of PD, monomeric α-synuclein assembles into higher ordered structures that ultimately become pathologic and drive neuronal cell death in a cell autonomous fashion. Pathologic α-synuclein can spread from cell to cell contributing to the progressive pathogenesis of PD, which causes microglia- and astrocyte-mediated neuroinflammation in a non-cell autonomous fashion. However, what drives the abnormal assembly of pathologic α-synuclein and death in neurons as well as the neuroinflammation in non-neuronal cells that are activated by pathologic α-synuclein are not known. Microglia are the resident macrophages and primary immune cells of the central nervous system. We showed that misfolded α-syn activates microglia, which release interleukin 6 (IL-6). IL-6, via its trans-signaling pathway, induces changes in the neuronal iron transcriptome that promote ferrous iron uptake and decrease cellular iron export via cellular iron sequestration response (CISR). Genetic deletion of IL-6, or treatment with the iron chelator deferiprone, reduces pathological α-syn toxicity in a mouse model of sporadic PD. These data suggest that IL-6-induced CISR leads to toxic neuronal iron accumulation, contributing to α-syn-induced neurodegeneration. Astrocytes are the most abundant glial cells in the brain and play a variety of physiological roles. In pathologic conditions, however, reactive astrocytes formed by response to stimulus or injuries in the CNS promote disease pathogenesis. Activated microglia induce neurotoxic reactive astrocyte by secreting interleukin-1α (IL-1α), TNF-α and C1q and that reactive astrocytes are found in postmortem brains of human neurodegenerative diseases including PD. We showed that pathological α-synuclein contributes to formation of neurotoxic reactive astrocytes and preventing α-synuclein-induced microglial activation and reactive astrocyte conversion protected against dopaminergic neurodegeneration and behavioral deficits in a mouse model of sporadic PD. More recently, we also found that reactive astrocytes formed by oligomeric amyloid-β (Aβ) contribute to neurotoxicity and synaptic degeneration in a mouse model of Alzheimer's disease (AD). Taken together, these findings demonstrate that reactive astrocytes contribute to pathogenesis and progression of multiple neurodegeneration.

☆ Session 489 Neural Mechanisms of Decision Making: Choice

8:00 AM - 12:00 PM

SDCC Halls B-H

☆ Presentation 489.21 / WW33 Higher long-term global reward improves consistency of reward-dependent choice strategies in mice and monkeys

8:00 AM - 12:00 PM

***J. WOO**[1], V. D. COSTA[3], B. A. BARI[4], J. Y. COHEN[5], A. SOLTANI[2];
[1]Dartmouth Col., [2]Psychological and Brain Sci., Dartmouth Col., Hanover, NH; [3]Dept. of Behavioral Neurosci., Oregon Hlth. and Sci. Univ., Beaverton, OR; [4]Sch. of Med., Baltimore, MD; [5]Neurosci., Johns Hopkins Univ., Baltimore, MD

Abstract

Local effects of reward feedback on learning and decision-making are often investigated by computing quantities such as win-stay or lose-switch probabilities or by fitting choice behavior using reinforcement learning (RL) models, all of which consider response or adjustment to individual reward feedback. However, how reward history on a longer timescale affects animal's choice behavior is relatively less known mainly because of the difficulty of measuring such effects using reinforcement learning models. To address this question, we re-analyzed choice behavior of mice (n=16) and monkeys (n=4) performing two dynamic foraging tasks. We extended our previous metrics based on information entropy (Trepka et al., ***Nat Comm*** 2021) to incorporate reward history spanning more than one trial. Specifically, we defined the entropy of global and local reward-dependent strategies (EGLORDS) equal to the conditional entropy of stay/switch strategy given the immediate reward feedback as well as global reward state (GRS) based on the history of reinforcement. Lower EGLORDS values correspond to decreased uncertainty and thus more consistency in the utilized strategy. To estimate the timescale on which animals integrate past reward, we fitted RL models with additional components that modulates choice behavior by expected reward. We used the estimated timescales from the best RL model to infer the global reward state and compute EGLORDS in each block of trials. We found consistent effects of global expected reward across both species: when animals were earning more rewards than expected (high GRS), their choice strategy became significantly more consistent in both rewarded and unrewarded trials as reflected in lower EGLORDS ($p < .001$; Wilcoxon signed rank test). Additionally, we found that reaction time (RT) was significantly shorter when animals were in the high GRS (mice: $p < .001$ for rewarded/unrewarded trials; monkeys: $p < .001$ for rewarded trials; one-sample T-test). Further analyses using GLM confirmed that expected reward is a significant predictor of RT even when immediate reward is accounted for: higher expected rewards accompanied shorter RT in both mice ($p < .001$) and monkeys ($p < .001$; one-sample T-test). These findings show that in addition to immediate reward feedback, global reward state has a significant impact on choice strategy, perhaps via modulations of motivation and thus, elucidate the role of motivation in choice behavior.

☆ Session 492 Cortical Networks and Behavior

8:00 AM - 12:00 PM

SDCC Halls B-H

☆ Presentation 492.17 / XX31 Neural correlates of multimodal object recognition in the perirhinal cortex

8:00 AM - 12:00 PM

***H.-Y. LIM**, I. LEE;
Dept. of Brain and Cognitive Sci., Seoul Natl. Univ., Seoul, Korea, Republic of

Abstract

Object recognition is normally accomplished in a multimodal and cross-modal fashion in natural settings. Known as the critical region for object recognition, the perirhinal cortex (PER) receives direct inputs from the cortical perceptual areas specialized in processing specific sensory modalities. However, the neural mechanisms are largely unknown regarding how those individual sensory-perceptual modalities are bound to represent an object and, once learned, the degree to which an object representation is activated by cross-modal cues in the PER. To examine these issues, we recorded spiking activities of single neurons in the PER while rats performed a multisensory object recognition task. Specifically, we trained eight male Long-Evans rats to recognize two different objects, each associated with unique visual and auditory features (i.e., boy-shaped figure with 5kHz frequency sine-wave tone versus egg-shaped figure with 10kHz frequency sine-wave tone). The rat initiated the onset of the multimodal object stimulus by poking the center nose-poke hole and, once the object stimulus appeared, poked its nose into either the left or right reward port on the basis of the identity of the multimodal object. Once trained, a 24-tetrode-carrying hyperdrive was implanted to target the PER. Once the neural recording commenced, only either visual or auditory modality was used during the object sampling phase in some trials, intermixed with the multimodal conditions. Rats performed successfully in both multimodal (86±5.4%, p<0.0001 compared to 50% chance level in a one-sample t-test) and unimodal conditions (visual: 67.2±4.6%, p<0.0001; auditory: 68.3±13.7%, p=0.007), although their performance was better in the multimodal trials than in the unimodal trials (p=0.0006, one-way repeated-measures ANOVA). Our preliminary analysis suggests that the neural firing patterns are correlated with the diverse combinations of modality conditions (i.e., multimodal, visual-only, or auditory-only) in object-representing neurons of the PER. We are currently characterizing further the neural firing patterns of the different subclasses of neurons in association with different modality conditions during object recognition and the relationships between the neural firing patterns and behavioral performance.

☆ Session 493 Learning and Memory: Hippocampal and Prefrontal Circuits

8:00 AM - 12:00 PM

SDCC Halls B-H

☆ Presentation 493.05 / XX42 How to interpret the results of causal optogenetic manipulations?

8:00 AM - 12:00 PM

***C. JOU**[1], E. PARK[2], D. DVORAK[2], A. A. FENTON[2];
[1]City Univ. of New York, New York, NY; [2]New York Univ., New York, NY

Abstract

Optogenetics have provided an unprecedented ability to causally and selectively manipulate specific cell populations to test their hypothesized function. For example, the so-called “engram cell” literature reports that hippocampus neurons that are active during training of a memory task can be optogenetically tagged such that they can be later stimulated to discharge in novel conditions. Amazingly, optogenetic stimulation causes behavioral expression of the memory. Are the tagged neurons the cells that store memory? What is the correct interpretation of such results? Consider two hippocampus place cells, one with a firing field in the north, the other with a field in the south of an arena. Both are active during training trials, but not at the same time. Once tagged, both cells will be stimulated to cofire. Why would one interpret this novel cofiring to be familiar and related to prior experience? Optogenetic manipulations may be precise manipulations, but they manipulate a complex neuronal population with adaptive, non-linear, and inertial interactions. Accordingly, we evaluate the effects of these manipulations by recording ensembles of CA1 cells during optogenetic stimulation of CA1 in Arc-CreERT2-ChR2-EYFP mutant mice. We find that optogenetic stimulation of active place avoidance memory-tagged hippocampus CA1 neurons activates ~14% of cells with sub-second latency. The CA1 network rapidly adapts with cells increasing, decreasing, or maintaining their baseline activity, despite continued stimulation with 15-ms light pulses in 4-Hz or 10-Hz trains for 10min. Even the opto-tagged neurons adapt by progressively decreasing their response to light pulses from 94% to 70%. The discharge pattern of the CA1 population is invariant to the stimulation, preserving their intrinsic ensemble discharge relationships, as well as the low-dimensional manifold organization of their population dynamics. This network resistance to faithfully follow optogenetic stimulation correctly predicted that the optogenetic stimulation is sufficient to elicit the conditioned active place avoidance memory in a neutral environment where the avoidance is not otherwise expressed. We conclude that causal manipulations such as optogenetic engram-cell stimulation should be interpreted as the expression of the population dynamics of a complex system, rather than the precise causal demonstration of a functioning circuit.

☆ Presentation 493.06 / XX43 Inside out: CA1 remapping changes the registration between internally-organized population discharge and the environment without reorganizing most neural discharge relationships

8:00 AM - 12:00 PM

***S. CARRILLO SEGURA**[1], E. R. LEVY[1], E. PARK[1], W. REDMAN[2], J. HURTADO[1], S. CHUNG[1], A. A. FENTON[1];
[1]Ctr. For Neural Sci., New York Univ., New York, NY; [2]Interdepartmental Grad. Program in Dynamical Neurosci., Univ. of California, Santa Barbara, Santa Barbara, CA

Abstract

How hippocampus represents spatial knowledge is unclear. The active subset of principal cells discharge in cell-specific locations called “place fields.” Standard “***external***” place field-based hypotheses assume place cells respond to places, only consider the active subset of place cells, and assume place fields are stable within environments. We performed a classic remapping experiment, using GCaMP6f and miniature microscopes to record CA1 ensemble activity while mice explored a box and a cylinder in 36 5-min sessions spread across 3 weeks. We consider the data in light of the standard hypothesis and an alternative “***internal***” hypothesis that assumes neural activity is internally-organized, founded on the cofiring relationships amongst all CA1 principal cells, and compatible with non-stable spatial tuning. This hypothesis asserts that neural computations are informed by the properties of low-dimensional trajectories of conjoint neural population activity through the neural state space. We find that CA1 place fields are unreliable across weeks, identify a <25% minority of the CA1 population, and remap between environments, permitting decoding of the current environment based on firing fields. Decoding from the cofiring patterns of the entire population is at least as accurate because of multi-stable dynamics that resemble remapping expectations, despite modest cofiring changes across environments. The cells that contribute the most to discriminating the environments are the ~30% “anti-cofiring cells,” whose 1-s timescale discharge is negatively correlated to the rest of the cells. The anti-cofiring subset is environment specific (9% in both environments), and place cells are no better than chance to be anti-cofiring. Other than the anti-cofiring subset, CA1 cofiring is stable across the environments, is organized on a low-dimensional manifold that is indifferent to the environments and stable across weeks. The environments are discriminated by the anti-cofiring cells that anchor the neural manifold within the neural state space. Firing field remapping across environments is not a reorganization of neural coactivity, contradicting the definition of remapping; instead the internally-organized activity manifold changes where it anchors in neural state space and its registration to the environment. These findings demand we reject standard external hypotheses and design experiments to investigate the internal hypothesis that hippocampus

represents information about external variables by registering the internally-organized neural activity to external features, controlled by anti-cofiring discharge.

☆ Session 499 Development and Application of Optogenetic Tools

8:00 AM - 12:00 PM

SDCC Halls B-H

☆ Presentation 499.01 / ZZ16 Structure-guided design of pump-like channelrhodopsins with properties enabling markedly improved optogenetic control in the brain

8:00 AM - 12:00 PM

***Y. KIM**[1], P. Y. WANG[2], E. F. X. BYRNE[2], Y. JO[2], C. RAMAKRISHNAN[2], S. QUIRIN[2], H. E. KATO[3], K. DEISSEROTH[4];
[1]Stanford Univ., Palo Alto, CA; [2]Stanford Univ., Stanford, CA; [3]Univ. of Tokyo, Tokyo, Japan; [4]Stanford, Stanford, CA

Abstract

The recently discovered pump-like channelrhodopsins (PLCRs), including ChRmine and KCRs, exhibit puzzling properties (unusually-large photocurrents, extreme light-sensitivity, and exclusive ion selectivity to monovalent cations) that have opened up new opportunities in optogenetics. Although PLCRs have gained broad interest and application in neuroscience research (since Marshel et al., ***Science*** 2019), little is known about the molecular mechanisms by which these unusual channelrhodopsins operate. Structural mechanisms and structure-guided engineering of channel conduction, light sensitivity, and speed in this family of proteins would likely lead rapidly to creation of powerful new resources for optogenetics. Here we present several designed PLCRs based on our recently-published 2.0 Å resolution cryo-electron microscopy structure of ChRmine (Kishi et al., ***Cell*** 2022). The structure reveals novel architectural features including the retinal binding pocket, ion conduction pathways and putative selectivity filters, which enabled us to engineer variants with red-shifted action spectra, faster- and slower-closing kinetics, and markedly-changed ion selectivity. Our structure-based design of PLCRs will open the door to diverse applications in neuroscience and point the way toward further structure-guided creation of novel channelrhodopsins for optogenetic applications across biology.

☆ Presentation 499.07 / ZZ22 Mapsi: miniscope with all-optical patterned stimulation and imaging

8:00 AM - 12:00 PM

J. ZHANG[1], ***J. KIM**[1], R. N. HUGHES[1], N. KIM[1], I. P. FALLON[2], K. BAKHURIN[1], F. ULLOA SEVERINO[1], H. H. YIN[1];
[1]Dept. of Psychology and Neurosci., [2]Dept. of Neurobio., Duke Univ., Durham, NC

Abstract

Recent advances in optical techniques for monitoring or modulating neural activity have led to numerous neuroscience findings. Particularly, all-optical approaches combining in vivo calcium imaging and optogenetics have enabled recording neuronal activity with cellular resolution as well as selective manipulation of neurons in the same animal. However, current tools often require stationary bench-top systems such as two-photon miniscopes which limit the portability of the system and animal behaviors. To address these limitations, we have developed a Miniscope with All-optical Patterned Stimulation and Imaging (MAPSI) by integrating a one-photon endoscope with a digital micromirror device. MAPSI enables simultaneous calcium imaging and photo-stimulation. Using this system, we were able to successfully image striatal neurons from the direct or indirect pathway while simultaneously activating any neuron of choice within the field of view. MAPSI can identify neurons tuned to a particular behavior and mimic the activity pattern of neurons to recreate the behavior. MAPSI can also produce arbitrary spatiotemporal stimulation patterns generated by an experimenter. Thus, MAPSI will be a useful tool for all-optical investigation of neural circuit function in freely behaving animals.

☆ Presentation 499.16 / ZZ30 Data-driven identification and perturbation of multi-regional and cell-type-specific neural population dynamics in reward history computation

8:00 AM - 12:00 PM

***Y. JO**, E. L. SYLWESTRAK, S. VESUNA, S. QUIRIN, A. DRINNENBERG, T. X. LIU, J. SHI, D. K. KIM, C. RAMAKRISHNAN, R. CHEN, K. V. SHENOY, D. SUSSILLO, K. DEISSEROTH;
Stanford Univ., Stanford, CA

Abstract

Neural computations for storing and processing history of reward and punishment are essential for the survival of animals. The timescale of such computations tends to be substantially longer than that of intrinsic membrane time constants of single neurons or even of typical single trials or tasks, suggesting the need for specific mechanisms generating persistent activity of relevant neural populations. Here we measured multi-regional and cell-type-specific neural population activity in awake mice performing reward history-guided decision-making tasks, using Neuropixels extracellular electrophysiology and two-photon Ca^{2+} imaging. With these datasets in hand, we conducted data-driven dynamical systems modeling using LFADS (latent factor analysis via dynamical systems) to reverse-engineer the population dynamical structures. We identified relevant persistent activity in multiple brain regions including retrosplenial cortex (RSP; N=6 mice), anterior lateral motor cortex (ALM; N=8), and medial habenula (MHb; N=9). Within MHb, genetic dissection of cell types revealed cell-type-specific line attractor dynamics underlying reward history integration. Learned dynamical systems models were utilized to make predictions on temporal evolution of activity and behavior, which in turn guided perturbation experiments. One-photon optogenetic inhibition of the reward history-integrating populations resulted in degraded behavioral performance (p=0.025, N=5), consistent with the hypothesized importance of the underlying circuitry and computation. Two-photon holographic optogenetic perturbation could be designed based on the identified dynamical structures to be orthogonal or parallel to the line attractor (N=3). Taken together, our integrated approach using a tight experiment-theory loop presents a framework by which the large-scale neurophysiology experiments can be efficiently guided by quantitative data-driven models for multi-regional and cell-type-specific investigation of neural population dynamics underlying fundamental behaviorally-relevant computations.

☆ Presentation 499.18 / ZZ32 Cardiogenic control of affective behavioral states

8:00 AM - 12:00 PM

***R. CHEN**[1], B. HSUEH[1], D. D. TANG[1], M. RAFFIEE[2], Y. JO[3], Y. KIM[1], M. INOUE[4], C. RAMAKRISHNAN[2], L. TAN[5], M. M. ZEINEH[6], M. GOUBRAN[7], K. DEISSEROTH[8];
[1]Stanford Univ., Palo Alto, CA; [2]Stanford Univ., Stanford, CA; [3]Applied Physics, Stanford Univ., Palo Alto, CA; [4]Bioengineering, Stanford Univ., Menlo Park, CA; [5]Bioengineering, Stanford Univ., Palo Alto, CA; [6]Radiology, Stanford Univ., Stanford, CA; [7]Med. Biophysics, Univ. of Toronto, Toronto, ON, Canada; [8]Stanford, Stanford, CA

Abstract

Physiological theories of emotion have suggested that bodily signals (e.g., changes in heart rate) might influence emotional states such as fear and anxiety. However, this hypothesis- widely debated for more than a century- has remained experimentally intractable. To alter cardiac rhythms, nonspecific interventions such as drugs or painful shocks would be required. Even with high-resolution tools like optogenetics, optical control of heart rate in freely moving animals would not have been possible (until recently), since existing opsins were not sensitive enough to control a large organ like the heart with enough precision and power.
To determine how altered cardiac rhythms might affect emotional or affective states, we developed a noninvasive optogenetic pacemaker utilizing 1) ChRmine under control of the mouse cardiac troponin T promoter delivered via AAV9 for enhanced tropism in cardiac tissue (AAV9-mTNT::ChRmine-2A-oScarlet) and 2) wearable micro-LED optics. Using the ultrapotent opsin ChRmine enabled precise control of cardiac rhythms up to 1000 beats per minute in freely-moving mice within a safe range of illumination power similar to conventional optogenetics. We tested the behavioral impact of truly precise and specific induced cardiac changes on behavior and affective state. We found that this primary and direct tachyarrhythmia indeed potently enhanced anxiety-like behavior in mice (n=16), demonstrating causal impact of the body to brain axis. We observed behavioral changes only in risky contexts, suggesting that both exteroceptive and interoceptive processes were synergistically required to modulate behavioral state changes. To identify potential brain regions involved in cardiac interoception, we performed a whole brain activity screen in in double transgenic TRAP2:Ai14 mice, and identified posterior insular cortex as a potential mediator of bottom-up cardiac signal processing (n=8). We then showed that simultaneous optogenetic inhibition of posterior insular cortex with iC++ during optical cardiac pacing was sufficient to reverse the induced behaviors, implicating this region as a necessary site for mediating cardiogenic anxiety-like and apprehensive behavior (n=8). Our findings offer insights into the specific mechanisms by which such bodily signals can causally influence complex behaviors, and reveal that body and brain must be considered together. We also present robust and generalizable tools for non-invasive, temporally precise control of precision-targeted cells, tissues, and organs throughout the body.

☆ Session 514 Post-Lesion Cortical Dynamics During Reaching

1:00 PM - 2:45 PM

SDCC 7

☆ Presentation 514.07 Bistability of beta oscillations and movement-related population spiking in motor areas

2:30 PM - 2:45 PM

***H. CHOI**[1], J. KIM[1], P. KHANNA[1], L. NOVIK[2], K. THIESEN[2], R. J. MORECRAFT[3], K. GANGULY[1];
[1]Neurol., Univ. of California, San Francisco, San Francisco, CA; [2]California Natl. Primate Res. Ctr., Univ. of California, Davis, Davis, CA; [3]Lab. of Neurolog. Sci., Univ. of South Dakota, Vermillion, SD

Abstract

Beta oscillations are a well-known feature of movement preparation and have been clinically used to track motor recovery. Moreover, it is increasingly clear that the movement-related spatial and temporal dynamics of population spiking activity in the motor cortex are important for movement control. Changes in population spiking are also known to track motor recovery and can be a target for neuromodulation using electrical stimulation. However, it remains unclear how beta oscillations and movement-related population spiking activity interact. The goal of this study was to characterize how beta oscillations and neural population dynamics interact and to develop a model for neuromodulation that accounts for their interaction. We measured local field potentials (LFP) and population spiking activity in the motor cortex of non-human primates performing reach and grasp tasks. We also performed such recordings from the premotor cortex in animals recovering from an M1 lesion. We tracked spiking activity and behavior throughout the recovery process. We then analyzed the interactions between changes in beta power and spiking activity during movements In general, we found that in expert animals there were rapid and sharp transitions from population spiking to changes in beta power. We characterized this process using a model of bistability, which is characterized as the presence of two states that can rapidly transition from one to the other. We also found that the reemergence of bistability correlated closely with the recovery of reach and grasp function. Notably, we found that low frequency alternating current electrical stimulation could modulate the bistable relationship between beta and population spiking. We also developed a computational model that could inform how best to deliver stimulation for a bistable process. Overall, our results indicate a close relationship between cortical beta oscillations and population spiking activity during skilled (recovered) reach and grasp behaviors. The bistable nature of this relationship suggests rapid transitions between states that are important to consider for movement control and for neuromodulation.

☆ Session 523 Synaptic Plasticity: Spike-Timing, Homeostatic and Other Mechanisms

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 523.11 / B37 Regulation of immediate early gene NPTX2 trafficking by PV circuit and cholinergic modulation in vivo

1:00 PM - 5:00 PM

***S.-E. ROH**, A. DELGADO, P. WORLEY;
Johns Hopkins Med. Institutions, Baltimore, MD

Abstract

NPTX2 (Neuronal Pentraxin 2) is an immediate early gene that is expressed in excitatory neurons and exocytosed onto the excitatory synapses of parvalbumin-interneurons (PV-IN). NPTX2 clusters AMPAR of PV-IN and mediates homeostatic scaling, supporting excitation-inhibition balance. Later NPTX2 is shed from synapses into the cerebrospinal fluid (CSF), where NPTX2 is detectable by ELISA. The CSF NPTX2 is significantly reduced and correlates with cognitive performance in individuals with Alzheimer's disease and schizophrenia. Previous ***in vivo*** imaging studies established NPTX2-SEP (Super-Ecliptic pHluorin) as a marker of synaptic NPTX2 and found that the trafficking in V1 is reduced on day 1 of monocular deprivation at the same time as the pyramidal to PV-IN connectivity is reduced. This raises a possibility that loss of PV-IN activity can lead to LTD of the excitatory synapse and subsequent NPTX2 shedding via spike-timing-dependent plasticity mechanism. In this study, we employed multiple approaches to modulate the PV-IN activity *in vivo* to investigate the effect of post-synaptic activity on NPTX2 trafficking using two photon microscopy together with chemogenetics and optogenetics. Direct inhibition of PV-IN by hM4d(Gi) resulted in a remarkable reduction of NPTX2-SEP signals, which is regarded as shedding. Optogenetic activation of cholinergic neurons using C1V1 as a natural way to inhibit PV-IN also induced shedding of NPTX2. Administration of low-dose nicotine, known to suppress PV-IN, also downregulated synaptic NPTX2 levels. Conversely, when PV-INs were chemogenetically activated with hM4d(Gq), NPTX2 accumulated in the synapses. This series of observations reveal the regulation of NPTX2 shedding by the level of post-synaptic PV-IN activity.

