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Better Therapeutic Applications through Better Understanding of the Brain

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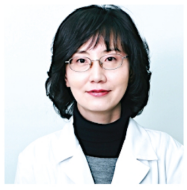

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Integrative neuroimaging: bridging the gap between the lab and the clinic

Heidi Johansen-Berg

University of Oxford

Correspondence and requests for collaboration should be addressed to ***heidi.johansen-berg@ndcn.ox.ac.uk***

Neuroimaging offers a route to bridge the gap between laboratory neuroscience and human health. This is possible because non-invasive neuroimaging methods such as MRI are increasingly able to provide us with measures that are sensitive to cellular phenomena but that can be acquired rapidly and non-invasively in living individuals.

This talk will discuss application of neuroimaging to provide a bridge between the laboratory and the clinic, and to exploit big data neuroimaging resources to identify predictive markers of disease.

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Dissecting the complexity of the postsynaptic proteome

Seth G.N. Grant

University of Edinburgh

Correspondence and requests for collaboration should be addressed to ***seth.grant@ed.ac.uk***

The postsynaptic terminal of excitatory synapses is an enigma. Each postsynaptic terminal of excitatory synapses houses hundreds of thousands of proteins, comprised of ~1000 proteins types that are highly conserved across vertebrate species. What is the function of this remarkable molecular complexity, how did genome evolution generate this complexity, and why has genome evolution preserved it?

The presentation will address the physical organization of the proteome, the results of the largest genetic study of verterbrate synapses, and a new method for mapping synapse molecular diversity across the whole mouse brain. These approaches lead to a new model of synapse function and behavior. In addition, we show that these mechanisms are directly disrupted by a large number of mutations causing common and rare human disorders.

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A novel synapse regulatory protein, Cyclin Y/CCNY links functional and structural plasticity of synapses

Mikyoung Park

Center for Functional Connectomics, Brain Science Institute, Korea Institute of Science and Technology, Seoul, Korea

Correspondence and requests for collaboration should be addressed to ***mpark@kist.re.kr***

Cyclin Y (CCNY) is a member of the cyclin protein family, known to regulate cell division in proliferating cells. Interestingly, CCNY is expressed in neurons that do not undergo cell division. Here, we found that CCNY inhibits activity-dependent exocytosis of AMPA receptors in neurons and negatively regulates LTP. Confocal imaging and 3D structure rendering reveal CCNY localization adjacent to postsynaptic sites in dendritic spines. Using a pH-sensitive GFP conjugated AMPA receptor, we showed that CCNY inhibits AMPA receptor exocytosis in spines triggered by LTP-inducing stimuli. In addition, live-cell imaging and FRAP assay revealed that CCNY regulates actin remodeling associated with synaptic plasticity. Our findings indicate that CCNY tightly regulates both synaptic insertion of AMPA receptors and the structural plasticity of dendritic spines, suggesting that CCNY may couple the structural and functional changes that occur during synaptic plasticity.

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How Neocortex Retrieves Memory to Detect Novelty

Samuel F. Cooke

King's College London

Correspondence and requests for collaboration should be addressed to ***samuel.cooke@kcl.ac.uk***

Familiarity with stimuli that bring neither reward nor punishment enables organisms to detect novelty and devote cognition to important elements of the environment. Here we describe an experimentally constrained form of familiarity in mice that is manifest as highly selective long-term behavioural habituation to visual stimuli. Parallel recordings in primary visual cortex (V1) reveal a similarly selective form of long-term plasticity, which occurs as habituation develops within layer 4 of V1. Evidence indicates that this stimulus-selective response potentiation relies upon mechanisms of canonical Hebbian synaptic plasticity and that these same mechanisms support habituation. However, this robust form of cortical plasticity is also an emergent property that requires feedback. Moreover, there is a clear requirement for the selective activity of inhibitory neurons in the retrieval of stored information. Surprisingly, potentiation coincides with, but is not caused by, pronounced shifts in on-going cortical state, which reflect the state of cortical inhibition and serve as a gate for the detection of novelty. Given that habituation deficits are a core feature of several psychiatric disorders, and that disrupted inhibition may contribute to underlying pathology in some of these disorders, there is potential translational utility to studying this very simple yet fundamental form of learning and memory.

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Neurotransmitter co-release mediated by midbrain dopamine neurons

Jae-Ick Kim[1], Subhashree Ganesan[2], Lu Chen[2], Jun Ding[2]

[1] Department of Biological Sciences, Ulsan National Institute of Science and Technology, Korea
[2] Department of Neurosurgery, Stanford University School of Medicine, US

Correspondence and requests for collaboration should be addressed to ***jikim220@unist.ac.kr***

One of fundamental questions in neuroscience is how distinct neurotransmitters control and orchestrate neuronal functions to generate proper behaviors for survival in complex environment. It is understood that repeated binge-like drinking is a gateway to alcoholism, but it is less well established precisely how repeated ethanol exposure leads to an increased likelihood of alcohol preference. Alterations in the dopaminergic system are particularly relevant to alcohol preference because dopamine (DA) is involved in multiple forms of addiction. It is known that, in addition to DA, DA neurons can co-release fast-acting neurotransmitters including glutamate and gamma-aminobutyric acid (GABA), suggesting that these additional neurotransmitters co-released by DA neurons may be involved in developing alcohol preference. In this talk, I will describe my work about co-transmission of inhibitory neurotransmitter, GABA, from dopaminergic terminals and its physiological role in alcohol-related behaviors. Then, I will offer ideas of how this dopaminergic inhibition can regulate the activity of spiny projection neurons (SPNs) in the striatum.

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Three-dimensional in vitro modeling of the central nervous system

Eun-Mi Hur

Korea Institute of Science and Technology

Correspondence and requests for collaboration should be addressed to ***ehur@kist.re.kr***

Advances in 3D tissue engineering have yielded a growing list of organ/tissue-mimics. Brain, which is composed of anatomically distinct elements interconnected by neural networks, represents perhaps the most complex organ to reconstruct. Although several strategies have been developed to model the modular or layered architecture of neuronal somata, limited success has been made towards mimicking the organized or aligned nature of nerve fibers. During development, axons follow precise paths and become directionally aligned, and alterations in such alignment are associated with a broad range of neurological diseases. Despite the importance, little attention has been paid to organizing axon fibres and neural connectivity in culture, especially in 3D. In this talk, I will introduce a simple yet effective method to align fiber tracts in 3D neural constructs, a method which can be applied to model normal and diseased neural circuits. By exploiting the elastomeric property of polydimethylsiloxane and kinetics of collagen fibrillogenesis, the hippocampal CA3–CA1 circuit has been reconstructed in a monolithic gel, in which collagen scaffolds aligned in 3D serve as contact guidance cues to direct axon growth. Moreover, our results suggest that structural alignment is important for achieving functional connectivity between CA3 and CA1 neural populations in vitro.

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Neurodegeneration: from molecules to medicines

Giovanna Mallucci

University of Cambridge

Correspondence and requests for collaboration should be addressed to ***gm522@medschl.cam.ac.uk***

This talk will summarise my lab's recent progress in understanding mechanisms of neurodegeneration and how this is informing new therapeutic approaches. The central concept is the identification of common pathways across the spectrum of these disorders (which include Alzheimer's and related diseases) relevant for both mechanistic insights and therapy. These include both 'toxic' processes that can be targeted to prevent neuronal death, and regenerative processes that can be harnessed for repair. I will briefly present data from mouse models targeting both of these aspects and their relevance for human disease. I will focus on modulating the Unfolded Protein Response pharmacologically, including and the recent discovery of repurposed drugs ready for clinical trials. I will also touch on the strategy of harnessing pathways that drive synapse regeneration, as occurs in hibernation, for the therapy of neurodegenerative disease.

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A New Avenues for Brain Disease and Therapy by Enhancer and enhancer RNA

Jae-Yeol Joo

Department of Neural Development and Disease, Korea Brain Research Institute, Daegu, Korea

Correspondence and requests for collaboration should be addressed to ***joojy@kbri.re.kr***

Genome-wide features of their origin and expression patterns ascribed a prominent role for long noncoding RNAs (lncRNA) to the regulation of protein-coding genes, and also suggest a potential link to many human diseases. The brain is one of the richest sources of lncRNAs, many of which have already shown a close relationship with genes or genetic loci implicated in a wide range of neurological disorders. Enhancer RNAs (eRNAs) are a class of lncRNA expressed from active enhancers, whose function and action mechanism are yet to be firmly established. The one of the outstanding mechanism for eRNA revealed in *Molecular Cell* paper, 2014. The eRNAs facilitate the transition of paused RNA polymerase II (RNAPII) into productive elongation by acting as a decoy for the negative elongation factor (NELF) complex upon induction of immediate early genes (IEGs) in neurons. The *c-fos* gene (also known as *Fos*) is induced by a broad range of stimuli and is a reliable marker for neural activity. The multiple enhancers located near the *c-fos* gene can be activated in distinct combinations in response to various stimuli or in different brain regions. As a consequence of such a mechanism, each stimulus exhibits a differential functional requirement of TFs, each of which also shows a distinct binding specificity in the *c-fos* gene area. The epigenetic mechanism of eRNAs should help in understanding the physiological nature of *c-fos* induction in relation to neural activity and plasticity.

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Parkinson's disease: What has genetics done for us?

Nick Wood

UCL Institute of Neurology
Queen Square
London WC1N 3BG

Correspondence and requests for collaboration should be addressed to ***n.wood@ucl.ac.uk***

It is the 20th anniversary since the first gene for Parkinson's disease (PD) was found (alpha synuclein). Since then there has been regular identification of novel genes and improvements in our understanding of underlying PD risk. Knowledge around these genes is directing biological experimentation and aiding pathway discovery.

Complementing this mendelian approach have been genome-wide association studies, which over the last 8-10 years have also identified a very large number of loci also contributing to disease risk. The results of all this work in the short term have been to identify key molecules which when mutated or perturbed alter pathways to produce disease. This is providing immensely useful and novel insights into pathogenetic mechanisms.

However there are significant limitations to working in neurodegenerative disease including access to tissue, the generally slow progression and insidious nature of the diseases, and the paucity of biologically relevant biomarkers to monitor the disease course. All of these have hampered investigating the mechanism and to date there are no disease modifying treatments of any significance in any of the major neurodegenerative diseases.

I will describe emerging approaches which are being harnessed to help use genetics to inform on biomarker discovery and drug target identification. These build on the techniques of mendelian randomisation to identify causal links between gene variation, pathogenesis, and drug response.

Refs:

Nalls, Mike A.; Pankratz, Nathan; Lill, Christina M.; et al. Large-scale meta-analysis of genome-wide association data identifies six new risk loci for Parkinson's disease. Nature Genetics 46, Issue 9: 989-993 (2014)

Noyce et al Estimating the causal influence of body mass index on risk of Parkinson's disease: A Mendelian randomisation study. PLoS Medicine, 13 June 2017

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Exon Junction Complex regulates a recursive mechanism of alternative splicing

Lorea Blazquez[1,2], Warren Emmett[1,2], Rupert Faraway[1,2], Nejc Haberman[1,2], Christopher R. Sibley[1], Jernej Ule[1,2]

[1]Department of Molecular Neuroscience, UCL Institute of Neurology, Queen Square, London, WC1N 3BG, UK
[2]The Francis Crick Institute, 1 Midland Road, London, NW1 1AT, UK

Correspondence and requests for collaboration should be addressed to ***j.ule@ucl.ac.uk***

Recursive splicing (RS) allows removal of introns in a two-step process. This requires definition of a 'RS-exon', which reconstitutes a new 5' splice site (RS-5ss) after its splicing to the preceding exon. Interestingly, over 5% of human annotated exons can reconstitute a RS-5ss. While most of these annotated RS-exons are constitutive, many of them become skipped upon perturbation of the Exon Junction Complex (EJC). EJC represses recursive splicing of these exons by assembling on the partly spliced pre-mRNA, and preventing recognition of the RS-5ss. This function involves all of the core EJC components, as well as the peripheral factors PNN and RNPS1. We find that the proportion of annotated RS-exons increases in vertebrates, indicating an increased EJC-dependent repression of recursive splicing. The alternative RS-exons have distinct tissue-specific inclusion patterns, with lowest inclusion in the brain, and haploinsufficiency of EJC components in mice leads to increased skipping of RS-exons in the brain, which affects several genes previously linked to the microcephaly phenotype. Notably, the binding patterns of splicing regulators at alternative RS-exons is more similar to constitutive rather than alternative exons, which is consistent with the role of recursive mechanism in their alternative splicing. Thus, EJC-dependent repression of recursive splicing enables regulation of splicing after exon definition, and this has particular implications for brain development and evolution.

