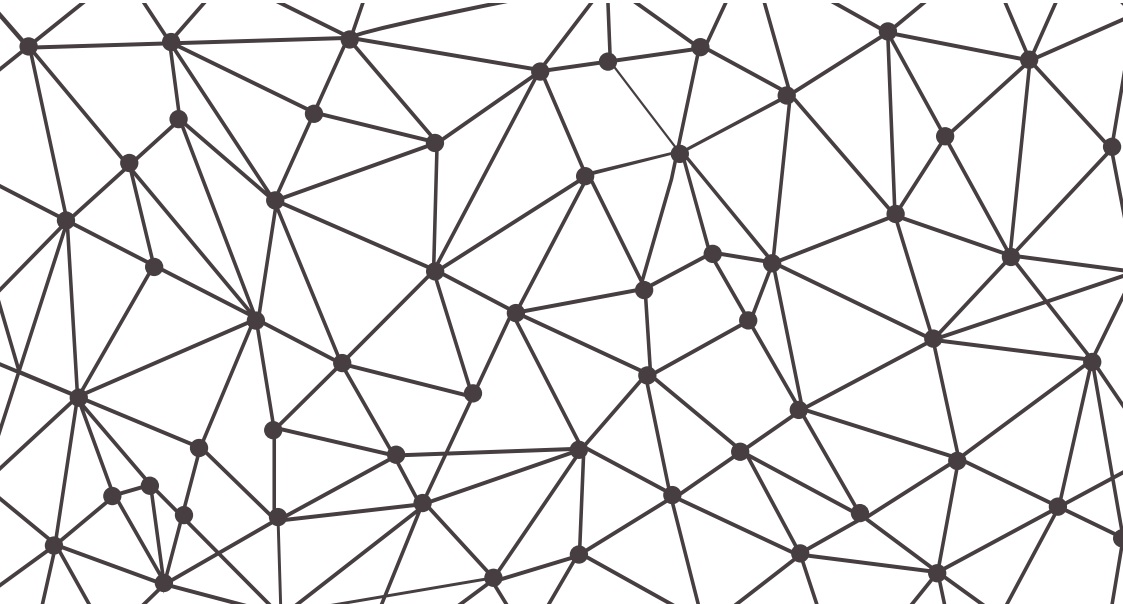
CHAMPALIMAUD
NEURO-
SCIENCE
SYMPOSIUM

Champalimaud
Foundation

2016

Abstract Book



Invited Talks Line-up

Plenary Talk

Development and organization of the entorhinal-hippocampal space circuit
Edvard Moser
Norwegian University of Science and Technology, Norway

Talk Session I

Towards the whole mouse brain connectome
Winfried Denk
Max Planck Institute of Neurobiology, Germany

Large-scale neural circuit dynamics during skill learning
Jose Carmena
University of California, Berkeley, USA

Whole brain dynamics underlying visuomotor behaviors in zebrafish
Michael Orger
Champalimaud Center for the Unknown, Portugal

Talk Session 2

Visual processing in Drosophila courtship
Barry Dickson
Janelia Research Campus, USA

Talk Session 3

Internal models of voluntary self-motion in the primate cerebellum: Implications for perception and action
Kathy Cullen
McGill University, Canada

Neural mechanisms for dynamic acoustic communication in flies
Mala Murthy
Princeton University, USA

Talk Session 4

Circuit mechanisms for incremental learning
Pico Caroni
Friedrich Miescher Institute for Biomedical Research, Switzerland

Molecular mechanisms of AMPA receptor delivery during LTP
Rob Malenka
Stanford School of Medicine, USA

Winner take all competition for neuronal allocation to an engram
Sheena Josselyn
University of Toronto, Canada

Talk Session 5

Hypothalamic feeding circuits driving cortical development and complex behaviors
Tamas Horvath
Yale School of Medicine, USA

Rules of connectivity in mouse visual cortex
Tom Mrsic-Flogel
University of Basel, Switzerland

Talk Session 6

Immune checkpoint blockade for fighting Alzheimer's disease: The communication between the brain and the circulation for brain function and repair
Michal Schwartz
Weizmann Institute, Israel

Genome editing for lineage tracing and schizophrenia genetics
Alex Schier
Harvard University, USA

Good dad, bad dad: genetic basis of parental care in wild mice
Hopi Hoekstra
Harvard University, USA

Talk Session 7

Mitochondrial function in the nucleus accumbens links stress and anxiety with coping behaviors
Carmen Sandi
Ecole Polytechnique Fédérale de Lausanne, Switzerland

