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PROCEEDINGS OF

THE UK-KOREA **NEUROSCIENCE FORUM**

NEW CONCEPTS OF NEUROSCIENCE FOR BASIC RESEARCH AND THERAPEUTIC ADVANCES

The 8th UK-KOREA Neuroscience Symposium

The Latimer Room,
Clare College, Cambridge,
United Kingdom

15-16 Sept. 2015

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The 8th UK-KOREA Neuroscience Symposium

Professor Youngchan Lee

President of Korea Health Industry Development Institute (KHIDI), Republic of Korea

Dear colleagues and friends,

I would like to extend a warm welcome to everyone attending the 8th UK-Korea Neuroscience Symposium. Over the past ten years UK-Korea Neuroscience Symposia have played a vital role in bridging the gap between neuroscience and medical research in the UK and Korea, as well as being committed to ensuring our research helps to address global ageing issues with excellence and impact.

This symposium will feature insightful speakers from a diverse cross section of neuroscience including neurodegenerative disease research. Basic, medical, and translational advancements will be highlighted, from which we will foster next-generation neuroscience research and strengthen our collaborative relationship.

As the president of Korea Health Industry Development Institute (KHIDI), on behalf of the event organisers, I would like to thank all of our participants, keynote speakers, and guests. Without your attendance and participation in our ongoing symposia we would not have been able to build this innovative platform for fruitful collaborations between the two nations.

In conclusion, we look forward to meeting each and every one of the symposium participants. I strongly encourage everyone to reach out to the UK-Korea network and hope that you will experience rewarding discussions and interesting findings during this event. Thank you very much for your generous support and contribution.

Best regards,

Professor Doochul Kim

President of Institute for Basic Science (IBS), Republic of Korea

I would like to congratulate everyone involved in hosting "The 8th UK-Korea Neuroscience Symposium", which will bring together distinguished scientists from the UK and Korea. I am confident that this symposium will foster new research relationships, and encourage our nations to increasingly share knowledge, ideas, and resources. In this regard, I am delighted that the Institute for Basic Science (IBS) is actively supporting this symposium since hosting last year's at IBS Center for Synaptic Brain Dysfunctions. As the president of IBS, I offer my wholehearted support to the symposium so that we can share our research outcomes and make progress in neuroscience research. I wish this year's symposium every success, and trust everyone will find the event thoroughly rewarding.

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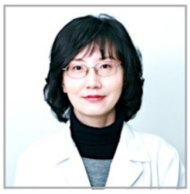

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The UK-Korea Programme Committee members are delightful to welcome you to the 8th UK-Korea Neuroscience Symposium in Cambridge, UK. This symposium sees the continuation of our collaboration for over ten years, since 2005. We would like to thank the UK Medical Research Council (MRC), Korea Health Industry Development Institute (KHIDI) and Institute for Basic Science (IBS) for their long-term funding and support for UK-Korea Neuroscience. This has helped to develop the UK-Korea Neuroscience collaboration from 'knowing each other' to working together through research activity. In this context, we have established a new collaboration platform 'UKorea (www.ukorea.ac.uk)', which will further establish lively connections among neuroscience research groups in the UK and Korea. In particular, the Committee would like to invite more young scientists to join the UKorea Neuroscience Symposium, as we aim to bridge to the next generation that will be vital for the continuation of our partnership.

Plenary Speaker: Professor Trevor Robbins
Head of Department, Experimental Psychology
Univ. of Cambridge

Professor TW Robbins F.R.S. works in the areas of cognitive and behavioural neuroscience, with a special emphasis on psychopharmacology. He is particularly interested in the cognitive functions of the frontal lobes of the brain, in understanding the neural basis of motivation and reward, in the neuropsychological basis of drug addiction and obsessive-compulsive disorder, and in the treatment of neurocognitive disorders such as Alzheimer's and Parkinson's diseases, schizophrenia and attention deficit disorder with 'cognitive enhancing' drugs. Much of his work is devoted to understanding how such drugs actually work, based on their actions on the chemical neurotransmitter systems of the brain. These systems include the monoamines dopamine, noradrenaline and serotonin, as well as acetylcholine. Professor Robbins uses a variety of techniques in his work, ranging from the invention of a computerized neuropsychological test battery ('CANTAB') for assessing cognition in patients to functional brain imaging and molecular neuropharmacology, and it seeks to translate basic neuroscience findings into clinical application.

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15-Sep	Tue.	The Latimer Room, Clare College, Cambridge
8:45	REGISTRATION	
9:00	**Opening**	**John O'Keefe (Chair of Programme Committee)**
	Invited Young Scientist Talk 1	***Session Chair - Graham Collingridge***
9:10	**Seung-Hee Lee** (KAIST-Korea)	*Virtual perception induced by artificial stimulation of mouse sensory cortices*
	Session 1	***Session Chair: Morgan Sheng & Eunjoon Kim***
9:30	**Anne Bertolotti** (MRC LMB Cambridge)	*Correcting protein quality control failure to prevent neurodegenerative diseases*
9:50	**Yong-Seok Oh** (DGIST, Korea)	*Hilar mossy cell as a neural substrate of mood regulation*
10:10	**Laura Andreae** (King's College London)	*Building synaptic connections: a new role for spontaneous neurotransmitter release*
10:30	Coffee break	
10:50	**Jinhyun Kim** (KIST, Korea)	*mGRASP for mapping synaptic connectivity at multiple scales*
11:10	**Michael Johnson** (Imperial College London)	*Integrated systems genetics identifies hippocampal gene co-expression networks for human declarative memory*
11:30	**Jaewon Ko** (Yonsei University, Korea)	*Leucine-rich repeat transmembrane proteins (LRRTMs) as central mammalian synapse organizers*
11:50	**Matt Jones** (Bristol)	*Assembly-ing information across limbic-cortical circuits*
12:10	**Min Whan Jung** (IBS-KAIST, Korea)	*Distinct roles of parvalbumin- and somatostatin-positive neurons in working memory*
12:30	Lunch	*Clare College-Main hall*
	Session 2	***Session Chair: Kei Cho & Bruno Frenguelli***
13:40	**Philip Regan** (Bristol)	*Regulation of synaptic long-term depression by tau protein*
14:00	**Won Do Heo** (IBS – KAIST, Korea)	*Optogenetic Control of Intracellular Signaling Proteins*
14:20	**Michael Häusser** (UCL)	*All-optical interrogation of neural circuits*
14:40	**Jee Hyun Choi** (KIST, Korea)	*Gamma oscillation studied by high density EEG in mice*
15:00	Coffee break	
15:20	**Jenni Harvey** (Dundee)	*Food for thought: Leptin and synaptic function in health and disease*
15:40	**Eunji Cheong** (Yonsei University, Korea)	*Thalamocortical circuit in vigilance control*
16:00	**Tiago Branco** (MRC LMB, Cambridge)	*A mouse neural circuit for computing escape decisions during foraging*
16:20	**Tae Kim** (Kyung Hee Univ., Korea)	*Cortically projecting basal forebrain parvalbumin neurons: novel regulators of cortical gamma band oscillations*
16:40	**Closing remarks**	**Morgan Sheng, Eunjoon Kim**
18:00	**Dinner**	**Clare College-Main hall *(invitation only)***