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Circadian Timing System

Kyungjin Kim

Korea Brain Research Institute (KBRI) and Department of Brain & Cognitive Sciences, DGIST, Daegu, Korea

Correspondence and requests for collaboration should be addressed to ***kyungjin@kbri.re.kr***

Circadian rhythm is involved in the regulation of physiology and behavior in mammals. The mammalian circadian timing system is organized in a hierarchy: The central circadian pacemaker residing in the suprachiasmatic nucleus(SCN) of the anterior hypothalamus orchestrates numerous subsidiary local clocks in several regions of the brain and peripheral tissues. The molecular clock machinery has two interlocking feedback loops that drive the circadian oscillation in cell-autonomous and self-sustainable manner even at the single-cell level. It works through the transcription/translation and post-translational modifications that contribute to the fine regulation of molecular circadian clockwork. Following a brief overview of recent advance in chronobiology, I will discuss our data on the novel functional link between the mood regulation by midbrain dopamine(DA) and circadian timing system.

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Combining bioengineering and organoids to model human brain development in a dish

Madeline A. Lancaster

MRC Laboratory of Molecular Biology

Correspondence and requests for collaboration should be addressed to ***mlancast@mrc-lmb.cam.ac.uk***

The human brain is one of the most enigmatic organs in the animal kingdom. In an effort to study the unique biology of the human brain, we have developed so-called cerebral organoids: three-dimensional self-organizing developing human brain tissue in a dish. These tissues nicely model early events in human brain development, particularly the organization of progenitor zones and the behaviour of neural stem cells. However, until recently it was difficult to model neural migration and neural positioning in the cortical plate. We have recently incorporated bioengineering into the method in order to more reproducibly generate cerebral cortex. Furthermore, reconstitution of the basement membrane allows for the formation of a properly aligned cortical plate and the ability model radial neuronal migration in vitro. This system thus allows for the study of human specific processes of neurogenesis as well as later neuronal migration and even maturation.

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Non-Coding RNAs in the brain: Functional implications of miR-19 in the migration of newborn neurons in the adult brain

Jinju Han[1*#], Hyung Joon Kim[1,3], Simon T. Schafer[1,2,3], Apua Paquola[1], Gregory D. Clemenson[1], Tomohisa Toda[1], Jinseo Oh[1], Aimee R. Pankonin[1], Bosuk Lee[1], Stephen T. Johnston[1], Anindita Sarkar[1], Ahmet M. Denli[1] and Fred H. Gage[1*]

[1] Laboratory of Genetics, Salk Institute for Biological Studies, 10010 North Torrey Pines Road, La Jolla, California 92037, USA
[2] Institute of Physiology, University of Greifswald, 17495 Karlsburg, Germany
[3] These authors contributed equally.
[#] Current Address: Graduate School of Medical Science and Engineering (GSMSE), KAIST, 291 Daehak-ro, Yuseong-gu, Daejeon 34141, Republic of Korea

Correspondence and requests for collaboration should be addressed to ***jinjuhan@kaist.ac.kr***

Altered microRNA profiles have been implicated in human brain disorders. However, the functional contribution of individual microRNAs to neuronal development and function is largely unknown. Here we report biological functions for miR-19 in adult neurogenesis. We determined that miR-19 is enriched in neural progenitor cells (NPCs) and downregulated during neuronal development in the adult hippocampus. By manipulating miR-19 in NPCs for gain- and loss-of- function studies, we discovered that miR-19 regulates cell migration by directly targeting Rapgef2. Concordantly, dysregulation of miR-19 in NPCs alters the positioning of newborn neurons in the adult brain. Furthermore, we found abnormal expression of miR-19 in human NPCs generated from schizophrenic patient-derived induced pluripotent stem cells (iPSCs) that have been described as displaying aberrant migration. Our study demonstrates the significance of posttranscriptional gene regulation by miR-19 in preventing the irregular migration of adult-born neurons that may contribute to the etiology of schizophrenia.

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Critical role of secretory carrier membrane protein 5 in the release site clearance during high neuronal activity at the presynaptic active zone

Daehun Park[1], Unghwi Lee[1], Haiyan Zhao[2], Jung Ah Kim[1,5], Byoung Ju Lee[1], Won Kyung Ho[1,4], Kwangwook Cho[3] and Sunghoe Chang[1,4,5]

[1]Department of Physiology and Biomedical Sciences, Seoul National University College of Medicine, Seoul, South Korea 110-799, [2]Physical Examination Center, Department of Internal Medicine, Yanbian University Hospital, Yanji, Jilin Province, PR China, [3]Centre for Synaptic Plasticity, Faculty of Health Sciences, University of Bristol, Bristol, UK [4]Biomembrane Plasticity Research Center, Seoul National University College of Medicine, Seoul, South Korea 110-799, [5]Neuroscience Research Institute, Medical Research Center, Seoul National University College of Medicine, Seoul, South Korea 110-799

Correspondence and requests for collaboration should be addressed to ***sunghoe@snu.ac.kr***

Despite being highly abundant synaptic vesicle membrane protein and a candidate gene for autism, the physiological function of secretory carrier membrane protein 5 (SCAMP5) remains mostly unknown. Here, using optical imaging and electrophysiological experiments, we demonstrate that SCAMP5 plays a critical role in synaptic vesicle (SV) clearance from release sites during sustained neuronal activity. Truncation analysis revealed that the 2/3 loop domain of SCAMP5 flanked by two transmembrane domains is required for its interaction with adaptor protein 2 and clathrin heavy chain. Knockdown (KD) of SCAMP5 exhibited pronounced synaptic depression during high frequency stimulation and a slower recovery of the SV pool. These were attributed to strong frequency-dependent short-term depression of SV release caused by SCAMP5 KD-induced defects in release site clearance even under the condition of sufficient release-ready SVs. Super-resolution microscopy clearly proved the defects in SV clearance from the active zone by SCAMP5 KD. Thus, reduced expression of SCAMP5 impairs the efficiency of SV clearance from the active zone, leading to rapid short-term depression of synaptic release, which could represent a novel cellular mechanism of synaptic dysfunction observed in autism.

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Imaging the somatosensory system with 7T MRI: neurochemicals, maps, and perception

James Kolasinski

Cardiff University Brain Research Imaging Centre; FMRIB Centre, Oxford

Correspondence and requests for collaboration should be addressed to ***kolasinskij@cardiff.ac.uk***

To date, investigating the fine-grain detail cortical maps, such as the body map in primary somatosensory cortex (SI), has largely remained the domain of electrophysiologists working with animal models. However, with recent advances in the spatial resolution of fMRI, afforded by the advent of 7 tesla systems, it is now feasible to resolve the detailed functional architecture of SI at the level of individual human participants.

Here I present the results of a series of 7 tesla MRI studies focused on understanding the organisation and plastic potential of human SI, using the representations of the individual fingers as a model system. I will briefly outline the mapping paradigm applied before moving on to discuss two key experiments. The first experiment probes the possibility for short-term changes in the cortical maps of the fingers in response to changes in hand use. The second experiment asks whether the cortical neurochemical milieu might drive the observed inter-individual differences in the cortical maps of the individual fingers, and whether this variability is associated with individual differences in tactile perceptual acuity.

This range of studies showcases the exciting potential of ultra-high field 7 tesla MRI to address questions previously unfeasible using human neuroimaging.

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Building better fMRI-based biomarkers in translational neuroimaging

Choong-Wan Woo

Institute for Basic Science / Sungkyunkwan University

Correspondence and requests for collaboration should be addressed to ***choongwan.woo@gmail.com***

For the last two decades, functional Magnetic Resonance Imaging (fMRI) revolutionized how we study human cognition and emotion. However, as evidence accumulates, many of the human brain-function mappings that fMRI studies have produced appear to be flawed due to their poor sensitivity, specificity, and reproducibility. A new emerging paradigm, which we termed predictive modeling, has a potential to resolve these issues. This new approach is based on specific uses of machine learning techniques combined with experimental designs optimized for prediction, yielding well-defined neuroimaging signatures of brain-outcome relationships that can be prospectively tested in new individuals, studies, and translational applications. In this talk, I will introduce how we have been using the new predictive modeling approach to the study of pain and related emotions across multiple basic and clinical studies, and show how this new approach can integrate ideas from machine learning, 'big data,' reproducible research, and open science to bring translational goals within reach.

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Local transformations of entorhinal grid cells in polarized enclosures

Marius Bauza, Julija Krupic, Stephen Burton and John O'Keefe

University College London

Correspondence and requests for collaboration should be addressed to ***m.bauza@ucl.ac.uk***

Entorhinal grid cells are active in multiple locations arranged in a hexagonal lattice. They are thought to represent a universal metric for space based on their remarkable periodicity and invariance of spatial firing pattern. Recent experiments challenge this notion by demonstrating that grid cell symmetry is disrupted in polarized enclosures. Currently it is not clear whether grid distortions are correlated between different cells, which would potentially preclude their usage as a metric system, hence it is crucial to simultaneously record from a large number of grid cells.

Here we present large scale grid cell recordings collected using Neuropixels, a new generation silicon probe. This probe allows chronic recordings from an unprecedented number of cells from freely moving animals.

Up to 50 spatially periodic cells were recorded simultaneously in different polygonal enclosures for more than 10 weeks after the implantation. We found that local changes in the geometry of the environment induce local transformations in grid cell pattern by causing individual grid fields to change their locations. The co-localized grid field shifts were strongly correlated and were independent of the scale. Finally, we will propose a computational mechanism explaining local transformations in the grid based on the structure of the enclosure.

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Object-brain interface for learning-free steering of mice

Sae-Geun Park[1], Yong-Cheol Jeong[1], Dae-Gun Kim[2], Min-Hyung Lee[1], Anna Shin[1], Geunhong Park[1], Seohui Bae[1], Cheol-Hu Kim[2], Phill-Seung Lee[2] and Daesoo Kim[1]

[1]Department of Biological Sciences, KAIST, Daejeon 34141, Korea; [2]Department of Mechanical Engineering, KAIST, Daejeon 34141, Korea

Correspondence and requests for collaboration should be addressed to ***heartworm@kaist.ac.kr***

Animals continuously explore extant objects to find resources. Here, we report a technique for learning-free steering of behaviors by exploiting a neural circuit that motivates interaction with objects. Photostimulation of medial preoptic area (MPA) neurons induces a strong craving for an object located at the front of the visual field. Inspired by this finding, we devised an MPA-induced drive-assisted steering (MIDAS) technology, in which a head-mounted object and circuit photostimulation can be controlled wirelessly. MIDAS-equipped mice navigate along the programmed path to pursue the head-mounted object in novel and fearful situations, but consciously obtain information en route. Thus, the MIDAS system provides a tool for learning-free behavioral control and for studying the neural mechanisms of object exploration and related disorders.

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Molecular basis of Obsessive-Compulsive Disorder: Involvement of TrkB/Slitrk5 in corticostriatal dysfunction

Minseok Song

Department of Structure & Function of Neural Network, Korea Brain Research Institute, Daegu, Korea

Correspondence and requests for collaboration should be addressed to ***minseoksci@kbri.re.kr***

Obsessive Compulsive Disorder (OCD) displays a substantial heritable component but few specific molecular genetic risk factors have been identified. Knockout mice lacking Slitrk5 expression display an OCD-like phenotype involving pathologic grooming that is responsive to serotonin reuptake inhibitors and corticostriatal dysfunction. To examine whether Slitrk5 function contribute to the genetic risk for OCD, we re-sequenced the complete protein coding sequence of SLITRK5 in a population sample of human OCD subjects. Direct functional testing of identified OCD-specific rare non-synonymous mutations in Slitrk5 found that all mutations showed impaired synaptogenic activity as well as diminished binding to PTPδ, a trans-synaptic binding partner of Slitrks. These results demonstrate that rare mutations in SLITRK5 contribute to the genetic risk for OCD in human populations. We previously reported that Slitrk5 modulates BDNF-dependent biological responses through direct interaction with TrkB receptors. Under basal conditions, Slitrk5 interacts primarily with PTPδ; however, upon BDNF stimulation, Slitrk5 shifts to cis-interactions with TrkB. Interestingly, genetic facilitation of TrkB signaling rescued repetitive phenotype of Slitrk5 KO mice while deletion of BDNF expression in OCD circuit induced increase in grooming behavior. The networks of genes implicated in OCD remain obscure, however, these findings suggest that BDNF-dependent regulation of TrkB, Slitrk5, and PTPδ interactions at the synapse may mediate proper functioning of key corticostriatal circuits implicated in OCD.