Midbrain dopamine neurons control judgment of time
Joe Paton
Champalimaud Center for the Unknown, Portugal

Two-photon optogenetics with millisecond temporal precision and cellular resolution
Valentina Emiliani
Centre National de la Recherche Scientifique, France

Selected Talks Abstracts

Talk Session I

Competitive disinhibition in early sensory processing mediates behavioral choice and sequences in Drosophila

Casey Schneider-Mizell, Tihana Jovanic, Mei Shay, Jean-Baptiste Masson, Albert Cardona, Marta Zlatic
Janelia Research Campus, Ashburn, VA, USA

Even a simple sensory stimulus can elicit distinct innate behaviors and behavioral sequences. During such elementary sensorimotor decisions competitive interactions amongst neurons that promote distinct behaviors must ensure the selection and maintenance of one behavior while suppressing others. The site and circuit implementation of such competitive interactions are still an open question. Combining comprehensive electron microscopy reconstruction of relevant inhibitory interneuron networks, modeling, electrophysiological recordings and behavioral studies we determined the circuit mechanisms that contribute to the Drosophila larval sensorimotor decision to startle, explore and perform an anisotropic sequence of the two in response to a mechanosensory stimulus. Together these studies reveal: 1) competitive interactions between reciprocally connected feedforward inhibitory interneurons mediate behavioral choice, 2) lateral disinhibitory interneurons promote sequence transitions to later behaviors and 3) specialized local feedback disinhibitory interneurons provide a positive feedback loop that maintains the later behavior and prevents reversals to the first. The combination of these interconnected circuit motifs can implement both the selection of a behavior and the serial organization of the behavior into a sequence.

Talk Session I

Adequate brain-wide connectivity of new neurons transplanted into adult brain circuits is shaped by the lesion environment

Sofia Grade[1, 2], Leda Dimou[1, 2, 3], Karl-Klaus Conzelmann[4], Magdalena Götz[1, 2, 3]
[1]Biomedical Center, Ludwig-Maximilians University Munich, Munich, Bavaria, Germany, [2]Institute for Stem Cell Research, Helmholtz Center Munich, Neuherberg, Bavaria, Germany, [3]SYNERGY, Excellence Cluster of Systems Neurology, Ludwig-Maximilians University Munich, Munich, Bavaria, Germany, [4]Max von Pettenkofer Institute and Gene Center, Ludwig-Maximilians University Munich, Munich, Bavaria, Germany

Neurons lost upon injury or disease are not replaced in the mammalian brain. While transplantation of new neurons from several cell sources is a widespread approach for cell replacement, the critical question of how those neurons connect in a brain-wide manner has not yet been answered. In fact, as most regions in the adult mammalian brain lack neurogenesis, the environment may be unsuited to support integration into existing networks.
To tackle this question we transplanted neurons from the mouse embryonic neocortex into the lesioned or intact primary visual cortex of adult mice. Neurons survive, differentiate into upper layer projection neurons, and acquire mature pyramidal morphologies and dendritic spines. When neurons are transplanted into a selective lesion with induced apoptotic death of upper layer projection neurons, they project mainly intracortically, appropriate for their upper layer identity. Using monosynaptic rabies virus tracing to map their brain-wide input, we show that they receive area-specific, and quantitatively faithful afferent projections matching those of endogenous projection neurons. Among these, the dorsal lateral geniculate nucleus, relaying the visual information from the retina, innervates the transplanted neurons with high accuracy, maintaining topographic maps. This striking similarity to the endogenous monosynaptic input is also observed when neurons are transplanted into a traumatic brain injury, while innervation strength is rather poor when neurons are transplanted into the intact visual cortex. Altogether our data indicate that neurons can integrate with great specificity into neocortical circuits challenged by an injury, a central finding for the prospect of adult brain regeneration.

Talk Session 2

Multichromatic color vision modulates C. elegans foraging on pigmented food sources