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16-Sep	Wed.	The Latimer Room, Clare College, Cambridge
	Invited Young Scientist Talk 2	***Session Chair: Graham Collingridge***
9:00	**Sue-Hyun Lee** (KAIST-Korea)	*Representation of information during memory retrieval compared to perception*
	Session 3	***Session Chair: John O'Keefe & Lisa Saksida***
9:20	**Ingo Greger** (MRC LMB, Cambridge)	*Assembly, structure and organization of AMPA receptor heteromers*
9:40	**Taekwan Lee** (DGMIF, Korea)	*Molecular-Level Functional Magnetic Resonance Imaging: Spatio-temporal mapping of dopamine release*
10:00	**Gwenaëlle Douaud** (Oxford)	*From prediction to treatment, and basic understanding of disease spread: what can be gained from using MRI in neurodegenerative disorders?*
10:20	Coffee break	
10:40	**Inah Lee** (Seoul Nat. University, Korea)	*Scenic hippocampal formation: Neural circuits for scene-dependent decision making*
11:00	**Chris Heath** (Cambridge)	*Touchscreen-based assessment of motivation and emotion in rodents*
11:20	**Hyosang Lee** (DGIST, Korea)	*Genetic dissection of the neural circuits mediating mouse social behaviours*
11:40	**Michael Hastings** (MRC LMB, Cambridge)	*Circadian clocks in the brain: genes, cells and circuits*
12:00	Lunch *Clare College-Main hall*	***Congratulatory address: Prof. Doochul Kim (President, IBS)***
13:20	***Plenary Lecture***	***Chair: Graham Collingridge***
Trevor Robbins (Cambridge; Neuropsychopharmacology) "***Translational Neuropsychopharmacology: Potential and Limitation***"		
	Session 4	***Session Chair: Dennis Chan & John Wood***
14:00	**Michael Owen** (Cardiff)	*What genetics tells us about the biology of schizophrenia*
14:20	**Seung-Jae Lee** (Seoul Nat. University, Korea)	*Mechanisms of propagation of synucleinopathies*
14:40	**Peter St. George-Hyslop** (Cambridge)	*Multi-disciplinary approaches to understanding mechanisms of risk genes identified by GWAS and WES/WGS*
15:00	Coffee break	
15:20	**Jin-Hee Han** (KAIST, Korea)	*Synaptic manipulation of memory trace*
15:40	**Tara Spires-Jones** (Edinburgh)	*Staying connected: the role of synapse degeneration in Alzheimer's disease*
16:00	**Changjoon Justin Lee** (KIST, Korea)	*Tonic GABA from reactive astrocytes: the next generation therapeutic target for Alzheimer's disease*
16:20	**John Wood** (UCL)	*New Insights into Peripheral pain mechanisms*
16:40	**Uhtaek Oh** (Seoul Nat. University, Korea)	*The Role of Anoctamin 1 in Sensory Transduction*
17:00	**Paul Matthews** (Imperial College London)	*Microglia, neurodegeneration and new perspectives on an old molecule*
17:20	**Ja Wook Koo** (KBRI, Korea)	*Essential role of mesolimbic brain-derived neurotrophic factor in depressive behaviors*
17:40	**Closing remarks**	**John O'Keefe, Peter St George-Hyslop**
18:30	**Symposium dinner**	**Old Library, Pembroke College *(invitation only)***

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Virtual Perception Induced by Artificial Stimulation of Mouse Sensory Cortices

You-Hyang Song, Hye-Won Jeong, Jae-Hyun Kim, Ilsong Choi, Seung-Hee Lee

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Primary sensory cortices are the first cortical areas where the modality-specific sensory information arrives, but the causal relationship between activities in distinct sensory cortical areas and sensory perception is not fully understood yet. We devised artificial sensory discrimination task, in which the head-fixed mice were trained to discriminate channelrhodopsin-2 (ChR2)-mediated activation of the primary visual cortex (V1) and the primary auditory cortex (A1). We found that mice can learn to discriminate spatially and temporally distinct artificial stimuli that were given to the excitatory neurons (but not the inhibitory neurons) in each sensory cortex and transform learned artificial stimuli into the actual modality-specific sensory information. Furthermore, simultaneous activation of V1 and A1 is integrated and reported as A1-like stimuli in the head-fixed mice. Our data indicate that optogenetic activation of the cortical neurons can induce the artificial perception, and auditory information plays a dominant role in the visuo-auditory sensory integration in the head-fixed, behaving animal.