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Forebrain-specific ablation of phospholipase Cγ1 causes manic-like behavior

Jung Hoon Jung[1,#], Yong Ryoul Yang[2,#], Su-Jeong Kim[1], Hyun Jin Kim[1], Joo Han Lee[1], Oh-Bin Kwon[1], Yeon Kyung Lee[3], Jeongyeon Kim[4], Eung-Kyun Kim[2], Hyun-Jun Jang[2], Du-Seock Kang[2], June-Seek Choi[3], C. Justin Lee[4], Hae-Young Koh4, Pann-Ghill Suh[2,*], Joung-Hun Kim[1,*]

[1] Department of Life Sciences, Pohang University of Science and Technology (POSTECH), Pohang, Gyungbuk, 37673, Republic of Korea
[2] School of Life Sciences, Ulsan National Institute of Science and Technology, Ulsan, 44919, Republic of Korea
[3] Department of Psychology, Korea University, Seoul, 02841, Republic of Korea
[4] Center for Functional Connectomics, and Center for Neural Science, Korea Institute of Science and Technology (KIST), Seoul, 02792, Republic of Korea

Correspondence and requests for collaboration should be addressed to ***jh.jung@postech.ac.kr***

Manic episodes are one of the major diagnostic symptoms in a spectrum of neuropsychiatric disorders that include schizophrenia, obsessive-compulsive disorder, and bipolar disorder (BD). Despite a possible association between BD and the gene encoding phospholipase Cγ1 (PLCG1), its etiological basis remains unclear. Here, we report that mice lacking PLCγ1 in the forebrain ($Plcg1^{f/f}$; CaMKII) exhibit hyperactivity, decreased anxiety-like behavior, reduced depressive-related behavior, hyperhedonia, hyperphagia, impaired learning and memory, and exaggerated startle responses. Inhibitory transmission in hippocampal pyramidal neurons and striatal dopamine receptor D1-expressing neurons of *Plcg1*-deficient mice was significantly reduced. The decrease in inhibitory transmission is likely due to a reduced number of γ- aminobutyric acid (GABA)-ergic boutons, which may result from impaired localization and/or stabilization of postsynaptic CaMKII at inhibitory synapses. Moreover, mutant mice display impaired BDNF-TrkB-dependent synaptic plasticity in the hippocampus, which could account for deficits of spatial memory. Lithium and valproate, the drugs presently used to treat mania associated with BD, rescued the hyperactive phenotypes of $Plcg1^{f/f}$; CaMKII mice. These findings provide evidence that PLCγ1 is critical for synaptic function and plasticity and that the loss of PLCγ1 from the forebrain results in manic-like behavior.

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New insights into how calcium affects physiological/ pathological function of α-synuclein

A. Stephens[1], G. Fusco[2], N. Curry[1], A. De Simone[2], G. Kaminski Schierle[1]

[1]Chemical Engineering and Biotechnology, University of Cambridge, Cambridge, UK
[2]Department of Life Sciences, Imperial College London, London, UK

Correspondence and requests for collaboration should be addressed to ***asds2@cam.ac.uk***

Alpha-Synuclein (aSyn) is a major component in familial and sporadic forms of Parkinson's disease (PD). It is a structurally disordered protein primarily localised in the pre-synapse, but its physiological and pathological function is still not clear. In PD the selective decline of dopaminergic neurons in the substantia nigra pars compacta may in part be due to their increased cytoplasmic calcium fluctuations due to their pacemaking activity.

We aim to investigate how calcium influences aSyn function/ dysfunction using NMR, super-resolution microscopy and biochemical techniques. We first show that calcium binds to the C-terminus of aSyn and displays a K_d of ~ 100 μM, revealed by NMR. Phase partitioning assays and lipid pull downs indicate aSyn becomes more hydrophobic upon calcium binding which can be reversed by the addition of EGTA. Using isolated synaptic vesicles (SV) from rat brains and NMR we reveal not only the N-terminus interacts with lipids, but also the C-terminus upon calcium binding. We also show that aSyn is more prone to aggregation in the presence of SV using super-resolution microscopy and the increased aggregation propensity of aSyn in the presence of calcium is determined using ThT assays.

To conclude, the physiologically relevant calcium binding concentrations indicate calcium is likely important in the function of aSyn. Calcium binds to the C-terminus of aSyn and enhances lipid interactions indicating that it may have a role in endo/exocytosis of SV. However, calcium binding also increases the rate of aggregation of aSyn, suggesting there is a fine balance between physiological and pathological function.

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Neuronal hypoactivity in NGL-1 KO mice disrupts normal expression of anxiety

Yeonsoo Choi, Haram Park, Hwajin Jung, Hanseul Kweon, Eunjoon Kim

Institute for Basic Science (IBS) / Korea Advanced Institute of Science and Technology (KAIST)

Correspondence and requests for collaboration should be addressed to ***yeonsoo.korea@gmail.com***

NGL-1 (Netrin-G ligand 1) is a postsynaptic adhesion molecule present only in the mammal brain and shows an expression pattern that, interestingly, is mostly complementary to its family member NGL-2. Although NGL-1 itself has not been implicated in psychiatric diseases, its known binding partners both extracellular (Netrin-G1) and intracellular (CKDL5) are heavily implicated so, suggesting that NGL-1, too, will have prominent roles in the synapse. To undertake this investigation, we produced NGL-1 KO mice and found that these mice showed strongly abnormal behavioral phenotypes, including hyperactivity, anxiolysis, and learning and memory impairments. When placed under electrophysiological analysis, we found that KO neurons showed altered neural transmission in the hippocampal CA1 pyramidal neurons. Interestingly, when stained for c-fos after exposure to anxiogenic environments, KO mice showed a brain-wide decrease in activity in response to stimulus, corroborating with the electrophysiological results. Certain brain regions, including the ACC and the BNST, showed stark differences between the WT and KO mice. These results highlight the importance of NGL-1 in the normal function of the brain and the role it plays in formation of circuitry required for anxiety.

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CYFIP2: A potential link between Aβ and tau pathologies in Alzheimer's disease

Anshua Ghosh

King's College London

Correspondence and requests for collaboration should be addressed to ***anshua.ghosh@kcl.ac.uk***

Alzheimer's disease (AD) is histopathologically characterised by Aβ plaques and tangles comprising hyperphosphorylated tau; however it is in fact synaptic degeneration that best correlates with the cognitive impairment, making its understanding critical in the development of clinical treatment. Early changes in the AD brain involve alterations in protein synthesis at synaptic sites that may be dependent on RNA-binding proteins such as FMRP and its interactors. Previous work from our group has found that the Cytoplasmic FMRP-Interacting Protein 2 (CYFIP2) is reduced by about 50% in the AD post mortem hippocampus when normalised for synaptic loss. CYFIP2 is a highly conserved protein that is abundant in synapses and developmentally expressed. While not much is known about its precise physiological role in the brain, it has been proposed to have functions in regulating local protein synthesis and modulating cytoskeletal dynamics. Using CYFIP2 heterozygous knockout mice to model the condition, we find that reducing CYFIP2 increases post-transcriptionally the expression of proteins having FMRP-regulated mRNAs, such as Amyloid Precursor Protein (APP) and αCaMKII in hippocampal synapses. $CYFIP2^{+/-}$ mice also have increased BACE1 protein in hippocampal synapses, and elevated $A\beta_{1\text{-}42}$ in total hippocampi. Additionally there is evidence for increased tau phosphorylation in hippocampal synapses of these mice. Taken together, reducing CYFIP2 in the mouse brain is sufficient to increase amyloid production and tau phosphorylation, recapitulating two key aspects of the disease. Therefore reduced CYFIP2 expression may be a key mediator of early changes in the AD brain and a potential link between Aβ and tau pathologies.

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Replenishment of microRNA-188-5p restores the synaptic and cognitive deficits in 5XFAD Mouse Model of Alzheimer's Disease

Hyunju Kim[1], Kihwan Lee[1], Kyongman An[2], Oh-Bin Kwon[2], Sungjun Park[2], Jin Hee Cha[3] Myoung-Hwan Kim[3], Yoontae Lee[2], Joung-Hun Kim[2], Kwangwook Cho[4, 5], Hye-Sun Kim[1, 6*]

[1]Department of Pharmacology, College of Medicine, Seoul National University, Seoul, 110-799, Republic of Korea
[2]Department of Life Science, POSTECH, Pohang, Gyeongbuk, 790-784, Republic of Korea
[3]Department of Physiology, College of Medicine, Seoul National University, Seoul, 110-799, Republic of Korea
[4]Henry Wellcome Laboratories for Integrative Neuroscience and Endocrinology (LINE), Faculty of Medicine and Dentistry, University of Bristol, Whitson Street, Bristol BS1 3NY, UK
[5]Centre for Synaptic Plasticity, School of Clinical Sciences, Faculty of Medicine and Dentistry, University of Bristol, Whitson Street, Bristol BS1 3NY, UK
[6]Seoul National University Bundang Hospital, College of Medicine, Seoul National University, Seongnam, Gyeonggi, 463-707, Republic of Korea

Correspondence and requests for collaboration should be addressed to ***hj-k89@hanmail.net***

MicroRNAs have emerged as key factors in development, neurogenesis and synaptic functions in the central nervous system. In the present study, we investigated a pathophysiological significance of microRNA-188-5p (miR-188-5p) in Alzheimer's disease (AD). We found that oligomeric Aβ1-42 treatment diminished miR-188-5p expression in primary hippocampal neuron cultures and that miR-188-5p rescued the Aβ1-42-mediated synapse elimination and synaptic dysfunctions. Moreover, the impairments in cognitive function and synaptic transmission observed in 7-month-old five familial AD (5XFAD) transgenic mice, were ameliorated via viral-mediated expression of miR-188-5p. miR-188-5p expression was down-regulated in the brain tissues from AD patients and 5XFAD mice. The addition of miR-188-5p rescued the reduction in dendritic spine density in the primary hippocampal neurons treated with oligomeric Aβ1-42 and cultured from 5XFAD mice. The reduction in the frequency of mEPSCs was also restored by addition of miR-188-5p. The impairments in basal fEPSPs and cognition observed in 7-month-old 5XFAD mice were ameliorated via the viral-mediated expression of miR-188-5p in the hippocampus. Furthermore, we found that miR-188 expression is CREB-dependent. Taken together, our results suggest that dysregulation of miR-188-5p expression contributes to the pathogenesis of AD by inducing synaptic dysfunction and cognitive deficits associated with Aβ-mediated pathophysiology in the disease.

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C9orf72 poly GA RAN-translated protein plays a key role in Amyotrophic Lateral Sclerosis via aggregation and toxicity

Youn-Bok Lee[1*], Pranetha Baskaran[2*], Jorge Gomez[1], Han-Jou Chen[1], Agnes Nishimura[1], Bradley Smith[1], Claire Troakes[1], Yoshitsugu Adachi[1], Alan Stepto[1], Leonard Petrucelli[4], Jean-Marc Gallo[1], Frank Hirth[1], Boris Rogelj[3], Sarah Guthrie[2], Christopher E Shaw[1]

[1]Maurice Wohl Clinical Neuroscience Institute, King's College London, London SE5 9RX [2]Department of Developmental Neurobiology, King's College London, Guy's Campus, London SE1 1UL, UK. Department of Biotechnology, Jožef Stefan Institute, Jamova 39, SI-1000 Ljubljana, Slovenia[3]. Department of Neuroscience, Mayo Clinic Florida, Jacksonville, FL 32224, USA[4]

Correspondence and requests for collaboration should be addressed to ***younbok.lee@kcl.ac.uk***

An intronic GGGGCC (G4C2) hexanucleotide repeat expansion inC9orf72 is the most common genetic cause of Amyotrophic Lateral Sclerosis and Frontotemporal Dementia (C9ALS/FTD). Repeat associated non AUG (RAN) translation of G4C2 RNA can result in five different dipeptide repeat proteins (DPR: poly GA, poly GP, poly GR, poly PA, and poly PR), which aggregate into neuronal cytoplasmic and nuclear inclusions in affected patients, however their contribution to disease pathogenesis remains controversial. We show that among the DPR proteins, expression of poly GA in a cell culture model activates programmed cell death and TDP-43 cleavage in a dose-dependent manner. Dual expression of poly GA together with other DPRs revealed that poly GP and poly PA are sequestered by poly GA, whereas poly GR and poly PR rarely co-localised with poly GA. Dual expression of poly GA and poly PA ameliorated poly GA toxicity by inhibiting poly GA aggregation both in vitro and in vivo in chick embryonic spinal cord. Expression of alternative codon-derived DPRs in chick embryonic spinal cord confirmed in vitro data, revealing that each of the dipeptides caused toxicity, with poly GA being the most toxic. Further, in vivo expression of G4C2 repeats of varying length caused apoptotic cell death, but failed to generate DPRs. Together these data demonstrate that C9-related toxicity can be mediated by either RNA or DPRs. Moreover, our findings provide evidence that poly GA is a key mediator of cytotoxicity and that cross-talk between DPR proteins likely modifies their pathogenic status in C9ALS/FTD.