☆ Session 527 Reactive Astrocytes

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 527.08 / C37 Hypothalamic GABRA5-positive neurons control obesity via astrocytic GABA

1:00 PM - 5:00 PM

***M. SA**[1], E.-S. YOO[2], W. KOH[1], M. G. PARK[1], H.-J. JANG[3], Y. YANG[3], J. LIM[1], W. WON[1], J. KWON[1], M. BHALLA[1], H. AN[1], Y. SEONG[1], S. LEE[4], K. PARK[5], P.-G. SUH[3], J.-W. SOHN[2], C. J. LEE[1];
[1]Ctr. for Cognition and Sociality, Inst. for Basic Sci. (IBS), Daejeon, Korea, Republic of; [2]Biol. Sci., Korea Advanced Inst. of Sci. and Technol., Daejeon, Korea, Republic of; [3]Ulsan Natl. Inst. of Sci. and Technol. (UNIST), Ulsan, Korea, Republic of; [4]Res. Animal Resource Ctr., [5]Convergence Res. Ctr. for Diagnosis, Treatment and Care Syst. of Dementia, Korea Inst. of Sci. and Technol. (KIST), Seoul, Korea, Republic of

Abstract

The lateral hypothalamic area (LHA) regulates food intake and energy expenditure. Although LHA neurons innervate adipose tissues, the identity of neurons that regulate fat is undefined. Here we identify that GABRA5-positive neurons in LHA (GABRA5^{LHA}) polysynaptically project to brown and white adipose tissues in the periphery. GABRA5^{LHA} are a distinct subpopulation of GABAergic neurons and show decreased pacemaker firing in diet-induced obesity (DIO) mouse model. Chemogenetic inhibition of GABRA5^{LHA} suppresses energy expenditure and increases weight gain, whereas gene-silencing of GABRA5 in LHA decreases weight gain. In DIO mouse model, GABRA5^{LHA} are tonically inhibited by nearby reactive astrocytes releasing GABA, which is synthesized by MAOB. Gene-silencing of astrocytic MAOB in LHA reduces weight gain significantly without affecting food intake, which is recapitulated by administration of a MAOB inhibitor, KDS2010. We propose that firing of GABRA5^{LHA} facilitates energy expenditure and selective inhibition of astrocytic GABA is a molecular target for treating obesity.

☆ Session 528 Brain Aging: Molecular and Cellular Changes

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 528.16 / D3 Dna break-induced loss of epigenetic information as a cause of neuronal aging

1:00 PM - 5:00 PM

***J.-H. YANG**[1], P. T. GRIFFIN[1], J. A. AMORIM[1], M. HAYANO[2], L. A. RAJMAN[1], A. R. PFENNING[3], D. A. SINCLAIR[1];
[1]Harvard Med. Sch., Harvard Med. Sch., Boston, MA; [2]Keio Univ., Tokyo, Japan; [3]Computat. Biol. Dept., Carnegie Mellon Univ., Pittsburgh, PA

Abstract

There are numerous hallmarks of aging in mammals, but no unifying cause has been identified. In budding yeast, aging is associated with a loss of epigenetic information that occurs in response to genome instability, particularly DNA double-strand breaks (DSBs). Mammals also undergo predictable epigenetic changes with age, including alterations to DNA methylation patterns that serve as epigenetic "age" clocks, but what drives these changes is unknown. Using a transgenic mouse system called "ICE" (for inducible changes to the epigenome), we show that a tissue's response to non-mutagenic DSBs reorganizes the epigenome and accelerates molecular, physiological, and cognitive changes normally seen in older mice, including the advancement of the epigenetic clock. These findings implicate DSB-induced epigenetic drift as a conserved cause of aging from yeast to mammals.

☆ Session 533 Huntington's Disease : Molecular Mechanisms

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 533.07 / E46 Analysis of gene networks and pathways in the striatum of HD mice exposed to a super-enriched

1:00 PM - 5:00 PM

environment

***H. KIM**[1], S. H. WEE[1], J.-C. CHAI[1], T. YOO[1], R. ZUKIN[2], J.-Y. HWANG[1];
[1]Dept. of Pharmacol. and Neurosciences, Creighton Univ. Sch. of Med., Omaha, NE; [2]Dominick P. Purpura Dept. of Neurosci., Albert Einstein Col. of Med., Bronx, NY

Abstract

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder characterized by progressive motor, psychiatric, and cognitive decline. Marked neuronal loss in the striatum and cerebral cortical structures is the main neuropathological hallmark of HD. Environmental factors can alter gene expression through epigenetic responses and can change the mechanisms of experience-dependent plasticity such as synaptic plasticity and neurogenesis. An enriched environment has been shown to delay the onset and progression of motor symptoms and to improve neurological function and cognitive deficits in HD mice. However, the impact of an enriched environment on transcriptional changes in the R6/2 transgenic mouse model of HD is yet unclear. To address this issue, we performed genome-wide transcriptome analysis using next-generation RNA-seq in striatal tissue from HD and wild-type (WT) mice reared in either an enriched (EE) or normal (NE) housing environment. We then performed bioinformatic analysis on the differentially expressed genes (DEGs, fold change of ±2 and FDR < 0.01) using the Ingenuity Pathway Analysis (IPA). We first investigated how gene expression is changed in HD mice during the development of HD symptoms. Canonical pathway analysis showed that the activity of the synaptogenesis signaling pathway is reduced in HD mice reared under the normal environment at 12 weeks ***vs.*** 4 weeks. An analysis in disease and functions showed that the gene network of these DEGs is implicated in movement disorders and the degeneration of neurons. These results indicate that genes changed in HD mice correlate with the pathogenesis of HD. Next, we analyzed 268 DEGs identified as 'EE'-common genes, which are changed in both HD and WT mice reared in an EE vs. NE. The IPA analysis of these common DEGs showed that genes associated with networks of long-term potentiation, the release of neurotransmitters, and learning and memory are activated, while genes associated with networks of behavior deficits, movement disorders, and neurological signs are inhibited. Taken together, we anticipate that the identification of genes and gene networks that are altered in HD mice in response to enriched environments will assist us in understanding how enriched environments can improve HD symptoms and neurological functions and will contribute to the development of novel therapeutic strategies to ameliorate motor and cognitive deficits associated with this debilitating and devastating disease.

☆ Presentation 533.17 / E54 Huntington's disease produces multiplexed transcriptional vulnerabilities of striatal D1-D2 and Striosome-Matrix Neurons

1:00 PM - 5:00 PM

***A. MATSUSHIMA**[1], S. S. PINEDA[1,2], J. R. CRITTENDEN[1], H. LEE[1,2], K. GALANI[1,2], J. MANTERO[1,2], M. KELLIS[1,2], M. HEIMAN[1,2], A. M. GRAYBIEL[1];
[1]MIT, Cambridge, MA; [2]Broad Inst. of MIT and Harvard, Cambridge, MA

Abstract

Striatal cell-type-specific vulnerability in Huntington's disease (HD) preferentially affects dopamine D2R-expressing projection neurons (SPNs), compatible with manifest motor symptomatology in HD. A second, less fully studied feature of striatal vulnerability involves the compartmental organization of the striatum, with neurochemically specialized labyrinthine 'striosomes' thought to be affected especially in relation to premanifest mood symptomatology.To disentangle the cell-type-specific vulnerability in HD, we performed single-nucleus RNA sequencing on striatal samples from two murine models (zQ175 and R6/2) and rare Grade 1 HD patient tissue, and examined striosome and matrix sub-clusters within parent D1 and D2 SPN clusters. In the Grade 1 human HD, striosomal SPNs were the most depleted SPN population. Surprisingly, for both mouse models, transcriptomic distinctiveness was diminished more for striosome-matrix SPNs than for D1-D2 SPNs. Compartmental markers tended to cancel endogenous identities of striosomal and matrix SPNs; striosomal makers were downregulated in striosomal SPNs and upregulated in matrix SPNs, and matrix markers were upregulated in striosomal SPNs and downregulated in matrix SPNs. On the contrary, markers for D1-D2 SPNs exhibited less identity obscuring; they appeared up- and down-regulated in a non-systematic way. The degree of dysregulation (i.e., absolute values of up- or down-regulations) was largest in D2R-expressing SPNs, recapitulating the D2-dominent vulnerability in HD, and reflected in genes upregulated in specific cell types and downregulated in others.These results suggest that striosomes are the first to die in human HD, and that striosome-matrix identities are more vulnerable than those of D1-D2, a pattern that could reflect a differentiation deficiency during development due to loss of function of normal Huntingtin, as proposed previously. Given that D2-dominent transcriptional dysregulation is observed from only about the age of onset, the two axes of striatal organization might be affected differentially in time and in nature, with the striosome-matrix axis affected during development, leading to deficient compartmental identities, and the D1-D2 axis affected later, around the age of onset of motor symptoms.

☆ Presentation 533.21 / E58 Cell Type-Specific Transcriptomics Reveals that Mutant Huntingtin Leads to Mitochondrial RNA Release and Neuronal Innate Immune Activation

1:00 PM - 5:00 PM

***H. LEE**[1,2], R. J. FENSTER[1], S. S. PINEDA[3,2], W. S. GIBBS[5], S. MOHAMMADI[3,2], J. DAVILA-VELDERRAIN[3,2], F. J. GARCIA[4], M. THERRIEN[2], H. S. NOVIS[5], F. GAO[1,6], H. A. WILKINSON[7], T. VOGT[7], M. KELLIS[3,2], M. J. LAVOIE[5], M. HEIMAN[1,4,2];
[1]Picower Inst. for Learning and Memory, Cambridge, MA; [2]Broad Inst. of MIT and Harvard, Cambridge, MA; [4]Dept. of Brain and Cognitive Sci., [3]MIT, Cambridge, MA; [5]Ann Romney Ctr. for Neurologic Dis., Brigham and Women's Hosp. and Harvard Med. Sch., Boston, MA; [6]Bioinformatics Resource Ctr., The Beckman Inst. at Caltech, Pasadena, CA; [7]CHDI Management, Inc./CHDI Fndn., Princeton, NJ

Abstract

Huntington's disease (HD) is a fatal neurodegenerative disorder caused by CAG trinucleotide repeat expansions in the huntingtin (*HTT*) gene. Although mutant huntingtin (*mHTT*) has been linked to both toxic gain-of-function and loss-of-function effects, it is still not fully understood how ***mHTT*** leads to the death of striatal spiny projection neurons, the most vulnerable cell type in HD. To gain new molecular insights, we conducted a large-scale cell type-specific transcriptomic profiling study across both human HD and mouse models of HD at various stages of disease progression, using two complementary techniques: cell type-specific Translating Ribosome Affinity Purification (TRAP-seq, a methodology used to purify ribosome-bound mRNAs in

bulk from a specific cell type) and single nuclear RNA sequencing (snRNA-seq, a methodology used to capture nuclear RNAs at the single-cell level).
Our systematic analyses of caudate/putamen (striatal) cell type-specific gene expression changes in human HD and mouse models of HD revealed a large number of both non-cell type-specific and cell type-specific responses that are induced by ***mHTT***. Among these we observed the release of mitochondrial RNA (mtRNA, a potent mitochondrial-derived innate immunogen) and a concomitant upregulation of innate immune signaling in ***Drd2***-expressing striatopallidal "indirect pathway" spiny projection neurons (iSPNs, the most vulnerable cell type in HD). Normally these mtRNAs are sequestered inside the mitochondria. In response to ***mHTT***, however, mtRNAs were released from SPN mitochondria into the cytoplasm. When released to the cytosol, mitochondrial nucleic acids can be sensed by various innate immune sensors, including the double-stranded RNA-dependent protein kinase PKR (which senses mtRNA) or cGAS-STING (which senses mtDNA), which can then trigger downstream innate immune responses that may lead to cell death. The iSPN-enhanced release of mtRNA correlates with ***mHTT*** CAG repeat length, is associated with disease model age, and even occurs at very early stages of HD model progression when the level of gene expression dysregulation is small. Our work reveals a new mechanism that may contribute to ***mHTT*** toxicity in HD and points to new therapeutic opportunities.

☆ Session 535 Tau: Cellular and Molecular Mechanisms II

1:00 PM - 5:00 PM

SDCC Halls B-H

★ Presentation 535.08 / F28 Role of phosphorylation in activity-dependent release of human tau from Drosophila larval neuromuscular junction

1:00 PM - 5:00 PM

R. UDDIN, *D. LEE;
Ohio Univ., Athens, OH

Abstract

Alzheimer's disease (AD) is one of the most common forms of dementia that shows progressive memory loss. A key pathological hallmark of AD, neurofibrillary tangles (NFTs) are intracellular aggregates of hyper-phosphorylated tau protein. NFTs are initially formed in the brain's temporal lobes and then progressively spread throughout the brain. Based on these findings, it has been proposed that intracellular tau is released into extracellular space as oligomers from the affected neurons and then taken up by the nearby healthy neurons. Finally, transferred tau serves as a seed in a healthy neuron for its continuous propagation. However, mechanisms of tau propagation are still not well elucidated. In our study, we wanted to see how neuronal activity and phosphorylation affect tau release as both neuronal excitability and phosphorylation are increased in the early stage of AD. We used the 3rd instar ***Drosophila*** larval neuromuscular junction (NMJ) as an ***in vivo*** model system to investigate mechanisms underlying tau release. We have chosen ***Drosophila*** NMJ because it is glutamatergic and greatly resembles neuronal and synaptic functions in human central nervous system. To increase neuronal excitability, we expressed channelrhodopsin (ChR2) in addition to wild-type human tau (hTau) in the glutamatergic motor neurons of flies by using a driver D42-Gal4. ChR2 was activated by blue light (470nm, 3x 10 min with 1 hour interval) to induce hTau release. Our ELISA results showed a significant increase of hTau release into the hemolymph from NMJ compared to the control group. Furthermore, we tested the role of different phosphorylation sites (pSites) of tau protein on the activity-dependent release by using phospho-specific antibodies (e.g., AT8 or PHF-1). We have demonstrated that tau released by neuronal stimulation is highly phosphorylated at different sites in the proline-rich domain (PRD) and C-terminal. Based on our findings, it can be said that neuronal excitability and phosphorylation play a significant role in hTau release. We are currently examining the importance of individual pSites in PRD and C-terminal by using ***Drosophila*** transgenic lines carrying one or two mutations in the pSites (e.g., UAS-hTau[S202A/T205A]). Overall, our novel ***Drosophila*** NMJ model will provide an important ***in vivo*** experimental platform to examine molecular and cellular mechanisms underlying tau release and the impact of tau phosphorylation on its activity-dependent release.

☆ Session 537 ALS Mechanisms and Models I

1:00 PM - 5:00 PM

SDCC Halls B-H

★ Presentation 537.07 / F49 A genetic screen of human neurodegenerative disease alleles identifies factors that drive rapid neuromuscular junction degradation in Drosophila

1:00 PM - 5:00 PM

***I. SANGHVI**[1], S. WU[1], S. PERRY[1], N. TRAN[1,2], D. DICKMAN[1];
[1]Dept. of Neurobio., [2]USC Neurosci. Grad. Program, USC, Los Angeles, CA

Abstract

A variety of neurological and neurodegenerative diseases have been modeled in ***Drosophila***, with human disease-associated alleles causing phenotypes that may recapitulate disease etiology. While much insight has been gained through transgenic expression of these alleles in all neurons or the visual system, synaptic function and degeneration in these models has not been systematically assessed at a common synapse. We have systematically screened human neurodegenerative disease models at the ***Drosophila*** neuromuscular junction (NMJ), a powerful model glutamatergic synapse that permits sophisticated genetic, electrophysiological, and imaging approaches. We expressed disease-related transgenes in motor neurons corresponding to a variety of human disease including Alzheimer's, Parkinson's, Frontotemporal Dementia, ALS, Huntington's, and Myotonic Dystrophy, assessing synaptic bouton number and retractions. Out of ~100 transgenes screened, a handful of lines exhibited significant NMJ degeneration. Detailed morphological and electrophysiological analyses, as well as secondary behavioral and learning assays, were consistent with severe NMJ degeneration. Finally, we probed whether rapid NMJ degeneration was protected or exacerbated following activation of the dual leucine zipper kinase (DLK) and SARM signaling programs, associated with neural injury and degeneration. Ultimately, we hope to establish well defined ***Drosophila*** NMJ models of human disease to fully characterize their impacts on synaptic degeneration, function, and plasticity.

★ Presentation 537.27 / G6 Mitochondrial dysfunction in a Drosophila model for ALS

1:00 PM - 5:00 PM

***M. SWARTZLANDER**, J. M. SABANDAL, A. A. BUTLER, R. L. DAVIS;
UF Scripps Biomed. Res., UF Scripps Biomed. Res., Jupiter, FL

Abstract

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder affecting motor neurons and has been linked to mutations in TAR DNA-binding protein 43 (TDP43). ALS patients exhibit progressive muscle weakness resulting in an eventual loss in voluntary motor function, as well as other cognitive and behavioral symptoms. As treatment options are limited, patients often die within a few years after diagnosis. TDP43 has been associated with mitochondrial impairment. Additionally, a growing body of literature in GWAS studies, animal models, and cell culture implicate mitochondrial dysfunction as a central player in the onset of ALS and other neurodegenerative diseases. However, studies of ALS using mammalian models can be prohibitively costly and time consuming, often spanning hundreds of days. Here, we describe behavioral and cellular phenotypes observed in a series of assays using ***Drosophila melanogaster*** with induced expression of mutant TDP43(G298S) in motor neurons during adulthood. We observed decreased lifespan, motor impairment, and changes in mitochondrial morphology that are like other ALS models. The phenotypes observed are progressive as in ALS, declining with age. Induced expression of TDP43(G298s) in adult *Drosophila* provides a useful tool for ***in vivo*** studies of TDP43 pathology, reducing the time and cost required for similar experiments with a mammalian model by an order of magnitude.

☆ Session 540 CNS Pain and Touch Mechanisms in Preclinical Models

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 540.17 / J1 Functions of Tacr1- and Gpr83-expressing spinoparabrachial neurons and their neuropeptide signaling in acute and neuropathic pain

1:00 PM - 5:00 PM

***S. CHOI**[1], J. TURECEK[1], A. R. MAGEE[1], D. A. YARMOLINSKY[2], C. J. WOOLF[2], D. D. GINTY[1];
[1]Neurobio., Harvard Med. Sch., Boston, MA; [2]F.M. Kirby Neurobio. Ctr., Boston Children's Hosp., Boston, MA

Abstract

Pain is initiated by the activation of nociceptors that innervate the skin and internal organs. Nociceptive signals are propagated into the spinal cord and then transmitted to the brain by spinal cord projection neurons (PNs). These spinal PNs are attractive therapeutic targets for pain treatment because nociceptive signals emanating from the periphery are channeled through these spinal cord output neurons ***en route*** to the brain to produce pain sensations. Spinoparabrachial (SPB) neurons, a major population of spinal PNs that innervate the lateral parabrachial nucleus of the pons, represent an ideal neuronal population for developing new approaches to treat pain because they convey touch and pain information to higher brain centers that control the affective aspects (i.e., emotional “feelings”) of touch and pain. Previously, we showed that *Tacr1*$^+$ and *Gpr83*$^+$ SPB neurons form two largely-nonoverlapping subdivisions of the SPB pathway that cooperate to convey tactile, thermal and noxious signals from the spinal cord to the brain. To further define the contribution of each SPB subdivision to pain sensation and associated behavioral responses to noxious stimuli, we have begun to examine the effects of acute silencing of *Tacr1*$^+$ and *Gpr83*$^+$ SPB neurons, individually or simultaneously, on nocifensive behaviors using a newly generated dual recombinase-dependent SYP1-miniSOG mouse line that enables selective, light-dependent silencing of synaptic transmission. In addition, to determine if neuropeptide signaling mediated by either TACR1, GPR83 or both in the spinal cord is required for pain transmission, we also have begun to examine acute and neuropathic pain behaviors following spinal cord-specific deletions of the ***Tacr1*** and ***Gpr83*** genes using mouse lines that harbor conditional alleles of ***Tacr1*** and ***Gpr83*** in conjunction with spinal cord specific Cre lines. Collectively, these behavioral analyses will provide insights into the functions of *Tacr1*$^+$ and *Gpr83*$^+$ SPB neurons and neuropeptide signaling mediated by the TACR1 and GPR83 GPCRs in acute and neuropathic pain and may reveal novel therapeutic targets for treating pain.

☆ Session 547 Cross-Modal Processing I

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 547.12 / T6 Flexible integration of audiovisual inputs in the parietal cortex mediates multisensory decisions under audiovisual conflicts

1:00 PM - 5:00 PM

***I. CHOI**, J.-H. KIM, Y.-H. SONG, S.-H. LEE;
Biol. Sci., KAIST, Daejeon, Korea, Republic of

Abstract

Multisensory integration is a fundamental process underlying optimal decision-making in mammals. However, the state-dependent flexibility in multisensory decisions remains elusive. Here, we found that the mouse posterior parietal cortex (PPC) mainly represents visual information of the audiovisual stimuli, which was suppressed when the mice make auditory-dominant decisions in audiovisual conflict. Interestingly, locomotion suppresses auditory inputs to the PPC and switches auditory-dominant decisions to visual-dominant ones. In the auditory cortex (AC), locomotion suppressed neurons projecting to the PPC (AC_{PPC}) but not those projecting to the striatum (AC_{STR}). By circuit-specific optogenetic manipulation, we double-dissociated that the AC_{PPC} mediates auditory-dominant decisions in audiovisual conflicts and the AC_{STR} mediates unisensory auditory decisions. Moreover, axons of the secondary motor cortex (M2) projected to and suppressed the AC_{PPC} neurons, and this M2 input to the AC was critical for locomotion-dependent switches in multisensory decisions. Collectively, our data demonstrate that locomotion suppresses auditory afferents to the PPC to enhance visual decisions under audiovisual conflicts without disrupting unisensory decisions. This modulation promotes flexible perceptual decisions in actively moving animals exposed to multisensory stimuli.

☆ Session 551 Sensing and Detecting Movement

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 551.07 / X5 Characterization of TMEM43 as a novel ion channel

1:00 PM - 5:00 PM

M. W. JANG, J. WON, Y.-E. HAN, C. J. LEE;
Ctr. for Cognition and Sociality, Inst. for Basic Sci., Daejeon, Korea, Republic of

Abstract

TMEM43 is a transmembrane protein with 4 transmembrane (TM) domains. A nonsense ***TMEM43*** variant p.(Arg372Ter) has been shown to cause auditory neuropathy spectrum disorder (ANSD) in two Asian families from South Korea and China. A knock-in mouse with the p.(Arg372Ter) variant that recapitulates a progressive hearing loss in humans, revealed that TMEM43 interacts with the Connexin26 and Connexin30 gap junction channels in the cochlea and mediates passive conductance current, that is critical for normal hearing. In this study, we examined if TMEM43 can function as an ion channel. Heterologous expression of TMEM43 demonstrated that TMEM43 is permeable to Na^+, K^+, and Cs^+ ions, indicating that TMEM43 is a non-selective cation channel. The TMEM43-mediated current decreased gradually with lowering external solution pH, further characterizing TMEM43 as an external-pH sensing channel. Utilizing the endogenous cysteine residue at TM3, we could predict that the pore-forming residue lies near TM3 and Loop2 domain. Importantly, stochastic channel-opening of the lipid-bilayer-reconstituted purified TMEM43 protein was observed, strengthening the proposal of TMEM43 as an ion channel. Lastly, heterologous expression of ***TMEM43***-p.(Arg372Ter) resulted in a loss of channel activity in dominant-negative fashion, as in the hearing loss phenotype. These results together provide molecular and functional properties of TMEM43 and identify TMEM43 as a novel ion channel.

☆ Session 554 Autonomic Regulation of Sleep: Behavior II

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 554.09 / AA11 The extract of chrysanthemum morifolium and linarin enhanced the sleep duration in rodent models via Cl^- channel activation

1:00 PM - 5:00 PM

M. KIM, *S. OH;
Ewha Womans Univ, Sch. of Med., Ewha Womans Univ, Sch. of Med., Seoul, Korea, Republic of

Abstract

Interest in sleep-promoting compounds derived from natural compounds is increasing owing to various side effects of prescription drugs for sleep disorders such as benzodiazepines. Dried Chrysanthemum morifolium flowers have traditionally been used in Korea for the treatment of insomnia. Thus, in this study, the sleep-promoting activity of ***Chrysanthemum morifolium*** extract and its active substance Linarin was assessed by measuring sleep latency time and duration in a pentobarbital-induced sleep mice model. Additionally, the effects of orally administered ***Chrysanthemum morifolium*** extract on rapid-eye-movement (REM) and non-REM sleep were analyzed by electroencephalography (EEG) in rats. In a dose-dependent manner, ***Chrysanthemum morifolium*** extract and Linarin showed longer sleep duration in the pentobarbital-induced sleep test compared to administered with pentobarbital alone groups at both hypnotic and subhypnotic doses. The low and high doses of ***Chrysanthemum morifolium*** extract administration significantly increased sleep quality, especially the relative power of low-frequency (delta) waves, compared with the normal group. Linarin and muscimol both increased chloride (Cl^-) uptake in the SH-SY5Y human cell line and the chloride influx was reduced by bicuculline. After administration of ***Chrysanthemum morifolium*** extract, the hippocampus, frontal cortex, and hypothalamus from rodents were collected and blotted for GAD (glutamic acid decarboxylase) and $GABA_A$ receptors subunit expression levels. The expression of GAD, α1- and β2-subunits of the $GABA_A$ receptor was modulated in the mouse brain. In conclusion, ***Chrysanthemum morifolium*** extract augments pentobarbital-induced sleep duration and enhances the sleep quality in EEG waves. These effects might be due to the activation of Cl^- channel.