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Correcting protein quality control failure to prevent neurodegenerative diseases

Anne Bertolotti

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The deposition of misfolded proteins is a defining feature of many age-dependent human diseases, including the increasingly prevalent neurodegenerative diseases. Why aggregation-prone proteins accumulate in aged cells remains largely unclear. Cells normally strive to ensure that proteins get correctly folded and have powerful and sophisticated mechanisms to maintain homeostasis under adverse conditions. However, with age, the cellular defence systems against misfolded proteins gradually fail, leading to the accumulation of misfolded proteins with devastating consequences for cells and organism.

In principle, improving the cells' ability to deal with misfolded proteins should represent a generic approach to reduce the pathology in diverse protein misfolding diseases. My lab has identified powerful strategies to improve the cells' ability to deal with misfolded proteins and implemented one of such strategy in mice to safely prevent two unrelated neurodegenerative disease. Some of our approaches shed light on novel aspects of protein quality control systems while others pave the way for the development of rational therapeutics.

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Hilar mossy cell as a neural substrate of mood regulation

Seojin Oh[1], Jeffrey Arace[2], Paul Greengard[2], Yong-Seok Oh[1]

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Selective serotonin reuptake inhibitor (SSRI) medications for the depressed patients generally show severe therapeutic delay, in spite of their immediate effect on serotonergic neurotransmission, suggesting the involvement of complicated downstream mechanisms for the onset of their therapeutic effects. However, our knowledge of the molecular mechanisms underlying the efficacy of long-term treatment with SSRIs, is still rudimentary. Our previous studies revealed the profound roles of p11 (S100A10) protein for mood regulation and antidepressant actions. SMARCA3, a chromatin-remodeling factor, is found as a molecular target for the p11-dependent antidepressant actions. In the dentate gyrus, p11 are highly enriched in the hilar mossy cells and the SSRI fluoxetine increases the amount of the ternary complex of p11/annexin A2/SMARCA3. Behavioral responses to chronic SSRI administration are altered by Smarca3 gene knockout in the mossy cells, as in p11 knockout model. Interestingly, cell-type specific modulation of the mossy cell activity results in changes in mood/anxiety-related behaviors. By isolating cell type-specific transciptome with TRAP approach, we now are identifying the physiological target genes of the ternary complex in the mossy cells, mediating the SSRI actions. The current study will contribute to our understanding the cell type-specific transcriptional mechanism for the antidepressant actions of SSRI-p11 signalling pathway.

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Building synaptic connections: a new role for spontaneous neurotransmitter release

Laura Andreae, Juan Burrone

MRC Centre for Developmental Neurobiology, King's College London

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Spontaneous neurotransmitter release is a core element of synaptic communication in mature neurons, but little is known of its function during neuronal development. Using genetically encoded reporters of presynaptic release, we found that developing axons exhibit exceptionally high levels of spontaneous vesicle cycling. This high-level, spontaneous axonal release of the neurotransmitter glutamate can signal at long-range to NMDA receptors on developing dendrites, prior to synapse formation and, indeed, axo-dendritic contact. Blockade of NMDA signalling during this early period of spontaneous vesicle cycling leads to a reduction in dendritic arbor complexity, indicating an important role for early spontaneous release in dendritic arbor growth.

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mGRASP for mapping mammalian synaptic circuit at multiple scales

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Mapping mammalian synaptic connectivity has long been an important goal of neuroscientists since it is considered crucial for explaining human perception and behavior. Our new genetically controlled method to resolve synapses at the level of LM, termed mammalian GFP reconstitution across synaptic partners (mGRASP), is synapse-specific labeling with two complementary GFP components. mGRASP is based on two non-fluorescent split-GFP fragments (called spGFP1-10 and spGFP11) tethered to synaptic membranes in each of two neuronal populations. When two neurons, each expressing one of the fragments, are tightly opposed across a synaptic cleft, fluorescent GFP is reconstituted. mGRASP can relatively quickly reveal the precise locations and numbers of synapses along postsynaptic dendrites, sites responsible for determining many important characteristics of signal processing. Thus, mGRASP technology is suitable for mapping large-scale connectivity patterns at multiple scales: micro-scale for synapse-by-synapse or neuron-by-neuron analysis; and meso-scale for revealing local circuits. We performed a comprehensive fine-scale circuit mapping of hippocampal regions using the mGRASP. This mapping revealed spatially non-uniform and clustered synaptic connectivity patterns. Furthermore, synaptic clustering was enhanced between groups of neurons that shared a similar developmental/migration time window, suggesting a mechanism for establishing the spatial structure of synaptic connectivity. Such connectivity patterns are thought to effectively engage active dendritic processing and storage mechanisms, thereby potentially enhancing neuronal feature selectivity. Based on these prime connectivity characteristics, our study recently focuses on understanding synaptic connectivity profiles associated with neurological disorders using mGRASP.

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Integrated systems genetics identifies hippocampal gene co-expression networks for human declarative memory

Michael Johnson

Deputy Head, Centre for Clinical Translation, Division of Brain Sciences, Imperial College Faculty of Medicine

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Genetic contributions to variable human memory are poorly understood. Here, we use a systems-level analysis of genome-wide gene expression to infer cross species conserved hippocampus gene-regulatory networks. Two of these networks, M1 and M3, consisting of 1,148 and 150 genes respectively, are enriched for genetic susceptibility variants for verbal declarative memory. Analysis of biological terms and canonical pathways enriched among the genes of M1 and M3 reveal M1 is highly enriched for KEGG pathways related to calcium signalling and LTP, as well as for genes comprising the post-synaptic density and NMDAR/ARC complex, whereas M3 genes are collectively poorly annotated for known biological functions. The expression of M1 and M3 genes is highly temporally regulated during human brain development. Following birth, the expression of M1 and M3 is stable throughout life, suggesting an enduring role for these genes in the formation of new memories. The identification of co-expression networks associated with variable human memory provides a framework for the identification of gene regulatory factors influencing variable human memory.