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Inhibition of Drp1 Ameliorates Synaptic Depression, Aβ Deposition, and Cognitive Impairment in an Alzheimer's Disease Model

Seung Hyun Baek[1], Jae In Jeong[1], So Jung Park[2], Sung Hyun Kim[3], Dong-Hyung Cho[2] and Dong-Gyu Jo[1,4]

[1]School of Pharmacy, Sungkyunkwan University, Korea; [2]Graduate School of East-West Medical Science, Kyung Hee University, Korea, [3]Department of Physiology, School of Medicine, Kyung Hee University, Korea, [4]Department of Health Sciences and Technology, SAIHST, Sungkyunkwan University, Korea

Correspondence and requests for collaboration should be addressed to ***backtion@gmail.com***

Excessive mitochondrial fission is a prominent early event and contributes to mitochondrial dysfunction, synaptic failure, and neuronal cell death in the progression of Alzheimer's disease (AD). However, it remains to be determined whether inhibition of excessive mitochondrial fission is beneficial in mammal models of AD. To determine whether dynamin-related protein 1 (Drp1), a key regulator of mitochondrial fragmentation, can be a disease-modifying therapeutic target for AD, we examined the effects of Drp1 inhibitor on mitochondrial and synaptic dysfunctions induced by oligomeric amyloid-β(Aβ) in neurons and neuropathology and cognitive functions in Aβ precursor protein/presenilin 1 double-transgenic AD mice. Inhibition of Drp1 alleviates mitochondrial fragmentation, loss of mitochondrial membrane potential, reactive oxygen species production, ATP reduction, and synaptic depression in Aβ-treated neurons. Furthermore, Drp1 inhibition significantly improves learning and memory and prevents mitochondrial fragmentation, lipid peroxidation, BACE1 expression, and Aβ deposition in the brain in the AD model. These results provide evidence that Drp1 plays an important role in Aβ-mediated and AD-related neuropathology and in cognitive decline in an AD animal model. Therefore, inhibiting excessive Drp1-mediated mitochondrial fission may be an efficient therapeutic avenue for AD.

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Investigations of Non-Classical Axis of Renin Angiotensin System in Alzheimer's Disease

Noura Al Mulhim, Dr. Scott Miners, Patrick Kehoe

Dementia Research Group,
School of Clinical Sciences,
University of Bristol
Learning and Research Building,
Southmead Hospital

Correspondence and requests for collaboration should be addressed to ***na15725@bristol.ac.uk***

The classical axis of RAS (ACE-1/Ang II/AT1R) has been highlighted as exerting damage effects on the brain in both animal and human studies. Hyperactivity of this axis contributed to the pathogenesis of Alzheimer's disease (AD). However, the involvement of the non-classical axis of RAS (ACE-2/Ang (1-7)/ MasR) in the etiology and progression of AD remain to be clarified. Therefore, investigating components of the non-classical axis of RAS is important for understanding the role of this system in the pathogenesis of AD.

Human Post-Mortem brain tissue used in this study was obtained from the South West Dementia Brain Bank, University of Bristol, with local Research Ethics Committee approval. The AD cases (n= 97) and the age-matched controls (n= 49) were selected. In this cohort, we measured Ang (1-7) levels in the mid-frontal cortex (Brodmann area 9) using in-house direct ELISA. A commercially available ELISA kit was used to measure MAS1 levels. Data on Ang II and ACE-2 activity had been previously obtained for all cases.

In this study, Ang (1-7) levels were unchanged in AD group compared to age-matched controls. However, Ang II/Ang (1-7) ratio (as a proxy indicator of ACE-2 activity) was significantly increased in AD group ($P < 0.001$), indicating a reduction of ACE-2 activity in AD. For the first time, we showed that the MAS1 levels were significantly reduced in AD ($P = 0.01$). This reduction in MAS1 levels was correlated with reduction in ACE-2 activity ($r = 0.27$, $P = 0.01$).

Together, our findings suggested that dysregulation of ACE-2/ Ang(1-7)/MasR) axis might be implicated in the pathogenesis of AD. Thus, maintaining the activity of the non-classical axis of RAS may be essential for targeting therapeutic strategies of AD.

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Assessment of High-fat diet-induced Alzheimer's disease in outbred ICR mice using touchscreen-based automated battery system

Saeram Lee[1,2], Eosu Kim[2,4], Ho Taek Song[3], ChulHoon Kim[2,5], Jong Eun Lee[1,2,*]

[1]Department of Anatomy, [2]BK21 PLUS Project for Medical Science, and Brain Research Institute, [3]Department of Radiology, [4]Department of Psychiatry, [5]Department of Pharmacology, Yonsei University, College of Medicine, Seoul, Korea

Correspondence and requests for collaboration should be addressed to ***saeramlee@yuhs.ac***

Studies show that beta amyloid aggregation at any stage is insufficient to develop a sporadic Alzheimer's disease (AD) which accounts for more than 85% of all type of AD. Moreover, recent studies show that sporadic AD arises from dysregulation of brain glucose metabolism that the amyloid hypothesis does not explain and that it occurs before amyloid plaques accumulates in the brain. In our previous results, mice were fed on 60% high-fat diet (HFD) and subjected to dynamic nuclear polarization-enhanced hyperpolarized 13C magnetic resonance spectroscopic imaging (DNP-MRSI). Abnormal pyruvate-lactate conversion was observed in the medial temporal lobe. Accumulation of beta amyloid was found in CA1 and DG. These results demonstrate that HFD-induced metabolic stress plays pivotal role of AD-like pathogenesis.

Although many pathological states are now detectable through imaging and biochemical analyses, neuropsychological tests are still widely used to confirm the diagnosis, especially for AD and schizophrenia. The touchscreen-based automated battery system, which is more accurate and less invasive than conventional methods, is used to assess cognition of the mouse with dysregulated metabolism. This system was introduced in humans to evaluate cognitive function and recently back-translated in monkeys and rodents. We used outbred ICR mice fed on HFD and conducted the paired associates learning (PAL) test for early assessment and detection of metabolic Alzheimer's disease. Also, the Fixed Ratio (FR) test was conducted before PAL to examine mice's motivation towards the task. We found how dysregulation of metabolism by consuming excessive fats affects the mice's motivation, learning ability and memory function.

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Dendritic spines require normal DISC1 function during development of their parent dendritic branch for plasticity in adulthood

A.M. de Haan[1], N.R. Hardingham[1], K. Fox[1]

[1]Cardiff University, Cardiff, United Kingdom

Correspondence and requests for collaboration should be addressed to ***DeHaanAM@cardiff.ac.uk***

Disrupted-In-Schizophrenia-1 (DISC1) plays an important role in brain development and is implicated in mental disorders such as schizophrenia and autism. We investigated effects of disrupting DISC1 conditionally using a transgenic mouse with a dominant negative fragment of the DISC1 c-terminal (DISC1cc). The mutant protein can be activated via tamoxifen injection and is only active for 6-48 hours.

Disruption of DISC signalling at postnatal day 7 (P7) results in a schizotypic phenotype (Li et al., 2007) and a loss of LTP and experience-dependent plasticity in L2/3 of adult barrel cortex (Greenhill et al., 2015). In contrast, disruption at P28 has no effect on experience-dependent plasticity, suggesting a critical period for plasticity itself (Greenhill et al., 2015). Disruption at P7 specifically affected 2nd/3rd order basal dendrites, which showed lower spine density and had fewer mushroom spines compared to 4th/5th order dendrites on the same cells and compared to 2nd/3rd order dendrites in wild-type mice.

To test whether these effects are due to a particular vulnerability of 2nd/3rd order dendrites, or because they were developing at the time of the DISC1 inhibition at P7, we delayed the tamoxifen injection (and thus the disruption of DISC1) until P9 or P11-13.

Delayed disruption affected the 4th/5th order dendrites, which develop later, thus suggesting that DISC1 disruption only affects spine density and morphology during the development of the parent dendrite. Preliminary analysis of spine dynamics in vivo appears to show that this might be related to an abnormal stability of long thin spines with small heads.

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Apolipoprotein E polymorphism and human hippocampal neurogenesis – the generation of dentate gyrus neuronal cells from human induced pluripotent stem cells and APOE expression in neuronal differentiation

Hyunah Lee[1], Graham Cocks[2], Lucia Dutan Polit[2], Jack Price[2], Sandrine Thuret[1]

[1]Laboratory of Adult Neurogenesis and Mental Health, Department of Basic and Clinical Neuroscience, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK
[2]Department of Basic and Clinical Neuroscience, Cell and Behaviour Unit, The James Black Centre, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK

Correspondence and requests for collaboration should be addressed to ***hyunah.lee@kcl.ac.uk***

Background: Adult hippocampal neurogenesis has been implicated in Alzheimer's disease (AD) progression as a potential target of early intervention and prevention. Growing body of evidence suggests that apolipoprotein E (APOE), the ε4 allele of which is a major genetic risk factor of late-onset AD, might play an important role in hippocampal neurogenesis. However, the impact of APOE4 on this process remains unclear.

Methods: Human induced pluripotent stem cells (iPSCs) were differentiated into dentate gyrus granule cells (DGCs), and the expression of APOE and a set of NPC and DG neuronal markers were examined by immunohistochemistry and gene expression analysis.

Results: We optimized a method of generating DGCs that expressed the DGC marker PROX1 from APOE3/3 human iPSCs. The time-course gene expression pattern of APOE was found to decrease markedly as the cells became more differentiated. Based on these preliminary findings, we now aim to quantify and compare the expression of neurogenic markers in iPSCs with different APOE isoforms and generate a phenotypic profile of these cells while they undergo hippocampal neurogenesis. Furthermore, the gene-environment interaction between APOE genotype and nutrient-derived metabolites that are physiologically relevant to AD and hippocampal neurogenesis will be investigated in subsequent experiments.

Conclusions: We have generated PROX1-positive DG neuronal cells from human iPSCs using an optimized differentiation method and observed a decrease in the level of gene expression of APOE during neuronal differentiation.

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Sexually dimorphic behavior, neuronal activity, and gene expression in Chd8-mutant mice

Hwajin Jung, * Haram Park,* Yeonsoo Choi, Hyojin Kang, Eunee Lee, Hanseul Kweon, Junyeop Daniel Roh, Jacob Ellegood, Woochul Choi, Jaeseung Kang, Issac Rhim, Su-Yeon Choi, Mihyun Bae, Sun-Gyun Kim, Jiseok Lee, Changuk Chung, Taesun Yoo, Hanwool Park, Yangsik Kim, Seungmin Ha, Seung Min Um, Jiwon Mo, Yonghan Kwon, Yong Chul Bae, Hyun Kim, Jason P. Lerch, Se-Bum Paik, and Eunjoon Kim

Institute for Basic Science (IBS) / Korea Advanced Institute of Science and Technology (KAIST)

Correspondence and requests for collaboration should be addressed to ***haram9071@kaist.ac.kr***

Mutations in CHD8, belonging to a family of chromatin-remodeling proteins, have consistently been associated with autism spectrum disorders, to the extent that CHD8 disruptions are being categorized as a distinct subtype by itself. Naturally, intense interest abounds, but the connection between the gene and the disease remains poorly understood. Here we report the study of the Chd8$^{+/N2373K}$ mice, carrying a heterozygous frame-shift mutation (Asn2373LysfsX2) in the Chd8 gene identified in two autistic male patients. Interestingly, although the mice showed subtly aberrant behavior, they were almost wholly specific to males, reminiscent of the high male-to-female ratio of autistic patients. In addition, male and female Chd8$^{+/N2373K}$ mice display strikingly opposite changes in transcriptomic profiles, synaptic transmission, and neuronal firing. Our results suggest that a human CHD8 mutation leads to male-biases behavioral abnormalities in mice that are associated with sexually divergent changes in gene expression, synaptic transmission, and neuronal firing, indicating a sexual dimorphism under CHD8 control.

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Wnt signalling mediates LTP-dependent spine plasticity and AMPAR localisation through Frizzled-7 receptors

McLeod F[1], Bossio A[1], Marzo A[1], Ciani L[1], Sibilla S[1], Hannan S[2], Wilson GA[1], Ernest Palomer[1], Smart TG[2], Gibb A[2] and Salinas PC[1]

Departments of [1]Cell and Developmental Biology and [2]Neuroscience, Physiology and Pharmacology, University College London, London, WC1E 6BT, UK.