Dipon Ghosh, Xin Jin, Michael Nitabach
Yale University, Connecticut, USA

Caenorhabditis elegans nematode worms forage for food bacteria in colorful habitats. While worms exhibit rapid escape responses to extremely bright blue light that require the lite-1 gene, it is unknown whether worms use light, and in particular color, to inform them about their environment. Here we show that worms use multichromatic color vision to guide food-related decision making. We found that simulated white daylight much less intense than required to elicit lite-1-dependent escape responses potentiates avoidance of pathogenic P. aeruginosa bacterial lawns, while foraging on non-pathogenic bacteria is unaffected by light. This white light enhancement of avoidance is dependent on both the blue toxic pigment pyocyanin secreted by P. aeruginosa and the C. elegans lite-1 gene. White light also potentiates avoidance of non-pathogenic E. coli bacterial lawns doped either with pyocyanin or with toxic paraquat mixed with inert blue food dye, but not with colorless paraquat alone. Remarkably, both short- and long-wavelength components are necessary for white-light-potentiated avoidance, while increasing the ratio of long- to short-wavelength light suppresses avoidance. This establishes the existence of an unknown long-wavelength sensor that allows the worm to determine not just illuminance, but also the spectral properties of its light environment, and reveals a means by which color vision could contribute to C. elegans behavioral ecology.

Talk Session 2

Distinct neuronal subpopulations of one brainstem nucleus control opposing motor programs

Paolo Capelli[1,2], Chiara Pivetta[1,2], Maria Soledad Esposito[1,2], Silvia Arber[1,2]
[1]Biozentrum, University of Basel, Basel, Switzerland, [2]Friedrich Miescher Institute for Biomedical Research, Basel, Switzerland

Walking is one of the most basic motor behaviors, yet circuit-level organization and function of descending motor pathways regulating locomotion remain largely elusive. The reticular formation in the brainstem plays an essential role in movement control through interaction with spinal circuitry and upper motor centers. We discovered the existence of a complex but precise connectivity matrix between specific neuronal populations of the brainstem and spinal circuits. We hypothesize that motor command lines in the brainstem may be organized according to modules and are functionally linked to the implementation of diverse motor programs. Here we show that in mice, intermingled excitatory and inhibitory descending projection neurons within the ventral domain of the reticular formation are embedded into precise circuitry. Identified neuronal subpopulations can be characterized by the input from defined upper motor centers and establish output to different neuronal populations in the spinal cord. This anatomical dichotomy is paralleled by the role of these two neuronal subpopulations in the control of movement. To interfere with the function of identified neuronal subpopulations, we expressed various optogenetic tools through combinatorial use of mouse genetics and viral targeting strategies. Behavioral interference by temporally precise manipulation demonstrates that the two identified and intermingled neuronal subpopulations control opposing motor actions in freely moving mice. Together, our work shows the existence of precisely organized yet spatially intermingled neuronal circuit elements in the brainstem involved in distinct animal behaviors.

Talk Session 2

Concentration change detectors in the olfactory bulb

Ana Parabucki[2], Alex Bizer[2], Genela Morris[2], Matt Smear[1], Roman Shusterman[1]
[1]University of Oregon, Eugene, OR, USA, [2]University of Haifa, Haifa, Israel

Locating objects of interest in space is a vital aspect of sensation. In most mammals, olfaction plays an important role in localization, yet how the brain mediates this ability remains poorly understood. In mammals, odor source localization depends partly on comparison of odor concentration across the two nostrils. However, mammals can still find odor sources and follow odor trails with one nostril blocked. This remaining ability shows that mammals also perform temporal comparison of odor concentration, from sniff to sniff, to guide them to an odor source. Yet studies in freely moving animals do not allow sufficient stimulus control for precise study of olfactory neuronal or behavioral responses. To simulate the concentration changes an animal would experience during navigation, we have developed an odor delivery system that allows rapid switching of odor concentration, such that concentration can be changed on each sniff. Using this system, we have found that a subset of neurons in the olfactory bulb is sensitive to concentration changes, modulating their activity when the odor concentration changes across sniffs. Our results indicate that olfactory neurons explicitly detect concentration change, providing a signal that may guide navigational decisions in downstream olfactory circuits. Revealing how the OB represents odor dynamics will open the way for unraveling the circuit mechanisms underlying this important sensory computation. Ultimately, these studies promise to reveal general principles underlying the brain's ability to store, compare, and read out dynamic sensory input.

Talk Session 3

A propriospinal internal feedback circuit for skilled reaching

Eiman Azim[1], Juan Jiang[2], Bror Alstermark[2], Thomas Jessell[3]
[1]Molecular Neurobiology Laboratory, Salk Institute for Biological Studies, La Jolla, CA, USA, [2]Department of Integrative Medical Biology, Section of Physiology, Umeå University, Umeå, Sweden, [3]Departments of Neuroscience and Biochemistry and Molecular Biophysics, Howard Hughes Medical Institute, Kavli Institute for Brain Science, Mortimer B. Zuckerman Mind Brain Behavior Institute, Columbia, New York, NY, USA

The impressive precision of skilled forelimb behaviors relies on feedback-driven corrections that are rapid enough to refine even the swiftest of arm movements. One potential source of rapid feedback information would be to convey copies of motor output internally, reducing dependence on delayed sensory information. Putative internal copy pathways, however, have been difficult to isolate experimentally, leaving their contributions to movement unclear.