☆ Session 555 Fear and Aversive Learning and Memory: Acquisition

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 555.12 / CC5 Activation of PBN CGRP neurons promotes the arrangement of defensive behavior appropriate to the context

1:00 PM - 5:00 PM

***H. CHO**, G. PYEON, I.-H. BAEK, Y. JO;
Sch. of Psychology, Korea Univ., Seoul, Korea, Republic of

Abstract

Fear is expressed by a wide spectrum of behaviors and it is crucial to orchestrate defensive behaviors that match distinct threat circumstances. Freezing is highly effective in response to repeated electric footshock by an invisible predator, whereas darting, in which an animal rapidly moves forward in an attempt to flee from perceived danger, is most appropriate when chased by a predator. The neurons expressing calcitonin gene-related peptide (CGRP) in the parabrachial nucleus (PBN) are known as a general alarm signal which respond to aversive stimuli and alert the forebrain of ongoing or potential threats. To determine whether CGRP^{PBN} neurons relay aversive information and contribute to defensive response, we bilaterally injected adeno-associated virus carrying Cre-dependent channelrhodopsin and implanted fiber-optic cannulae over PBN of $\text{Calca}^{\text{cre/+}}$ mice. We activated CGRP^{PBN} neurons for 30 s and confirmed that repeated 30 Hz stimulation of CGRP^{PBN} neurons evoked robust time-locked freezing behavior in mice. We investigated whether activation of CGRP^{PBN} neurons promote adaptive defensive behavior that fits the context using a naturalistic threat paradigm. Chasing threat paradigm mimics an imminent threat situation where mice are placed in a circular track and chased by a predator-like robot. The ecological setting allows the observation of darts, which were defined as rapid movements preceded by immobility. We subjected mice to threat conditioning in which a tone (10 s, 70 dB) was paired with a predator-like robot chasing (3 s, 0.58 m/s). We activated CGRP^{PBN} neurons of $\text{Calca}^{\text{cre/+}}$ mice (n = 5) during the chasing threat and observed a significant decrease in freezing compared to the control group (n = 7) when the tone was presented alone the next day. Instead, CGRP^{PBN}-activated mice showed greater darting compared to the control group. Followed by an extinction training, the control group displayed decreased darting whereas darting by CGRP^{PBN}-activated mice was maintained and significantly greater compared to the control group. Indeed CGRP^{PBN}-activated mice showed significantly less freezing compared to the control group. We discovered that mice that received CGRP^{PBN} stimulation learned to dart in response to the cue associated with the chasing threat and showed impaired extinction learning. Our findings suggest that CGRP^{PBN} neurons are the core alarm system in which the enhanced alarm signal by CGRP^{PBN} neurons elicited behavioral responses appropriate to distinct threat stimuli.

☆ Session 557 Neural Basis of Reward II

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 557.19 / GG1 Altered basal ganglia output during self-restraint

1:00 PM - 5:00 PM

B.-M. GU[1], *J. BERKE[2];
[1]Dept. of Neurol. and Neurolog. Sci., Stanford, Stanford, CA; [2]Neurol., UCSF, San Francisco, CA

Abstract

Our capacity for behavioral inhibition is considered central to cognitive control and is compromised in a range of neurological and psychiatric disorders. Behavioral inhibition can be ‘reactive’ - e.g. aborting imminent actions in response to a Stop signal - or ‘proactive’ - e.g. restraining actions in anticipation of a possible Stop signal. Reactive inhibition has been shown to involve fast cue responses in frontal cortex and basal ganglia pathways, including from the subthalamic nucleus (STN) to the basal ganglia output nucleus substantia nigra pars reticulata (SNr) (Schmidt et al. 2013). The underlying mechanisms of proactive inhibition are less well understood, but have been proposed (Aron 2011) to involve the pathway from striatum via globus pallidus pars externa (GPe) “indirectly” to SNr. To examine how changes in basal ganglia output contribute to self-restraint, we recorded SNr neurons (n=619, from 10 adult male Long-Evans rats) during a proactive behavioral inhibition task (Gu et al., 2020). Rats responded to Go! cues with rapid leftward or rightward movements, but also prepared to cancel one of these movement directions, for which a Stop! cue might occur. This action restraint - visible as direction-selective slowing of reaction times - altered both rates and patterns of SNr spiking. Overall firing rate was elevated before the Go! cue, and this effect was driven by a subpopulation of direction-selective SNr neurons. In neural state space, this corresponded to a shift away from the restrained movement. Furthermore, SNr activity showed an increase in spike variability during proactive inhibition. Increased spike variability corresponded to variable state-space trajectories, slowing reaction times via reduced preparation to move. These findings open new perspectives on basal ganglia mechanisms for movement preparation and cognitive control, at a single cell level and also in population dynamics.

☆ Session 558 Emotion Processing in the Human Brain

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 558.02 / HH2 Introspection makes your brain more like you: Periodic thought sampling enhances accuracy of functional connectome fingerprinting and behavior prediction at rest

1:00 PM - 5:00 PM

***H.-J. KIM**[1,2], C.-W. WOO[1,2], E. S. FINN[3];
[1]Inst. for Basic Sci. (IBS), Ctr. For Neurosci. Imaging Res. (CNIR), Suwon-si, Gyeonggi-do, Korea, Republic of; [2]Biomed. Engin., SungKyunKwan Univ. (SKKU), Suwon-si, Gyeonggi-do, Korea, Republic of; [3]Psychological and Brain Sci., Dartmouth Col., Hanover, NH

Abstract

Heterogeneity of brain structure and function has long been recognized, and the ability to predict individual differences in trait variables from brain measures is one of the most critical steps toward individualized neuroscience. Functional connectome fingerprinting is one such approach, which demonstrates that functional connectivity (FC) can serve as a ‘fingerprint’ to identify each individual from a large group of people. Researchers have shown that FC data collected with naturalistic stimuli (e.g., movie-watching) outperforms resting-state FC in both fingerprinting and behavioral prediction. However, there have been few studies on how introspective thinking shapes FC and its fingerprinting performance though it has been proposed that introspection could effectively induce idiosyncratic brain states. We collected fMRI data from 61 participants while they underwent two types of rest scans: one in which they were asked to report what they were thinking in a few words every 45 seconds (“thought-sampling”), and one pure rest scan without any thought probes. We applied the fingerprinting approach in which the accuracy was defined as the number of within-subject correlations being greater than any other between-subject correlations between two separate runs (thus the chance level was approximately 1/61). The fingerprinting result showed that the thought-sampling scan provided higher fingerprinting accuracies (95.1-100%, permutation $p < 0.001$ against chance) compared to the rest-only scan (88.5-93.4%). This result was consistent in the retest data from a subset of participants ($n = 29$, test-retest interval of 3 months on average). In both the thought-sampling and rest-only runs, functional connections among the medial frontal, frontoparietal, and default mode networks played an important role in distinguishing each individual from others. Lastly, data collected during the thought-sampling scan accurately predicted individual differences in traits measured with multiple behavioral surveys, whereas predictions based on rest-only data were not as accurate. These results suggest that even without external stimuli, a mere change of cognitive states that enhance introspection can induce individually unique FC patterns. Overall, we show that adding intermittent thought probes to rest scans to enhance introspection produces more FC-based accurate predictions of self-identity and trait-like features compared to pure rest, providing a possibility of using thought sampling not only in healthy populations but also in clinical populations given that it is a simple but potent method for capturing individually distinct FC features.

☆ Session 560 Stress and Trauma Related Disorders: Animal Models

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 560.08 / KK7 Establishment of the female mouse model of social avoidance induced by female-directed female aggression

1:00 PM - 5:00 PM

*J. KIM, K. POKHAREL, S. MICHAEL, **C. KIM**;
Dept. of Neurosci. & Regenerative Med., Augusta Univ., Augusta, GA

Abstract

Although women are more likely than males to suffer from stress-related disorders such as posttraumatic stress disorder and depression, the majority of preclinical research on the impact of stress has been conducted on male subjects. Chronic social defeat stress (CSDS) is a rodent model of psychosocial stress that causes social avoidance and anhedonia. However, this model has been challenged in female mouse studies since neither male nor female resident mice attack intruder females. In this study, we aim to establish the female mouse model of social avoidance. We used ovariectomized (OVX) CD-1 female mouse with single- or a pair-housed setting with male CD-1 mouse. Given that the selection of aggressor is the critical step for the CSDS model, we first determined the attack latency and the number of attacks during the selection of aggressor. In the single-housed OVX mice, 34 percent of mice met the criterion of the selection of aggressor. There was a significant negative correlation between attack latency and the number of attacks (R^2=0.5660, P=0.009), suggesting that attack latency can be a good indicator of the number of attacks. However, single-housed OVX mice did not show reliable, aggressive behaviors (e.g., attack bites) during the CSDS. As a result, we did not find any behavioral changes in the social interaction test, elevated plus-maze test, and spontaneous alternation Y-maze test, suggesting the importance of aggressive behavior toward the intruder. In contrast, during the selection of aggressor, 42 percent of OVX mice in a pair-housed condition with male CD-1 mice satisfied the criterion and displayed consistently aggressive behaviors. CSDS produced susceptible (67 %) and resilient (33 %) phenotypes during the social interaction test. In addition, both susceptible and resilient mice showed anxiogenic-like behaviors in the elevated plus-maze test. Our study suggests that OVX CD-1 mice in a pair-housed setting show reliable, territorial aggression toward female intruders, producing susceptibility and resilience to social avoidance.

☆ Session 563 Opioids: Reward and Reinforcement II

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 563.03 / NN13 A comprehensive dissection of cell type, circuit, and molecular mechanisms of action of opioids in the cerebral cortex

1:00 PM - 5:00 PM

***N. OCHANDARENA**[1], J. NIEHAUS[2], R. PICKEN[2], Z. YAO[3], D.-W. KIM[3], H. ZENG[4], G. SCHERRER[5];
[1]UNC Neurosci. Curriculum, [2]UNC Neurosci. Ctr., UNC Chapel Hill, Chapel Hill, NC; [3]Allen Inst. for Brain Sci., Seattle, WA; [4]Allen Inst. For Brain Sci., Seattle, WA; [5]UNC Neurosci. Center, Dept of Cell Biol. and Physiol., The Univ. of North Carolina at Chapel Hill, Chapel Hill, NC

Abstract

Opioids are indispensable analgesics that can also produce harmful side effects including tolerance, addiction, and death through respiratory depression. Understanding the organization and function of neural circuits underlying these different effects may reveal strategies to disassociate opioid-induced analgesia from unwanted side effects. Opioids elicit their effects through the μ, κ, and δ opioid receptors (MOPr, KOPr, and DOPr), which are expressed in neurons throughout the nervous system. Opioids act on different regions of the cerebral cortex to alter sensorimotor function, motivation, and affect, but the molecular identity, connectivity, and functional contributions of the neurons involved are unclear. Specifically, although cortical regions such as the infralimbic, prelimbic, anterior cingulate, insular, somatosensory, and motor cortices have been studied for their contribution to the sensory, affective and cognitive dimensions of pain experience, how opioids modulate cortical activity remains poorly understood. Because several of these regions also contain circuits that contribute to opioid addiction, delineating analgesia-and addiction-promoting circuits is challenging. To address this issue, here we use single-cell RNA-sequencing (scRNA-seq), circuit tracing, recording and manipulation of neural activity in freely behaving mice to establish the mechanisms of action of opioids in the cerebral cortex. Although scRNA-seq has been used to investigate the cellular heterogeneity of the cortex, the distribution and molecular characteristics of OPr-expressing neurons across different cortical regions and layers remains unclear. Furthermore, the low sequencing depth of droplet-based high-throughput scRNA-seq

approaches limits reliable detection of lowly expressed transcripts, like the OPr-encoding genes ***Oprm1***, ***Oprk1***, and ***Oprd1***. We analyzed scRNA-seq data from cortical samples prepared by SMART-seq technology, which yields full length transcriptomes with exceptional sensitivity for sparse transcripts. We assessed ~80,000 neurons sorted from 15 cortical regions to comprehensively characterize the molecular identity of neurons expressing each OPr gene across neocortical areas. Using marker genes identified from these data, we applied intersectional genetic approaches to determine the spatial distribution of different OPr-expressing subpopulations across cortical regions and resolve region- and layer-specific cell types. Together, these experiments resolve the molecular and spatial configuration of opioid-sensitive cortical neurons for dissecting their contributions to opioid-induced behaviors.

☆ Session 564 Biological and Computational Models of Decision Making

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 564.11 / PP16 Fronto-striatal decoupling during arbitration between goal-directed and habitual decision-making in obsessive-compulsive disorder

1:00 PM - 5:00 PM

***T. KIM**[1], S. LEE[1], S. LHO[2], S.-Y. MOON[2], M. KIM[2], J. KWON[3];
[1]KAIST, Daejeon, Korea, Republic of; [2]Seoul Natl. Univ. Hosp., Seoul, Korea, Republic of; [3]Seoul Natl. Univ., Seoul, Korea, Republic of

Abstract

A theory that excessive habits serve as a building block of compulsions has drawn attention to identifying a brain model underlying habit-bias in obsessive-compulsive disorder (OCD) to bridge the cognitive model and neurotherapeutics. To extend the current understanding that an imbalance in goal-directed versus habitual neural systems underlies habit-bias,[1] it needs to clarify how the imbalance occurs during an arbitration process between the two strategies. When goal-directed learning is deemed to be dominant, the ventrolateral prefrontal cortex (vlPFC) tracking reliability (i.e., probability of successful outcome predictions) of the two strategies downregulates the putamen engaged in habitual learning.[2] We aimed to determine whether this neurocircuit is aberrantly attenuated in OCD during the arbitration. In this study, thirty patients with OCD (age 26.9 ± 6.2 years, 12 females) and thirty healthy controls (age 25.0 ± 4.7 years, 17 females) underwent fMRI scans while simultaneously performing the sequential two-step decision task, designed to observe model-based (goal-directed) and model-free (habitual) learning.[2] We employed a computational model devised to account for the arbitration process, which makes inferences about the reliability of each learning based on the history of its prediction errors and determines that the control is given to a more reliable strategy. We estimated brain activity encoding variables of the computational model (reliability and action value of each learning) and analyzed psychophysiological interaction effects of the model-choice preference on the vlPFC-putamen coupling. Compared to healthy controls, patients with OCD exhibited a stronger habit-bias ($P = .006$), attributed to less reliable predictions in goal-directed than habitual learning. When behaviors should be model-based, patients exhibited a weaker strength of the fronto-striatal negative coupling than healthy controls ($t = 4.43$, $P_{\text{FWER}} = 0.001$). This hypoconnectivity was correlated with more severe compulsivity ($r = -0.56$, $P = 0.001$). We suggest that the attenuated top-down control of the habit controller by the prefrontal arbitrator underlies habit-bias in OCD. Enhancing the fronto-striatal connectivity may be a potential neurotherapeutics for compulsivity. **References [1]** Voon V, Derbyshire K, Ruck C***, et al***. Disorders of compulsivity: a common bias towards learning habits. ***Mol Psychiatry*** 2015;20(3):345-352. **[2]** Lee SW, Shimojo S, O'Doherty JP. Neural computations underlying arbitration between model-based and model-free learning. ***Neuron*** 2014;81(3):687-699.

☆ Presentation 564.23 / QQ9 Medial prefrontal cortex activity mediates social stress-induced decrease in disadvantageous inequality aversion

1:00 PM - 5:00 PM

***K. KIM**[1], J.-H. LEE[2], W.-Y. AHN[2,3], H. KIM[1];
[1]Sch. of Psychology, Korea Univ., Seoul, Korea, Republic of; [2]Dept. of Psychology, [3]Dept. of Brain and Cognitive Sci., Seoul Natl. Univ., Seoul, Korea, Republic of

Abstract

It has been reported that social stress can have contradictory effects on social behavior, increasing prosocial or antisocial behaviors. Such findings may be attributed to the modulatory role of stress in context-dependent value computation because cortisol hormone affects a wide range of neural regions including the medial prefrontal cortex (MPFC). In this study, by incorporating stress treatment with a modified social discounting task, we investigated the neural mechanism underlying the association between the physiological responses to social stressors and inter-subject variability in money-sharing behavior. 41 male participants performed the Montreal imaging stress task (MIST), in which they were asked to solve arithmetic problems under time pressure and received negative social feedbacks. About 20 minutes after stress onset, samples of their saliva were collected to measure changes in cortisol concentration from the baseline. Then, participants performed a modified social discounting task, which was designed to measures money sharing with targets of varying social distance when money sharing results in inequal (i.e., disadvantageous inequal condition) or equal (i.e., equal condition) consequence. We used computational modeling and hierarchical Bayesian analysis to identify the three distinctive dimensions of motivation: 1) the sensitivity to target's social distance, 2) the sensitivity to reward for self, and 3) the degree of disadvantageous inequality aversion as measured by the tendency of avoiding an option that gives more money to a target than to self. Behavioral results showed a negative correlation between the degree of increase in cortisol concentration and the degree of disadvantageous inequality aversion. The degree of increase in cortisol concentration was negatively correlated with the degree of the dorsomedial prefrontal cortex (DMPFC) activity in tracking the value of reward for self in the disadvantageous inequal condition. In turn, those with higher degree of disadvantageous inequality aversion exhibited higher degree of DMPFC activity and lower degree of VMPFC activity in tracking the value of reward for target in the disadvantageous inequal condition. Finally, a mediation analysis confirmed that the association between the degree of increase in cortisol level and the degree of disadvantageous inequality aversion was indirectly mediated by the DMPFC activity. These findings suggest that the DMPFC plays a key role in promoting disadvantageous inequality aversion, which can be interrupted by socially induced stress, resulting in self-protective prosocial motivation.

☆ Session 565 Cortical Control of Decision Making in Rodents

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 565.02 / RR2 Role of vasoactive intestinal polypeptide (VIP)-expressing neurons in the prefrontal cortex in probabilistic reversal learning

1:00 PM - 5:00 PM

J. YI[1,2], ***Y. YOON**[3,1,2], S. CHOE[1], M. JUNG[3,1];
[1]Ctr. for Synaptic Brain Dysfunctions, Inst. for Basic Sci., Daejeon, Korea, Republic of; [2]These authors contributed equally, Daejeon, Korea, Republic of; [3]Dept. of Biol. Sci., Korea Advanced Inst. of Sci. and Technol., Daejeon, Korea, Republic of

Abstract

The prefrontal cortex (PFC) plays a crucial role in flexible control of behavior. Of various types of neurons in the PFC, VIP-expressing neurons are thought to exert powerful influences on PFC circuit operations by disinhibitory control of other inhibitory interneurons. Here, to obtain insights on the role of VIP-expressing neurons in flexible control of behavior, we investigated modulation effects and activity dynamics of VIP-expressing neurons in the medial PFC (mPFC) in adult male mice performing reversal learning under a probabilistic classical conditioning paradigm. Chemogenetic (n = 7) and optogenetic modulation (n = 5) of VIP-expressing neurons in the mPFC significantly impaired reversal learning. Calcium imaging (n = 10) revealed diverse patterns of activity dynamics of mPFC VIP-expressing neurons during reversal. As a population, VIP-expressing neurons conveyed strong signals related to reward prediction error (RPE) during, but not before or after, reversal learning. These results suggest that VIP-expressing neurons may modulate mPFC neural activity in an RPE-dependent manner, thereby contributing to flexible control of behavior.

☆ Presentation 565.11 / SS3 Roles of ventrolateral orbitofrontal cortex, basolateral amygdala, and anterior cingulate cortex in flexible stimulus-based learning

1:00 PM - 5:00 PM

***C. G. AGUIRRE**[1], J. L. ROMERO-SOSA[1], J. H. WOO[4], J. MUNIER[2], J. PEREZ[1], G. EDLER[1], M. G. GOLDFARB[1], K. DAS[1], M. G. GOMEZ[1], T. YE[1], J. PANNU[2], P. R. O'NEILL[3], I. SPIGELMAN[2], A. SOLTANI[4], A. IZQUIERDO[1];
[1]Psychology, [2]Section of Biosystems and Function, Sch. of Dent., [3]Shirley and Stefan Hatos Ctr. for Neuropharmacology, Dept. of Psychiatry and Biobehavioral Sci., UCLA, Los Angeles, CA; [4]Dept. of Psychological and Brain Sci., Dartmouth Col., Hanover, NH

Abstract

Reversal learning (RL), impacted in various neuropsychiatric disorders, measures subjects' ability to form flexible associations between cues/stimuli and reward. The contribution of orbitofrontal cortex (OFC), basolateral amygdala (BLA), and anterior cingulate cortex (ACC) to RL and its dependence on the nature of association (i.e., stimulus-based), the modality (i.e., visual), and uncertainty associated with the reward contingencies (i.e., deterministic vs. probabilistic) has not been extensively studied in rats. Here we examined the roles of ventrolateral OFC (a subregion not as often probed as MO and LO), BLA, and ACC in the flexible learning of stimulus-based associations using chemogenetic manipulation. Male and female Long-Evans rats (N=39, 20 females) were prepared with bilateral inhibitory hM4Di DREADDs or eGFP on a CaMKIIa promoter targeting the major output neurons of each region. Rats first met a discrimination criterion, before being tested on both fully predictive deterministic (100/0) and probabilistic (90/10) reversals, during which they selected a visual stimulus associated with a sucrose reward by nosepoking a touchscreen. Thirty minutes prior to each reversal session rats were administered clozapine-N-oxide (CNO) or vehicle (VEH) solution (3mg/kg, i.p.), using a within-subject, counterbalanced design. Specifically, if a rat received CNO on the 1st reversal, it was administered VEH on the 2nd reversal (CNO1-VEH2), or vice versa (VEH1-CNO2). Only animals with confirmed bilateral targeting were included in the behavioral analyses, and efficacy of CNO to reduce activity in these regions was confirmed by ex vivo calcium imaging in slice. Rats learned the initial stimulus discrimination in 8.4 ± 1.5 sessions to 75% for hM4Di and 8.7 ± 0.6 sessions for eGFP. Generalized Linear Models were conducted for each brain region and included all factors (reversal number, virus, drug, drug order, sex) for every measure. Preliminary analyses revealed significant reversal number and/or drug order interactions for learning measures (i.e., probability of choosing the better option, rewards collected), attentional (i.e., initiation latencies), and motivational (i.e., reward latencies) measures for all brain regions. Although post-hoc analyses are ongoing, we found that CNO1-VEH2 animals exhibit poorer learning and less adaptive strategies compared to VEH1-CNO1 animals following vlOFC and ACC inhibition, but not BLA inhibition. Engagement of vlOFC and ACC during the first experience of a reversal was crucial as it set how future adjustments occurred, consistent with the theorized roles for frontocortical regions in expected uncertainty.

☆ Session 569 Social Cognition: Animal Behavior I

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 569.22 / WW2 The impact of the LC-NAergic system in controlling empathic fear.

1:00 PM - 5:00 PM

***J.-H. KIM**[1], M. KIM[1], H.-S. SHIN[1,2];
[1]Ctr. for Cognition and Sociality, Inst. for Basic Sci. (IBS), Daejeon, Korea, Republic of; [2]SL Bigen, Incheon, Korea, Republic of

Abstract

Observational fear is a useful behavioral paradigm for assessing affective empathy in rodents. The anterior cingulate cortex (ACC) is involved in empathic responses to pain or fear in a conspecific animal. The ACC receives various neuromodulatory inputs from subcortical structures, including the locus coeruleus-noradrenaline (LC-NA) neurons. The LC is the main origin of noradrenergic neurons, and NA is a key neuromodulator playing critical roles in various higher brain functions in the central nervous system (CNS) including arousal, attention, cognition, and memory. However, the relevance of the LC-NA system to empathic behavior is not known. Here, we show that the LC-NA system is crucial for maintaining freezing behavior during observational fear. We found increasing LC-NA neurons' terminal activity during observational fear in the ACC. Additionally, the optogenetic inhibition of LC-NA input in the ACC affected only the maintenance of observational fear responses but not the initial response in observer mice, indicating that the LC-NA system in the ACC controls the degree of socially transmitted fear. By monosynaptic rabies tracing we identified the bed nucleus of the stria terminalis (BNST) as the upstream input to the LC-NAergic projections to the ACC. Notably, we found that there is no anatomical connection between the ACC and the BNST. Abolishing the LC-projecting BNST neurons elicited a failure of contiguous freezing response during observational fear, suggesting that the BNST is involved in controlling empathy through the LC-NA system. This work expands our understanding of the neural circuits involved in observational fear beyond the amygdala and the ACC, revealing the role of a novel neural pathway centered on the LC-NAergic system in affective empathy.