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Leucine-rich repeat transmembrane proteins (LRRTMs) as central mammalian synapse organizers

Jaewon Ko

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Recent research has identified a diverse array of synaptogenic adhesion molecules and investigated their mechanisms of action in different synaptogenesis contexts. Among them, leucine-rich repeat transmembrane proteins (LRRTMs), in particular, have emerged as being important for excitatory synapse development. The LRRTM family composed of four members (LRRTM1 to LRRTM4) require distinct sets of presynaptic ligands to instruct presynaptic assembly. Moreover, the LRRTM family members also exhibit discrete region-specific expression patterns in the hippocampus and cerebellum. Intriguingly, a subset of LRRTMs is involved in AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor trafficking and function. Furthermore, analyses of *in vivo* LRRTM functions in knockout mice have revealed subtle anatomical and significant functional and behavioral defects. Not surprisingly, all four LRRTMs are associated with various neuropsychiatric disorders. Although the significance of LRRTMs in excitatory synapse development and function has been clearly recognized, it is still unclear whether LRRTM family members are functionally redundant in a region-specific manner, or whether distinct LRRTM proteins perform synaptic functions by employing shared and/or distinct sets of molecular mechanisms. In this talk, I would introduce our previously published studies and present unpublished data on LRRTM3 to address a few issues left from prior studies.

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Assembly-ing information across limbic-cortical circuits

Matthew Jones

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The hippocampus contains prize-winning place cells, the parietal cortex contains exquisitely turn-selective neurons and the prefrontal cortex contains all-over-the-place cells. How are these different flavours of spatial code integrated over the course of learning to inform behaviour?

I will describe analyses of simultaneous recordings of network activity in rat hippocampus, prefrontal and parietal cortex, highlighting the roles of coordinated oscillations during wake and sleep in binding different features of the cognitive map.

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Distinct roles of parvalbumin- and somatostatin-positive neurons in working memory

Dohoung Kim, Heejeong Jeong, Jeong-Wook Ghim, Seung-Hee Lee, Min Whan Jung

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Recent studies have begun to reveal distinct roles of different interneuron subtypes in various regions of the brain. However, specific roles of different inhibitory interneuron subtypes in working memory remain unclear. We examined discharge characteristics and stimulation effects of two major interneuron subtypes, parvalbumin (PV)- and somatostatin (SOM)-positive neurons, in the medial prefrontal cortex (mPFC) of mice performing a spatial working memory task. PV neurons showed weak target-dependent delay-period activity and were strongly inhibited by reward. By contrast, SOM neurons showed strong target-dependent delay-period activity and only a subtype of them was inhibited by reward. In addition, optogenetic stimulation of SOM, but not PV, neurons suppressed ipsilateral target-dependent delay-period activity more strongly than contralateral target-dependent one. Our results demonstrate distinct discharge characteristics and stimulation effects of PV and SOM neurons related to working memory and reward processing. These findings suggest roles of PV neurons in modulating response gain and gating reward-based learning and SOM neurons in maintaining the content of working memory in the prefrontal cortex.

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Regulation of synaptic long-term depression by tau protein

Philip Regan[1], Thomas Piers[1], Jee Hyun Yi[1], Dong-Hyun Kim[1], Seonghoo Huh[2], Se Jin Park[3], Jong Hoon Ryu[3], Daniel J. Whitcomb[1], Kwangwook Cho[1]

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The microtubule associated protein tau has been known to be a principal pathological component of numerous neurodegenerative disorders, including Alzheimer's disease (AD), for nearly 30 years. However, the nature by which tau contributes to neuronal pathogenesis still remains to be fully understood, hindering the development of novel therapeutic intervention strategies. For these reasons, it has become imperative to better understand the role that tau plays in neuronal physiology, from which insights into disease mechanisms can be better ascertained.

I will describe how tau has come to be realised as a post-synaptic protein, far-removed from its canonical axonal segregation. Here, a combination of biochemical and electrophysiological approaches has revealed a requirement for tau in the induction of long-term depression (LTD) of synaptic transmission in the hippocampus. I will further describe how tau phosphorylation at specific residues is integral to this novel function, and what the behavioural and pathophysiological consequences of these findings may be.

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Optogenetic Control of Cell Signaling in Mammalian Cells

Won Do Heo

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Recently, the advent of light responsive elements in cell biology has led us to design a rapid and reversible control system to modulate protein functions by stimulating specific wavelength of light in a spatiotemporal manner. Using a light responsive element we developed a versatile platform to inactivate proteins in living cells, light-activated reversible inhibition by assembled trap (LARIAT), which sequesters target proteins into complexes formed by multimeric proteins and a blue light–mediated heterodimerization module. Through the LARIAT, we exquisitely and reversibly inactivated guanine nucleotide exchange factors, Rho small GTPases, PI3-kinase and microtubules with high spatiotemporal resolution. Employing single-domain antibodies further expanded our platform to the inhibition of target proteins containing specific epitopes. I will also discuss in the talk new optogenetic tools we have developed to activate cell signaling and cell functions in mammalian cells. We expect these new optogenetic tools could specifically control the functions of endogenous target proteins in neuron and provide a powerful way to control a broad range of signaling proteins *in vivo*.