Correspondence and requests for collaboration should be addressed to ***f.mcleod@ucl.ac.uk***

The structural and functional plasticity of synapses are critical for learning and memory. Induction of long-term potentiation (LTP) promotes spine growth and AMPAR accumulation at excitatory synapses, leading to increased synaptic strength. Glutamate initiates these processes, but the contribution from extracellular modulators is not fully established. Wnt proteins are required for spine formation, however their impact on activity-mediated spine plasticity and AMPAR localization is unknown. Here we show that LTP induction rapidly increases synaptic Wnt7a/b protein levels. Blockade of endogenous Wnts or genetic loss of Frizzled-7 (Fz7) receptor impairs LTP-mediated synaptic strength, spine growth and AMPAR localization at synapses. Live imaging of surface SEP-GluA1 and single particle tracking reveal that Wnt7a rapidly promotes synaptic AMPAR recruitment and trapping. Notably, Wnt7a induces CaMKII-dependent loss of Ras-GTPase SynGAP from spines. Our studies identify Wnts, through Fz7, as key signalling molecules in LTP-mediated synaptic accumulation of AMPARs and spine plasticity.

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Early dysregulation of microRNAs in the posterior cingulate gyrus of Alzheimer's disease and vascular dementia

Jose Gerardo-Aviles, Shelley Allen, Patrick Gavin Kehoe

Dementia Research Group, Institute of Clinical Neurosciences, School of Clinical Sciences, University of Bristol, Southmead Hospital, Bristol, UK

Correspondence and requests for collaboration should be addressed to ***jose.gerardo-aviles@bristol.ac.uk***

Over one hundred microRNAs have been found to be dysregulated in Alzheimer's disease although inconsistencies exist between studies due to variably sized cohorts, hybridization techniques lacking specificity and inadequate microRNA calibrators. We aimed to evaluate the expression of a 7 microRNA signature in post-mortem brain tissue of Alzheimer's disease and vascular dementia patients.

MicroRNA selection was based on transcripts involved in amyloid production, transport and degradation, tau phosphorylation, blood brain barrier integrity and immune response. Only high confidence microRNAs were considered and further selection criteria was determined by the number of reads reported in MiRbase and number of predicted transcripts by TargetScan. miRvana isolation kit and Quant-iT RiboGreen assay were used for RNA isolation and quantification. qRT-PCR was performed using TaqMan microRNA assays.

Using RNU6b as calibrator, a consistent expression pattern with Alzheimer Braak stage was found for 5 microRNAs with increases in Braak II and VI, but no difference in vascular dementia (miR-16, miR- 29a, miR-34a, miR-125b with $p<0.001$ and miR-29b $p=0.002$). A significant decrease and alternate pattern was found for miR-132 ($p=0.02$) and miR-212 ($p=0.01$) in both Alzheimer's and vascular dementia.

Pathway analysis of transcripts targeted by the 5 microRNAs (DAVID software) found high enrichment scores in zinc metabolism, neurotrophin signalling, serine/threonine kinases and phosphatases. All target the retinoic acid receptor-related orphan receptor-alpha, which regulates expression of apolipoproteins, activates the transcriptional activity of HIF1A, interacts with PPARgamma and is reduced by angiotensin II. Additionally, our data suggest that miR-16 is not an appropriate calibrator.

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nArgBP2 regulates excitatory synapse formation by controlling dendritic spine morphology

Sang-Eun Lee[a,b], Yoonju Kim[a,b,c], Jeong-Kyu Han[a,d], Hoyong Parke, Unghwi Lee[a,b], Myeongsu Na[a,b], Soomin Jeong[a,b], ChiHye Chunge, Gianluca Cestra[f,g,1], and Sunghoe Chang[a,b,d,1]

[a]Department of Physiology and Biomedical Sciences, Seoul National University College of Medicine, Seoul 01030, South Korea; [b]Biomembrane Plasticity Research Center, Seoul National University College of Medicine, Seoul 01030, South Korea; [c]KM Convergence Research Division, Korea Institute of Oriental Medicine, Daejeon 34054, South Korea; [d]Interdisciplinary Program in Neuroscience, Seoul National University College of Medicine, Seoul 01030, South Korea; [e]Department of Biological Sciences, Konkuk University, Seoul 05029, South Korea; [f]Istituto di Biologia ePatologia Molecolari, Consiglio Nazionale delle Ricerche, 00185 Rome, Italy; and [g]Department of Biology and Biotechnology, University of Rome "Sapienza", 00185 Rome, Italy

Correspondence and requests for collaboration should be addressed to ***sangeun45@snu.ac.kr***

Neural Abelson-related gene-binding protein 2 (nArgBP2) was originally identified as a protein that directly interacts with synapseassociated protein 90/postsynaptic density protein 95-associated protein 3 (SAPAP3), a postsynaptic scaffolding protein critical for the assembly of glutamatergic synapses. Although genetic deletion of nArgBP2 in mice leads to manic/bipolar-like behaviors resembling many aspects of symptoms in patients with bipolar disorder, the actual function of nArgBP2 at the synapse is completely unknown.

Here, we found that the knockdown (KD) of nArgBP2 by specific small hairpin RNAs (shRNAs) resulted in a dramatic change in dendritic spine morphology. Reintroducing shRNA-resistant nArgBP2 reversed these defects. In particular, nArgBP2 KD impaired spinesynapse formation such that excitatory synapses terminated mostly at dendritic shafts instead of spine heads in spiny neurons, although inhibitory synapse formation was not affected. nArgBP2 KD further caused a marked increase of actin cytoskeleton dynamics in spines, which was associated with increased Wiskott–Aldrich syndrome protein-family verprolin homologous protein 1 (WAVE1)/p21-activated kinase (PAK) phosphorylation and reduced activity of cofilin. These effects of nArgBP2 KD in spines were rescued by inhibiting PAK or activating cofilin combined with sequestration of WAVE.

Together, our results suggest that nArgBP2 functions to regulate spine morphogenesis and subsequent spine-synapse formation at glutamatergic synapses. They also raise the possibility that the aberrant regulation of synaptic actin filaments caused by reduced nArgBP2 expression may contribute to the manifestation of the synaptic dysfunction observed in manic/bipolar disorder.

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Emerging protein dynamics in Alzheimer's disease

Celia Martinez Perez[1,2], Garry Whitehead[1,2], Daniel Whitcomb[1,2], Kwangwook Cho[1,2]

[1]Henry Wellcome Laboratories for Integrative Neuroscience and Endocrinology (LINE), School of Clinical Sciences, Faculty of Health Sciences [2]Centre for Synaptic Plasticity, University of Bristol, Whitson Street, Bristol, BS1 3NY, United Kingdom

Correspondence and requests for collaboration should be addressed to ***cm15978@bristol.ac.uk***

Despite Alzheimer's disease (AD) being the most common form of dementia, our understanding of the molecular mechanisms that underlie the severe cognitive impairments of AD patients remains very incomplete. A general consensus is that AD pathology impairs synaptic plasticity; i.e. the intrinsic ability of synapses to modulate the strength of their connections in responses to changes in their activity. This is widely considered to be the underpinning physiological mechanism of learning and memory. Accordingly, the disruption of synaptic plasticity has been proposed as the basis for the cognitive decline associated with AD. Amyloid beta (Aβ) has been shown to be a key molecule in driving the impairment of synaptic function but the signalling processes that mediate Aβ-induced neurotoxic effects are not fully characterised. Compelling evidence is now positioning metabotropic glutamate receptor 5 (mGluR5), a G-protein coupled receptor (GPCR), as an emerging mediator of such effects. Our aim is to understand whether aberrant regulation of mGluR5 contributes to synapse weakening and progression of pathology in AD. As a first step, we examined the levels of mGluR5 and related molecules in post-mortem brain samples from AD patients and age-matched control subjects. This study showed a decrease in mGluR5 levels, together with an overall decrease in postsynaptic but not presynaptic proteins in late AD pathology. We are currently working on pre-symptomatic Braak stage II-III brain tissue. This study will provide further insight into the pre and postsynaptic protein dynamics in different stages of AD pathology.

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Shared novel variant analysis identified novel genes in familial amyotrophic lateral sclerosis from whole exome sequencing

CH Wong[1], SD Topp[1], YB Lee[1], BN Smith[1], S Mueller[1], G Cocks[1], N Ticozzi[2], J Landers[3], The FALS Exome Sequencing Consortium, CE Shaw[1]

[1] Maurice Wohl Clinical Neuroscience Institute, Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK
[2] Department of Neurology, IRCCS Instituto Auxologico Italiano, Milan, Italy
[3] Department of Neurology, University of Massachusetts Medical School, Worcester, USA

Correspondence and requests for collaboration should be addressed to ***chun_hao.wong@kcl.ac.uk***

Whole exome sequencing (WES) has proven to be a powerful technology for identification of novel genes and mutations in Mendelian disorders such as amyotrophic lateral sclerosis (ALS). We have performed WES in a total cohort size of 1008 ALS patients, including 750 index cases for which the pathogenic mutation has yet to be identified, and 68 affected relatives of these. Due to the late onset nature of neurodegenerative disease and lack of large kindreds from which to perform linkage analysis, we have chosen to perform shared variant analysis to only consider unique exonic and splice site changes that are high quality, found in three or more familial ALS probands, and that are novel, defined as being absent from ExAC, EVS, UK10K, 1000 genomes and 670 local control exomes (n=> 70,000). As a proof of principle, our analysis has identified 7 known disease-causing mutations in common ALS genes including *SOD1*, *FUS* and *TARDBP*. Additionally, we have identified 2 novel candidate genes that are not previously known to be causative of ALS. By combining the power of genetics and follow-up functional assessment, we are currently characterising these novel candidate genes, and novel mutations within those genes both, which are associated with both familial and sporadic ALS.

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Amyloid-β-mediated pathophysiology in the perirhinal cortex: Aberrant interplay between metabotropic glutamate receptor 5 (mGluR5) and muscarinic acetylcholinereceptor (mAChR) function

Jee Hyun Yi [1,2], Daniel J. Whitcomb [1,2] and Kwangwook Cho [1,2]

[1]Henry Wellcome Laboratories for Integrative Neuroscience and Endocrinology, School of Clinical Sciences, Faculty of Health Sciences, [2]Centre for Synaptic Plasticity, University of Bristol, Whitson Street, Bristol, BS1 3NY, United Kingdom

Correspondence and requests for collaboration should be addressed to ***JeeHyun.Yi@bristol.ac.uk***

The pathophysiology of Alzheimer's disease (AD), the predominant form of dementia, involves progressive neurodegeneration in the brain and cognitive impairment. In particular, the perirhinal cortex, a structure in the medial temporal cortex of the brain, is susceptible to AD-mediated pathogenesis and this leads to object recognition memory deficits (Romberg et al., 2012). We previously reported that A dysregulates physiological LTD (mAChR-dependent LTD) in the perirhinal cortex, leading to the aberrant encoding of object information (Romberg et al., 2012). However, it is not known how AD-mediated pathophysiology affects the cellular processes of recognition memory.

Since mGluR5 interferes with mAChR function in the perirhinal cortex (Jo et al., 2006), it is of interest whether amyloid- (A)-mediated pathophysiology is associated with aberrant activation of mGluR5 function. We found that A induces the mGluR5-mediated interference of mAChR function. In addition, this was associated with the inhibition of mAChR-dependent long-term depression (LTD), which has been implicated in an underlying cellular mechanism of object recognition. Our data also suggest that the inhibition of mGluR5 restores mAChR function and mAChR-mediated LTD expression. Finally, an infusion of an mGluR5 negative allosteric modulator in vivo restores novel object recognition in a 5xFAD transgenic AD mouse model, and also restores mAChR-LTD ex vivo. These data suggest that mGluR5 might have important implications for mAChR function in Aβ-mediated pathophysiology and therapeutic intervention in AD.

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Classifying interneurons of the dorsal CA1 hippocampus from extracellular recordings

Gido M. van de Ven, Vítor Lopes-dos-Santos, David Dupret

MRC Brain Network Dynamics Unit, Department of Pharmacology, University of Oxford, OX1 3TH Oxford, UK

Correspondence and requests for collaboration should be addressed to ***gidovandeven@gmail.com***

A variety of interneuron types has been identified in the rodent hippocampus based on differences in their post-synaptic targets, their expression of molecular markers and their spike timing relative to rhythmic fluctuations of the local field potential. Such interneuron types are thought to have distinct contributions to the temporal organization of principal cell firing. However, current progress in testing the role of each interneuron type has been hindered by the difficulty to assign interneurons to anatomically well-defined types when solely recorded with extracellular recordings (i.e., without further labelling) in behaving rodents.

Here we present results from a data set of 679 putative interneurons recorded using multichannel extracellular techniques from the dorsal CA1 region of the hippocampus of 38 mice. We employ an unsupervised clustering framework to attempt sorting interneurons into distinct types based on their (1) spike train dynamics, (2) spike waveform, (3) spatial tuning of their spike discharge, (4) spike coupling to well-known hippocampal oscillations, (5) coupling to the summed population activity of principal cells and (6) firing response to sharp wave-ripple oscillatory events.