☆ Session 572 Timing and Temporal Processing: Cortex, Hippocampus, Striatum

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 572.01 / WW47 Medial Entorhinal Cortex is necessary to learn novel temporal Delayed Non-Match to Sample task

1:00 PM - 5:00 PM

***E. R. BIGUS**[1], A. A. CHAGOVETZ[2], J. G. HEYS[2];
[1]Interdepartmental Neurosci. Program, [2]Dept. of Neurobio., Univ. of Utah, Salt Lake City, UT

Abstract

The medial temporal lobe (MTL) of the brain encodes individual experiences into memory so they can be flexibly used to guide future behavior. Although experiences and memories are rooted in a sense of time, it remains unknown how the MTL memory system encodes elapsed time on the order of seconds to minutes, called interval time. Numerous recent studies have uncovered a role of the medial entorhinal cortex (MEC) in interval timing tasks, suggesting this region helps the MTL track time. However, these studies also demonstrate that MEC is not always necessary for performance of interval timing tasks, raising uncertainty about the role of MEC in timing. To date, it is unknown under what circumstances MEC is necessary for interval timing. To address this gap, we propose that multiple memory systems are capable of driving interval timing behavior, depending upon timing demands. MTL structures including MEC may be necessary when animals quickly and flexibly learn and recall durations, while tasks requiring more rigid temporal responses may instead be mediated by a procedural memory system. We are examining this framework by testing the hypothesis that MEC is necessary for interval timing when animals must quickly and flexibly encode durations in a manner suited to the demands of the MTL memory system. Due to the lack of behavioral paradigms designed for studying MTL timekeeping in mice, we first established a novel temporal Delayed Non-Match to Sample (tDNMS) task in which mice quickly and relatively flexibly make decisions based upon relative stimulus durations. To test the necessity of MEC, we then trained mice expressing either a control virus or inhibitory DREADDs on the tDNMS task (n = 16 control mice; n = 15 DREADD mice; a mix of male and female C57BL/6). Administration of the DREADD agonist DCZ selectively impaired the ability of DREADD mice to learn the tDNMS task but did not affect performance post-learning. Results show a clear necessity of MEC in learning the tDNMS task, supporting the hypothesis that MEC is necessary for timing when behavioral demands are appropriate. In parallel we have used cellular-resolution Ca2+ imaging experiments to determine the neural dynamics in MEC that may underlie tDNMS performance. Our preliminary results indicate that populations of MEC neurons fire in regular, time-locked sequences across trials. Interestingly, we find that many time cells display context-dependent timing activity that is able to decode trial-type. Together, this work supports the overarching hypothesis that MEC plays a role in interval timing behavior through regular sequential neural activity across populations of MEC time cells.

☆ Session 573 Spatial Cognition

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 573.06 / Web Only A virtual place preference task dependent on the interactions between the prefrontal cortex and hippocampus in a VR environment

1:00 PM - 5:00 PM

***S. PARK**[1], S.-W. JIN[1], H. HWANG[1], J. SHIN[1], H.-W. LEE[2], I. LEE[1];
[1]Seoul Natl. Univ., Seoul Natl. Univ., Seoul, Korea, Republic of; [2]Neurobio., Univ. of Utah, Salt Lake City, UT

Abstract

We hypothesize that the iHPC-mPFC interactions are critical for an animal to navigate a space in a goal-directed fashion. To test this, we trained rats (n=6) to navigate to an unmarked goal location in a VR environment to receive water rewards. The rat navigated a circular VR arena by running on a ball-shaped treadmill. The rat started from the center of the arena, facing either north or south, to visit the unmarked reward zone on the west (WRZ). Rats typically showed a stereotyped turning behavior (turning to the right) as a trial started and then adjusted the length of the trajectory depending on the starting heading direction. Once the rat was trained, the rat was trained to go to a new reward zone on the east (ERZ). Afterward, a 24-tetrode-carrying hyperdrive was implanted, targeting the mPFC and iHPC. After recovery, tetrodes were lowered to the target regions and rats were retrained. As the main recording commenced, the rat was required to visit the WRZ. Then, rats were required to reverse the goal zone again to the ERZ until they reached the performance criterion. When we checked how accurately the rat arrived at the reward zone by measuring the angular difference between the center of the reward zone and the first contact

point of the circular boundary of the arena, there was a significant difference between the sessions in which rats performed below and above the performance criterion ($p<0.0005$, Kruskal-Wallis test). However, a similar analysis on the departure angle at the start point did not result in performance-related correlates, suggesting that rats used allocentric visual scenes encountered during the navigation to adjust their travel paths for wayfinding to the goal zone in our task. This allocentric strategy was also confirmed when we examined the navigation patterns of rats at different learning stages. Specifically, rats tended to show an egocentric strategy by entering the closest reward zone (ERZ or WRZ) associated with each start heading direction (ERZ and WRZ when heading north and south at the start, respectively) before learning. However, as rats learned the task (reaching the goal zone > 75%), they inhibited the egocentric tendency to travel to the nearest goal zone to take a longer path to reach the goal zone on the opposite side in those trials in which their initial departing orientations carried them farther from the goal zone as they started their navigation in a stereotypic way (i.e., right turn). Such a strategic shift made the rat's hitting rate for the goal zone significantly higher after learning compared to the pre-learning stage ($p<0.0001$, Chi-square test). We plan to analyze spiking activities of single units recorded from the iHPC and mPFC in this task.

☆ Session 576 Visualizaing Neural Connectivity With High Resolution

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 576.14 / XX63 Visualization of astrocyte-neuron contact using eGRASP

1:00 PM - 5:00 PM

***J. KIM**, Y. SUNG, H. PARK, D. CHOI, J.-I. KIM, H. LEE, S. YE, B.-K. KAANG;
Seoul Natl. Univ., Seoul-si, Korea, Republic of

Abstract

Astrocytes are known to contribute to synaptic functions and plasticity through tripartite synapses. Tripartite synapses are the site of communication among presynaptic, postsynaptic neurons and astrocyte by contact-dependent and diffusible factors. Therefore, identifying tripartite synapses and understanding its dynamics is important to understand the synaptic functions and astrocytic contribution. However, current techniques to observe tripartite synapses are limited and laborious, hindering the research. Therefore, we developed specialized tool, Astrocyte-eGRASP (enhanced Green Fluorescent Protein Reconstitution Across Synaptic Partners), which can visualize astrocyte-neuron contact by fluorescence. By expressing pre-eGRASP and post-eGRASP in astrocyte and neuron, we could label neuron-astrocyte contact in vitro and in vivo. Astrocyte-eGRASP enabled us to analyze astrocyte-neuron contact in individual astrocyte, identify tripartite synapses in specific neurons, such as excitatory and inhibitory neurons. This study will provide the tool to expand the research on astrocytic participation in synaptic functions.

☆ Presentation 576.02 / XX51 Ultrastructural membrane expansion microscopy (umExM) for electron microscopy-like imaging of brain circuits

1:00 PM - 5:00 PM

***T. W. SHIN**[1,2], C. ZHANG[3], B. AN[3], Y. LU[3], B. GUNER-ATAMAN[3], C. M. MITCHELL[2], D. LEIBLE[2], H. WANG[2], C.-C. YU[2], L.-H. TSAI[2,4,5], E. S. BOYDEN[1,2,3,6];
[1]Dept. of Media Arts and Sci., [2]Dept. of Brain and Cognitive Sci., [3]McGovern Inst. for Brain Res., MIT, Cambridge, MA; [4]Picower Inst. for Learning and Memory, Cambridge, MA; [5]Broad Inst. of Harvard and Massachusetts Inst. of Technol., Cambridge, MA; [6]Howard Hughes Med. Inst., Cambridge, MA

Abstract

Electron microscopy is the primary technology currently used to delineate the detailed shapes of neurons in brain circuits, down to synaptic resolution, important for connectomics. Ideally, however, such imaging would be possible on a conventional light microscope, so that anyone could delineate the detailed shapes of neurons, and how they are connected, in neural circuits. In addition, ideally, it would be possible to image such neural circuits at scale, and identify and localize biomolecules in the detailed ultrastructural context of neural circuits. Recently, building from our invention of expansion microscopy (ExM), we have shown that lipid stains can be constructed that enable electron microscopy-like images to be taken on ordinary light microscopes, and for biomolecules to be identified and localized through fluorescent antibody staining, but with a low resolution of ~80 nm or so (bioRxiv 829903). Here we report a new generation of lipid stains, as well as a newly optimized ExM protocol, that aim to achieve images with comparable resolution to electron microscopy - sufficient to delineate the shapes of neurons, with molecular contrast, and pointing the way towards the possibility of dense connectomics via light microscopy. In particular, we have now generated two lipid stains that, mixed together, delineate the boundaries of neurons with excellent contrast. We also have generated a novel lipid preservation process to preserve ultrastructure in the context of fixation and expansion steps, as well as an optimized gelation chemistry recipe with an 8x expansion factor. Finally, we optimize the entire procedure to maximize the lipid membrane integrity. We demonstrate the ability of this novel protocol, which we call ultrastructure membrane expansion microscopy (umExM), to map out the shapes of neurons and the locations of key biomolecules with ~50 nm resolution, sufficient to resolve axons, with ~20 nm resolution achieved through an iterative version of umExM (iumExM), which may be sufficient to facilitate connectomics. Combined with barcoding strategies also under development in our lab, we aim to share this protocol throughout neuroscience to assist with the democratization of neural morphology measurement and connectomics

☆ Presentation 576.11 / XX60 16-fold expansion microscopy (16exm) enables single-shot ultrahigh resolution imaging on conventional microscopes

1:00 PM - 5:00 PM

***S. WANG**[1,2], T. SHIN[1,3], C. ZHANG[1], H. YODER[1], K. LEUNG[1], N. HAN[1], Y. LIU[1], L. L. KIESSLING[2,4], E. S. BOYDEN[1,5];
[1]McGovern Inst. of Brain Res., [2]Dept. of Chem., [3]Media Arts and Sci., MIT, Cambridge, MA; [4]Broad Inst. of MIT and Harvard, Cambridge, MA; [5]HHMI, Cambridge, MA

Abstract
SW and TWS contributed equally to this work. Expansion microscopy (ExM) is in widespread use throughout biology because its isotropic physical magnification enables nanoimaging on conventional microscopes (Science, 347(6221), 543-548), with many hundreds of experimental papers and preprints appearing to date. To date, all methods either expand specimens to a limited range (typically ~4-10x in linear expansion factor, yielding ~30-70 nm resolution; the upper limit in expansion factor is limited by the lower gel density with bigger expansion factors, which in turn results in more fragile expanded samples), or achieve larger expansion factors through iterating the expansion factor over and over (typically ~15-20x in linear expansion factor, yielding ~20 nm resolution). In addition, recent expansion protocols such as expansion revealing (ExR; bioRxiv 2020.08.29.273540), which separate biomolecules from each other before staining, make target biomolecules more available and enable them to be better stained, in some cases converting invisible biomolecules into visible ones. We here present a new expansion protocol that supports post-expansion staining, and achieves ~16x expansion factor, sufficient to enable ~20-nm-resolution imaging on a conventional microscope, in a single expansion step. We show the utility of this protocol, which we call 16ExM, in mapping neural architecture in Thy1-YFP transgenic mice and other preparations and contexts of importance in neuroscience.

☆ Session 504 The Mechanisms of Gut-Brain Axis in Neurological Disorder - Inhee Mook-Jung

2:00 PM - 4:30 PM

SDCC 6CF

☆ Presentation 504.07 ApoE isoform and microbiota-dependent progression of neurodegeneration in a mouse model of tauopathy

3:45 PM - 4:05 PM

D. Seo;
Washington University in St. Louis, Saint Louis, MO.

Abstract
A growing body of research point towards the existence and role of the gut-brain connection in several neurological diseases. Alterations in gut flora and failure to establish a functioning gastrointestinal (GI) tract system may contribute to the pathogenesis of brain disease. This minisymposium provides scientific insights into new therapeutic approaches through a holistic understanding of the mechanistic link between the GI health and neurological disease.

☆ Session 508 Sonogenetics: Fundamentals and Applications - Zhihai Qiu

2:00 PM - 4:30 PM

SDCC 28

☆ Presentation 508.06 The development of sonothermogenetics

3:25 PM - 3:45 PM

H. Chen;
Washington University In St. Louis, Washington University in St. Louis, Saint Louis, MO.

Abstract
Sonogenetics refers to the use of genetically-coded, ultrasound sensitive ion channels for noninvasive and selective control of neural activity. It is still in its infancy stages, basic studies and developments are underway and the field is evolving rapidly. The performance including spatiotemporal resolution, selectivity, specificity, and safety are being characterized.

WEDNESDAY, NOV. 16, 2022

☆ Session 593 Parkinson's Disease and Mechanisms

8:00 AM - 10:45 AM

SDCC 7

☆ Presentation 593.02 Paan/mif nuclease inhibition prevents neurodegeneration in parkinson’s disease

8:15 AM - 8:30 AM

***H. PARK**[1], T.-I. KAM[2], H. PENG[2], J. O. LIU[2], V. L. DAWSON[2], T. M. DAWSON[2];
[1]Johns Hopkins Univ., [2]Johns Hopkins Univ. Sch. of Med., Johns Hopkins Univ., Baltimore, MD

Abstract
Parthanatos Associated AIF (apoptosis-inducing factor) Nuclease (PAAN), also knownas macrophage migration inhibitor factor (MIF) is a member of the PD-D/E(X)Knucleases that acts as a final executioner in parthanatos. PAAN’s role in Parkinson’sdisease (PD) and whether it is amenable to chemical inhibition is not known. Here weshow that neurodegeneration induced by pathologic α-synuclein (α-syn) occurs viaPAAN/MIF nuclease activity. Genetic depletion of PAAN/MIF and a mutant lackingnuclease activity prevent the loss of dopaminergic neurons and behavioral deficits inthe α-syn preformed fibril (PFF) mouse model of sporadic PD. Compound screeningled to the identification of PAANIB-1, a first-in class, brain-penetrant PAAN/MIFnuclease inhibitor that prevents neurodegeneration induced by α-syn PFF, AAV-α-synoverexpression or MPTP intoxication in vivo. Our findings could have broad relevancein human pathologies where parthanatos plays a role for development of new celldeath inhibitors targeting the druggable PAAN/MIF nuclease.

☆ Presentation 593.10 Cell autonomous role of LRRK in dopaminergic neuronal survival

10:15 AM - 10:30 AM

***J. KANG**[1], G. HUANG[1], Y. TONG[1], L. MA[1], L. CUI[1], A. SHAHAPAL[1], P. CHEN[1], J. SHEN[1,2];
[1]Brigham and Women's Hosp., Harvard Med. School/BWH, Boston, MA; [2]Program in Neuroscience, Harvard Med. Sch., Boston, MA

Abstract

Mutations in the ***leucine-rich repeat kinase 2*** (*LRRK2*) gene are the most common genetic cause of Parkinson's disease. Genetic studies revealed that LRRK2 regulates the autophagy-lysosomal pathway, and that germline deletion of ***LRRK2*** and its functional homologue ***LRRK1*** results in progressive loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc), along with earlier lethality and reduced body weight. In this study, we created dopaminergic neuron-specific ***LRRK*** conditional double knockout (cDKO) mice, in which LRRK1 and LRRK2 are selectively inactivated in dopaminergic neurons by Cre recombinase expressed under the control of the endogenous ***DAT*** promoter, to determine whether LRRK is required for dopaminergic neuronal survival in a cell autonomous manner. We found that dopaminergic neuron-specific ***LRRK*** cDKO mice of both sexes exhibit normal body weight and mortality, but they develop age-dependent loss of dopaminergic neurons in the SNpc, as evidenced by the normal number of dopaminergic neurons in ***LRRK*** cDKO mice at 15 months of age and decreases of dopaminergic neurons in the SNpc at the ages of 20 months (-14%) and 25 months (-23%), compared to littermate controls. However, the reduction of dopaminergic neurons in the SNpc of ***DAT-Cre*** driven ***LRRK*** cDKO mice occurs at a later age of onset and is less severe, compared with ***LRRK*** DKO mice lacking LRRK1 and LRRK2 in all cells (***e.g.*** no reduction of dopaminergic neurons in cDKO mice at 15 months of age vs. ~20% loss of dopaminergic neurons in DKO mice at 15 months). In addition, dopaminergic neurodegeneration in ***LRRK*** cDKO mice is accompanied with increases in apoptosis, microgliosis, and accumulation of autophagic and autolysosomal vacuoles in surviving DA neurons. These results demonstrate an intrinsic, essential role of LRRK in the protection of dopaminergic neurons during aging, and suggest a non-cell autonomous role of LRRK in contribution to dopaminergic neuronal survival.

☆ Session 594 Mechanisms of Brain Injury and Recovery

8:00 AM - 9:30 AM

SDCC 33

☆ Presentation 594.03 Ischemic preconditioning maintains adaptive mitophagy while suppressing maladaptive mitophagy induced by transient global cerebral ischemia.

8:30 AM - 8:45 AM

***T. JOVER-MENGUAL**[1,2], H.-R. BYUN[3], B. L. COURT-VAZQUEZ[4], M. DELGADO-ESTEBAN[5,6], J.-Y. HWANG[7], R. S. ZUKIN[1];
[1]Dominick P. Purpura Dept. of Neurosci., Albert Einstein Col. of Medicine., Bronx, NY; [2]Dept. de Fisiología, Univ. de Valencia, Valencia, Spain; [3]Dep. of Pathology & Lab. Med., Cedars Sinai Med. Ctr., Los Angeles, CA; [4]Weo, Univ. of Miami, Miami, FL; [5]Inst. de Biología Funcional y Genómica (IBFG CSIC), Univ. of Salamanca, Salamanca, Spain; [6]Inst. de Investigaciones Biomédicas de Salamanca (IBSAL), Salamanca, Spain; [7]Creighton Univ. Sch. of Med., Creighton Univ., Elkhorn, NE

Abstract

Transient global cerebral ischemia affects millions of people each year and arises as a consequence of cardiac arrest. Global cerebral ischemia (GCI) causes selective, delayed death of hippocampal CA1 pyramidal neurons resulting in severe cognitive deficits. To date, there is no known treatment for the neurodegeneration associated with this devastating insult.
Loss of mitochondrial function is an early event during cerebral ischemia, ultimately triggering neuronal cell death. Mitochondria are involved in ATP production, ROS generation, inflammation, as well as apoptosis. Selective degradation of damaged or dysfunctional mitochondria through autophagy is known as mitophagy.
Ischemic preconditioning (IPC) is a well-known phenomenon in which a brief, sublethal ischemic insult confers robust neuroprotection to hippocampal CA1 neurons against a subsequent severe ischemic challenge. Unmasking the endogenous mechanisms triggered during IPC could help to understand how the brain protects itself. However, the molecular mechanisms underlying ischemic tolerance by preconditioning are not fully understood.
In our previous study, we showed that GCI triggers a transient increase in biochemical markers of autophagy, pS317-ULK-1, pS14-Beclin-1, and LC3-II, a decrease in the cargo adaptor p62, and an increase in autophagic flux, a functional readout of autophagy, in selectively vulnerable hippocampal CA1 neurons. However, the role of mitophagy in neuronal death after cerebral ischemia has not yet been delineated.
Here we show that mitophagy is activated in response to GCI in the hippocampal CA1 pyramidal neurons ***via*** PINK/PARKIN/p62/Optineurin and BNIP3 signaling pathways. Consistent with this, recruitment of dynamin-related protein-1 (Drp1), a marker for mitochondrial fission, was detected in the mitochondrial fraction. Additionally, ischemia induces phosphorylation of NFκB and increases the expression of the proinflammatory IL-1β in the cytoplasmic fraction. However, a poor translocation of NFκB to the nucleus and no change in the mitochondrial fraction expression was observed. We further show that IPC induced a decrease of PINK, P62, Optineurin, BNIP3, and Drp1 expression in the mitochondrial fraction and IL-1β expression in the cytoplasmic fraction of the CA1 neurons. In contrast, NFκB was increased in the mitochondrial fraction suggesting a role of NFκB signaling in the mitochondria, possibly by mitochondrial dynamics regulation. These findings indicate that GCI induces maladaptive mitophagy while IPC can maintain adaptive mitophagy, most likely; through mechanisms related to mitochondrial dynamics and modulation of inflammation.

☆ Session 597 Perception and Behavior in Human Social Interactions

8:00 AM - 10:30 AM

SDCC 25

☆ Presentation 597.04 Neural correlates of social information processing and gossip

8:45 AM - 9:00 AM

***J. LEE**[1,2], Y. SONG[1], J. JEONG[1,2];
[1]Bio and Brain Engin., [2]Program of Brain and Cognitive Engin., KAIST, Daejeon, Korea, Republic of

Abstract

Gossip, a conversation between two people sharing social information about an absent person (i.e., a target), is a ubiquitous form of social interaction easily found in daily life. Gossip is generally considered a malicious behavior that violates solidarity norms within a group or community; at the same time, studies have suggested that gossip serves important functions such as social control and social bonding. Although gossip is a clear example of decision-making that has reasons for it (e.g., social control and social bonding) and against it (e.g., risks of breaking solidarity norms and retaliation from the gossip's target), there is a limited number of studies attempting to find neural evidence that gossiping involves such benefit-cost frameworks. Here, we used fMRI techniques to investigate how the brain processes various types of social information and decision variables (i.e., benefits and costs) for gossip. To systematically generate input stimuli varying in traits, we identified three basic building blocks of social information: target, content, and valence. With the data obtained from 50 participants, we performed a series of contrast analyses and found specific areas showing greater activities for particular types of information: bilateral occipital pole for gossip about morality and social norm, precuneus and angular gyrus for daily social affairs, posterior cingulate gyrus and frontal pole for ingroup friends, lateral PFC and dmPFC for negative events, etc. Next, we performed conjunction analysis to find if there is any area specialized for processing costly gossip. We found dmPFC showing greater activity when the information that may cause negative consequences in the future (e.g., a possible social conflict between the sender and the target after gossiping) was given, suggesting the area's involvement in the cost processing of gossip. Finally, to find an area processing benefits of gossip, we calculated gossip spreading rates that represent the total benefit (or estimated value) of taking the action. We found vmPFC showing correlated activities, which suggests its role in processing total benefit for gossip decisions. Our results provide neural evidence that there are dedicated areas for processing specific types of social information and that gossip involves benefit and cost processing, which is a key feature of value-based decision making. The evidence of such decision variable processing also suggests the presence of a system for integrating these signals in gossip decision-making, and research towards identifying such processes in the brain may be an interesting point for further study.

☆ Session 599 Mechanisms of Glial Development

8:00 AM - 12:00 PM

SDCC Halls B-H

☆ Presentation 599.20 / A18 Identification of astrocyte subtypes in the Drosophila melanogaster visual system

8:00 AM - 12:00 PM

***J. SAUNDERS**[1], Y. Z. KURMANGALIYEV[3], A. D. R. GARCIA[2], C. R. VON REYN[1];
[1]Sch. of Biomed. Engineering, Science, and Hlth. Systems, [2]Dept. of Biol., Drexel Univ., Philadelphia, PA; [3]Howard Hughes Med. Institute, Dept. of Biol. Chem., UCLA, Los Angeles, CA

Abstract

The diversity of glial cells, particularly astrocytes, has gained increasing recognition. Astrocytes are the most abundant glia cell type and regulate synapse formation, maturation, and function. Growing evidence from rodent studies shows a remarkable diversity and complexity of astrocyte subpopulations. In contrast, if astrocytes in ***Drosophila melanogaster***comprise multiple subpopulations is unknown. ***Drosophila melanogaster*** is a good model for studying astrocyte diversity due to emerging connectomes and conserved astrocyte properties between vertebrates and invertebrates. Evidence for astrocyte subtypes in ***Drosophila*** comes from sc-RNAseq datasets in the developing visual system that identified 19 glial clusters (Kurmangaliyev 2020). An independent study in the adult visual system also identified 19 glial clusters (Özel 2021), suggesting similarities between transcriptionally defined glial populations in the pupal and adult brain. These findings have raised questions about possible diversity among the six well-defined glial classes in ***Drosophila***. Here, we focus on identifying astrocyte populations among the 19 glial clusters in the pupal and adult brain of ***Drosophila.*** We establish a bioinformatics and immunohistochemistry pipeline to investigate astrocyte heterogeneity. We utilize three known genetic markers to classify astrocytes among unlabeled glia clusters. The markers ***alrm, Eaat1,*** and ***Gat*** separate astrocytes among various glial populations in newly eclosed flies (96 hours after pupal formation (hAPF)), but only ***Eaat1*** and ***Gat*** reliably separate astrocytes during adulthood. Using these markers, we identify two putative astrocyte clusters in both datasets that are predicted to be astrocytes. A correlation analysis reveals the predicted astrocytes in each dataset have the highest correlations when comparing their genetic profiles. We then sought to identify genetic differences between the predicted astrocytes. A differential gene analysis identified 3 genes differentially expressed between predicted astrocytes at 96 hAPF and 30 genes differentially expressed between predicted adult astrocytes. Future work will examine protein expression and ***in vivo*** localization of these genes to determine whether clusters represent subtypes of astrocytes or astrocytes in different states. We will then use the bioinformatics pipeline to investigate other glia cell types in these datasets as we suspect them to exhibit similar diversity. Overall, this work provides insights for identifying diversity among glia populations and aids in the understanding on the mechanisms glia cells have in regulating neuronal connectivity.