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All optical interrogation of neural circuits

Adam Packer, Lloyd Russell, Henry Dalgleish, Michael Häusser

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Neural circuits display complex spatiotemporal patterns of activity on the millisecond timescale during behaviour. Understanding how these activity patterns drive behaviour is a fundamental problem in neuroscience, and remains a major challenge due to the complexity of their spatiotemporal dynamics. The ability to simultaneously image and manipulate patterns of activity in neural circuits at cellular resolution would open up new frontiers in neuroscience. I will describe a strategy for “all-optical” interrogation of neural circuits in vivo with single-spike and single-neuron precision. Two-photon calcium imaging is combined with two-photon optogenetic activation using coexpression of a red-shifted opsin and a genetically encoded calcium indicator. A spatial light modulator allows tens of user-selected neurons to be targeted for spatiotemporally precise optogenetic activation, while simultaneous fast calcium imaging provides high-resolution network-wide readout of the manipulation with negligible optical cross-talk. Proof-of-principle experiments in mouse barrel cortex demonstrate interrogation of the same neuronal population during different behavioral states and targeting of neuronal ensembles based on their functional signature. This approach extends the optogenetic toolkit beyond the specificity obtained with genetic or viral approaches, enabling high-throughput, flexible and long-term optical interrogation of functionally defined neural circuits in vivo.

Reference: Packer et al. (2015), Nature Methods 12:140-6. doi: 10.1038/nmeth.3217.

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Gamma Oscillation Studied by High Density EEG in Mice

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Cortical gamma oscillations (30 – 80 Hz) are crucial to consciousness, attention, perception, and memory formation, and failure in gamma regulation is a hallmark of neurological and psychiatric disease. Recent studies using optogenetics have shown that gamma oscillations are induced by selective activation of fast-spiking interneurons containing calcium-binding protein parvalbumin (PV) and the subcortical PV cells, particularly cortex projecting PV cells in basal forebrain (BF-PV cells), are responsible to trigger the cortical gamma band oscillation. However, the cortical regions in the gamma oscillation reign of BF-PV cells are not known. Here, we combined the optogenetic interrogation with high density EEG in freely moving mice to detmine the spatio-frequency characteristics of cortical gamma band oscillation driven by BF-PV cells. We found that gamma band oscillation of BF-PV cells induced cortical gamma oscillation in the frontal cortex, whereas slow oscillation of these neurons induced diffusive and variant cortical activation mostly in the centro-parietal cortex. We further applied pulse train sound locking to the optogenetic stimulation. An in-phase activation of BF-PV cells lead more phasic response to the auditory sound, whereas out-of-phase activation suppressed the auditory evoked frontal responses. Thus, these findings indicate that BF-PV cells generate the frontal gamma oscillation and may be involved in their functional role.

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Food for Thought: Leptin and synaptic function in health and disease

Gemma McGregor, Yasaman Malekizadeh, Andrew Irving, Jenni Harvey

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The endocrine hormone leptin regulates food intake and body weight via its hypothalamic actions. However, leptin receptors are widely expressed in the brain and evidence is growing that leptin influences many central processes including cognition. In particular, leptin is reported to have cognitive enhancing properties as it facilitates the cellular events underlying hippocampal-dependent learning and memory, including significant effects on AMPA receptor trafficking and activity-dependent synaptic plasticity. Recent evidence indicates that leptin also regulates excitatory synaptic transmission at the temporoammonic input to hippocampal CA1 neurons. However, leptin-driven regulation of hippocampal synaptic function is markedly attenuated with age. Moreover, dysfunctions in the leptin system are correlated with an increased risk of developing neurodegenerative disorders such as Alzheimer's disease (AD). Here, we will discuss the cognitive enhancing role of the hormone leptin and also the therapeutic potential of targeting the leptin system in AD.

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Thalamocortical circuit in vigilance control: GABAA-mediated tonic inhibition in the ventrobasal thalamus

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The transition from attentive wake state to unconscious state accompanies synchronized rhythmic oscillations in thalamocortical circuit. A classical model for thalamocortical oscillations states that reciprocal interaction between synaptically connected GABAergic thalamic reticular nucleus (TRN) neurons and glutamatergic thalamocortical (TC) neurons generates oscillations, which is then transmitted from TC to cortical neurons. T-type Ca^{2+} channel-mediated low-threshold spikes in TC neurons have long been implicated in the genesis of thalamocortical oscillations and must be preceded by GABAergic inputs hyperpolarizing the membrane potential to de-inactivate T-channels. In TC neurons, tonic GABA inhibition as well as phasic inhibition have been observed and are known to be mediated via subunit-containing extrasynaptic $GABA_A$-receptors. However, the source of tonic GABA and its regulation have not been fully understood.

Here we investigated the source of tonic GABA inhibition and found that, contrary to the generally accepted idea that tonic GABA would mainly arise from synaptic spill-over, a major portion of tonic GABA is released from GABA-containing astrocytes in VB nuclei and that astrocytic GABA is released through the Ca^{2+}-activated chloride channel, bestrophin 1 (mBEST1). Additionally, we investigated the contribution of astrocytic GABA release to the generation of thalamocortical oscillations, which highlights its role in vigilance control.

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A mouse neural circuit for computing escape decisions during foraging

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Deciding when to escape from threatening situations is essential for animal survival. Staying in places with a high likelihood of facing threats, such as predators, can result in harm and ultimately, death, while prematurely fleeing from a safe place leads to resource loss. The neural basis of escape decisions under different levels of threat is poorly understood. To investigate this, we have implemented a foraging behavioural assay where mice are exposed to threatening overhead looming stimuli of different contrasts. Quantitative behavioural analysis and modelling show that the probability, reaction time and strength of defensive escape increase with stimulus contrast, in a manner compatible with gradual accumulation of evidence towards the presence of a threat. Using cell type-specific *in vivo* optogenetics and *in vitro* whole-cell recordings we have identified *Vglut2*$^{+}$ neurons in the medial Superior Colliculus (mSC) and dorsal Periaqueductal Gray (dPAG) as two monosynaptically connected circuit nodes that control the likelihood and strength of goal-directed defensive escape. Our data supports a model where evidence of a threat is accumulated in the mSC, and leads to activation of dPAG neurons that engage the escape motor program once a threshold is crossed.