We have been exploring a class of spinal interneurons, cervical propriospinal neurons (PNs), which receive input from descending systems and extend bifurcating axons; one branch projects caudally to forelimb motor neurons and the other projects rostrally to the lateral reticular nucleus (LRN), a major cerebellar input, providing an anatomically simple means by which to convey copies of pre-motor signals internally. We found that a subpopulation of excitatory V2a interneurons correspond to PNs in mice, and their ablation disrupts reaching, but not grasping or locomotion, as revealed by a high-resolution kinematic motor assay. To determine whether manipulation of the PN internal copy branch has any impact on motor output, we used a focal optogenetic approach to recruit the internally-directed PN branch selectively, eliciting a severe disruption of reaching mediated by a rapid cerebellar-motor loop (Azim et al., 2014). The rapidity of this effect suggests a capacity for this pathway to adjust motor output continuously during a reach. We are now combining anatomical, electrophysiological and behavioral approaches to define how these feedback pathways are engaged by specific elements of forelimb movement and explore how their recruitment contributes to motor correction.

Talk Session 4

Learning based on error representations in apical dendrites of L5 pyramidal neurons

João Sacramento, Walter Senn
University of Bern, Bern, Switzerland

Classically, dendrites are considered to represent nonlinear processing units that enhance the computational power of neurons. But computational power can also be obtained by stacking together simplified neurons, and it remains elusive in what sense dendrites are beneficial. A first step in understanding the dendritic morphology of layer 5 pyramidal neurons is the observation that top-down input to the apical tree increases the gain of the firing rate in response to bottom-up input. We suggest that, beyond receiving attentional signals, the apical dendrite of L5 pyramidal neurons is also involved in deep learning where error signals are projected back to lower layers. In cortical networks, however, no such neuron-specific error signal could experimentally be identified so far. An alternative view is that the apical tree reconstructs the error signal based on a comparison between predictive lateral input and top-down input. When embedded in a local microcircuit, lateral projections targeting the apical dendrite learn to cancel top-down teaching input. The unpredicted novel component serves either as an attentional signal via gain modulation, or as an error signal which drives bottom-up plasticity. The proposed design matches features of anatomical cortical connectivity and is suggestive of a multi-compartment pyramidal-neuron-like structure. We demonstrate the ability of our networks to solve in continuous time a memory task otherwise unsolvable using simpler networks or learning rules. Our work opens the possibility that synaptic plasticity is approximating the backpropagation of errors algorithm in cortical networks.

Talk Session 5

GABA cells in lateral hypothalamus regulate feeding, locomotion and arousal

Marta Carus Cadavieco[1], Maria Gorbati[1], Suzanne van der Veldt[1], Natalia Denisova[1], Franziska Ramm[1], Franziska Bender[1], Karl Deisseroth[2], Alexey Ponomarenko[1], Tatiana Korotkova[1]

[1]Behavioural Neurodynamics Group, Leibniz Institute for Molecular Pharmacology (FMP)/ NeuroCure Cluster of Excellence, Berlin, Germany, [2]Howard Hughes Medical Institute; [3] Department of Bioengineering; [4] Department of Psychiatry and Behavioral Sciences, W080 Clark Center, 318 Campus Drive West, Stanford University, Stanford, USA

How the brain initiates, maintains and coordinates innate behaviors is largely unknown. Lateral hypothalamus (LH) is crucial for the regulation of innate behaviors, including food intake, locomotion and sleep-wake cycle. Combining optogenetics with neuronal recordings in behaving mice (Korotkova et al., Neuron 2010), we characterized state- and behavior-dependent activity of LH GABA cells. We found that optogenetic stimulation of LH GABA cells at various frequencies as well as stimulation of projections of these neurons changed transitions between innate behaviors. We showed that optogenetic stimulation of LH GABA cells and their connections regulates arousal (Herrera et al., Nature Neuroscience, 2016) whereas theta-rhythmic input onto LH cells regulates locomotion (Bender et al., Nature Communications, 2015). Combining optogenetics and chemogenetics (DREADDs) with multisite electrophysiological recordings in behaving mice, we report role of LH GABA cells and their projections in the feeding behavior. We further show that activation of LH GABA cells regulates feeding behavior by reorganization of functional cell assemblies in LH.