☆ Session 604 Autism: Models

8:00 AM - 12:00 PM

SDCC Halls B-H

☆ Presentation 604.01 / B49 Requirement of AGO1 for sociability and structuring the brain architecture

8:00 AM - 12:00 PM

***H. DO**[1], D. KIM[1], M. JU[1], R. JAPPELLI[3], H. YANG[2], Y. JEON[2], G. SON[1], J. SON[1], I. AHN[1], C. LIM[3], Y. JU[2], Y.-M. HAN[2], S.-H. LEE[2], D. LEE[2], F. H. GAGE[3], J. HAN[1];
[1]Grad. Sch. of Med. Sci. and Engin., [2]Biol. Sci., Korea Advanced Inst. in Sci. and Technol., Daejeon, Korea, Republic of; [3]LOG-G, Salk Inst., La Jolla, CA

Abstract

Diverse de novo variations on the ***AGO1*** gene have been identified in human patients with neurodevelopmental disorders, including intellectual disability and autism spectrum disorders (ASD). While molecular functions of AGO1 in RNA interference are very well understood, the biological roles of AGO1 in brain development and diseases remain largely unknown. Here, we present the requirement of AGO1 for sociability and structuring brain architecture during early development. First, we confirmed that AGO1 depletion in neurons results in behavioral changes in animals, similar to patients carrying AGO1 variants. Ago1 knockout (KO) in neurons leads to hyposociability of animals, which is one of the representative phenotypes of ASD. Next, we produced AGO1 KO human embryonic stem cells by applying the CRISPR/Cas9 technique and differentiated them into forebrain organoids, which mimic the 3D structure of the developing brain. Ablating AGO1 remarkably disrupts the ventricle-like structure of human forebrain organoids. Approximately half of the ventricle-like structures are unclosed, and the ventricular zone-like structures are significantly thicker in AGO1 KO organoids. At the cellular level, AGO1 KO leads to a change in neuronal morphology and electrophysiological property. AGO1 KO neurons contain shorter neurites and fire less compared to the controls. Supporting the phenotypes, differentially expressed genes (DEGs) in AGO1 KO neural progenitor cells (NPCs) and neurons were related to the extracellular matrix, cell adhesions, and neuronal differentiation. Among the DEGs, RELN, a key signaling molecule for neuronal migration and development, decreased with the most remarkable fold change in NPCs. By performing chromatin immunoprecipitation, we found that AGO1 binds to the chromatin. One of the regions associated with AGO1 in NPCs is the promoter of LIN28A that regulates the translation of mRNAs destined for the endoplasmic reticulum. We are currently working on untangling gene networks related to the phenotypes observed in AGO1 KO neurons. Nevertheless, our data clearly show that AGO1 is essential in the early stages of brain development, forming a ventricle-like structure.

☆ Presentation 604.09 / B57 Effects of CLCN4 variants on human neurodevelopmental process

8:00 AM - 12:00 PM

***D. KIM**[1], H. DO[1], C. KANG[1], I. AHN[1], Y. KOH[1], J. KIM[3], G. SON[1], J.-H. SON[1], M. JU[1], D. KIM[3], J.-E. PARK[1], J. HAN[2,1];
[2]Grad. Sch. of Med. Sci. and Engin., [1]KAIST, Daejeon, Korea, Republic of; [3]UNIST, Ulsan, Korea, Republic of

Abstract

Variations in different positions along the ***CLCN4*** have been identified in patients with intellectual disability, autistic traits, and epileptic seizures. ***CLCN4*** is a gene encoding voltage-gated chloride channel 4, CLC-4. The expression profile of the ***CLCN4*** shows the highest expression level in the brain among the other tissues, and patients carrying ***CLCN4*** variants present symptoms related to brain dysfunction. However, the biological roles and characteristics of CLC-4 in brain development and diseases remain largely unknown. In this study, to investigate the effects of ***CLCN4*** variations on the neurodevelopmental process, we generated human embryonic stem cells (hESCs) carrying ***CLCN4*** variants by applying the CRISPR/Cas9-based genome editing technique. At first, we differentiated the hESCs carrying the ***CLCN4*** variant to neural progenitor cells (NPCs) and obtained adequate NPCs similar to the control. Next, NPCs were differentiated into neurons. The neurons with the ***CLCN4*** variant displayed abnormal morphology of extended neurites at the early stage of neurogenesis. Surprisingly, the neurons with ***CLCN4*** variants suddenly died before maturation. Even in the forebrain organoids, where non-neuronal cells in the structure can support neuronal development, TUJ1 positive cells were drastically reduced if ***CLCN4*** carries genetic variations. The single-cell RNA sequencing results indicate that the brain organoids with ***CLCN4*** variants contain reduced number of neurons at the early time point in the pseudo-time-based trajectory. In summary, our results show that ***CLCN4*** is essential for the neuronal viability at the early stage of neurodevelopment. Furthermore, in this presentation, we will also discuss the expected molecular mechanisms underlying the cell death of neurons with ***CLCN4*** variants that we are currently investigating.

☆ Presentation 604.25 / C9 Dysfunction of NMDA receptors in neuronal models of an autism spectrum disorder patient with a DSCAM mutation and in Dscam-knockout mice.

8:00 AM - 12:00 PM

***M. KIM**[1], C.-S. LIM[3], J. CHOI[1], M. ISLAM[1], Y.-K. LEE[4], K.-W. SHIM[2], J.-H. LEE[5], Y.-S. LEE[6], K. LEE[7], J.-A. LEE[4], B.-K. KAANG[1];
[1]Sch. of Biol. Sci., [2]Interdisciplinary Program in Bioinformatics, Seoul Natl. Univ., Seoul, Korea, Republic of; [3]pharmacology, Wonkwang Univ. Sch. of Med., Jeonbuk, Korea, Republic of; [4]Biotech. and Biol. Sci., Hannam Univ., Daejeon, Korea, Republic of; [5]Life and Nanopharmaceutical Sci., Kyung Hee Univ., Seoul, Korea, Republic of; [6]Physiology, Beiomedical Science, Neurosci. Res. Inst., Seoul Natl. Univ. Col. of Med., Seoul, Korea, Republic of; [7]Dept. of Anatomy, Sch. of Med., Kyungpook Natl. Univ., Daegu, Korea, Republic of

Abstract

One of the neurodevelopmental disorder, autism spectrum disorders (ASD), shows heterogeneous pathologies so that ASDs require individualistic and patient-specific research. Recent improvement, human-induced pluripotent stem cell (iPSC) technology, provides a distinct platform for modeling ASDs to study complex neuronal phenotypes. Here, we generated telencephalic induced neurons (iNs) from iPSCs derived from an ASD patient with a heterozygous point mutation in the DSCAM gene. The mRNA of DSCAM and the density of DSCAM in neurites were significantly decreased in ASD compared to control iNs. RNA sequencing analysis showed that several synapse-related genes including NMDA receptor subunits were downregulated in ASD iNs. Moreover, NMDA receptor (R)-mediated currents were also reduced in ASD compared to control iNs. Normal NMDA-R-mediated currents were rescued by expressing wild-type DSCAM in ASD iNs, and reduced currents were observed by truncated DSCAM expression in control iNs. shRNA-mediated DSCAM knockdown in control iNs resulted in the downregulation of an NMDA-R subunit, which was rescued by the overexpression of shRNA-resistant DSCAM. In fact, DSCAM was co-localized with NMDA-R components in the dendritic spines of iNs whereas their co-localizations were significantly reduced in ASD iNs. A neural stem cell-specific Dscam heterozygous knockout mice show deficits in social interaction and social memory with reduced NMDA-R currents. These data suggest that DSCAM mutation causes pathological symptoms of ASD by dysregulating NMDA-R function.

☆ Session 610 Transcriptional and Translational Control of Synaptic Plasticity and Behaviors

8:00 AM - 12:00 PM

SDCC Halls B-H

☆ Presentation 610.07 / E12 Essential role for the neurodevelopmental disorder-linked gene, MEF2C, in GABAergic neuron function and neurotypical social behavior

8:00 AM - 12:00 PM

***Y. CHO**, E. TSVETKOV, T. R. SATO, S. BERTO, A. ASSALI, C. W. COWAN;
Dept. of Neurosci., Med. Univ. of South Carolina, Charleston, SC

Abstract

The MEF2 (Myocyte Enhancer Factor 2) family of transcription factors regulate gene expression controlling cell differentiation and synapse development. Loss-of-function mutations or deletions of the ***MEF2C*** gene cause a neurodevelopmental disorder, termed ***MEF2C*** Haploinsufficiency Syndrome (MCHS). MCHS includes symptoms of autism spectrum disorder (ASD), intellectual disability, seizures, and motor and sensory abnormalities. MEF2C is highly expressed in excitatory forebrain neurons and GABAergic neurons, but the effects of MEF2C hypofunction in GABAergic cells for MCHS-like phenotypes is unknown. To study the role of MEF2C in GABAergic cell populations during mouse development, we bred ***Vgat*** (vesicular GABA transporter)-Cre mice, which express Cre recombinase broadly in early developing GABAergic neurons, with a floxed ***Mef2c*** loss-of-function mouse to create offspring that are GABAergic cell-specific ***Mef2c*** heterozygous mutants (***Mef2c***$^{fl/+}$;***Vgat***-Cre or ***Mef2c*** cHet^{Vgat}). We then subjected the ***Mef2c*** cHet^{Vgat} and littermate control mice to a battery of tests measuring MCHS-relevant phenotypes, including social preference, learning and memory, and sensory sensitivity. Interestingly, ***Mef2c*** cHet^{Vgat} female, but not male, mice displayed significant deficits in sociability. Using additional cell type-specific Cre driver lines, we are in the process of further defining the relevant GABAergic cell subtypes relevant to sociability deficits. Moreover, in the ***Mef2c*** cHet^{Vgat} female mice, we observed significant alterations in excitatory/inhibitory balance and physiological properties of GABAergic interneurons in the prefrontal cortex (PFC), a brain region linked to social behavior deficits in multiple mouse models of ASD. Using a single-cell RNA-Seq approach, we also observed significant differentially expressed genes (DEGs) in multiple GABAergic cell types in PFC, and the most affected GABAergic population showed significant DEG enrichment for risk genes linked to ASD, schizophrenia, and intellectual disability. Together, our findings reveal an important, sex-specific role for MEF2C in GABAergic cells in neurotypical social behavior in mice.

☆ Session 613 Alzheimer Disease Multiomics

8:00 AM - 12:00 PM

SDCC Halls B-H

☆ Presentation 613.03 / E57 Cell-type specific protein changes in an acute model of Alzheimer’s disease

8:00 AM - 12:00 PM

***J. SHIN**[1,2], V. L. DAWSON[1,2,3,4], T. M. DAWSON[1,2,3,5,6], C. NA[1,2], T.-I. KAM[1,2];
[1]Neurodegeneration and Stem Cell Programs, Inst. for Cell Engin., [2]Dept. of Neurol., [3]Solomon H. Snyder Dept. of Neurosci., [4]Dept. of Physiol., [5]Dept. of Pathology, [6]Dept. of Pharmacol. and Mol. Sci., Johns Hopkins Univ. Sch. of Med., Baltimore, MD

Abstract

Alzheimer’s disease (AD) is the most common neurodegenerative disorder. Amyloid-β (Aβ) is known as a central hallmark of AD brains, but the underlying pathological mechanisms still remain to be elucidated. The focus of the majority of AD research has been targeted towards the selective loss of specific neuronal populations, but less effort has been spent in understanding the non-neuronal mechanisms mediated by microglia and astrocytes. While knowledge of proteomic changes that occur in pathological conditions might provide a better understanding of AD pathogenesis, systemic analysis of the brain proteome of AD models is lacking. Here we analyzed the alterations in cell-type-specific proteome induced by Aβ in primary mouse cortical, microglial and astrocyte cultures using TurboID-based protein labeling approach. In addition, lentiviruses expressing TurboID under neuron-, astrocyte, or microglia-specific promoters were delivered to mouse brains via stereotaxic injections, followed by intracerebroventricular injection of oligomeric Aβ that acutely induce AD-like cognitive symptoms. LC-MS/MS-based proteomics in each cell type of Aβ-infused mice brains and further validation via biochemical analysis can offer novel insights into cellular mechanisms underlying AD.

☆ Session 616 APP/Abeta Cellular and Animal Models I

8:00 AM - 12:00 PM

SDCC Halls B-H

☆ Presentation 616.01 / F29 Alterations in behavioral flexibility and hippocampal sharp-wave ripples during naturalistic risky decision-making in a mouse model of Alzheimer’s disease

8:00 AM - 12:00 PM

***E. KIM**[1,3], B. P. SCHUESSLER[1], S. PARK[4], J. CHO[4], J. J. KIM[1,2];
[1]Dept. of Psychology, [2]Program in Neurosci., Univ. of Washington, Seattle, WA; [3]Sch. of Psychology, Korea Univ., Seoul, Korea, Republic of; [4]Dept. of Brain and Cognitive Sci., Ewha Womans Univ., Seoul, Korea, Republic of

Abstract

While much research on Alzheimer’s disease (AD) has focused on neuropathological markers and consequent loss of memory functions, there is limited information as to how AD adversely affects brain cell activities involved in other cognitive functions, such as risky decision-making. Previously, we reported that 5XFAD mouse model of AD, expressing five mutations in human APP and PS1 (4-8 months old male and female mice), showed impairment in discerning safety-danger boundaries and making optimal foraging decisions when tested in ecologically-relevant ‘approach food-avoid predator’ paradigms (Schuessler et al., 2021). Given the critical role of hippocampal sharp-wave ripples (SWRs) and prefrontal cortical activity in decision-making and “contextual emotional experience” (Schmidt & Redish, 2021; Girardeau et al., 2017), we investigated whether and how SWRs and SWRs-associated neuronal interactions in the prefrontal-hippocampal circuit are altered by amyloid pathology in the 5XFAD mice. To do so, male and female 5XFAD and wild-type (WT) mice, implanted with tetrode arrays in the medial prefrontal cortex (mPFC) and CA1 area of the dorsal hippocampus (dCA1) ipsilaterally, underwent successive sessions of nest habituation, foraging preference baseline, and predator testing in a figure-8 maze where two different pellets (grain-based vs. chocolate-flavored) were placed in the two arms. Tetrodes were gradually advanced towards their target structures, and neural activities were recorded during the predator testing session, which consisted of pre-predator (8-11 trials), predator (5-8 trials), and post-predator (10 min in nest) stages. During the predator trials, every time the animal approached the preferred pellet, the predator surged forward. In response to the predator, the WT mice switched their foraging strategy from the preferred to non-preferred pellets. In contrast, the 5XFAD mice continued to choose their preferred pellets, indicating an inability to adjust their foraging behavior as a function of danger. During the post-predator trials, 5XFAD mice demonstrated decreased frequency and shortened duration of dCA1 SWRs events compared to the WT mice. However, comparable proportions of mPFC units exhibited SWRs-associated activity in the two groups, indicating that surviving hippocampal SWRs can modulate mPFC activity in the 5XFAD mice. These results of impaired behavioral flexibility and reduced hippocampal SWRs during risky decision-making in AD mice suggest that restoring hippocampal SWRs may be a novel therapeutic strategy for AD.

☆ Presentation 616.02 / F30 5XFAD transgenic mouse model of Alzheimer's disease: a longitudinal analysis of naturalistic foraging behavior

8:00 AM - 12:00 PM

***B. P. SCHUESSLER**[1], L. BELLMONT-OLSON[3], J. J. KIM[1,2], E. KIM[1];
[1]Dept. of Psychology, [2]Program in Neurosci., Univ. of Washington, Seattle, WA; [3]Sch. of Grad. Psychology, Pacific Univ., Hillsboro, OR

Abstract

Studies utilizing animal models of Alzheimer’s disease have primarily focused on the disease’s impact on higher cognitive functions, particularly learning and memory. Less studied in animal models is the impact of the disease on other behavioral processes, such as motivation (Boyle et al., 2003), eating pattern (Tsang et al., 2010) and circadian rhythm (Coogan et al., 2013). The present study sought to comprehensively investigate these understudied processes over an extended period using the Five Familial AD (5XFAD) mouse model of Alzheimer’s disease. To do so, male 5XFAD transgenic mice (3-4 months old) were housed under closed economy conditions, wherein animals were required to obtain their daily food solely via lever pressing (Schuessler et al., 2020). To assess motivation levels and circadian appetitive (foraging) behavior, a fixed ratio 50-continuous reinforcement (FR50-CRF) chained schedule of reinforcement was used. Under this schedule, animals were required to initially press 49 times without reinforcement. On the 50th press they were rewarded with a food pellet and entered into the CRF phase, where each press was reinforced with one pellet. This schedule imposed naturalistic food procurement/consumption costs. Additionally, the lever schedule reset after 1 minute of no pressing. This meant animals needed to exert sustained effort to obtain food. Locomotor and foraging behavior in closed economy chambers were measured automatically and near continuously (23-47 hours per day/session) for several weeks. Overall, there were minimal differences between 5XFAD hemizygous mice (n=8) and their wild type littermates (n=8); there were no significant differences between groups in the total amount of food pellets obtained, failed transitions into CRF and distance travelled (locomotor activity) per day. However, 5XFAD mice engaged in significantly more eating bouts per day (“meals”) relative to their wild type littermates, which also resulted in significantly more lever presses per day. Analysis of circadian rhythm under reverse 12-hour light/dark conditions shows that while both genotypes displayed comparable circadian behavior, 5XFAD mice foraged more during the last three hours of the dark cycle (ZT 22-24). This study suggests that at 3-4 months of age, male 5XFAD mice do not show general deficits in food motivation or locomotor activity, but rather subtle changes in daily foraging pattern.

☆ Presentation 616.21 / F47 Co-activation of selective nicotinic acetylcholine receptors improves hippocampal brain rhythms and memory in the mouse of Alzheimer’s disease.

8:00 AM - 12:00 PM

***R. LEE**, S. KIM;
Colorado State Univ., Colorado State Univ., Fort Collins, CO

Abstract

It has been suggested that reduced activity in GABAergic inhibitory interneurons disrupts neural oscillations in the hippocampus, which leads to memory loss in Alzheimer's disease (AD). A prominent AD pathology in the human brain is the loss of cholinergic neurons and nicotinic acetylcholine receptors (nAChR). Aβ is known to interact with these receptors and impair their function. nAChRs are expressed more in GABAergic inhibitory interneurons, thus cholinergic deficiency is a prime suspect for Aβ-induced impairment of inhibitory dysfunction in the hippocampus and cognitive decline in AD. Our previous findings, using cultured mouse hippocampal neurons show Aβ selectively interacts with α7- and α4β2-nAChRs, but not α3β4-nAChRs, and decreases activity in inhibitory interneurons, but induces hyperexcitation in excitatory neurons. We thus hypothesize that Aβ reduces hippocampal GABAergic activity by selectively inhibiting α7- and α4β2-nAChRs, resulting in hippocampal oscillatory disruption and memory loss in AD. To test our hypothesis, the AD mouse model, 5XFAD transgenic mice, and wild type (WT) littermates were treated intraperitoneally with α7- and α4β2-nAChR agonists. Saline was given to control mice. Fear conditioning was performed to see if agonists improved memory. We found that 5XFAD mice showed clear deficit in contextual memory which was successfully reversed by co-stimulation of α7- and α4β2-nAChR agonists. Stereotaxic surgery was then performed to measure local field potentials of theta and gamma oscillations, key components for learning and memory. During memory consolidation, theta, slow and fast gamma activities were significantly reduced in 5XFAD mice. Co-activation of α7- and α4β2-nAChR agonists was sufficient to restore normal rhythmic activities in 5XFAD mice. Ca^{2+} imaging with nicotine uncaging further reveals that cultured hippocampal neurons expressed α7- and α4β2-nAChRs in parvalbumin-positive (PV+) and somatostatin-positive (SST+) cells, respectively. These two major types of GABAergic inhibitory interneurons play key roles in hippocampal network activity and learning and memory. Thus, co-activation of the two receptors is important for restoring hippocampal activity and memory in 5XFAD mice.

☆ Session 618 LRRK2 Mechanisms, Targets, and Pathways

8:00 AM - 12:00 PM

SDCC Halls B-H

☆ Presentation 618.08 / G12 Characterization of a novel small-molecule LRRK2 inhibitor WI-211094 as a potential therapeutic agent for Parkinson's disease

8:00 AM - 12:00 PM

***J. SEO**[1], J. LEE[1], B. YOU[1], J. HEO[1], S. HAN[1], K. PARK[1], H. SHIN[1], D. HO[2], H. CHOI[3], G. LEE[4], S. KANG[1];
[1]Whan In Pharmaceut. Co., Ltd., Seoul, Korea, Republic of; [2]InAm Neurosci. Res. Center, Sanbon Med. Center, Col. of Medicine, Wonkwang Univ., Gunpo, Korea, Republic of; [3]Col. of Pharm. and Inst. of Pharmaceut. Sciences, CHA Univ., Pocheon, Korea, Republic of; [4]Office of Small & Medium Enterprises Support, Korea Res. Inst. of Chem. Technol., Daejeon, Korea, Republic of

Abstract

Inhibition of leucine-rich repeat kinase 2 (LRRK2) is a potential target for disease-modifying therapy in Parkinson's disease (PD) since mutations in its kinase domain are known to cause familial and idiopathic PD (iPD). Here, we report WI-211094, a novel, highly potent (IC50=26 nM for WT and 6.4 nM for G2019S mutant), selective, and central nervous system (CNS)-penetrant small-molecule LRRK2 inhibitor. In an lipopolysaccharide (LPS)-treated BV2 cell model, inhibition of LRRK2 by WI-211094 decreased both reactive oxygen species (ROS) and TNF-alpha levels. Moreover, WI-211094 improved the mitochondrial dysfunction, implying its anti-neuroinflammatory effects. WI-211094 possesses high oral bioavailability in rodents and beagle dogs, and it exhibited in vivo efficacy in a PD animal model, the rotenone-induced mouse model. WI-211094 treatment rescued the expression level of tyrosine hydroxylase (TH) impaired by rotenone and reduced the phosphorylation level of alpha-synuclein in the substantia nigra (SN), indicating that WI-211094 could attenuate the toxicity of alpha-synuclein by interrupting its aggregation. In mice, WI-211094 was well tolerated up to 1000 mg/kg once daily for 2 weeks without histopathological alterations in tissues, especially lung adverse effects. Taken together, we suggest that WI-211094, a novel, advanced, and generally safe LRRK2 inhibitor, might be a potential therapeutic candidate for both iPD patients and familial PD patients with LRRK2 mutation.

☆ Session 621 Neuroinflammation: Immunomodulators, Anti-Inflammatories

8:00 AM - 12:00 PM

SDCC Halls B-H

☆ Presentation 621.21 / K1 Inhibiting peripheral and central MAO-B ameliorates joint inflammation and cognitive impairment in rheumatoid arthritis

8:00 AM - 12:00 PM

***W. WON**[1], H.-J. CHOI[2], J.-Y. YOO[2], D. KIM[1], T. KIM[1], Y. JU[1], K. PARK[3], H. LEE[3], S. JUNG[4], C. J. LEE[1];
[1]Ctr. for Cognition and Sociality, Inst. for Basic Sci., Daejeon, Korea, Republic of; [2]CHA Univ., Seongnam, Korea, Republic of; [3]Korea Inst. of Sci. and Technol., Seoul, Korea, Republic of; [4]CHA Bundang Med. Center, CHA Univ., Seongnam, Korea, Republic of

Abstract

Rheumatoid arthritis (RA) is an autoimmune disorder characterized by chronic inflammation and the destruction of joints and systemic organs. RA is commonly accompanied by neuropsychiatric complications, such as cognitive impairment and depression. However, the role of monoamine oxidase (MAO) and its inhibitors in controlling neurotransmitters associated with these complications in RA have not been clearly identified. Here, we report that peripheral and central MAO-B are highly associated with joint inflammation and cognitive impairment in RA, respectively. Ribonucleic acid (RNA) sequencing and protein expression quantification were used to show that MAO-B and related molecules, such as gamma-aminobutyric acid (GABA), were elevated in the inflamed synovium of RA patients. In primary cultured fibroblast-like synoviocytes in the RA synovium, MAO-B expression was significantly increased by tumor necrosis factor (TNF)-α-induced autophagy, which produces putrescine, the polyamine substrate for GABA synthesis. We also observed that MAO-B-mediated aberrant astrocytic production of GABA was augmented by interleukin (IL)-1β and inhibited CA1-hippocampal pyramidal neurons, which are responsible for memory storage, in an animal model of RA. Moreover, a newly developed reversible inhibitor of MAO-B ameliorated joint inflammation by inhibiting cyclooxygenase (Cox)-2. Therefore, MAO-B can be an effective therapeutic target for joint inflammation and cognitive impairment in patients with RA.