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Cortically projecting basal forebrain parvalbumin neurons: novel regulators of cortical gamma band oscillations

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Cortical gamma band oscillations (GBO, 30–80 Hz, typically ~40 Hz) are involved in higher cognitive functions such as feature binding, attention, and working memory. GBO abnormalities are a feature of several neuropsychiatric disorders associated with dysfunction of cortical fast-spiking interneurons containing the calcium-binding protein parvalbumin (PV). GBO vary according to the state of arousal, are modulated by attention, and are correlated with conscious awareness. However, the subcortical cell types underlying the state-dependent control of GBO are not well understood. Here we tested the role of one cell type in the wakefulness-promoting basal forebrain (BF) region, cortically projecting GABAergic neurons containing PV, whose virally transduced fibers we found apposed cortical PV interneurons involved in generating GBO. Optogenetic stimulation of BF PV neurons in mice preferentially increased cortical GBO power by entraining a cortical oscillator with a resonant frequency of ~40 Hz, as revealed by analysis of both rhythmic and nonrhythmic BF PV stimulation. Our results suggest that this presumptively inhibitory BF PV input controls cortical GBO, likely by synchronizing the activity of cortical PV interneurons. BF PV neurons may represent a previously unidentified therapeutic target to treat disorders involving abnormal GBO, such as schizophrenia.

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Representation of information during memory retrieval compared to perception

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Memory retrieval allows humans to re-experience previously experienced events or stimuli. Although such retrieval is thought to evoke similar neural activation in sensory cortical areas to those elicited during the actual experience, it remains unclear how item specific information is represented during retrieval compared to actual experience. Here we performed an event-related functional magnetic resonance imaging (fMRI) experiment to conduct a detailed comparison of the representations between retrieval and perception. Using multi-voxel pattern analysis, we found that the response of object-selective cortex could be used to decode the identity of individual objects during both perception and retrieval. However, in hippocampus, object identity could be decoded during retrieval of long-term memory only but not perception or retrieval of short-term memory. Moreover, in object-selective cortex but not hippocampus, there was significant correspondence between the representations during perception and retrieval. Furthermore, the accuracy and fidelity of retrieval was correlated with the decoding accuracy in object-selective cortex but not hippocampus. Thus, these results suggest that while retrieval of item specific information activates a similar fine-grained representation with that during perception in visual areas, the hippocampal representation is dynamic across time.

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Structure, dynamics and organization of AMPA receptor heteromers

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AMPA receptors are glutamate-gated ion channels that mediate excitatory transmission and synaptic plasticity in vertebrate brains. The receptor channel forms tetramers of four core subunits, GluA1-4, that are associated with a variety of auxiliary subunits. AMPAR are preferential heteromers of varying subunit combinations, which increases their signaling range and regulates trafficking at synapses. Expression of different subunit combinations is associated with synaptic plasticity and with various pathologies. A core interest of the lab has been to understand the rules governing receptor AMPAR assembly. A driving force is the N-terminal domain, which drives heteromeric assembly via a large subunit interface. I will discuss the role of the NTD in assembly and highlight data that implicate this domain in allosteric regulation of AMPARs which involves auxiliary subunits.

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Molecular-Level Functional Magnetic Resonance Imaging: Spatio-temporal mapping of dopamine release

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Dopamine signaling is critical to brain systems controlling voluntary movement, learning, and the experience of reward. Although extensive studies of dopaminergic neural activity have been performed using electrophysiology and pharmacological approaches, very little information has been obtained about spatial characteristics of dopamine signaling in the brain. To address this issue, I applied a family of protein-based contrast agents that can detect dopamine in MRI. Here I use these probes to perform molecular-level functional imaging of dopamine release during delivery of a widely-studied artificial reward, electrical stimulation of the medial forebrain bundle (MFB) in rats. Statistical analysis revealed significant stimulation-associated MRI signal changes across the ventral striatum, with the strongest responses observed in the nucleus accumbens core. Average time series data indicated signal changes of up to 2%, consistent with peak dopamine concentrations of approximately 10 μM binding to the sensor. Parallel measurements using electrochemical detection verified that dopamine concentrations determined by MRI were realistic, and confirmed that the contrast agent binds dopamine in vivo. These experiments offer a novel and qualitatively unique spatiotemporal view of phasic dopamine signaling, and provide direct evidence for the spatial heterogeneity of dopamine release in the ventral striatum.

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Scenic hippocampal formation: Neural circuits for scene-dependent decision making

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The hippocampal formation is critical for episodic memory. Episodic memory requires going back to a specific time and place in one's mind and retrieving specific details of a past event. Our current hypothesis is that memory for visual scene is essential for remembering a specific event in episodic memory, and the hippocampus and its associated areas are important during the processes. Our laboratory investigates the neural mechanisms of scene-dependent decision making. By using a behavioral task in which the rat is required to choose between different responses on the basis of visual scenes, we have shown that the hippocampus is necessary for scene-dependent decision making (even when no spatial behavior is not required). Physiologically, single units in CA1 alter both spatial and nonspatial firing patterns in association with visual scenes in a learning-dependent manner. That is, well-learned scenes induce bigger changes both in the spatial and nonspatial firing patterns, compared to newly learned scenes. We are currently investigating the representational differences across different subareas in the hippocampal formation and its associated cortical areas (including the perirhinal cortex, postrhinal cortex, entorhinal cortex, etc.). We aim to learn how these neural firing characteristics are translated into decision behavior in a goal-directed task.

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Touchscreen-based assessment of emotion and motivation in rodents

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While synonymous with memory loss, dementia can also result in the development of significant neuropsychological symptoms including changes in motivation and emotional regulation. These often present early and are particularly distressing to patients and their caregivers. Amelioration of these disruptions would therefore yield a substantial quality of life improvement for sufferers and their families. To facilitate this, further understanding of the underlying neurobiological mechanisms and the effects of pathology is required. While many animal models that would enable such investigations exist, few have been examined for analogous symptoms.