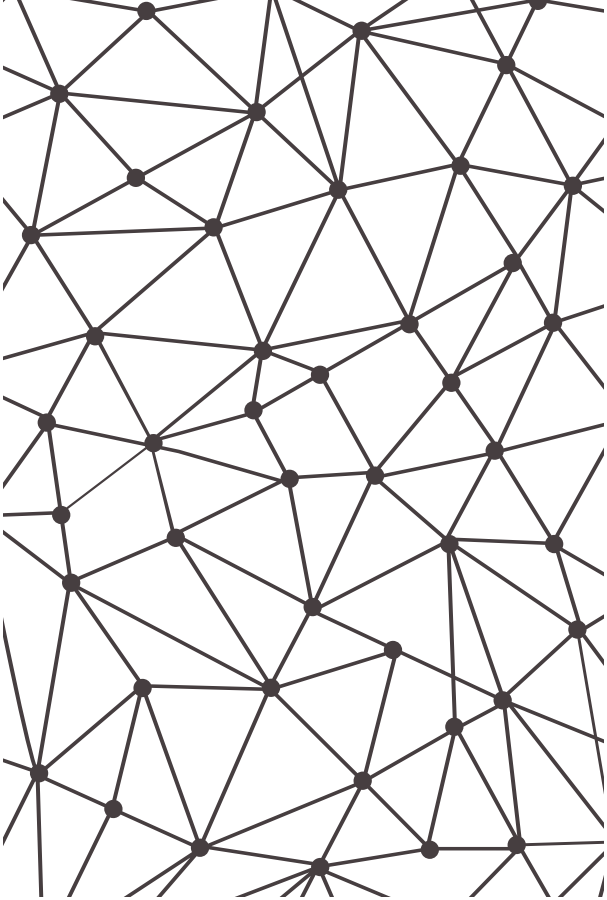
We gratefully acknowledge support by The Human Frontier Science Program (HFSP; RGY0076/2012, TK), the DFG (Exc 257, TK and AP, SPP1665, AP) and GIF (I-1326-421.13/2015, TK).

Talk Session 6

Evolution of acid sensing olfactory circuits in Drosophila

Lucia Prieto-Godino[1], Raphael Ritz[1], Benoite Bargeton[1], Liliane Abuin[1], Roman Arguello[1], Steeve Cruschet[1], Matteo dal Peraro[2], Richard Benton[1]
[1]CIG, UNIL, Lausanne, Switzerland, [2]EPFL, Lausanne, Switzerland

Animals adapt their behaviors to specific ecological niches, but the underlying genetic and cellular basis of nervous system evolution is poorly understood. We have compared the olfactory circuits of the specialist fly species Drosophila sechellia, which feeds and breeds exclusively on the acid-rich fruit of Morinda citrifolia, with its generalist cousins D. melanogaster and D. simulans, which are associated with a wide range of fermenting fruits. We have identified both loss and gain of sensory responses to acids in D. sechellia and link these to single nucleotide differences within a tandem cluster of olfactory receptor genes. Unexpectedly, we find that one of these receptors bears a premature stop codon (PTC), and yet encodes a functional receptor, due to efficient neuron specific translational read-through of the PTC. These peripheral functional differences are accompanied by regulatory and developmental modifications that shape the species-specific neuroanatomical organization of acid-sensing pathways. Our work links chemosensory ecology to genetic changes influencing nervous system structure and function across evolutionary time.