☆ Presentation 621.09 / J5 Redirecting Microglia Phenotype via Inhibition of NFAT1 Ameliorates Deficits in Mouse Models of synucleinopathies

8:00 AM - 12:00 PM

***C. KIM**[1], M. IBA[1], M. SZABO[1], Y. LEE[2], R. A. RISSMAN[3], S.-J. LEE[4], S. YOU[2], M. COOKSON[1], E. MASLIAH[1];
[1]Natl. Inst. on Aging, NIH, Natl. Inst. on Aging, Bethesda, MD; [2]Cedars-Sinai Med. Ctr., Los Angeles, CA; [3]UCSD Sch. of Med., Sch. of Med., La Jolla, CA; [4]Seoul Natl. Univ. Col. of Med., Seoul, Korea, Republic of

Abstract

Abnormal deposition of α-synuclein (α-syn) and neuroinflammation are key contributors to the pathogenesis of Parkinson's disease (PD) and other synucleinopathies such as Dementia with Lewy bodies and Multiple system atrophy. We recently demonstrated that Leucine-rich repeat kinase 2 (LRRK2), a PD-associated gene mediated microglial neurotoxic neuroinflammation via modulation of and nuclear factor of activated T-cells 1 (NFAT1) activity in synucleinopathies. Therefore, we evaluated the possibility of NFAT1 inhibition as a new potential therapeutic strategy for synucleinopathies in current study. To investigate the effect of NFAT1 inhibition in the pathogenesis of synucleinopathies, we intraperitoneally delivered cell-permeable NFAT1 inhibitor, 11R-VIVIT into the wildtype and α-syn transgenic mice (α-syn-tg). Administration of 11R-VIVIT decreased the levels of NFAT1 and microglial pro-inflammatory cytokine gene expressions such as Tnfα and Il-6 in the α-syn-tg. However, neurodegeneration of α-syn-tg was inhibited by NFAT1 inhibition in α-syn-tg. In addition, treatment of 11R-VIVIT ameliorated motor learning behavior in α-syn-tg. Furthermore, accumulation of pathogenic forms of α-syn was also significantly reduced by 11R-VIVIT treatment in α-syn-tg. Most interestingly, microglial transcriptome analysis obtained from isolated microglia from wildtype and α-syn-tg treated with either saline or 11R-VIVIT suggested that inhibition of NFAT1 reduced microglial cytokine gene expression, but also ameliorates cell motility and phagocytosis abilities in α-syn-tg. Indeed, inhibition of NFAT1 re-directed pre- and fully- activated microglia to resting microglia, therefore increased microglial phagocytosis and migration, but also decreased microglial pro-inflammatory cytokine gene expressions. Hence, we propose that inhibition of NFAT1 will be a novel therapeutic strategy for Parkinson’s disease and related synucleinopathies.

☆ Session 623 Microglia: Regulation and Function

8:00 AM - 12:00 PM

SDCC Halls B-H

☆ Presentation 623.19 / N3 Sat1 alleviates neuropathic pain by regulating microglia activation

8:00 AM - 12:00 PM

***J. SHIN**, S. KIM, H. SHIN, D. KIM;
Chungnam Natl. Univ. Col. of Med., Chungnam Natl. Univ. Col. of Med., Daejeon, Korea, Republic of

Abstract

Microglia are glial cells and responsible for the immune defense and inflammatory responses in the central nervous system (CNS). The activation of microglia has been considered to develop and maintenance of neuropathic pain, moreover, prolonged microglia activation can cause chronic neuroinflammation and increase production of pro-inflammatory mediators. Here, we succeeded in alleviating neuropathic pain by inhibiting the microglial activation through the downregulation of SAT1 with PLGA nanoparticles. To relive neuropathic pain behavior, SAT1 shRNA encapsulated PLGA nanoparticles (shSAT1 NPs) were prepared and characterized. We revealed that shSAT1 NPs significantly inhibited excessive production of TNF-α and IL-1β in LPS incubated BV2 cells. In addition, neuropathic pain induced by spinal nerve injury was effectively reduced in rats and mice, and the decrease of microglia activity was also confirmed by histological and cytokine analysis. Taken together, these data suggest that SAT1 downregulation in microglia with PLGA nanoparticles efficiently relives neuropathic pain, and it would be therapeutic value for treating neuropathic pain.

☆ Presentation 623.21 / N5 Amitriptyline repositioning prolongs analgesic effect by enhanced targeting microglia

8:00 AM - 12:00 PM

***S. KIM**, J. SHIN, N. SHIN, H. SHIN, D. KIM, S. LEE;
Chungnam Natl. Univ. of Med., Chungnam Natl. Univ. of Med., Daejeon, Korea, Republic of

Abstract

Amitriptyline (AMI) has been applied to various pain conditions, including neuropathic pain, but the clinical outcomes remain unsatisfactory, and the underlying molecular mechanisms are unclear. Therefore, we investigated the development of a drug repositioning for neuropathic pain based on low dose of AMI encapsulated in poly (D, L lactic-co-glycolic acid) (PLGA) nanoparticles (AMI NPs), since PLGA nanoparticles are known to be enhancing delivered to microglia. The analgesic effects of AMI and AMI NPs on neuropathic pain were evaluated with behaviors and inflammatory responses using a rat model of spinal nerve ligation (SNL). Analgesic effect on SNL-induced neuropathic pain was persisted for 4 h in AMI-injected rats. By contrast, AMI NPs significantly alleviated mechanical allodynia for 3 days. Both microglial activation and pro-inflammatory mediators were notably reduced in the spinal dorsal horn, according to histological and cytokine analyses. This study showed that AMI NPs can provide a prolonged analgesic effect by enhanced targeting of microglia. Moreover, neuropathic pain was improved by AMI NP-mediated regulation of pro-inflammatory cytokine release from activated microglia. Our view implies that sustained release of AMI from microglia-targeted NPs provides drug repositioning along with long-term analgesic effects while reducing potential side effects of the drug.

☆ Session 633 Auditory: Human Speech and Music

8:00 AM - 12:00 PM

SDCC Halls B-H

☆ Presentation 633.03 / X7 Emergence of music-selectivity in deep neural networks trained for natural sound detection

8:00 AM - 12:00 PM

***G. KIM**, D.-K. KIM, H. JEONG;
KAIST, KAIST, Daejeon-City, Korea, Republic of

Abstract

Music exists in almost every society, has universal acoustic features, and is processed by distinct neural circuits in humans even with no experience of musical training. These characteristics suggest an innateness of the sense of music in our brain, but it is unclear how this innateness emerges and what functions it has. Here, using an artificial deep neural network that models the auditory information processing of the brain, we show that units tuned to music can spontaneously emerge by learning natural sound detection, even without learning music. By simulating the responses of network units to 35,487 natural sounds in 527 categories, we found that various subclasses of music are strongly clustered in the embedding space, and that this clustering arises from the music-selective response of the network units. The music-selective units encoded the temporal structure of music in multiple timescales, following the population-level response characteristics observed in the brain. The music-selectivity of the network gradually increased throughout the training process for natural sound detection. Based on this, we confirmed that the process of generalization is critical for the emergence of music-selectivity and that music-selectivity can work as a functional basis for the generalization of natural sound. We found that ablation of the music-selective units significantly deteriorates the natural sound detection performance of the network. This suggests that music and other natural sounds share key features, and thus music-selective units can play a functionally important role not only in music processing but also in natural sound detection. Further investigation showed that training with speech helps the network units to acquire long-range temporal features of music. Our findings suggest that our sense of music can be innate, universally shaped by

evolutionary adaptation to process natural sound.
https://www.biorxiv.org/content/10.1101/2021.10.27.466049v2

☆ Session 639 Cerebellum: Interactions With Other Brain Areas

8:00 AM - 12:00 PM

SDCC Halls B-H

☆ Presentation 639.13 / FF10 Noradrenergic tone modulates cerebellar nuclear activity-dependent performance in delay eyeblink conditioning

8:00 AM - 12:00 PM

***J. LEE**, H.-J. BOELE, W. T. FLEMING, G. J. BROUSSARD, F. D'OLEIRE UQUILLAS, S. S.-H. WANG;
Princeton neuroscience institute, Princeton Univ., Princeton, NJ

Abstract

Noradrenergic tone regulates learning and performance in forebrain structures, but little is known about how this pathway affects cerebellar function. We administered a delayed eyeblink conditioning task to mice, and simultaneously recorded activity from populations of locus coeruleus (LC) axons and deep-nuclear neurons in the interpositus nucleus (InT) using fiber photometry. We used a genetic strategy to express GCaMP8f in LC axons and jRGECO1a in local neurons of the InT to allow multiplex imaging of both target cell types in InT. A 280 ms blue LED light served as the conditioned stimulus (CS), and a co-terminating corneal airpuff (30 ms) as the unconditioned stimulus (US). Conditioned responses (CRs) developed over the course of 18 daily sessions, with 90-100 trials per session. CS-evoked InT signals grew on a session-by-session basis (linear mixed-effects model, LME, effect size: Cohen's d = 1.16, p = 1.0e-06) and with learning stage (sessions with less than 20 CR% were classified as before learning, 20 to 60% as during learning, and more than 60% as after learning; linear regression by stage, effect size: Cohen's d = 0.59, p = 0.06). However, on a trial-by-trial basis, InT signals only weakly predicted CR amplitude (LME for trial-by-trial: d = 0.18, p = 3.8e-15). To test whether pre-CS noradrenaline levels also couple InT activity and CRs, we quantified the ability of pre-CS LC activity ("LC tone") to moderate the trial-by-trial relationship between CS-evoked InT and CR amplitude. LC tone was Z-scored and defined as low (less than minus one-half SD of LC signal), medium (more than minus one-half SD to less than one-half SD of LC signal), or high (more than one-half SD of LC signal). InT signals and CR amplitude were unrelated at low LC tone (d = 0.07, p = 0.18) but became more strongly coupled for medium (d = 0.24, p = 8.2e-07) and high tone (d = 0.29, p = 1.2e-05). Combined with our previous finding that CS-evoked LC signals become larger with eyeblink conditioning (J. Lee, H.-J. Boele, and S.S.-H. Wang 2021 Soc. Neurosci. Abstract P510.06), we posit that LC activity regulates InT-driven learned responses on a trial-by-trial basis.

☆ Session 646 Stress-Modulated Pathways: Hypothalamus and Bed Nucleus

8:00 AM - 12:00 PM

SDCC Halls B-H

☆ Presentation 646.09 / OO1 Restraint stress changes the excitability of hypothalamic POMC neuron and food intake

8:00 AM - 12:00 PM

***G. HA**, G.-H. KIM, R. SONG, E. CHEONG;
Yonsei Univ., Yonsei Univ., Seoul, Korea, Republic of

Abstract

Stress activates the hypothalamic-pituitary-adrenal system and induces the release of glucocorticoids, stress hormones, into circulation. Many studies have shown that stress affects feeding behavior. However, the underlying circuitry and molecular mechanisms are not fully understood. Orexigenic (simulating appetite) and anorexigenic (loss of appetite) signals reciprocally modulate feeding behavior. It is suggested that proopiomelanocortin (POMC) and neuropeptide Y (NPY) neurons in the arcuate nucleus (ARC) of the hypothalamus are the first-order neurons that respond to the circulating signals of hunger and satiety. Here, we examined restraint stress model and observed an alteration of food intake. We investigated whether stress affects the properties of POMC and NPY neurons in ARC and found that restraint stress changed the excitatory inputs onto POMC neurons and the action potential threshold, leading to changes in feeding behavior. Additionally, we have further studied to find out the effect of restraint stress in other brain regions related to regulate appetite and satiety.

☆ Session 651 Neural and Behavioral Variables Associated with Cocaine Use

8:00 AM - 12:00 PM

SDCC Halls B-H

☆ Presentation 651.06 / SS13 Brain structural and functional alteration in the cocaine self-administered common marmoset

8:00 AM - 12:00 PM

***S. GU**[1], S. YOON[2], J. LEE[3], H. EOM[3], J. GIM[1], S. KIM[4], E. YU[1], A. KIM[1], J. CHOI[3], Y. YI[3], J. SON[3], T. KIM[5], C.-W. PARK[1], J. HONG[1], Y.-S. JUNG[4], D. LEE[3], J. YUN[1];
[1]Col. of Pharm., Chungbuk Natl. Univ., Cheongju-si, Korea, Republic of; [2]Col. of Korean Med., Daegu Haany Univ., Daegu, Korea, Republic of; [3]Osong Med. Innovation Fndn., Cheongju-si, Korea, Republic of; [4]Pusan Natl. Univ., Busan, Korea, Republic of; [5]Catholic Univ. of Daegu, Gyeongsan-si, Korea, Republic of

Abstract

Brain dysfunction and structural changes are related with repetitive and stereotyped behaviors, cocaine-induced rapid head movement in common marmoset (Callithrix jacchus) can serve as a model for stereotype. In this study, we studied effects of binge cocaine administration on the marmoset behaviors, brain structural and functional alteration. Cocaine was self-administered (SA) intravenously to adult marmosets for 30 days. After the last cocaine administration, the behaviors were observed in freely moving marmosets for 2 h. We performed resting-state functional magnetic resonance imaging (rs-fMRI) to elucidate resting-state functional connectivity (rsFC), and metabolic profiles in the plasma. A total of 30.45 mg/kg of cocaine injected for one month induced repetitive stereotyped behaviors, such as rapid head movements. We confirmed that cocaine administration changed the brain connectivity at 23 areas including the cortex, and nucleus accumbens, and availability of cannabinoid receptor type 1 and expression of glutamate decarboxylase in the cortex, and glutamine/glutamate metabolism in the plasma. Furthermore, cocaine reduced white matter structure in the corpus callosum. In proteomics study, level of dihydropyrimidinase-related protein2 (DPYSL2) that is related with axon development and guidance regulation molecules are most altered in cocaine treated marmoset acute brain slice, and protein expression of DPYSL2 tended to decrease by treatment of cocaine. Interestingly, gene-gene interaction analysis revealed that crystallin alpha B (CRYAB), a chaperone expressed in oligodendrocyte is associated with DPYSL2, and we also confirmed that cocaine significantly induced expression of CRYAB and p-CRYAB in oligodendrocytes-positive cells in the cortex. Meanwhile, to develop a deep learning-based automatic striatal dopamine transporter (DAT) identification algorithm, we used the ^{18}F-FP-CIT PET images of cocaine SA marmosets and the U-net neural network. As a result, significant strong negative correlation between SA data and striatal DAT availability on PET image was shown, and the U-NET based segmentation for striatal DAT showed 0.96 of accuracy, 0.84 of intersection over union and 0.91of Dice. Taken together, the study suggests that the cocaine chronic SA induced disturbance in the cortex connectivity and modification in the corpus callosum white matter via regulation of endogenous cannabinoid system and GABAergic neurotransmission, axon development, moreover, an automatic identification algorithm for DAT could be helpful for image analysis for research to pharmacological researchers who are not imaging experts.

☆ Session 656 Prefrontal Cortex Role in Memory and Fear

8:00 AM - 12:00 PM

SDCC Halls B-H

☆ Presentation 656.08 / VV37 Amygdala-prefrontal cortex interactions during risky decision-making in rats encountering a predatory threat in a naturalistic environment

8:00 AM - 12:00 PM

***J. J. KIM**[1], E. KIM[1], S. PARK[2], J.-S. CHOI[3], J. CHO[2];
[1]Psychology, Univ. of Washington, Seattle, WA; [2]Brain Cognitive Sci., Ewha Womans Univ., Seoul, Korea, Republic of;
[3]Psychology, Korea Univ., Sungbuk-Ku, Seoul, Korea, Republic of

Abstract

Animals often change their foraging behaviors under predation pressure to maximize survival by decreasing exposure to threats and increasing procurement of available food. Previously, we investigated foraging behaviors in an ecologically-relevant setting and found that rats can discern conditional predatory (Robogator) threats and adjust their foraging strategy, which was abolished by amygdala lesions (Kim et al., 2016). Here, we explored the neural basis of conditional threat discrimination and foraging preference switch by simultaneously recording single-units in the basolateral amygdala (BLA) and the prelimbic (PL) area of the medial prefrontal cortex, two structures implicated in fear and decision-making processes, respectively (Mobbs and Kim, 2015). Male Long-Evans rats were implanted with tetrode arrays in the BLA and PL and underwent successive stages of (i) nest habituation, (ii) foraging preference baseline (choosing chocolate pellet vs. normal pellet), and (iii) Robogator encounter testing (preference baseline trials followed by Robogator trials). Neural activities of BLA and PL were recorded simultaneously during the Robogator encounter testing days. During the preference baseline trials, rats showed a general bias towards chocolate pellets over normal pellets. Upon approaching the preferred pellet and experiencing the Robogator surge, all animals shifted their foraging behaviors toward non-preferred pellets. When BLA and PL cells were analyzed by plotting the peri-event time histograms, the population levels of BLA neurons showed increased activity exclusively to the Robogator surge while the population levels of PL neurons displayed increased activity comparably to multiple events (i.e., preferred pellet, non-preferred pellet, and Robogator surge). A cross-correlation analysis revealed that a subset of simultaneously recorded BLA and PL cell pairs showed increased spike synchrony prior to foraging preference shift during the Robogator session, where (PL-led) BLA cells responded to the Robogator surge while (BLA-projecting) PL cells responded to multiple events. These results suggest that BLA neurons encoding imminent threats actively interact with PL units signaling multiple events to change foraging strategy under conditional threat.

☆ Presentation 656.10 / VV39 Ecological analysis of Pavlovian fear conditioning in rats

8:00 AM - 12:00 PM

***P. R. ZAMBETTI**[1], B. P. SCHUESSLER[2], B. E. LECAMP[3], A. SHIN[4], E. KIM[1], J. J. KIM[1];
[1]Psychology, Univ. of Washington, Seattle, WA; [2]Psychology, [3]Undergraduate Program in Neurosci., Univ. of Washington, Seattle, Seattle, WA; [4]Undergraduate Program in Human Biol., Stanford Univ., Stanford, CA

Abstract

Contemporary models of fear and their putative translational significance largely stem from rodent Pavlovian fear conditioning research, which simplifies behavioral, systems, circuit and genetic analyses of the acquisition, expression, generalization, extinction and return of a specific conditioned fear responses (CR; mainly, freezing). Although fear conditioning is widely considered crucial to survival, its functions surprisingly have not yet been ethologically validated. Some have even questioned its evolutionary relevance—if associative trial-and-error learning were the primary defensive mechanism, most animals would be killed before they learned which predators and situations must be avoided (e.g., Bolles, 1970). To address this critical gap in proof of concept, we incorporated a one-trial delay auditory fear conditioning procedure into an ethologically-relevant 'approach food-avoid predator' scenario. Specifically, male and female Long-Evans rats foraging for food in a large arena were presented with a tone conditioned stimulus (CS) paired with electric shock unconditioned stimulus (US) to their dorsal neck/body that reflexively elicited escape unconditioned response (UR) to the safe nest. On subsequent test days, the tone-shock paired animals failed to exhibit fear CR (neither fleeing nor freezing) to the CS introduced in the open arena. The same tone CS-shock US arrangement in a standard conditioning chamber, however, produced a robust freezing CR to the CS. To mimic a more naturalistic fearful scenario, other animals encountered a looming artificial owl paired with a dorsal neck/body shock, mimicking a realistic predatory-inflicted pain. The owl-shock paired animals instantly fled to the nest when presented with a tone for the first time. These results highlight the possibility of a nonassociative, rather than standard associative, fear process providing adaptive function in life-threatening situations that animals are likely to encounter in nature. The utilization of naturalistic fear paradigms that simulate dangers that animals and humans encounter in real life—where there are external hostile agents (predators in animals and perpetrators in humans)—will likely clarify, update, and revise fear concepts derived largely from fear conditioning studies (devoid of external agents) and in doing so facilitate future progress in the treatment of fear disorders.

☆ Session 657 Human Learning and Memory

8:00 AM - 12:00 PM

SDCC Halls B-H

☆ Presentation 657.09 / VV47 Repulsion of overlapping memory representations in the hippocampus depends on internal beliefs about the environment

8:00 AM - 12:00 PM

***W. GUO**, S. HAN, B. A. KUHL;
Dept. of Psychology, Univ. of Oregon, Eugene, OR

Abstract

The hippocampus is believed to play a critical role in disambiguating memories for similar events (Yassa & Stark, 2011). Consistent with this view, pattern-based fMRI studies have found that event similarity triggers an active "repulsion" of hippocampal representations (Chanales et al., 2017; Favila et al., 2016; Hulbert and Norman, 2014). Moreover, this repulsion is time-locked to successful behavioral discrimination of similar memories (Wanjia et al., 2021). One account of these findings is that repulsion of hippocampal representations specifically occurs when external stimuli are similar, but internal beliefs are distinct (Sanders et al., 2020). Here, we tested this idea using a spatial learning task in which human participants learned four different routes within the University of Oregon campus. Each route consisted of a series of sequentially presented images terminating at a specific destination (24 s, total). Critically, although each route terminated at a unique destination, the four routes contained two pairs of competing routes. For the first 6 s, the competing routes were identical (SAME segment); for the next 12 s, the routes followed identical paths but there were subtle differences in the images (OVERLAPPING segment); for the final 6 s, the routes followed divergent paths and were visually distinct (NON-OVERLAPPING segment). Importantly, to manipulate internal beliefs, each route was preceded by a probabilistic cue (75% valid) indicating the likely destination of the route. Thus, during the SAME segment, the competing routes were objectively identical, but beliefs were manipulated via the cues. Preliminary fMRI pattern similarity analyses (n = 6)
revealed that during the SAME segment—when competing routes were identical—there was a cue-driven repulsion effect in the hippocampus (selective to CA2, CA3, and dentate gyrus). Namely, when cues indicated different destinations (but the visual stimuli were identical), pattern similarity between competing routes was actually lower than pattern similarity between non-competing routes. Repulsion effects were also present during the OVERLAPPING segment (when competing routes were highly similar, but not identical); however, this effect was less dependent on the cues. Strikingly, repulsion effects were absent during the NON-OVERLAPPING segment (when competing routes were distinct). Repulsion effects were also absent, during any segment, in visual cortex. Together, our initial findings reveal that repulsion of hippocampal representations specifically occurs when visual stimuli are highly similar—or even identical—but beliefs about these stimuli are distinct.

☆ Session 659 Dentate Gyrus: Molecular and Circuit Mechanisms of Encoding

8:00 AM - 12:00 PM

SDCC Halls B-H

☆ Presentation 659.19 / WW41 Increasing adult hippocampal neurogenesis enhances social recognition memory by recruiting a feedforward inhibitory circuit

8:00 AM - 12:00 PM

***A. CHUNG**[1,2], S. MILLER[1,2], M. GHOSH[3], O. J. AHMED[3,4], A. SAHAY[1,2,5,6];
[1]Ctr. for Regenerative Med., MGH, Boston, MA; [2]Harvard Med. Sch., Boston, MA; [3]Dept. of Psychology, [4]Dept. of Biomed. Engin., Univ. of Michigan, Ann Arbor, MI; [5]BROAD Inst. of Harvard and MIT, Cambridge, MA; [6]Harvard Stem Cell Inst., Cambridge, MA

Abstract

Social recognition memory is critical for adaptive social behavior. The dentate gyrus is host to generation of new neurons, dentate granule cells, throughout life. Adult-born dentate granule cells (abDGCs) contribute to spatial or contextual memory formation, discrimination, and consolidation. In contrast, the neural circuit mechanisms by which adult-born dentate granule cells (abDGCs) contribute to social recognition memory are poorly understood. Here, we show that genetically increasing adult hippocampal neurogenesis improves social memory discrimination in a social memory interference task. Genetic expansion of a discrete population of age-matched population of abDGCs increased Parvalbumin inhibitory interneurons (PV IN) perisomatic contacts on CA2 pyramidal neurons. This enhanced PV IN structural plasticity was accompanied by an increase in functional inhibitory synaptic inputs onto CA2 pyramidal neurons. To understand how these changes in feed-forward inhibition in dentate gyrus (DG)-CA2 circuit affect network properties, we recorded local field potentials in CA1 during sleep and in the social memory task. Mice with genetically expanded population of age-matched abDGCs exhibited an increase in CA1 sharp-wave ripple (SWR) power during sleep and reduced Gamma range (30-100Hz) oscillatory neural activity during non-REM sleep. Social interactions increased the CA1 SWR rate in mice with more age-matched abDGCs relative to the control group. Our findings

begin to define neural circuit and network mechanisms by which new neurons in the adult dentate gyrus contribute to social information processing.

☆ Session 660 Timing and Temporal Processing

8:00 AM - 12:00 PM

SDCC Halls B-H

☆ Presentation 660.19 / WW57 Representations of semantic, spatial, and temporal distance in episodic memory retrieval are mediated by slow and fast theta oscillations

8:00 AM - 12:00 PM

***J. LEE**[1], S.-E. PARK[2], S. A. LEE[1];
[1]Seoul Natl. Univ., Seoul Natl. Univ., Gwanak-gu, Korea, Republic of; [2]Brain and Cognitive Sci., Seoul Natl. Univ., Seoul, Korea, Republic of

Abstract

Episodic memories can be defined by ***what*** happened, ***where*** it happened, and ***when*** it happened. Studies have shown that the different components of memory can be dissociated by their neural correlates and their heterogenous impairment in memory disorders. However, recent studies also raise the possibility that common domain-general mechanisms of cognitive mapping may be involved in the coding of semantic distance (***what***), spatial distance (***where***), and temporal distance (***when***). Given these findings, we hypothesized the simultaneous existence of both shared (domain-general) and unique (domain-specific) neural correlates across the ***what***, ***where***, and ***when*** components of episodic memory. To see such potential memory representations at work during memory retrieval, we tested 47 college students (21 female, age range 20-27) on a scene-based episodic memory task designed to assess the components separately. After showing them a series of 10 scenes, the ***what*** retrieval test required a choice between two objects the one that was missing from a particular scene; ***where*** retrieval required a choice between two scenes in which the spatial location of an object differed; and ***when*** retrieval required participants to choose which of two scenes came first during encoding. To measure neural activity during the memory retrieval phase (response time 2.3 sec on average), we recorded scalp EEG (32-channels) and calculated spectral power using Morlet wavelet transformation.We tested for correlations between cognitive distance (semantic, spatial, and temporal) and slow (2.5-5Hz) and fast (5-8.5Hz) theta power. First, during the first half of the retrieval phase (over the first second after stimulus onset) we found a unique neural signature of time - a negative correlation of slow theta power with temporal distance. In the second half of the retrieval period, we found that slow theta power was correlated with all three types of distance, while fast theta power was correlated with spatial and temporal distances. We take these results to be indicative of: 1) a domain-general, abstract representation of distance for cognitive mapping, 2) a spatiotemporal, perhaps navigational distance correlate in fast theta, and 3) an immediate (early) modulation of slow theta in temporal order memory retrieval. Although the first two markers replicate past studies using scalp EEG and iEEG, the third marker of temporal distance is novel and may signify a unique neuro-cognitive process required in temporal organization of memory.