To address this, we have developed a battery of behavioural tasks to assess various domains of emotion and motivation and are examining several mouse models for evidence of appropriate phenotypes. Our battery utilizes the rodent touchscreen apparatus which enables translation between rodent models and patients. Such standardization increases the likelihood that a promising laboratory intervention will have beneficial effects in the clinic. This may facilitate the development of efficacious therapeutics for these debilitating symptoms.

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Genetic Dissection of the Neuronal Circuits Mediating Mouse Social Behaviors

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Emotional behaviors are associated with internal states that are perceived in humans as feelings. Aggression and sexual behavior are highly conserved, prototypic emotional behaviors that proceed through a series of appetitive and consummatory phases associated with increasing levels of arousal. How this escalation is encoded in the brain and linked to behavioral action selection remains an important unsolved problem in neuroscience.

Using in vivo electrophysiological recordings and functional manipulations such as optogenetics, we found that neurons in the ventrolateral subdivision of the ventromedial hypothalamus (VMHvl) are activated during both mating and fighting, and that optogenetic activation of this structure can trigger attacking behavior in mice. In our study, we further dissected VMHvl using a molecular genetic marker and found that estrogen receptor 1-expressing neurons in VMHvl control the progression of a social encounter from its appetitive through its consummatory phases in a scalable manner that reflects the number or type of active neurons in the population. This study raises important new questions about the neuronal circuit mechanism controlling decisions between innate social behaviors in the hypothalamus.

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Circadian clocks in the brain: genes, cells and circuits

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Daily or circadian rhythms dominate our lives: the most obvious rhythm being the cycle of sleep and wakefulness, which is the ultimate arbiter of neural function. The principal internal clock controlling these rhythms is the suprachiasmatic nucleus (SCN) of the hypothalamus. This presentation will review current knowledge of the molecular genetic basis of the SCN timing system, and then consider how sub-populations of SCN neurons determine specific properties of the clock. Finally, it will address how the SCN interacts with other local clocks across the brain to control the timing of the sleep/ wake cycle and also direct sleep quality and sleep-dependent memory.

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What genetics tells us about the biology of schizophrenia

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Recent genomic studies have confirmed the highly polygenic nature of schizophrenia. Despite this complexity, studies using systems biology approaches have identified enrichment of genetic variants in functionally related sets of genes in schizophrenia cases. These findings are remarkable in that they converge upon a highly plausible set of biological processes and have now been replicated in several different datasets using independent approaches. They implicate functionally related set of proteins involved in synaptic plasticity, learning and memory. Among them are genes encoding members of N-methyl-D-aspartate receptor (NMDAR) and neuronal activity-regulated cytoskeleton-associated (ARC) protein complexes, targets of FMRP, and voltage-gated calcium channels. More recently, we have shown for the first time that case CNVs are enriched for genes involved in GABAergic neurotransmission. These findings indicate that disrupted GABAergic signalling is of direct causal relevance rather than a secondary effect or due to confounding. Additionally, we independently replicated and greatly extended previous findings of CNV enrichment among the NMDAR and ARC gene sets. Given the strong functional links between the major inhibitory GABAergic and excitatory glutamatergic systems, our findings converge on a broad, coherent set of processes, providing firm foundations for studies aimed at dissecting disease mechanisms.

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Mechanism of propagation of synucleinopathies

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Misfolding and aggregation of α-synuclein have been implicated as critical factors in the pathogenesis of Lewy body diseases (LBD), such as Parkinson's disease. However, the pathogenic modifications of this protein and the mechanism underlying its activity have not been fully characterized. Recent studies suggest that very low levels of α-synuclein, a cytosolic protein, are released from neuronal cells by unconventional exocytosis. This extracellular α-synuclein, released by the neurons, contributes to the major pathological features of LBD, such as neurodegeneration, progressive spreading of α-synuclein pathology, and neuroinflammation. In this talk, I will critically review a rapidly increasing body of literature, which propose extracellular α-synuclein as a novel therapeutic target of LBD and suggest interventional approaches to halt the progression of the disease.

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Synaptic manipulation of memory trace

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Isolating and manipulating key circuit components in a memory trace is critical to understand the nature of memory. To isolate the essential neural circuit components for fear memory association, we tested whether direct activation of presynaptic sensory inputs in LA is sufficient to form fear memory in mice. Photostimulation of axonal projections from the two main auditory brain regions, the medial geniculate nucleus of the thalamus and the secondary auditory cortex, was paired with aversive footshock. Twenty-four hours later the same photostimulation induced robust conditioned freezing and this fear memory formation was disrupted when glutamatergic synaptic transmission was locally blocked in the LA. Therefore, our results show that synapses between sensory input areas and the LA represent key circuit component in a fear memory trace that actually is sufficient to serve as a conditioned stimulus. Our results are consistent with the idea that the LA may be sufficient to encode and store associations between neutral cue and aversive stimuli during natural fear conditioning as a critical part of a broad fear memory engram. This synaptic component in a memory trace could be manipulated to reveal the nature of memory.

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Staying connected: the role of synapse degeneration in Alzheimer's disease

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The collapse of neural networks important for memory and cognition, including death of neurons and degeneration of synapses, causes the debilitating dementia associated with Alzheimer's disease (AD). We have demonstrated that synaptic changes are central to the disease process. Both amyloid beta and tau proteins contribute to synaptic dysfunction and collapse in transgenic models of AD *in vivo*.

Further, the march of neurofibrillary tangles through brain circuits appears to take advantage of recently described mechanisms of trans-synaptic spread of pathological forms of tau. These two key phenomena, synapse loss and the spread of pathology through the brain via synapses, make it critical to understand the physiological and pathological roles of amyloid beta and tau at the synapse.