Poster Abstracts

22 thu

Poster Session I

1	Aaron	McGee	*Layer 4 gates disinhibition and drives feed-forward developmental visual plasticity through nogo receptor*
2	Adil	Khan	*Learning changes the selectivity and interactions of GABAergic interneuron classes in visual cortex*
3	Adrienn	Kovács	*Direct presynaptic and indirect astrocyte-mediated mechanisms both contribute to endocannabinoid signaling in the pedunculopontine nucleus of mice*
4	Ahnjili	ZhuParris	*A web based meta-analysis of microdosing of psychedelic drugs as a form on nootropics*
5	Alexander	Goltsev	*Network model of interictal and recurrent ictal activity in epilepsy*
6	Ana	Fernandes	*Postingestive mechanisms in instrumental reinforcement learning*
7	Ana Catarina	Certal	*The CCU Fish Platform: supporting Neuroscience zebrafish research through continuous development of husbandry and health programs, and advanced services*
8	Ana Sofia	Machado	*Optogenetic manipulation of distinct deep cerebellar nuclei differentially effects coordinated locomotion in mice*
9	André	Ponte	*Why use benzodiazepines in alcohol withdrawal treatment?*
10	Andreas	Genewsky	*Midbrain structures control extremes in fear and anxiety*
11	Anna	Krysiak	*Serum Response Factor: regulator of dendritic spines' maturation.*
12	Antonia	Groneberg	*Early life social environment in larval zebrafish affects behavior in social and non-social contexts*
13	António	Jácomo	*Behind and beyond the brain. Against a conceptual distinction between practical and philosophical neuroethics.*
14	António	Dias	*Modulation of PMv activity during social interactions in female mice*
15	Bahman	Sadeghi	*Role of chronic ghrelin in memory and synaptic plasticity enhancement in hippocampal CA2: restoration of long-term potentiation following amyloid β-induced Alzheimer's disease*
16	Ballázs	Rózsa	*Fast 3D imaging of spine, dendritic, and neuronal assemblies in behaving animals*
17	Barbara	Pijet	*MMP-9 in Traumatic Brain Injury: friend or foe?*
18	Bassam	Atallah	*Task engagement predicted by global dopaminergic activity during temporal judgements*
19	Boon Chuan	Low	*Vesicular Trafficking of Cholinergic Machinery in Acetylcholine Signaling Requires Scaffold Protein BNIP-H (Caytaxin) working in Concert with Kinesin Motor, Rab GTPases and Secretory Proteins*

20	Bruno	Afonso	*Circuit principles of neuronal processing in larval drosophila melanogaster thermotaxis*
21	Camille	Mazo	*GABAB receptors tune cortical feedback to the olfactory bulb*
22	Carlos	Mão de Ferro	*PyControl-GUI, a graphical software tool to control and analyse behavioural experiments.*
23	Catarina	Albergaria	*Locomotor activity modulates performance in delay eyeblink conditioning in mice*
24	Christopher	Roome	*Exploring input-output relations of neurons in vivo*
25	Claudia	Vargas	*Retrieving a context tree from EEG data*
26	Dana	Darmohray	*Cerebellum-dependent locomotor adaptation on a split-belt treadmill in mice*
27	Daniela	Razolli	*Hypothalamic inflammatory makers and POMC are differentially regulated in response to dietary fats in obese prone as compared to obese resistant mice.*
28	Danielle	Mersch	*Single fly behavioral responses to odor blends*
29	Danylo	Khomiak	*Novel peptidomimetic MMP-9 inhibitors as potential anti-epileptogenic therapeutics*
30	David	Ehrlich	*Improved control of movement initiation underlies the development of balance in zebrafish*
31	Deanna	Anderlini	*Why do only some patients recover their arm motor function? Role of mirror neurons in BA44.*
32	Diana	Costa	*Development of new tools to measure social hierarchy in the home-cage.*
33	Dmitry	Osmakov	*Natural low molecular weight compounds, modulating the acid-sensing ion channel 3*
34	Dmitry	Kobak	*Geometry and state-dependence of sound representations in rat auditory cortex*
35	Eduardo	Dias-Ferreira	*Dissecting stored variables underlying reinforcement learning in Drosophila*
36	Efrén	Álvarez-Salvado	*Algorithms underlying olfactory navigation in walking fruit flies*
37	Elena	Lorenzi	*Septum responds to elementary motion cues related to the perception of animacy in visually naïve chicks*
38	Emilia	Rejmak	*Cleavage of nectin-3 is blocked by MMP-9 specific inhibitor in the hippocampus upon neuronal stimulation*
39	Erika	Dona	*Development of sex-specific connectivity in Drosophila*
40	Éva	Kókai	*Correlative morphological and electrophysiological study of proenkephalin (PENK) expressing neurons in the spinal dorsal horn*
41	Felipe	Schmitz	*Methylphenidate Induces Neurons and Astrocytes Loss in Hippocampus and Behavior Changes in Juvenile Rat*
42	Francisco	Esteves	*Neural circuits controlling Prolactin release during sexual behavior*