Although we do not find clear support for the possibility to identify discrete types of interneurons solely based on their extracellular recordings, we do find structure in this dataset indicative of clusters of interneurons with overlapping firing properties. We suggest that our framework for an unsupervised interneuron clustering, although not absolute, nevertheless provides a useful way of classifying hippocampal interneurons that could contribute to further our understanding of their diverse roles in network dynamics and behaviour.

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Cyclin Y, a novel actin binding protein, directly regulates actin cytoskeleton dynamics and modulates activity-dependent spine plasticity

A-Ram Lee[1], Young-Na Hur[1], Eunsil Cho[1,2], Seongeun Song[1], Jung-Hwa Hong[1], Saebom Lee[1], and Mikyoung Park[1,2]

[1]Center for Functional Connectomics, Korea Institute of Science and Technology, Seoul 02792, South Korea.
[2]Department of Neuroscience, Korea University of Science and Technology, Daejeon 34113, South Korea.

Correspondence and requests for collaboration should be addressed to ***091210@kist.re.kr***

In mammalian brain system, excitatory synapses are the major sites of information processing and storage. Dendritic spine morphology and size are heavily dependent on the dynamics of actin cytoskeleton. The actin cytoskeleton directly determines the morphological plasticity of small actin-rich protrusions, dendritic spines. Cyclin Y (CCNY), a member of the cyclin protein family that is known to regulate cell proliferation, was reported to regulate functional synaptic plasticity in neuronal cells (Cho et al., 2015). Here, we report that CCNY is a novel actin binding protein and differentially regulates activity-dependent spine plasticity by modulating the actin cytoskeleton dynamics. Using various techniques including immunocytochemistry, in vitro actin binding assay, proximity ligation assay and bimolecular fluorescence complementation assay, we found that CCNY is an actin binding protein and regulates actin dynamics by enhancing actin polymerization and inhibiting actin depolymerization at steady state. More importantly, unlike the steady state, CCNY inhibits both spine enlargement and actin polymerization during LTP-inducing stimulation, suggesting differential roles of CCNY towards the actin cytoskeleton in an activity-dependent manner. Taken together, our findings demonstrate that CCNY inhibits LTP-induced structural changes by controlling the actin cytoskeleton dynamics and further propose CCNY as a molecular linker between functional and structural plasticity of hippocampal synapses.

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Characterization of *in vivo* functions of SALM4

Eunkyung Lie,[1], and Eunjoon Kim[1,2]

[1]Center for Synaptic Brain Dysfunctions, Institute for Basic Science (IBS), Daejeon 305-701, Korea; [2]Department of Biological Sciences, Korea Advanced Institute for Science and Technology (KAIST), Daejeon 305-701, Korea

Correspondence and requests for collaboration should be addressed to ***justforhillary@gmail.com***

Synaptic proteins regulate a variety of steps of neuronal development, including neurite outgrowth and branching, synapse formation, as well as synaptic maturation. Neuronal synapses are composed of diverse synaptic proteins in complex interactions. It is becoming increasingly clear that, defects in synaptic protein complexes lead to abnormalities in synapses, neural circuits, and brain functions, a condition termed "Synaptopathy". Synaptopathies have recently been associated with diverse neuropsychiatric and neurological disorders including autism, ADHD, and mental retardation.

SALM4 (Synaptic Adhesion-Like Molecules; also known as Lrfn3 or leucine-rich and fibronectin III domain-containing 3) is a member of the SALM family of adhesion molecules known to regulate neurite outgrowth and branching and synapse formation and maturation. SALM4 does not possess synaptogenic activity, but SALM4 overexpression in cultured neurons increases the number of primary processes extending from the cell body. Importantly, however, whether and how SALM4 regulates aspects of neuronal development and circuit/brain functions in vivo remain to be addressed. In this study, we have generated and characterized SALM4 knock-out (KO) mice to explore in vivo functions of SALM4.

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Promoting Neuroplasticity and Neurological Recovery with Chondroitinase ABC: Systematic Review and Meta-analyses

Chan Hee Koh[1], Savva Pronin[1], Mark Hughes[2]

[1] College of Medicine and Veterinary Medicine, Division of Health Sciences, University of Edinburgh
[2] Translational Neurosurgery Unit, Centre for Clinical Brain Sciences, University of Edinburgh

Correspondence and requests for collaboration should be addressed to ***s1205416@sms.ed.ac.uk***

Damage to eloquent brain causes deficits in important neurological functions. Although neuroplasticity can ameliorate such deficits caused by disease or trauma, its extent is limited by a non-permissive microenvironment. Chondroitinase ABC (ChABC) digests perineuronal nets, leading to a more conducive microenvironment for neuroplasticity. This systematic review identifies and evaluates the effects of ChABC in animal models of acute brain injuries.

Four databases were searched for studies relating to ChABC and brain or brain injuries. Controlled studies in mammals with acute brain injuries treated with ChABC were included. Neurobehavioural outcomes were extracted and synthesised with meta-analyses. The effects of ChABC on macroanatomy, microanatomy, synapses, astroglia and myelination were analysed with descriptive synthesis.

Of 775 identified records, 16 studies administered ChABC after acute brain injury. 9 studies reported neurobehavioural outcomes. The estimated treatment effect on neurological recovery over the duration of included studies was 49.4% (CI: 30.3-68.4% with Hartung-Knapp-Sidik-Jonkman adjustment, p=0.0002). Sensitivity analyses showed the effects to be robust to assumptions. There was no significant publication bias (p=0.61), although it could not be excluded due to the small number of included studies. The evidence suggests that mechanisms of action may involve decreasing astroglial scar formation, promoting neuronal sprouting, and selective synaptic strengthening of sprouting neurites and activated neural pathways.

The summary of published evidence suggests that promoting neuroplasticity through ChABC is effective in enhancing neurological recovery after acute brain injury. More studies will be needed to exclude publication.

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Detecting neuronal assemblies using patterns of cross-correlations

Alexander Morley[1], Colin McNamara[1], David Dupret[1]

[1]MRC Brain Network Dynamics Unit, University of Oxford, Mansfield Road, Oxford OX1 3TH, UK

Correspondence and requests for collaboration should be addressed to ***alexander.morley@univ.ox.ac.uk***

The coordinated activity of subsets of neurons across multiple circuits is thought to support complex behaviours. These functionally coupled subsets are often referred to as cell assemblies. The detection of cell assembly patterns from single-unit recordings usually relies on finding significant co-firing within a particular time bin. Choosing a bin length based on synaptic integration times, e.g. 20 ms, makes these methods well-suited to detecting Hebbian-like cell assemblies within a single structure such as the hippocampus. However for assemblies that span multiple circuits it may be that the assembly-forming neurons interact at longer latencies or over successive temporal windows. Here we apply independent component analysis to the cross-correlation between each neuron pair at multiple lags in order to incorporate these interactions. We show that this method is able to capture cross-structural assemblies, and contrast its performance to other methods, using both spike-train simulations and in vivo recordings from the rodent hippocampus and ventral tegmental area. Importantly we found that different assemblies detected in this manner show distinct neurophysiological correlates such as their coupling to different phases of hippocampal theta oscillations, responses during sharp-wave ripples, and speed modulation.

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Single-cycle analysis of hippocampal theta oscillations suggests underlying network states

Vítor Lopes-dos-Santos, Gido M. van de Ven, Alexander Morley, Stéphanie Trouche, David Dupret

MRC Brain Network Dynamics Unit, Department of Pharmacology, University of Oxford, OX1 3TH Oxford, UK

Correspondence and requests for collaboration should be addressed to ***vitor.lopesdossantos@pharm.ox.ac.uk***

During active behavior in rodents, local field potentials (LFPs) recorded from the hippocampal formation are dominated by sustained theta oscillations (~5 to 12 Hz) and co-occurring faster rhythms (~30 to 140 Hz), referred to as gamma oscillations, which emerge as bursts nested within theta cycles. In the CA1 subfield of the dorsal hippocampus, the broad gamma range is commonly divided in three bands: low gamma (~30 to 50 Hz), which is believed to emerge from CA3 to CA1 projections; mid gamma (~50 to 100 Hz), believed to reflect entorhinal cortex to CA1 interactions; and fast gamma (~100 to 140 Hz), proposed to be generated by local activity within the CA1 pyramidal layer. Although these oscillations are often assumed to be consistent across theta cycles, visual inspection of raw LFP traces indicates that their magnitude can vary dramatically in a cycle-by-cycle basis. Thus, if we assume that in fact each gamma component has its own underlying mechanism, the spectral content of individual theta cycles might report a specific network state. Taking into consideration this rationale, we designed and applied an unsupervised method for the extraction of spectral signatures from individual theta cycles recorded from dorsal CA1 of behaving mice. Our analysis blindly retrieved independent components compatible with slow and fast gamma oscillations, as well as two additional components with main frequencies within the mid gamma range, and an unexpected additional “beta” component (main frequency ~22 Hz). This beta component was not a sustained oscillation but a large negative deflection in the LFP around the peak of theta waves that synchronized spiking activity in the CA1 layer. Overall, the five extracted components were remarkably robust in 17 sessions recorded from 10 different mice, even when some of them were not salient in standard cross-frequency coupling analysis. We performed CSD analysis for each pattern in order to evaluate if they have unique current sources. Furthermore, we showed that CA1 pyramidal cell activity predicts the strength of each component on a cycle-by-cycle basis, and that the information used for predicting each pattern has a distribution across neurons, thus indicating that the ensemble entrained in each oscillation is somewhat unique. Our data suggest that the CA1 circuitry can engage in different network states that are reflected in the oscillations nested in individual theta cycles.

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Brain networks and eating behaviors: A dynamic connectivity analysis approach

Bo-yong Park[a,b] and Hyunjin Park[b,c*]

[a] Department of Electronic, Electrical and Computer Engineering, Sungkyunkwan University, 16419, Korea
[b] Center for Neuroscience Imaging Research, Institute for Basic Science (IBS), 16419, Korea
[c] School of Electronic and Electrical Engineering, Sungkyunkwan University, 16419, Korea

Correspondence and requests for collaboration should be addressed to ***by6860@skku.edu***

Connectivity analysis is the representative method for quantifying the complex brain networks. Static connectivity analysis constructs correlation matrices by computing correlation of the whole time series of functional magnetic resonance imaging (fMRI) and dynamic connectivity analysis uses sub-time series to construct correlation matrices. Dynamic connectivity analysis has an advantage that it could reflect dynamic changes of cognitive states. In the current study, we adopted dynamic connectivity analysis to explore the links between brain networks and eating behaviors. We obtained 62 resting-state fMRI (rs-fMRI) data (31 healthy weight (HW) and 31 non-HW) from enhanced Nathan Kline Institute-Rockland Sample database. Brain networks were defined using a group independent component analysis (ICA). Dynamic correlation matrices were constructed by dividing the whole time series using a rectangular window with size of 111 s. The cognitive states were defined by grouping the dynamic correlation matrices into several clusters using k-means clustering algorithm. Thirteen functionally interpretable brain networks were generated and six cognitive states were defined. The betweenness centrality (BC) was computed to assess the importance of a given node (brain network) and they were correlated to eating disorder examination questionnaire (EDE-Q) scores. The BC values of state 5 showed strong correlation with EDE-Q eating concern ($r = 0.5636$ and $p = 0.0016$), shape concern ($r = 0.5469$ and $p = 0.0028$), and weight concern ($r = 0.4591$ and $p = 0.0330$) scores. The results might provide new insights to link between the brain networks and eating behaviors.

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Projection-based chemogenetic dissection of the noradrenergic system: Dissociation of analgesic and aversive circuits

Stefan Hirschberg[1], Yong Li[1], Andrew Randall[2], Eric J Kremer[3] and Anthony E Pickering[1]

[1] School of Physiology, Pharmacology & Neuroscience, University of Bristol;
[2] Institute of Biomedical Sciences, University of Exeter;
[3] IGMM, CNRS, UMR5535, Montpellier, France.

Correspondence and requests for collaboration should be addressed to ***rtaep@bristol.ac.uk***

The Locus coeruleus (LC) is the principal source of noradrenaline in the CNS. Anatomical studies indicate that the LC has distinct output modules with, for example, discrete populations that innervate the prefrontal cortex (LC-PFC) and the spinal cord (LC-SC). We functionally tested the hypothesis hypothesise that analgesic effects and stress-like adverse effects that are caused by increased noradrenergic activity are mediated by distinct LC modules.

Retrogradely-transported CAV2-based vectors were designed to express a genetically “engineered” excitatory ionophore (PSAM) specifically activated by the selective agonist (PSEM308) under a catecholaminergic neuron specific promoter. Chemogenetic activation of LC neurons was electrophysiologically verified then subsequently employed to activate LC-PFC and LC-SC neurons in naïve rats and in rats that underwent tibial nerve transection (TNT, a neuropathic pain model).