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Tonic GABA from reactive astrocytes: the next generation therapeutic target for Alzheimer's disease

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In Alzheimer's disease (AD), memory impairment is the most prominent feature that afflicts patients and their families. Although reactive astrocytes have been observed around amyloid plaques since the disease was first described, their role in memory impairment has been poorly understood. We have recently demonstrated that reactive astrocytes aberrantly and abundantly produce the inhibitory gliotransmitter GABA by monoamine oxidase-B (Maob) and abnormally release GABA through the bestrophin 1 channel. In the dentate gyrus of mouse models of AD, the released GABA reduces spike probability of granule cells by acting on presynaptic GABA receptors. Suppressing GABA production or release from reactive astrocytes fully restores the impaired spike probability, synaptic plasticity, and learning and memory in the mice. In the postmortem brain of individuals with AD, astrocytic GABA and MAOB are significantly upregulated. We propose that selective inhibition of astrocytic GABA synthesis or release may serve as an effective therapeutic strategy for treating memory impairment in AD. Conventional MAOB inhibitors show loss of effect and side effects during chronic treatment for AD. To develop better inhibitor of MAOB, we have screened for compounds that block MAOB reversibly with maximal selectivity for MAOB against MAOB. We have found several candidate compounds that show promising medicinal potential.

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Endogenous opioids contribute to insensitivity to pain in humans and mice lacking sodium channel $Na_V1.7$

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Loss of function mutations in the *SCN9A* gene encoding voltage-gated sodium channel $Na_V1.7$ cause congenital insensitivity to pain in humans and mice. Surprisingly, many potent selective antagonists of $Na_V1.7$ are weak analgesics. We investigated whether $Na_V1.7$, as well as contributing to electrical signaling, may have additional functions. We found that $Na_V1.7$ deletion has profound effects on gene expression, leading to an upregulation of enkephalin precursor *Penk* mRNA and met-enkephalin protein in sensory neurons. In contrast, sodium channel $Na_V1.8$ null mutant sensory neurons show no upregulated Penk mRNA expression. Application of the opioid antagonist naloxone potentiates noxious peripheral input into the spinal cord, and dramatically reduces analgesia in both male and female $Na_V1.7$ null mutant mice, as well as in human $Na_V1.7$ null mutants. These data suggest that $Na_V1.7$ channel blockers alone may not replicate the analgesic phenotype of null mutant humans and mice, but may be potentiated with exogenous opioids.

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Anoctamin 1 and its implication in neural function

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Anoctamin 1 (ANO1 or TMEM16A) was cloned to be a candidate for CaCC. ANO1 is activated by intracellular Ca2+, which is also voltage dependent. ANO1 is expressed in epithelia of salivary glands, pancreas, kidney, pulmonary airways, the retina, and sensory neurons where endogenous CaCC currents were found.

ANO1 is expressed in dorsal-root ganglion (DRG) neurons, highly co-expressed with TRPV1, a marker for nociceptors, suggesting the involvement in nociception. Surprisingly, ANO1 is activated by heat over 44^{o}C. Indeed, Ano1-deficient (Adv/Ano1$^{fl/fl}$) mice showed reduced responses to noxious heat. In addition, Ano1-deficient mice also elicited reduced inflammatory hyperalgesia and neuropathic allodynia. Thus, Ano1 plays an important role in mediating nociception in sensory neurons.

Because of high expression in nociceptors, ANO1 may be involved in itch signals. Indeed, we found that ANO1 mediates itch. Adv/Ano1$^{fl/fl}$ mice displayed a significant reduction in scratching behaviors to chloroquine or SLIGRL injection, but not histamine injection. These results demonstrate that ANO1 possibly mediate histamine-independent itch signaling in sensory neurons.

Finally, we present evidence that ANO1 plays a critical role in the development of brain during embryo.

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Microglia, neurodegeneration and new perspectives on an old molecule

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The “third element” of the brain identified by Hortega and characterized by Cajal includes microglia, now recognized for having unique roles in control of the environment of the neuronal-glial unit and in regulating key aspects of adaptive response. I will describe the development of molecular imaging approaches to visualizing the dynamics of microglial responses in human disease, which have re-focused attention on the 18 kD mitochondrial translocator protein. This work is providing novel disease insights, highlighting particularly the role of the innate immune response in neurodegeneration. However, there is an even richer story. The protein has been highly conserved through evolution, with functions expanding widely with differentiation of cell types to include roles in steroidogenesis and the regulation of mitochondrial oxidative phosphorylation and rapidly dividing cell apoptosis. Uniquely, humans carry a functional polymorphism that appears to have functional effects. We are exploring the influence that TSPO may have on signaling to modulate glial inflammatory responses and reconsidering the pharmacodynamics of TSPO ligands. The talk will illustrate how an unexpected series of fundamental questions about microglial biology grew out of work intended “simply” to better image the brain.

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Essential role of mesolimbic brain-derived neurotrophic factor in depressive behaviors

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Social stress is a risk factor for depression and several related syndromes in humans. A long-lasting and generalized aversion to social contact, produced by repeated aggressive encounters in rodents, has been proposed as a model for aspects of these disorders. However, the mechanisms underlying such social avoidance behavior remain incompletely understood. Here, we demonstrate that BDNF-TrkB signaling, but not dopamine (DA) signaling, in the mesolimbic DA circuit is required for the social avoidance that is produced by chronic social defeat stress (CSDS). Blockade of BDNF-TrkB signaling, but not DA signaling, from the ventral tegmental area (VTA) to the nucleus accumbens (NAc) prevented CSDS-induced social avoidance. The induction of BDNF-TrkB signaling by CSDS appears specific for the population of NAc medium spiny neurons that express the D1 dopamine receptor. Optogenetic phasic stimulation of the VTA-NAc circuit, which mimics the enhanced burst firing seen in defeated mice, exacerbated CSDS-induced social avoidance. This aggravated social avoidance was normalized by BDNF-TrkB blockade—by use of pharmacological and genetic tools—in the VTA-NAc circuit. Together, these findings suggest that BDNF-TrkB signaling, rather than DA signaling, in the VTA-NAc circuit is crucial for facilitating depressive-like outcomes after CSDS.