☆ Presentation 660.20 / WW58 Temporal binding of "where" as an indicator of episodic memory network engagement

8:00 AM - 12:00 PM

***J. SHIN**[1,2], S. LEE[2];
[1]KAIST, Korea Advanced Inst. of Sci. and Technol., Daejeon, Korea, Republic of; [2]Seoul Natl. Univ., Seoul, Korea, Republic of

Abstract

Episodic memory (EM) is a key cognitive function that enables us to remember the details of past experiences including objects, locations, and temporal order (***what, where,*** and ***when***). While humans can flexibly associate EM components into a single event memory, a detailed neural account of how ***what*** and ***where*** information are bound together in time is still unclear. In this study, we tested whether remembering a temporal sequence of ***where*** is dissociable from remembering ***what*** information in EM.
Subjects (n=33, 11 female) performed an EM task in a virtual environment in the fMRI scanner. They were asked to remember an event in which objects (***what***) moved one by one into an array of boxes (***where***) in a specific order (***temporal binding***). After an interference task, they were asked to recall the entire event in their mind while looking at the still scene of the room (retrieval), and then asked to respond by using a controller to reenact the entire sequence of objects and locations. Subjects performed at ceiling in choosing the correct objects and locations (***what*** and ***where***) but made errors in binding them into a temporal sequence (***what-when*** and ***where-when***). Interestingly, error patterns for what-when and where-when varied across individuals, and the subjects who showed preserved where-when binding even when they made errors tended to have higher full EM accuracy (***what-where-when***).
fMRI results showed that the retrieval of ***what-where-when*** associated event induced activation of the visual episodic memory network including MTL, OFC, precuneus, and fusiform gyrus. The EM trials with perfect memory showed higher EM network activation than the error trials, especially in the posterior part of the hippocampus (HPC) and entorhinal cortex. Next, the error trials with higher ***where-when*** preservation (i.e., better location sequence accuracy and worse object sequence accuracy) induced more activation in the right anterior HPC (particularly in the subiculum, t=2.69, p=0.007) as well as fusiform gyrus. ***Where-when*** binding was also associated with higher functional connectivity of the anterior HPC with the temporal and parahippocampal cortex. Moreover, individual differences were also reflected in the activation of the EM network. Subjects with higher ***where-when*** utilization showed higher activity in OFC and fusiform gyrus, even when accounting for their generally higher EM accuracy. Our study provides insight into how the temporal binding of different EM components is represented in the brain and suggests that spatiotemporal (***where-when***) binding is indicative of an active EM network and predictive of successful episodic memory.

☆ Presentation 660.21 / WW59 Distinct neural mechanisms underlying individual differences in the retrieval of temporal information in episodic memory

8:00 AM - 12:00 PM

***S.-E. PARK**, J. LEE, S. LEE;
Brain and Cognitive Sci., Seoul Natl. Univ., Seoul, Korea, Republic of

Abstract

Despite many previous studies that showed dissociable neural correlates of the ***what, where, and when*** components of episodic memory, there is still a lack of a domain-based explanation of individual differences in memory performance. Given the particularly fragile nature of temporal information (i.e. ***when*** in comparison with ***what*** and ***where)*** in Alzheimer's disease, finding specific neural markers of individual differences in temporal memory may be useful for both scientific and clinical purposes. We investigated EEG activity during the retrieval of episodic memory in 47 college students using a scene-based task designed to isolate ***what***, ***where***, and ***when***. Subjects were asked to remember 10 scenes during the encoding without being informed about the condition (i.e. ***what, where and when***). ***What*** retrieval required subjects to choose the correct object that was in a particular scene; ***where*** retrieval required them to choose the correct spatial location of an object from two possible scenes; and ***when*** retrieval require them to choose the scene that they saw first. We extracted the spectral EEG features by applying wavelet transform. First, we observed a significant correlation between ***what*** and ***where*** but not with ***when,*** suggesting that ***when*** retrieval may be functionally independent from the other two components. Based on the behavioral measures, we divided subjects into three groups using k-means clustering: The first two groups (Group G - good overall performance and B - bad performance) showed similar accuracy profiles across the three components. The third group performed well specifically in the ***when*** condition compared to the other components (Group GT - good temporal memory only). To test whether these "cognotypes" in behavior can be explained by their neural activities, we first compared the theta power (a well-known neural marker of memory) across the three groups. Subjects who performed well at ***what*** and ***where*** (Group G) showed higher theta power than the other groups during the retrieval (16 out of 32 channels for $p<0.05$), but this pattern was not observed for ***when*** task. Instead, performance on the ***when*** retrieval depended on how well the theta power was modulated across temporal distance between two scenes. Group G and TG (high performers for ***when***) showed modulation of their theta power for coding temporal distance (correlation against zero: $p<0.001$) while Group B did not show any neural pattern associated with temporal distance. In summary, we found a distinct behavioral pattern and its corresponding neural markers for temporal memory retrieval which can be potentially useful for explaining and predicting individual differences in vulnerability to episodic memory disorders.

Session 686 Neurogenesis and Differentiation

1:00 PM - 5:00 PM

SDCC Halls B-H

Presentation 686.03 / A12 Metabolic changes of human neurogenesis are linked to microRNA-124 function

1:00 PM - 5:00 PM

***G. SON**[1], Y. KIM[2], Y. NA[3], J.-H. SON[1], H. DO[1], D. KIM[1], G. D. CLEMENSON JR[2], S. T. SCHAFER[2], J.-S. KIM[3], F. H. GAGE[2], J. HAN[1];
[1]Grad. Sch. of Med. Sci. and Engin., KAIST, Daejeon, Korea, Republic of; [2]LOG-G, Salk Inst., La Jolla, CA; [3]Seoul Natl. Univ., Seoul, Korea, Republic of

Abstract

Metabolic reprogramming takes place during neurogenesis, but much about how noncoding elements affect the metabolic aspect of neurogenesis still needs exploration. microRNAs are one of the major constituents of noncoding elements and their expression pattern varies by the cell type. Interestingly, the metabolic power of mitochondria is also dependent on cell state. To survey the relationship between microRNAs and metabolism in neurogenesis, we used a microRNA sponge system to inhibit key functions of a neuron-specific microRNA: microRNA-124 (miR-124), at the initiating stages of neurogenesis. Surprisingly, miR-124 depleted neurogenesis resulted in the impairment of neurogenesis both ***in vivo*** and ***in vitro***. From the phenotype observed, we were curious to examine intracellular changes at a systemic level. We utilized human embryonic stem cell-derived neural progenitor cells (NPCs) to study changes in the proteome of one-week differentiated neurons with or without miR-124 during neurogenesis. Proteomic analysis was performed to identify the differentially expressed proteins (DEPs) of miR-124 knockdown (KD) neurons versus control. The KEGG pathway analysis was carried out with the list of DEPs and has revealed that the term oxidative phosphorylation (OXPHOS) was annotated with the highest significance. OXPHOS as the major change following the sequestration of miR-124 in the initiation of neurogenesis led us to investigate further onto the functional and morphological changes of mitochondria. For miR-124 KD neurons, the analyses of oxygen consumption rate (OCR) and mitochondrial membrane potential (MMP) resulted in a reduction of both OCR and MMP levels, denoting mitochondrial dysfunctions. In line with preceding findings, examining mitochondrial structures depicted immature and globular mitochondrial morphologies. We then compared the list of DEPs with online mitochondrial protein databases to sort for the candidates of unexplored mitochondrial proteins participating in neuronal differentiation. From the selection, an exemplary gene, GSTK1 – upregulated in miR-124 KD neurons, was overexpressed with CRISPRa system to validate how reliable the list is to be associated in metabolism during neurogenesis. An OCR analysis after overexpressing GSTK1 in both NPCs and neurons confirmed a reduction of mitochondrial cell respiration. In conclusion, we propose an association of miR-124 to metabolic changes in neurogenesis and also provide a putative list of mitochondrial proteins vital to the start of neuronal differentiation.

Presentation 686.04 / A13 The role of GPR110 in neurodevelopment in human stem cell and mouse models

1:00 PM - 5:00 PM

***Y. JOO**, E. AFLAKI, B. X. HUANG, H.-Y. KIM;
NIAAA, NIH, Rockville, MD

Abstract

G-protein coupled receptor 110 (ADGRF1, GPR110) is an adhesion GPCR involved in the development of neurons and cognitive function. Synaptamide, an endogenous ligand for GPR110, binds to the ***N***-terminal G-protein autoproteolysis-inducing (GAIN) domain of GPR110 and activates GPR110/cAMP signaling, promoting neurogenic differentiation of neural stem cells, neurite growth and synaptogenesis of developing neurons in mouse primary cells in culture. To further understand the role of GPR110 in neurodevelopment, we investigated the developmental phenotype and related molecular pathways using GPR110 knockout (KO) mouse model and human neural progenitor cells (hNPCs) where we found a high level of GPR110 expression. In hNPCs, GPR110 ligands dose-dependently increased cAMP production which was blocked by the pretreatment with *N*-terminal targeting GPR110 antibody. Deleting GPR110 *in vivo* or introducing inactive mutation to hNPCs that was identified in a schizophrenic patient population caused abnormal developmental phenotypes according to the RNA sequencing and imaging analysis. In addition to the downregulated neurogenesis and neurite growth, the expression of glutamate receptors and synaptic molecules associated with postsynaptic density were significantly reduced in GPR110 KO mouse brain or differentiating hNPCs with inactivating mutation. Our results indicate a significant role of GPR110 and its downstream signaling in neuronal differentiation and neuromaturation during development. The lack of GPR110 signaling leading to aberrant neuronal development may contribute to the psychiatric abnormality in adult stage.

☆ Session 693 Structural Plasticity: Synapses 1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 693.22 / C54 Synaptic connections in the lateral amygdala encode auditory fear memory 1:00 PM - 5:00 PM

***H. LEE**, D. CHOI, J. KIM, J.-I. KIM, Y. SUNG, J. CHOI, S. JAYAKUMAR VENKAT, P. PARK, H. JUNG, B.-K. KAANG;
Sch. of Biol. Sci., Seoul Natl. Univ., Seoul, Korea, Republic of

Abstract

Adaptation to an environment guarantees survival by acquiring appropriate behavioral response to a specific stimulus by encoding related memory in the brain. This memory formation and recall require activation of engram cells and synaptic potentiation among engram ensembles. How synaptic connection between engram cells encoding memory is modulated during memory formation and extinction remained unknown, due to the lack of appropriate molecular tool to directly examine specific synapses between engram cells. Applying a previously established synapse-labeling technique, dual-eGRASP (enhanced Green Fluorescent Protein Reconstitution Across Synaptic Partners), we found that synapses between engram cells in auditory cortex (AC) and lateral amygdala (LA) during auditory fear conditioning showed structural plasticity, observed as enlarged spine morphology of engram-engram spine in the LA. This enlargement of synaptic engram spines after fear memory formation was significantly reduced after fear extinction, while re-conditioning with the same tone and shock after extinction restored the morphology of the engram spines. Our results show spine-structural evidence of unlearning mechanism during extinction in the auditory fear memory circuit and propose synaptic connection between engram cells as synaptic engram, which demonstrates a functional unit encoding memory.

☆ Session 694 Structural Plasticity: Neurons and Networks 1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 694.16 / D14 The NHE1 is suppressed in spinal cord of neuropathic pain models 1:00 PM - 5:00 PM

***J. WU**[1], H. SHIN[1,2], N. SHIN[1,2], W. LEE[4], D. KIM[1,3,2];
[1]Dept. of Med. Science, Sch. of Medicine,, [2]Brain Res. Inst., [3]Dept. of Anat. & Cell Biology, Sch. of Medicine,, Chungnam Natl. Univ., Daejeon, Korea, Republic of; [4]Dept. of Anesthesia and Pain Med., Chungnam Natl. Univ. Hosp., Daejeon, Korea, Republic of

Abstract

One of the underlying pathophysiology of neuropathic pain is central disinhibition. Central inhibition is mainly accomplished via spinal interneurons and brainstem descending pathways as well as classical inhibitory transmitters such as: aminobutyric acid (GABA), glycine, adrenergic, 5-HT and enkephalin. On the other hand, the reduction of intracellular pH during neuroinflammation may either lead to neuronal death, a part of the pathological process. However, how intracellular pH changes affects central disinhibition in neuropathic pain remains unknown. Sodium hydrogen exchanger 1 (slc9a1, NHE1), widely involved in cell volume and pH regulation, is one of the most important acid extruders, inducing extracellular acidification in response to neuronal hyperactivity. Here, we first established a rat spinal nerve ligation SNL model. We found that NHE1 expression was reduced in the spinal dorsal horn of rats on days 3 and 10 after SNL, and furthermore, the vast majority of NHE1 was co expressed with the neuronal cells. In addition, there was a concomitant decrease in GAD67, which is responsible for the synthesis of GABA. When we found after intrathecal injection of NHE1 siRNA nanoparticles on day 3 after SNL surgery, this exacerbated pain in SNL model rats. From this, we speculate that NHE1 reduction in the spinal dorsal horn of SNL model rats may be one of the mechanisms that cause neuropathic pain, which specifically may involve the excitability of NHE1 through intraneuronal pH regulated inhibitory networks, such as the GABA system.

☆ Session 696 Epilepsy: *In Vivo* and Behavior 1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 696.09 / D46 Prenatal deletion of forebrain Ank2 causes seizure-related phenotypes by reshaping the synaptic proteome 1:00 PM - 5:00 PM

***S. YOON**[1], M. D. SANTOS[1], M. FORREST[1], C. PRATT[1], N. KHALATYAN[2], P. MOHLER[3], J. SAVAS[2], P. PENZES[1];
[1]Neurosci., [2]Neurol., Northwestern Univ., Chicago, IL; [3]The Ohio State Univ., Columbus, OH

Abstract

Rare genetic variants in *ANK*2, which encodes ankyrin-B, are associated with neurodevelopmental disorders, however, their pathogenesis is not well understood. To investigate the role of *Ank2* in the brain and behavioral development, we used *Ank2* brain-specific conditional knockout mouse models. The mice with prenatal deletion in cortical excitatory neurons and oligodendrocytes ($\text{Emx1}^{\Delta\text{ankyrin-B}}$), but not with postnatal deletion in forebrain excitatory neurons ($\text{CaMKII}\alpha^{\Delta\text{ankyrin-B}}$), displayed severe spontaneous seizures, increased mortality, hyperactivity, and social deficits, but no cognitive deficits. Calcium imaging of cortical slices from $\text{Emx1}^{\Delta\text{ankyrin-B}}$ mice showed increased neuronal calcium event amplitude and frequency, along with network hyperexcitability and hypersynchrony. Quantitative proteomic analysis of cortical synaptic membranes using tandem mass tags and liquid chromatography-triple stage mass spectrometry revealed upregulation of AMPA receptor and dendritic spine plasticity-regulatory proteins, and downregulation of intermediate filaments. Characterization of the ankyrin-B interactome identified interactors associated with autism and epilepsy risk factors and synaptic proteins, including GluA2. The AMPAR antagonist, perampanel, restored cortical network activity and partially rescued survival in $\text{Emx1}^{\Delta\text{ankyrin-B}}$ mice. Our findings suggest that abnormal network activity and synchrony, leading to seizures, could be a primary pathogenic mechanism in some forms of ASD, which can be reversed by the pharmacological targeting of proteomic alterations.

☆ Session 702 Abeta as a Therapeutic Target

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 702.10 / F28 Anti-amyloidogenic effect of BACE1 expression lowering compound identified using high-throughput gene expression assay

1:00 PM - 5:00 PM

***S. BAEK**, S. HONG, D.-G. JO;
Sch. of pharmacy, Sungkyunkwan Univ., SUWON-SI, Korea, Republic of

Abstract

Accumulation of Aβ (amyloid-beta) in a brain is one of the pathological hallmarks of Alzheimer's disease (AD). Aβ is generated through sequential cleavage of amyloid precursor protein (APP) by β-secretase (BACE1) and γ-secretase complex. BACE1 is one of the crucial targets for AD given that BACE1 expression is significantly upregulated in AD patients compared with non-AD. However, direct and complete inhibition of BACE1 activity can cause unpredictable or unintended effects because of numerous physiological substrates of BACE1. Therefore,a breakthrough without interfering BACE1 function is needed to overcome Alzheimer's disease. We screened xxxx small compounds, including drugs approved by the U.S. Food and Drug Administration to identify drugs that reduce promoter activity of BACE1. Here, we have found a new candidate drug which reduces promoter activity, mRNA, and protein levels of BACE1 in neuronal cells. We have confirmed that the drug decreases BACE1 gene expression, prevents accumulation of Aβ, and improves cognitive function in APP/PS1 transgenic mice. The ability of this compound reverses a wide range of deficits suggests that BACE1 expression-reducing agents may have therapeutic utility in the treatment of AD.

☆ Session 704 Parkinson's Disease: Alpha Synuclein Mechanism and Transmission

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 704.08 / F46 Optogenetic neuromodulation modifies α-synuclein spreading dynamics and is predicted by changes in whole-brain function

1:00 PM - 5:00 PM

E. DADGAR-KIANI[1], G. BIERI[2], R. MELKI[5], A. D. GITLER[3], ***J. LEE**[4];
[1]Bioengineering, Stanford Univ., Stanford, CA; [2]Stanford Univ., Menlo Park, CA; [3]Dept. of Genet., [4]Stanford Univ., Stanford Univ., Stanford, CA; [5]Inst. François Jacob, Fontenay-aux-Roses, France

Abstract

The seeding and spreading of misfolded proteins can lead to widespread pathology and has been implicated in many neurodegenerative diseases. However, many treatments for these diseases only compensate for circuit function changes caused by neurodegeneration, such as deep brain stimulation in Parkinson's Disease. Here we report on an optogenetic stimulation paradigm guided by brain clearing and quantification that allows for the tracking and modulation of whole brain α-synuclein pathology. In a mouse pre-formed fibril (PFF) model where injection of α-synuclein PFFs into the striatum results in widespread pathology, repeated daily optogenetic stimulation led to consistent changes in brain-wide pathology after two weeks. Aggregation decreased at both the site of stimulation and various ipsilateral regions of interest, while the contralateral cortex saw a consistent increase in pathology. Meanwhile, the treatment did not affect the total whole brain aggregate count. Aligning the modified spreading patterns with brain activity during stimulation, as measured by optogenetic fMRI, confirmed that the polarity and spatial localization of these changes in pathology could be predicted by whole brain functional changes. Altogether, these results demonstrate the ability to both modulate and readout whole brain pathology using a longitudinal neurostimulation paradigm, which can guide future treatments for neurodegenerative disease.

☆ Presentation 704.17 / F55 Whole-brain modeling of α-synuclein spreading, aggregation, and decay dynamics as informed by mesoscale connections and gene expression

1:00 PM - 5:00 PM

***E. DADGAR-KIANI**[1], G. BIERI[2], R. MELKI[5], A. D. GITLER[3], J. LEE[4];
[1]Stanford Univ., Stanford Univ., Stanford, CA; [2]Stanford Univ., Menlo Park, CA; [3]Dept. of Genet., [4]Stanford Univ., Stanford, CA; [5]Inst. François Jacob, Fontenay-aux-Roses, France

Abstract

An emerging view of neurodegenerative diseases is that seeding of misfolded proteins in discreet brain regions leads to widespread pathology. The mechanisms by which misfolded protein seeds form in distinct brain regions and cause differential whole-brain pathology remain elusive. We used whole-brain tissue clearing and high-resolution imaging to longitudinally map pathology in an α-synuclein pre-formed fibril injection model of Parkinson's disease. We used machine-learning based quantitative three-dimensional analysis of these images and identified distinct phases of spreading and decline. We then fit a network model with parameters that represent α-synuclein pathology spreading, aggregation, and decay. Remarkably, our model can predict α-synuclein spreading patterns from several distinct brain regions and can even pinpoint their origins. These models empower mechanistic understanding and accurate prediction of disease progression, paving the way for the development and testing of therapeutic interventions.

☆ Session 714 Neural Bases of Adaption and Modulation of Visual Circuits

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 714.03 / P9 The brain optimizes perception in astigmatism through compensatory gain modulation

1:00 PM - 5:00 PM

***S. SON**[1,2], W.-M. SHIM[1,2,3], H. KANG[4], J. LEE[1,2,3];
[1]Ctr. for Neurosci. Imaging Res., Suwon, Korea, Republic of; [2]Dept. of Biomed. Engin., [3]Dept. of Intelligent Precision Healthcare Convergence, Sungkyunkwan Univ., Suwon, Korea, Republic of; [4]Dept. of Optometry, Catholic Kwandong Univ., Gangneung, Korea, Republic of

Abstract

Most people have some amount of astigmatism, which systematically distorts retinal inputs to the brain. However, in everyday life, our perception is much less distorted. Here, we investigated how the brain compensated for the distorted orientation inputs after long-term exposure to astigmatism. We asked two groups of participants to perform an orientation adjustment task while recording an electroencephalogram (EEG) activity from 64-channels of active electrodes. One group had chronic astigmatism in which their retinal input had a meridian-specific distortion due to the deformation in the lens (chronic group). The other group had normal vision, where we temporarily induced astigmatic blur by applying a cylindrical lens (control group). The amount of astigmatism induced in the normal-visioned group was matched with that in the chronic group. In the control group, the neural orientation tuning responses represented in the multivariate EEG activities were severely skewed according to the optical characteristics of astigmatism. However, it was far less severe in the chronic group, even if the degree of deformation in retinal inputs were similar to those in the control group. Computational modeling on multivariate EEG responses revealed that the enhancement in the chronic group was due to a simple gain modulation mechanism that enhanced neural responses to the optically blurred orientation and reduced responses to the orthogonal orientation. We further found that the gain modulation gradually stabilized over exposure time. Even in the control group, we found that the gain modulation started to appear after the participants were exposed to astigmatic blur for approximately 30 minutes. Yet, this gain modulation had no visible relationship with the perceptual judgments. On the contrary, the gain modulation was observed throughout the trials in the chronic group and was closely related to both within- and across-participants variability of the perceptual report. These results provide insight into how the brain adapts to systematically biased inputs; the brain is sensitive enough to temporarily re-weight the neural orientation space to fight back the distortion, but it takes time to work stably and functionally. The current research provides a mechanistic understanding of neural compensation for the optical aberration, which can be utilized as a practical guide in clinical situations.

☆ Session 722 Posture and Gait: Kinematics, Biomechanics, Exercise, and Fatigue II

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 722.12 / AA9 Kinematic and neuromuscular responses of the neck and trunk during imitative horseback riding movements in children with cerebral palsy

1:00 PM - 5:00 PM

***S. YAN**[1,2], S. PARK[1,2], R. KEEFER[1], W. DEE[1], A.-M. ROJAS[1,2], W. Z. RYMER[1,2], M. WU[1,2,3];
[1]Northwestern Univ., Shirley Ryan AbilityLab, Chicago, IL; [2]Northwestern Univ., Dept. of Physical Med. and Rehabil., Chicago, IL; [3]Univ. of Illinois at Chicago, Dept. of Biomed. Engin., Chicago, IL

Abstract

Postural control is one of the factors restricting physical activities of children with cerebral palsy (CP). Hippotherapy has been used for improving postural control, gait speed, and gross motor function in children with CP. However, it is unclear whether different intensities/speeds of horseback riding movement would cause different postural responses in children with CP. Also, the optimal intensity/speed of horseback riding movement remains unclear. The purpose of this study was to examine kinematic and neuromuscular responses of the neck and trunk during sitting with different perturbation intensities and frequencies in children with CP. We hypothesized that horseback riding movements with greater intensity and lower frequency would result in greater trunk movements and muscle activities. In this study, a robotic toy horse was pulled forward and backward (anterior-posterior, AP) with external perturbation force repeatedly, which mimicked horseback riding movements. Twelve children with CP (age = 7.3 ± 2.8 years) who sat on the toy horse and kept an upright position completed two sessions. In session 1, four perturbation intensity levels (10%, 15%, 20%, and 25% of body weight (BW)) with a frequency of 1Hz were applied to the horse. Subjects exhibited the greatest pelvic range of motion (ROM) in the AP direction, the greatest sagittal ROM of neck, trunk, and pelvic angle, and the greatest muscle activities of the trunk flexor, neck flexor and extensor when perturbation intensities of 20% and 25% were applied ($p < 0.05$, $N = 12$). In session 2, six perturbation frequency levels (0.5Hz,

1Hz, 1.5Hz, 2Hz, 2.5Hz, and 3Hz) with the same perturbation intensity (20%) were applied. Subjects showed the greatest pelvis ROM in the AP direction and the greatest sagittal ROM of the neck, trunk, and pelvic angle when perturbation frequencies of 0.5Hz, 1Hz, and 1.5Hz were applied ($p < 0.05$, N = 12). Muscle activities of the trunk extensor differed among frequency levels ($p = 0.02$, N = 7). In conclusion, effects of horseback riding movements on postural responses may be intensity and frequency dependent. The medium to high force intensity and low force frequency can be applied in future hippotherapy interventions in children with cerebral palsy.