Activation of LC-SC neurons (10mg/kg PSEM308) increased thermal withdrawal latency but had no effect in conditioned place preference (CPP) and open field experiments (n=9). In contrast, activation of LC-PFC neurons was associated with aversive and anxiety-like behaviour (n=7) in CPP and open field testing without any analgesic effect.

In the TNT model, activating LC-SC neurons significantly reduced mechanical and cold-evoked hypersensitivity and improved weight bearing (n=7). The animals now also exhibited conditioned place preference for the PSEM308 paired environment.

This provides evidence that the LC is organised into functional modules and that it is possible to dissociate analgesic from aversive noradrenergic actions and this targeting the ps-LC is an effective therapeutic strategy in a neuropathic pain model.

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Cerebellar role in emotional memory processing at parallel fiber-Purkinje cell synapses

Jeong-Kyu Han[1,2,4*], Sun-Ho Kwon[3,4*], Yong-Gyu Kim[2], Da-Eun Jun[2], Sang-Kyu Ye[3,4], Sang Jeong Kim[1,2,4]

[1]Department of Brain & Cognitive Sciences, Seoul National University Graduate School, Seoul, Republic of Korea, [2]Department of Physiology, Seoul National University College of Medicine, Seoul, Republic of Korea, [3]Department of Pharmacology, Seoul National University College of Medicine, Seoul, Republic of Korea, [4]Neuro-Immune Information Storage Network Research Center, Seoul National University College of Medicine, Seoul, Republic of Korea

Correspondence and requests for collaboration should be addressed to ***tandoori@snu.ac.kr***

It is increasingly recognized that there is a critical relationship between cerebellum and emotion, particularly in fear responses and fear memory consolidation. However, underlying mechanism for molecular regulation of memory formation remains unclear. To address this issue, we targeted signal transducer and activator of transcription (STAT) family, which is known as a strong etiological factor for posttraumatic stress disorders (PTSD), characterized by a hypermnesia of the trauma. Herein, we hypothesize that cerebellar STAT3 contributes to PTSD- like memory formation. Using Purkinje cell-specific STAT3 knockout (KO) mice model in fear conditioning paradigm, we found that long-term fear memory was increased in STAT3- deficient group, and avoidance memories were significantly increased in STAT3 KO group after 24 hours. When learned fear, STAT3 KO group showed more exaggerated responses (fear- potentiated responses) than wildtype group. After fear conditioning, long-term potentiation (LTP) was reframed to long-term depression (LTD) at parallel fiber-Purkinje cell synapses of STAT3 KO mice. Reframing LTP/LTD was also confirmed in *in vitro* slice physiology. However, long-term potentiation of inhibitory synapses at molecular layer interneuron- Purkinje cell synapses of STAT3 KO mice were not involved in the consolidation of fear memory. To investigate that how Purkinje cell-specific STAT3 modulates bidirectional plasticity in memory formation, we considered the transcriptional regulations mediated by STAT3. Expression level of AMPA receptor gluA1/2 subunits was increased in STAT3 KO mice. All things considered, these results demonstrated that Purkinje cell STAT3 regulates PTSD-like memory formation revealing the novel mechanisms of traumatic memories.

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The Honeycomb Maze: a novel test of spatial navigation

Wood R[1], Wu R[2], Delekate A[3], Burton S[1,2], Bauza M[1,2], Krupic J[2], Chan D[4], O'Keefe J[1]

[1] Sainsbury Wellcome Centre for Neural Circuits and Behaviour, University College London, UK
[2] Cell and Developmental Biology, University College London, UK
[3] DZNE German Centre for Neurodegenerative Diseases, Bonn
[4] Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK

Correspondence and requests for collaboration should be addressed to ***ruth.wood@ucl.ac.uk***

The Honeycomb Maze (HM) is a novel behavioural paradigm for the study of spatial navigation. It consists of 37 tessellated hexagonal platforms, each individually raised or lowered to control choices as the animal moves from start to goal. It offers several advantages over current mazes. First, experimenter control over the choice of available platforms allows scaling of task difficulty. The associated parametric behavioural output may be better suited than tasks with binary (correct/incorrect) outputs for tracking disease progression in mouse models of Alzheimer's disease. Second, this dry maze permits concomitant recording of grid and place cell activity.

Place navigation on the HM requires an animal to navigate to an unmarked goal platform associated with a food reward from one of several start platforms. Each trial consists of a series of sequential choices in which the animal is confined to a single raised platform and given a choice between two of the six adjacent platforms. Correct behavior consists of choosing the platform with the smallest angle to the goal heading-direction.

Rats learn this task rapidly and their choice behavior shows an influence of three maze factors: the angle separating the two choice platforms, the distance from the goal, and the angle between the correct choice platform and the goal heading-direction. Task performance is significantly impaired in rats with hippocampal lesions, and a greater effect of the three maze factors is observed in HC-lesioned animals compared to controls suggesting the hippocampus plays a key role in the processing of vector space.

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Silent synaptic and behavioral alterations after chronic cocaine exposures by D1 MSN specific NR2B suppression

Hyun Jin Kim, Joung-Hun Kim

POSTECH, South Korea

Correspondence and requests for collaboration should be addressed to ***hanzlight@postech.ac.kr***

When after exposure to the addictive drugs, various cellular and molecular mechanisms dynamically occur in our brain. Excitatory inputs to the MSNs of nucleus accumbens, which is critical area for behavioral responses to the addictive drugs, are dramatically changes after repeated exposure to cocaine or addictive drugs. The generation of silent synapse which only has NMDAR including NR2B subunit and lacking of AMPAR is the most prominent plasticity of glutamatergic transmission to the MSN, especially D1 MSN, in NAc after (5days) chronic cocaine exposure. In addition, silent synapses highly correlated locomotor sensitization and conditioned place preference (CPP). However, there is little information on the role of NR2B subunits for silent synapses and behavioral changes in cocaine addiction. Here, using viral mediated conditional knock down (cKD) technique and optogenetics, we assessed whether the cKD of NR2B subunit alters the locomotor sensitization and generation of silent synapses in the D1 MSN of NAc shell area. Locomotor sensitization after 5days of non-contingent cocaine exposure, NR2B cKD virus injected mice show increased locomotor activity. In contrast, % silent synapse was reduced but generated the silent synapses. Moreover, we found evidences the contribution of distinct other NMDAR subunits (i.e. NR2C) through the selective antagonists tests in NR2B deleted D1 MSNs. In addition, the result of CPP was impaired on NR2B cKD mice. Together, these results indicate that NR2B is not critical for the generation of silent synapses but contribute to the glutamatergic changes for the acquisition of associated memory formation when after cocaine exposure.

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The thalamic reticular nucleus controls fear extinction

Joon-Hyuk Lee[1], Charles Latchoumane[1], Jungjoon Park[1,2], Kwang-Hyung Lee[2], Hee-Sup Shin[1]*

[1] Center for Cognition and Sociality, Institute for Basic Science (IBS), Daejeon 305-338, Korea
[2] Department of Bio and Brain Engineering, Korea Advanced Institute of Science and Technology (KAIST), Daejeon 305-338, Korea

Correspondence and requests for collaboration should be addressed to ***ijunhyuk@gmail.com***

The thalamic reticular nucleus (TRN), a shell-shaped GABAergic structure, provides one of the most significant inhibitory inputs to the thalamus, thereby playing a pivotal role in sensory processing, attention control, and sleep modulation. Although previous anatomical data suggest a possible role of the TRN in emotional processing, this issue remains unexplored. Here we show that a specific sub-region of the TRN is critical for fear extinction. With the neural tracing experiments, we observed that the rostroventral part of the TRN (TRNrv) projects to the limbic thalamus, including the paraventricular nucleus of the thalamus (PVT) known to be important in fear modulation. This contrasts with the projection of the neighbouring rostrodorsal part of the TRN (TRNrd) to the centrolateral thalamus (CL). Notably, optogenetic inhibition of the TRNrv neurons suppresses fear extinction, whereas the inhibition of the TRNrd neurons did not affect fear extinction. Recordings in vivo revealed an increased firing rate of the TRNrv neurons during fear extinction learning and boosting the firing rate led to enhanced fear extinction. Moreover, optogenetic inhibition of the TRNrv terminals in the PVT resulted in a persistent elevation of fear. Our results show a previously unknown role of the TRN, control of emotional behavior, and reveal a critical circuit for fear memory modulation.

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The Role of Endocytosis in Tau Misfolded State Propagation and Pathology

Colin Hockings, Na Yu, Claire Michel, Gabriele Kaminski Schierle

Department of Chemical Engineering and Biotechnology, University of Cambridge, Cambridge, United Kingdom

Correspondence and requests for collaboration should be addressed to ***ch431@cam.ac.uk***

We have previously shown that extracellular monomeric Tau has the capacity to enter neurons by endocytosis to trigger aggregation of the endogenous Tau protein. The speed at which exogenously added Tau adopts an aggregated form once internalised by neurons prompted us to investigate the pathway responsible for aggregation in more detail.

We used custom microfluidic devices to study the uptake and transfer of exogenously added Tau within neurons. In order to determine Tau aggregation state in various microcompartments of the cell we applied a specifically developed fluorescence lifetime sensor.

Our results show that exogenously added Tau first localises in endosomes/lysosomes within the soma department as shown by super-resolution microscopy. The presence of Tau in a locally acidic and crowded environment triggers the formation of Tau aggregates and increasing the pH in vesicles can block the aggregation of exogenously added Tau. Co-aggregation of exogenous and endogenous Tau within the axon severely affects normal mitochondrial transport along microtubules. Furthermore, Tau is axonally transported along microtubules, and aggregates further upon transfer to acceptor cells.

We conclude that there is increased pathology in the presence of extracellular Tau and thus capturing Tau in the extracellular space may provide new therapeutic strategies.

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To Sleep or to Wake Up: The Janus-Faced Nature of the Basal Forebrain Parvalbumin Neurons in Sleep-Wake Control

Chanmi Yeon, Jieun Jung, Sung Guk Lee, Jooho Lee, and Tae Kim*

Department of Biomedical Science and Engineering
Gwangju Institute of Science and Technology, South Korea

Correspondence and requests for collaboration should be addressed to ***ycmi0331@gmail.com***

The basal forebrain (BF) plays a pivotal role in sleep-wakefulness control. Recently, wake-promoting property of GABAergic parvalbumin (PV) neurons has been shown and we also reported cortical gamma oscillation enhancement at ~40Hz by BF PV neurons. Whereas, intermittent stimulation at 8Hz of thalamic reticular nucleus (TRN) receiving projection from BF PV neurons, increased sleep spindle and NREM sleep. Therefore, we investigated differential roles of BF PV neurons in sleep-wake control.

To selectively control BF PV neurons, we employed optogenetic methodology. A double-floxed ChR2-eYFP viral vector was stereotaxically injected into the BF of PV::Cre mice. After 2 weeks, we recorded sleep-wake profiles at baseline, followed by experimental days with either 40Hz or “spindle-like (intermittent 10 light pulses at 8Hz)” stimulation.

We compared relative amount of wake, NREM and REM sleep time. At the end of dark period, time awake decreased from 86% to 40% and NREM sleep time increased from 14% to 58%, meanwhile, REM sleep time showed similarly low proportion (0 and 2%, respectively). At the beginning of light period, time awake decreased from 23% to 11% and NREM sleep time increased from 76% to 81%. REM sleep time increased 1% to 8%.

We found that intermittent stimulation of BF PV neurons at 8Hz could increase NREM sleep and reduce wakefulness. Considering the wake-promoting effect was shown by a higher frequency (40Hz), we propose the differential roles of BF PV neurons on sleep-wake regulation depending on their firing rates.

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Yin-and-yang bifurcation of opioidergic circuits for descending analgesia at the midbrain of the mouse

Jonghyun Kim[1,2,3], Gireesh Gangadharan[1], Eui-Ju Choi[2], C. Justin Lee[3], Hee-Sup Shin[1]

[1.] Center for Cognition and Sociality, Institute for Basic Science, Daejeon 305-811, Korea
[2.] Laboratory of Cell Death and Human Diseases, Department of Life Sciences, School of Life Sciences, Korea University, Seoul 136-701, Korea;
[3.] Brain Science Institute, Korea Institute of Science and Technology, Seoul 136-791, Korea;

Correspondence and requests for collaboration should be addressed to ***comer0213@hanmail.net***

The midbrain periaqueductal gray (PAG) is a major component in the descending analgesia circuits for the endogenous, opioidergic pain control. The neurons projecting from the PAG to the rostral ventromedial medulla (RVM) are potentiated through disinhibition under opioidergic conditions and thereby exert pain reduction. In addition, the locus coeruleus (LC) has been proposed to play a role in endogenous pain control through noradrenergic inputs to the spinal cord(SC). Nevertheless, how the LC is integrated in the descending analgesia circuits remains elusive. In this study, we show that the opioidergic analgesia circuit is bifurcated at the PAG: a positive control through the PAG-RVM circuit and a negative control through the PAG-LC circuit. In the PAG, phospholipase C β4(PLCβ4) is selectively expressed in the neurons projecting to the LC. Mice with a mutation and a PAG-specific knockdown of PLCβ4 exhibited an enhancement of the swim-stress-induced analgesia (SSIA) as well as the anti-nociceptive effect of a morphine administration.