23 fri

Poster Session II

43	Franz	Weber	*A brainstem circuit consolidating NREM sleep*
44	Gabriel	Madirolas	*Bayesian estimation and logarithmic-like representation lead to geometric mean optimal averaging in group estimation tasks*
45	Gabriela	Ribeiro	*Flavor-nutrient conditioning is disrupted by weight-loss surgery*
46	Gautam	Agarwal	*A high-dimensional interface to study complex decisions*
47	Georg	Ammer	*Functional Asymmetries in Drosophila Motion Vision*
48	Guliz	Ozcan	*Physiological, behaviorally relevant targets of amyloid beta sleep regulation in vivo*
49	Hayrullah	Köse	*Kir channel upregulation in the heart of PTZ induced epileptic rats*
50	Henrique	Ribeiro	*Dopamine, glutamate and biotypes in the future of schizophrenia*
51	Hugo	Cruces -Solis	*Neuronal correlates of auditory implicit learning in the mammalian midbrain*
52	Ida	Barlow	*Dreammist, a novel peptide implicated in Zebrafish sleep*
53	Ingrid	Fetter -Pruneda	*The neurobiology of social behavior: Characterization of the oxytocin/vasopressin system in ants*
54	Jacques	Bourg	*Transient Competitive Amplification during states of cortical activation*
55	Jaroslaw	Barski	*Motor coordination impairment and autistic like traits in Purkinje cell specific TSC1 knockout mouse*
56	Jasmine	Loveland	*The first step to filial imprinting: a neurobiological investigation of c-Fos expression in dopamine neurons and substance P effects during the first visual experience of newly hatched chicks (Gallus gallus)*
57	Jessica	Rodgers	*Functional characterisation of human melanopsin variants, P10L and T394I, using targeted AAV delivery in vivo.*
58	Jitka	Skrabalova	*The effect of morphine on beta-adrenergic signaling in rat cerebral cortex*
59	Joanna	Lau	*Premotor population codes controlling elementary motor behaviours*
60	João	Calmeiro	*Channelrhodopsin engineering and characterization of novel optogenetic tools designed in silico*
61	João	Fayad	*LocoMouse: A 3D Markerless Video Tracker for Mice*

62	João	Valadeiro	*Magnetoresistive sensors integrated in bendable probes for local field detection in neurosciences*
63	Johannes	Seelig	*Neural circuits underlying visuomotor integration in Drosophila*
64	Jonathan	Green	*A circuit architecture for angular integration in Drosophila*
65	Jose	Pardo-Vazquez	*Level-invariant accuracy through level-dependent speed in a sound lateralization task*
66	Juan	Castiñeiras	*Decision making under sensory uncertainty by stochastic optimal agents*
67	Judith	Reichel	*Interplay of GABAergic neurons and hypothalamic stem cells in the ageing process*
68	Karolina	Nader	*Adult deletion of SRF regulates structural plasticity in neurons*
69	Kathrin	Steck	*Identification of chemosensory neurons that mediate yeast and amino acid feeding in Drosophila melanogaster*
70	Kensaku	Nomoto	*The role of PGR-expressing neurons in the ventromedial hypothalamus on female sociosexual behavior*
71	Kuo-Hua	Huang	*Effects of autism-related genetic modifications in zebrafish on social behavior and neural activity*
72	Lara	Franco	*Win or Lose – Behavior, cellular and molecular characterization of social subordinance*
73	Laura	Grima	*The encoding of future reward by dopamine release is shaped by action initiation and is implicated in action selection.*
74	Laura	Pozzi	*A Parvalbumine-expressing Cell Population in the Lateral Habenula Promotes Anxiety-Related Behaviors*
75	Lisa	Fenk	*Quantitative predictions orchestrate visual signaling in Drosophila*
76	Luara	Batista	*The chemoreflex as an animal model of panic attack: pharmacological validity and modulation by the endocannabinoid system*
77	Marco	Tripodi	*Life-long genetic access to neural circuits using Self-inactivating Rabies virus*
78	Victòria	Brugada -Ramentol	*Effects of changes in ownership and agency on human behavioral variability, a virtual reality study.*
79	Maria	Silva	*Population receptive field size and cortical magnification factor changes across polar angle in human early visual cortex*
80	Maria Leonor	Godinho	*Single Nucleotide polymorphisms in the OXTR gene associated with social phenotypes: a review*
81	Marina	Camargo	*Eye movement behavior in the early detection of Alzheimer's disease: the impact of time and cognitive effort*
82	Marion	Ponserre	*Organization of central amygdala circuits controlling feeding and appetitive behaviours*
83	Michael	Pereira	*A novel navigation task for studying planning in the rodent brain*