☆ Presentation 722.13 / AA10 Intermittent adaptation to pelvis perturbation during walking enhances retention and generalization of improved weight transfer in people with spinal cord injury

1:00 PM - 5:00 PM

***S. PARK**[1], S. YAN[3], W. DEE[1], R. KEEFER[1], W. Z. RYMER[2], M. WU[4];
[2]Shirley Ryan AbilityLab, [1]Shirley Ryan AbilityLab, Chicago, IL; [3]Home, Northwestern Univ., Evanston, IL; [4]Shirley Ryan Abilitylab- Chicago, Shirley Ryan Abilitylab- Chicago, Chicago, IL

Abstract

Many individuals with spinal cord injury (SCI) walk with restrained mediolateral weight transfer due to the impaired ability to maintain balance during walking. Continuous motor adaptation to external pelvis perturbation while walking was demonstrated to facilitate motor learning of improved weight transfer in people with SCI. However, the influence of intermittent adaptation to perturbation-induced new walking patterns on locomotor learning in individuals with SCI remains unknown. To address this, fifteen individuals with chronic incomplete SCI visited the lab once to complete two experimental conditions. Each condition included a) treadmill walking with either intermittent or continuous adaptation to externally perturbed walking patterns and b) overground walking before, immediately after, and 10 min after treadmill walking. During the treadmill walking, an external pulling force was applied to the pelvis toward the lateral side during the early-to-mid stance phase of the leg to perturb mediolateral weight transfer. The intermittent condition induced longer retention of improved weight transfer and enhanced muscle activation of hip abductor after the removal of pelvis perturbation load during treadmill walking ($P < 0.02$), whereas the continuous condition did not ($P = 0.50$). During overground walking, participants also showed improved weight transfer 10 min after treadmill walking for the intermittent condition ($P = 0.04$), but not for the continuous condition ($P = 0.76$). In conclusion, intermittent motor adaptation to pelvis perturbation load during walking practice may enhance preservation of improved weight transfer and generalization of motor learning in people with spinal cord injury.

☆ Session 728 Neuromodulation of Food and Water Intake and Energy Balance

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 728.03 / GG1 Neural Mechanism of Hunger-gated Food-seeking and Evaluating

1:00 PM - 5:00 PM

***Y. LEE**[1], Y. KIM[1], K. KIM[1], H. SONG[1], M. JANG[1], D.-S. HA[1], J. PARK[1], S.-H. JUNG[1], J. LEE[1], K. KIM[1], D.-H. CHEON[1], I. BAEK[1], M.-G. SHIN[2], E. LEE[2], S. KIM[3], H. CHOI[1];
[1]Seoul Natl. Univ., Seoul, Korea, Republic of; [2]Ajou Univ., Suwon, Korea, Republic of; [3]Seoul Natl. Univ. Col. of Med., Seoul, Korea, Republic of

Abstract

The physiological need for energy evokes motivated feeding behaviours that help to ensure survival. However, the neural mechanisms underlying the generation of food motivation remain poorly understood. We investigated these mechanisms by subdividing feeding-related motivated behaviours into food-seeking, evaluating, and swallowing. Micro-endoscopic results indicated that neurons containing leptin receptors (LepRs) in the lateral hypothalamus (LH) are the major food-specific subpopulation of $\mathrm{LH}^{\mathrm{GABA}}$ neurons. Optogenetic manipulation of $\mathrm{LH}^{\mathrm{LepR}}$ neurons bidirectionally regulated both food-seeking and evaluating. Furthermore, micro-endoscope data revealed that distinct $\mathrm{LH}^{\mathrm{LepR}}$ neurons encode seeking and evaluating. Computational modelling analysis demonstrated that $\mathrm{LH}^{\mathrm{LepR}}$ neurons encode motivation, whereas neurons containing agouti-related peptide and neuropeptide Y (AgRP/NPY) encode the need for food. Additionally, slice studies revealed that NPY decreases inhibitory input to $\mathrm{LH}^{\mathrm{LepR}}$ neurons via $\mathrm{LH}^{\mathrm{GABA}}$ interneurons. This mechanism explains the permissive gate role of hunger (food need) in seeking/evaluating motivation. Together, the present study provides a comprehensive neural mechanism of how physiological needs drive distinct motivated behaviours.

☆ Presentation 728.04 / GG2 Role of Lateral Hypothalamus GABAergic Neurons on Goal-directed and Non-goal-directed Behaviors in Non-human Primates

1:00 PM - 5:00 PM

***L. J.-S. HA**[1], H.-G. YEO[2], Y. LEE[1], J. WON[2], I. BAEK[1], Y. KIM[2], Y. JUNG[1], J. MIN[1], K. KIM[2], J. PARK[2], K. LIM[2], C.-Y. JEON[2], W. CHOI[2], S.-H. PARK[2], Y. LEE[2], H. CHOI[1];
[1]Seoul Natl. Univ., Seoul Natl. Univ., Seoul, Korea, Republic of; [2]Natl. Primate Res. Ctr., Korea Res. Inst. of Biosci. and Biotech. (KRIBB), Cheongju, Korea, Republic of

Abstract

Introduction: In recent years, the study of the role of LHA GABAergic neurons was vigorously executed in rodents. LHA GABAergic neuron activation in rodents is associated with food-seeking and abnormal behavior. However, its role in the non-human primate is yet to be discovered. **Objective:** we dissected the behavior phenotype of goal-directed and non-goal-directed behavior. We also observed the role of LHA GABAergic neurons in Non-human primates. **Method:** we used three adult macaque monkeys in the experiment. We injected the AAV virus consisting of GABA specific promoter(hDlx) and chemo-genetics activation(hM3Dq). We developed the behavior indices and analyzed the assessment using manual and deep learning-based methods. **Results:** LHA GABAergic neuron activation in non-human primates was observed in goal-directed and non-

goal-directed behavior. Goal-directed behavior for palatable food was significantly increased by LHA GABA neuron activation. Low speed with immobility to palatable food was increased by LHA GABA neuron activation connected to the meaning of compulsive food-seeking for palatable food. On the other hand, the vehicle-injected control monkey wandered with the palatable food and appeared to the stereotyped behavior as usual. No significant goal-directed behavior was observed with no object, toy, or water by LHA GABA neuron activation. In addition, non-goal-directed behavior of stereotyped and self-harming behavior was reduced in LHA GABAergic neuron activation. One monkey's vocalization relevant to stereotyped behavior was observed of reduced. **Conclusion:** LHA GABA neuron activation is presumed to increase food motivation and compulsive food-seeking for palatable food as a goal-directed behavior in non-human primates. In particular, as a non-goal-direct behavior, it is predicted to reduce the stereotyped and self-harming and eventually connected to the reduction in the vocalization of monkey B.

☆ Session 735 Cocaine: Pharmacology

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 735.15 / PP3 Silent synapse contribution to behavioral alterations after chronic cocaine exposure by D1-MSN specific GluN2B modulation

1:00 PM - 5:00 PM

***H.-J. KIM**, K.-B. SUNG, H.-Y. LEE, T. YOO, J. SHIN, J.-H. KIM;
POSTECH, POSTECH, Pohang, Korea, Republic of

Abstract

Silent synapse expresses only NMDAR subtype 2B (GluN2B)-containing NMDARs without AMPARs in the postsynaptic membrane. They are predominant during the developing stage of neurons and will be un-silencing by AMPARs recruiting (synaptic maturation) or disappear by synaptic elimination. However, silent synapses remerged significantly after repeated cocaine exposure. Cocaine induced silent synapse generation is prominent subsequential plasticity of striatal medium spiny neurons (MSNs), and ***De-novo*** synthesis of GluN2B is necessary for cocaine induced silent synapse formation. Its formation and maturation are highly correlated with addiction-like behavior expression and maintenance. However, GluN2B is hard to modulate since GluN2B encoded gene ***GRIN2B*** is lethal, critical for neuronal development, and expressed in various cell types. Thus, we adapted ***cre*** inducible GluN2B modulation by ***CRISPR-Cas9*** or ***shRNA*** system to overcome limitations that enable cell type (D1R-MSNs) and area-specific (NAc shell area) modulation without unwanted effects, such as developmental or global KO impacts of target gene deletion. By conditional GluN2B modulation during cocaine exposure, the silent synapse formation was disabled, but the cocaine induced behavioral changes were not all disrupted. From the electrophysiological and anatomical evidence, we will discuss and suggest how silence synapses contribute to behavioral changes during drug addiction progress.

☆ Session 736 Prefrontal Cortex Regulation of Brain Function

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 736.05 / QQ1 Representation of credit-deserving feature information and feature-specific reward prediction errors among prefrontal cortical areas during credit assignment

1:00 PM - 5:00 PM

***E. LEE**[1,3], W. F. ASAAD[1,3,4,2];
[1]Neurosci., [2]Neurosurg., Brown Univ., Providence, RI; [3]Carney Inst. for Brain Sci., Providence, RI; [4]Norman Prince Neurosciences Inst., Rhode Island Hosp., Providence, RI

Abstract

In reinforcement learning, the credit assignment problem, which is how an agent attributes the outcome of choice to a relevant event when there is a temporal gap or multiple inputs, has been a long-lasting question. The prefrontal cortex is well-suited for resolving this problem, but its neural mechanisms are still debated. To determine how the prefrontal cortex (PFC) helps to resolve this problem, we trained two monkeys on a credit assignment task and implanted large arrays of independently-positionable electrodes over the PFC, including ventral lateral PFC (vlPFC) and orbitofrontal cortex (OFC) (96 and 128 electrodes, respectively). Animals learned to attribute a choice outcome to one of several earlier cue features. Specifically, they were required to attend to both cue identity and cue location, but the location was relevant for only the immediate choice, whereas identity was relevant in future trials and so needed to be learned. Credit assignment, therefore, was required for identity but not location. Generic feedback for correct vs. incorrect outcomes was provided after the animal's choice, without conveying specific information about why that choice was correct or incorrect, thereby requiring an implicit linkage between outcome and remembered antecedent (cue identity) at that moment. We fit a hybrid reinforcement learning (RL) model to behavior and then applied those inferred RL parameters to two multi-regression models to understand the neural representation of cue identities, cue locations, choice outcomes, cue values, and reward prediction errors (RPEs). During initial cue presentation, vlPFC and OFC neuronal activity conveyed both cue identity and location. During feedback, neuronal activity conveyed feature-specific reward prediction errors (RPEs that also signaled which specific cue deserved credit) in both areas. Interestingly, in the vlPFC, location information necessary for the immediate response was evident during the delay but decreased after the choice was made. Moreover, during feedback, vlPFC activity conveyed cue identity and feature-specific RPEs earlier than OFC. This information is the key ingredient requiring credit assignment in this task. These results suggest that vlPFC may be more centrally involved than OFC during critical steps in the credit assignment process.

☆ Session 740 Learning and Memory: Hippocampal: Formation Circuitry

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 740.18 / VV10 Neurogenesis-mediated circuit remodeling reduces engram reinstatement and promotes forgetting

1:00 PM - 5:00 PM

A. AWASTHI[1], S. KO[1], A. GUSKJOLEN[1], J. DHALIWAL[1], J. DE LA PARRA[1], J. R. EPP[2], E. CHAHLEY[3], M. L. DE SNOO[1], M. SOLARI[1], P. PANESAR[1], J. S. SNYDER[4], X. DUAN[5], J. R. SANES[6], S. A. JOSSELYN[1], P. W. FRANKLAND[1];
[1]Neurosciences and mental health, Hosp. for Sick Children, Toronto, ON, Canada; [2]Cell biology and Anat., Univ. of Calgary, Calgary, AB, Canada; [4]Dept. of Psychology, [3]Univ. of British Columbia, Vancouver, BC, Canada; [5]Departments of Ophthalmology and Physiology, Weill Inst. for Neurosciences,, Univ. of California San Fransisco, San Fransisco, CA; [6]Ctr. for Brain Sci. and Dept. of Mol. and Cell. Biology,, Harvard Univ., Cambridge, MA

Abstract

Post-training increases in hippocampal neurogenesis are associated with forgetting of hippocampus-dependent memories in adult mice. This form of forgetting might be due to increased numbers of new neurons, remodeling of hippocampal circuitry or some combination of both. Here we tested the hypothesis that neurogenesis-mediated forgetting is caused by remodeling of hippocampal circuits by engineering mice in which adult-generated granule cells hypo- or hyper-integrate into hippocampal circuits. Using gene deletion, opto- and chemogenetic strategies, we find that hypo-integration of newborn neurons prevents post training exercise-induced forgetting of contextual fear memories. Conversely, inducing hyper integration of newborn neurons following contextual fear conditioning is sufficient to produce forgetting. Ex vivo patch clamp recordings from these gene deleted adult-generated granule cells confirmed hypo- or hyper-integration into the perforant path. Recording optogenetically evoked EPSCs from the same cells in downstream CA3 cells also established hypo- or hyper-integration at their output synapses. Because these interventions did not affect survival of newborn neurons, these findings suggest that neurogenesis-mediated remodeling of hippocampal circuits represents a continuous and active form of interference that alters accessibility of engrams underlying hippocampal memories. Consistent with this, using engram-labeling approaches, we found that exercise-induced forgetting was associated with reduced engram reactivation.

☆ Presentation 740.20 / VV12 Neurogenesis-mediated rewiring of hippocampal episodic engram circuitry drives memory generalization

1:00 PM - 5:00 PM

***S. Y. KO**[1,2], S. A. JOSSELYN[1,2,3,4], P. W. FRANKLAND[1,2,3,4];
[1]Neurosciences and Mental Hlth., The Hosp. for Sick Children, Toronto, ON, Canada; [2]Dept. of Physiol., [3]Dept. of Psychology, [4]Inst. of Med. Sci., Univ. of Toronto, Toronto, ON, Canada

Abstract

Episodic information is allocated to the hippocampal engram cells, embedded within DG-CA3-CA1 circuitry. However, it is unclear whether the hippocampal engram fidelity for an episode is maintained or remodeled over time. Adult-born new granule cells (abGCs) are continuously integrated into the existing hippocampal circuits throughout the lifetime and potentially interact with engram cells. Here, we attempted to rewire episodic engram circuits by modulating adult hippocampal neurogenesis ***after*** the memory formation. We first examined the impact of manipulating overall levels of adult neurogenesis. Our results show that reducing post-learning neurogenesis retains episodic fidelity (i.e., prevents memory generalization). Conversely, increasing post-learning neurogenesis reduces episodic fidelity (i.e., accelerating memory generalization) in both contextual fear conditioning and watermaze. Next, we evaluated the impact of altering how abGCs integrate into hippocampal circuits on episodic fidelity. Conditional knockout of the cadherin-9, a cell adhesion protein, only in abGCs blocked abGCs structural integration into the DG-CA3 after the memory formation and prevented the degradation of episodic fidelity. This suggests that post-learning structural changes in DG-CA3 circuitry mediates neurogenesis-mediated fidelity degradation. In addition, we investigated whether the addition of abGCs directly induces structural changes of the DG-CA3 engram circuitry. Using engram-specific whole-neuron synaptic connectivity visualization (i.e., enhanced green fluorescent protein reconstitution across synaptic partners; eGRASP technique) and engram projection visualization, we found that post-learning neurogenesis modulation rewires DG-CA3 engram connectivity, including both excitatory (i.e., large mossy fiber terminal structure) and inhibitory (i.e., filopodial contacts to parvalbumin-positive interneurons) connections. Consequently, the output of the CA3 engrams (i.e., CA3-CA1 engram connectivity) is maintained when neurogenesis is ablated in the post-learning window, whereas CA3-CA1 engram connectivity is reduced when neurogenesis level is elevated. Regardless of neurogenesis-mediated rewiring, optogenetic suppression of neurotransmitter release at presynaptic terminals of the CA3 engrams (i.e., CA1 region) using eOPN3 functionally interferes with both episodic and generalized memory retrieval. Together, our study suggests that adult hippocampal neurogenesis transforms episodic engram circuitry into generalized engram circuitry in the hippocampus, which reflects fidelity changes.

☆ Presentation 740.24 / VV16 Examining the Engram encoding specificity hypothesis in mice

1:00 PM - 5:00 PM

***J. JUNG**[1], Y. WANG[1,2], A. MOCLE[1,2], A. Y. CHUNG[3], S. KOHLER[4], P. W. FRANKLAND[1,2,5], S. A. JOSSELYN[1,2];
[1]The Hosp. For Sick Children, Toronto, ON, Canada; [3]Dept. of Cell and Systems Biol., [2]Univ. of Toronto, Toronto, ON, Canada; [4]Univ. Western Ontario, Univ. Western Ontario, London, ON, Canada; [5]Canadian Inst. for Advanced Res. (CIFAR), Toronto, ON, Canada

Abstract

Memories are thought to be stored in sparse groups of neurons (engrams); retrieval cues reactivate the engram to induce memory recall. According to a long-standing theory, memory is best recalled by retrieval cues that overlap with training cues (encoding specificity hypothesis). Although human behavioral and imaging studies generally support this hypothesis, they cannot examine encoding specificity at the level of the neuronal ensemble. Here we used engram visualization tools in mice to test directly whether retrieval cues that closely overlap with training cues produce robust memory recall via high engram reactivation. Using variations of cued fear conditioning tasks in which a tone conditioned stimulus (CS) is paired with footshock, we manipulated encoding and retrieval conditions along multiple domains, including pharmacological state, external sensory (varying tone CS and retrieval cue) and internal (varying optogenetic CS and retrieval cue) cue. Maximal engram reactivation and memory recall occurred when retrieval closely matched training conditions. These findings provide a biological basis for the encoding specificity hypothesis and highlight that memory recall involves an interaction between stored information (engram) and information available at retrieval (memory retrieval cue).

☆ Presentation 740.23 / VV15 The supramammillary nucleus (SuM) transforms environmental signals into effects on cognition and mood via regulation of hippocampal neurogenesis

1:00 PM - 5:00 PM

***J. DHALIWAL**[1], S. KO[2], M. SADERI[1], A. VALLAZZA[1], M. SOLARI[1], S. A. JOSSELYN[3], P. W. FRANKLAND[4];
[1]The Hosp. for Sick Children (Sickkids), Toronto, ON, Canada; [2]Program in Neurosciences and Mental Hlth., The Hosp. for Sick Children, Toronto, ON, Canada; [3]Neurosci. & Mental Hlth., [4]PGCRL - NMH 5th floor, The Hosp. For Sick Children, Toronto, ON, Canada

Abstract

Adult neurogenesis in the dentate gyrus (DG) of the hippocampus represents an important form of neuroplasticity that regulates both mood and cognition. Adult neurogenesis is bidirectionally regulated by environmental stimuli, including enrichment (which promotes neurogenesis) and stress (which suppresses neurogenesis). However, how these signals reach the DG to regulate neurogenesis is unknown. To address this, we used anatomical tracing to identify input projections to the DG from cortical, basal forebrain, midbrain and hypothalamic regions. We found that the activity of many of these regions was regulated by environmental enrichment and stress. In particular, the activity of one hypothalamic region, the supramammillary nucleus (SuM), was downregulated by chronic enrichment and upregulated by chronic restraint stress. The SuM sends both excitatory and inhibitory projections to the DG. We found that chronic chemogenetic inhibition of SuM excitatory (but not inhibitory) projections increased neurogenesis, similar to enrichment. Conversely, chronic activation of these same SuM projection neurons suppressed neurogenesis, similar to stress. Subsequent experiments established that these effects are mediated by an SuM (excitatory neuron) to DG (granule cell) to DG parvalbumin (PV) interneuron circuit, and that chemogenetic interventions targeting this circuit can mimic or block the effects of environmental signals on neurogenesis. Finally, we show that direct manipulation of SuM has bidirectional effects on mood and cognition, similar to enrichment and stress manipulations. Together, these studies identify the SuM as a key region that translates environmental signals into effects on mood and cognition via regulation of hippocampal neurogenesis.

☆ Presentation 740.07 / UU19 Subicular neurons represent multiplex task information by using theta rhythm in a hippocampal-dependent visual scene memory task

1:00 PM - 5:00 PM

***S.-M. LEE**[1], J. SEOL[2], I. LEE[1];
[1]Seoul Natl. Univ., [2]Seoul Natl. Univ., Seoul, Korea, Republic of

Abstract

The subiculum has long been considered a critical brain region through which the hippocampal information is transmitted to various cortical areas, but little is known about its exact roles in hippocampal-dependent memory tasks. Most hippocampal place cells tend to have single place fields, and they can represent visual scene or behavioral choice information via rate remapping. On the other hand, subicular place cells exhibit very different firing properties by showing broad and spatially invariant firing fields. Such discrepancies make it difficult to compare the two regions by using the traditional rate-based analytical methods. To address this issue, we adapted spiking-phase methods to parse multiple subfields from the single broad firing field of a subicular neuron. Specifically, we trained five male Long-Evans rats to make a behavioral choice to either left or right arm in a T-maze according to visual scene stimulus presented on LCD monitors. During the task, single-unit spiking activities and local field potentials were recorded simultaneously in the dorsal subiculum and hippocampal CA1 by an implanted multi-electrode drive equipped with 24 tetrodes. Among the putative complex spiking cells (CA1, n=270; subiculum n=151), two-thirds of subicular cells had multiple place fields after the field parcellation based on the spiking-phase method, and those cells showed enhanced rate remapping for task-related information (i.e., visual scene and choice response). Notably, multiple subfields of a single subicular neuron could carry different types of task variables respectively, which was rarely observed in the CA1. Combining these results, we conclude that subicular neurons may facilitate associative learning by multiplexing hippocampal-dependent information so that downstream structures receive more associative information between the critical task variables. Furthermore, since it has recently been reported that the neuronal population in the subiculum has a finer representation of navigational factors compared to the CA1, we aim further to investigate whether the subicular neurons recorded in the scene memory-based task also generate better populational decoding accuracy than the CA1 neurons in terms of animal's position and task variables. We also plan to examine the contribution of temporal codes to the decoding performance, which is expected to be significant for the position rather than task variables.

☆ Session 743 Hippocampus, Encoding, and Navigation

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 743.03 / WW6 Adding visual noise to a familiar virtual environment divides the neural population into global- and rate-remapping subpopulations in CA1, but not in CA3

1:00 PM - 5:00 PM

***J. SHIN**[1], H.-W. LEE[2], S.-W. JIN[1], I. LEE[1];
[1]Seoul Natl. Univ., Seoul Natl. Univ., Seoul, Korea, Republic of; [2]The Univ. of Utah, Salt Lake City, UT

Abstract

It has been demonstrated that the CA3 of the hippocampus plays a crucial role in forming discrete representations of modified

environments presumably through pattern separation and completion. In contrast, the neural population in the CA1 hardly shows such nonlinearity compared to the CA3, which is puzzling because the CA1 is the immediate downstream structure of the CA3. We tested whether adding visual noise to a familiar virtual environment would allow us to observe some CA3-like nonlinearity in the CA1 when representing the modified environment. In computational neuroscience, adding noise is a critical testing condition when simulating a network’s capability of processing modified inputs, but it is almost impossible to test in a real environment. Thus, we used virtual reality (VR) apparatus to parametrically manipulate the environment by adding visual noise (i.e., virtual fog). We recorded single units with tetrodes simultaneously from the CA1 and CA3 in rats (n=8). The head-fixed rats on a cylindrical treadmill navigated the VR environment projected through three surrounding LCD monitors. Rats were required to move forward along a 3m-linear track to obtain water rewards at two randomized sites per trial (20 μL/site). After allowing the rat to experience the familiar environment, a fog block started. In the fog block, we introduced different levels of 'foggy' conditions (e.g., 0% as a control in the post-fog block; 15%; 30%) by adding virtual fog to the familiar environment. As a result, the place-cell population of the CA1 split into two classes, one showing global remapping and the other exhibiting fog density-dependent rate remapping. By contrast, in the CA3, most place cells showed rate remapping in the fog conditions. Interestingly, those CA1 place cells that exhibited global remapping in the fog block maintained the changed firing patterns even when reexperiencing the original fog-free environment in the fog block, suggesting that the network was under the influence of a top-down or internal contextual shift. If one considers the rate-remapping class of place cells as pattern-completing cells and the global-remapping class as pattern-separating cells, our results suggest that the neural population in the CA1 can manifest both pattern-separating and pattern-completing classes of neurons in our virtual environment, and there is a possibility that the latter class is inherited from the dominant pattern-completion network in the CA3.