The PAG-LC projection neurons, which normally become quiescent in response to opiates, were resistant to this opioid effect when PLCβ4 is absent, which would lead to a persistent activity of noradrenergic neurons in the LC, enhancing analgesia. In fact, the enhanced SSIA analgesia in the PLCβ4(-/-) mice returned to the control level by blocking α2-noradrenergic receptors.

These findings indicate that opioidergic conditions suppress the descending analgesia through the PAG-LC pathway whereas they promote it through eh PAG-RVM pathway. Our findings suggest a new framework for the development of tools for pain control.

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Electrophysiological Signatures of Boundary Representation in the Human Subiculum

Sang Ah Lee[1,2], Jonathan Miller[2], Joshua Jacobs[2]

[1] Department of Bio and Brain Engineering, Korea Advanced Institute of Science and Technology
[2] Department of Biomedical Engineering, Columbia University

Correspondence and requests for collaboration should be addressed to ***sangah@gmail.com***

Environmental boundaries play a major role in spatial representation across a wide range of tasks, from early navigation abilities in children, to place learning in virtual reality environments, to 2D visual scene recognition.

The neural correlates of boundary representations (i.e., boundary/border cells) have been most widely studied in the rodent hippocampal formation. Nevertheless, converging evidence from a wide range of species and methodologies suggests that the neural correlates of spatial navigation are widely shared across vertebrates, including humans. While the human correlate of boundary cells have not yet been discovered, it may be possible to detect boundary-specific neural activity in the human brain, particularly in subiculum where the largest known population of boundary-representing neurons exist in rodents.

In this study we tested pre-surgical epilepsy patients implanted with intracranial depth electrodes in a virtual navigation task with varied goal locations across trials. Here we present comparisons of neural oscillations (at 1-4 Hz, 4-10 Hz, and 30-90 Hz frequency bands) on trials in which subjects encoded goal locations near spatial boundaries to trials in which they encoded goal locations in the central region of the virtual arena. We found higher theta power for goals near the boundaries of the arena; importantly, this effect was specific to the subiculum.

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Development and behavioural / pharmacological characterisation of an adult rat model of sucrose feeding-induced analgesia

Alexander J Davies[1], Jeongrak Park[2], Hue Wang[1], Jeong-Yun Lee[2], Anthony Pickering[3], Seog Bae Oh[1,2]

[1] Dental Research Institute and Department of Neurobiology and Physiology, School of Dentistry, Seoul National University, Republic of Korea.
[2] Department of Brain and Cognitive Sciences, College of Natural Sciences, Seoul National University, Republic of Korea.
[3] School of Physiology & Pharmacology, Medical Sciences Building, University of Bristol, United Kingdom.

Correspondence and requests for collaboration should be addressed to ***ajd09@snu.ac.kr***

Oral perfusion of sucrose is innately analgesic to neonatal rodents and is commonly used to provide pain relief in new born humans. In adults sucrose is a strong motivator to feed, even in potentially hazardous circumstances (i.e. threat of tissue damage). However, the neurobiological mechanisms of this endogenous reward-pain interaction are unclear. We have developed a model of sucrose (10% solution) feeding-induced analgesia in Sprague- Dawley rats (male; 6-9 weeks) using the Hargreaves's test of hind paw thermal sensitivity as a nociceptive assay. All experiments were approved by the Institutional Animal Care and Use Committee (SNU-151113-2). Rats were easily trained in the task and consistently displayed an increase in thermal threshold while drinking sucrose (10.7±0.5 s) compared to resting baseline (8.6±0.3 s, p=0.0002, paired t test, n=12). The sucrose effect was transient and thresholds returned to baseline within 1-2 min. In contrast, rats passively fed the same sucrose solution via an intraoral catheter (2 µl/s for at least 10 s) showed no change in thermal thresholds compared to sham or water controls. Interestingly, water drinking by water-deprived or sucrose expectant rats showed a similar analgesic response, suggesting the effect may be attributable to reward conditioning. Pre-treatment with the µ-opioid receptor antagonist naloxone, either via spinal (10 µg i.t.) or systemic (1 mg/kg i.p.) administration, did not prevent the increase in thermal thresholds during sucrose feeding compared to vehicle treatment. In summary, active sucrose feeding induces a transient state of thermal analgesia that appears to operate via a non-opioidergic neural pathway.

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Single-molecule FISH reveals human SHANK3 mRNA expression and neuronal localization varies during development and in SHANK3 heterozygous individual with autism

Samuel E. Taylor

Centre for Developmental Neurobiology, MRC Centre for Neurodevelopmental Disorders, King's College London, U.K.

Correspondence and requests for collaboration should be addressed to ***samuel.s.taylor@kcl.ac.uk***

Deletions and mutations in the SHANK3 gene are strongly associated with autism spectrum disorder (ASD) and cause Phelan McDermid Syndrome. The SHANK3 protein is a scaffolding protein found at the post-synaptic membrane of excitatory neurons. Single molecule fluorescence in situ hybridisation (smFISH) allows the visualization of single mRNA transcripts in vitro. Here we perform and quantify smFISH in human inducible pluripotent stem cell (hiPSC) derived cortical neurons, targeting the SHANK3 transcript. Both smFISH and conventional immunofluorescence staining demonstrated a developmental increase in SHANK3 mRNA and protein, respectively, in control human cortical neurons. Analysis of single SHANK3 mRNA molecules in neurons derived from an autistic individual heterozygous for SHANK3 indicated that while the number of SHANK3 mRNA transcripts remained comparable with control levels in the cell soma, there was a 50% reduction within neuronal processes.

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Tau regulates the extrasynaptic expression of AMPA receptors

Philip Regan[1,2], Garry Whitehead[1], Jee Hyun Yi[1], Thomas Piers[1,2], Kwangwook Cho[1,2]

[1]Henry Wellcome Laboratories for Integrative Neuroscience and Endocrinology, Translational Health Sciences, Bristol Medical School, [2]Centre for Synaptic Plasticity, University of Bristol, Whitson Street, Bristol, BS1 3NY, United Kingdom

Correspondence and requests for collaboration should be addressed to ***anplr@bristol.ac.uk***

The microtubule associated tau protein remains inextricably linked to numerous neurodegenerative diseases, collectively termed tauopathies. To better understand how tau may contribute to these pathological phenotypes, it is important to understand the precise physiological functions of tau. Here, we have built upon recent studies revealing a regulatory synaptic role for tau in the plasticity of glutamate receptor trafficking. Through combined electrophysiological and pharmacological assays of tau-shRNA transfected neurons in vitro, we have discovered an aberrantly increased extrasynaptic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR)-mediated excitatory post-synaptic current (EPSC) but no effect on synaptic AMPAR EPSC. Our data suggest that knocking down of tau expression may dysregulate a certain form of AMPAR trafficking, leading to an accumulation of extrasynaptic AMPARs. These findings raise the possibility of a molecular role for tau in regulating synaptic function through effects on extrasynaptic trafficking of AMPARs. They also highlight the broader implications of extrasynaptic AMPARs for synaptic physiology and pathophysiology.

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Schizophrenia-associated postsynaptic density protein, DLG2 affects cortical layer generation

Bret Sanders and Eunju Jenny Shin

Neuroscience and Mental Health Research Institute, Cardiff University, Hadyn Ellis building, Maindy Road, Cardiff CF24 4HQ

Correspondence and requests for collaboration should be addressed to ***shine@cardiff.ac.uk***

Postsynaptic density (PSD) proteins play a critical role in brain function and a number of PSD genes have been found to be associated with increased risk of neuropsychiatric disorders. So far, roles of PSD proteins during neural development have received little attention, probably due to their stereotyped roles in mature synapses. The current study hypothesised that PSD proteins will contribute to early neural development and neurogenesis. We particularly focussed on DLG2 (disk large homolog) since de novo deletions of DLG2 have been found to be highly associated in development of schizophrenia. First, we looked for expression of DLG2 in mouse embryos and in neural precursors derived from human embryonic stem cells. To our surprise, DLG2 mRNA was expressed in ventricular zone of E14.5 embryonic brain and DLG2 protein was expressed in cortical neural precursors derived from human embryonic stem cells. To this end, DLG2$^{-/-}$ hESCs were generated using the new genome editing technology, CRISPR/Cas9 system. DLG2$^{-/-}$ hESCs were differentiated into nestin+ neural precursors and gave rise to cortical projection neurons to a comparative manner to wildtype cells. However, specific cortical populations were affected by DLG2 deficiency. The proportion of TBR1^{+} layer 6 cortical neurons was reduced in DLG2$^{-/-}$ cultures whereas CTIP2^{+} layer 5 neurons were increased. These results show, for the first time, a role of the DLG2 in corticoneurogenesis. Currently the underlying mechanism of DLG2's role in cortigoneurogenesis is under investigation.

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Immersive VIrtual Reality Testing of Entorhinal Cortex and Hippocampal function in ageing and Mild Cognitive Impairment (VIRTECH-MCI)

David Howett, Andrea Castegnaro, Daniel Bush, Deepti Marchment, John King, Neil Burgess, Dennis Chan

University College London

Correspondence and requests for collaboration should be addressed to ***dh525@cam.ac.uk***

Background. The entorhinal cortex (EC) is the first region to show neurodegeneration in Alzheimer's disease (AD)[1]. As such, detection of EC dysfunction will aid diagnosis of AD in its pre-dementia stages and stratification of individuals for future interventional therapies aimed at slowing the progression of disease.
The demonstration that EC cells have spatially related firing patterns (head direction cells and grid cells[2]) underpins the role of this region in spatial navigation.
To test the hypothesis that navigation is impaired in pre-dementia AD, this study used a novel immersive virtual reality (iVR) platform to test path integration.

Methods. Patients diagnosed with mild cognitive impairment (MCI, n=8) and aged-matched healthy controls (n=25) underwent VR testing.
Navigation is tested using a path integration paradigm; participants sequentially walk up to, and "collect", three objects before being asked to return to the location of object 1. Participants are further challenged with three different return conditions (boundary cues present, boundary cues absent, removal of environment textural information to disrupt optic flow). Performance is measured in terms of distance and angle error between the estimated and actual location of Object 1.

Results. All participants completed the PI task with no nausea or tolerability issues, indicating that iVR is a suitable platform for older individuals. MCI patients exhibit larger errors in distance ($F(1, 970) = 241.40$, $p<0.001$) and angle ($F(1, 970) = 80.08$, $p<0.001$) from target. MCI patients with AD positive biomarkers exhibit impaired performance across all measures compared to non-AD MCI.

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Brain structural development in a mouse model of Autism spectrum disorder

Adam Tyson[1,2,3], Grainne McAlonan[3], Declan Murphy[2,3], and Laura Andreae[1,2]

[1]Centre for Developmental Neurobiology, Institute of Psychiatry, Psychology and Neuroscience, King's College London, U.K.
[2]MRC Centre for Neurodevelopmental Disorders, Institute of Psychiatry, Psychology and Neuroscience, King's College London, U.K.
[3]Department of Forensic and Neurodevelopmental Sciences, Institute of Psychiatry, Psychology and Neuroscience, King's College London, U.K.

Correspondence and requests for collaboration should be addressed to ***adam.tyson@kcl.ac.uk***

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterised by core impairments in social interaction and communication along with patterns of repetitive behaviour. Mutations of hundreds of genes have been linked to ASD, many of which are related to synaptic structure or function. One of these is Neurexin 1α (Nrxn1α), which codes for a synaptic cell adhesion protein. A potential link between these genetic mutations and the core symptoms may be abnormal brain structural development, one of the most reproduced findings in ASD.

To investigate the link between genetics and brain structure in ASD, the Nrxn1α knock-out (KO) mouse model was studied. The Nrxn1α KO mouse shows a behavioural phenotype relevant to ASD and is a promising model of the disorder. A novel tissue clearing method (CLARITY) was used to render brain tissue from this mouse transparent, allowing for high-resolution 3D imaging of multiple cellular markers in large volumes of brain tissue. Brain structure and cellular distribution was investigated in two areas thought to develop ab- normally in the Nrxn1α KO mouse, the cortex and striatum, at multiple time points during development.

Determining which brain areas are particularly affected following a deletion of Nrxn1α will help understand how the genetic abnormalities found in individuals with ASD cause the core symptoms of the disorder.