24 sat

Poster Session III

84	Marta	Pereira	*Eye movement behavior predictive of cognitive decline in Alzheimer's disease*
85	Matthias	Meier	*Neural correlates of a visual motion detector in Drosophila*
86	May	Dobosiewicz	*Roles of chemical and electrical synaptic connections in sensory-to-interneuron communication in a C. elegans chemotaxis circuit*
87	Minas	Salib	*Diversity of medial septal neurons: State-dependent activity in awake mice and axonal target regions*
88	Mohamed	Edfawy	*The role of mGluR signaling and associated network proteins in the regulation of neuronal morphology and spine maturation*
89	Natalia	Barrios	*Taking the pulse of flies during defensive behavior.*
90	Nicholas	Olivas	*Diminished Network Sparseness in V1 Encodes Correct Performance Following Reward-based Associative Learning*
91	Nicole	Lindsay	*Motor cortex-directed movement of the mystacial vibrissae through pre-motor neurons in the spinal trigeminal nuclei*
92	Nikolaos	Balaskas	*Selective sensory-motor connections determined by dendritic and axonal positioning*
93	Olga	Babaev	*Neuroligin 2 and IgSF9b bi directionally regulate anxiety- related processing*
94	Paul	Pichler	*Efferent Modulation of Mechanical Information in Zebrafish larvae*
95	Paulina	Koza	*Altered AMPARs subunit composition as a result of TDP-43 neuronal depletion*
96	Paulo	Aguiar	*A unifying thermodynamics model for voltage-gated and temperature-gated channels*
97	Pavel	Itskov	*Automatic high-throughput measurement and manipulation of feeding behaviour.*
98	Pedro	Henriques	*Visual Attention in Zebrafish larvae*
99	Petra	Fischer	*Neural correlates of sudden stopping in patients with Parkinson's disease*
100	Philip	Avigan	*Prefrontal-CA1 interaction supports flexible spatial learning within a CA1-dependent task framework*
101	Rachel	Bhushan	*Impaired Episodic memory in William's Syndrome mice models*
102	Renata	Ferreira -Sgobbi	*The effects of hormonal levels on ketamine-induced prepulse inhibition disruption in female rats*

103	Renato	Martinho	*Defining new asymmetry markers of the zebrafish habenula.*
104	Rita	Lima	*2-AG into the dorsolateral periaqueductal gray of rats reduce the expression of conditioned contextual fear*
105	Robert	Hinz	*Ontogeny of collective behavior reveals a simple attraction rule*
106	Sabine	Reichert	*A sleep-like state induced by neuronal hyperactivity*
107	Sabine	Cordes	*Misregulation of an activity-dependent splicing network as a common mechanism underlying autism spectrum disorders*
108	Samantha	Herbert	*The control of protein appetite by neuronal nutrient sensing*
109	Samuel	Walker	*State- and experience-dependent modulation of gustatory neurons underlies protein appetite.*
110	Sara	Hänzi	*Interactions of vestibular stimulationand locomotor corollary discharge in Xenopus laevis tadpoles*
111	Sara	Matias	*Firing patterns of serotonin neurons underlying cognitive flexibility*
112	Silky	Arora	*Looking beyond the classical areas of speech production: Insights from the case studies*
113	Silvana	Araújo	*Investigation into the role of Dopaminergic cells in VTA during sexual behavior in male mice*
114	Sofia	Soares	*Midbrain dopamine neurons control judgment of time*
115	Stephanie	Wegener	*Encoding angular velocity to drive a compass in the Drosophila central complex*
116	Tomasz	Stępkowski	*mitoLUHMES - an engineered neuronal cell line for the analysis of mitochondrial motility*
117	Verónica	Corrales -Carvajal	*Internal states drive nutrient homeostasis by modulating exploration-exploitation trade-off*
118	Maria	Ribeiro	*Noradrenergic modulation of reaction time is task dependent*
119	Vivek	Athalye	*Closed-loop pairing of motor cortex activity and phasic VTA activation reinforces specific spatiotemporal activity patterns*
120	Yaroslav	Andreev	*Natural antimicrobial peptide potentiates TRPA1 receptor and produces analgesic effects in mice*
121	Yiling	Yang	*High Resolution Estimation of the Hemodynamic Response Function across Brain Regions*
122	Yulia	Lerner	*Brain plasticity following physical training in individuals with mild cognitive impairment: Neuroimaging study*
123	Yulia	Logashina	*TRPA1 modulator from sea anemone Metridium senile reduces antinociceptive behavior in mice.*
124	Zita	Carvalho-Santos	*Commensal bacteria and essential amino acids control food choice behavior and reproduction*

22 thu

Posters
1 to 42

I

Layer 4 gates disinhibition and drives feed-forward developmental visual plasticity through nogo receptor

Michael Frantz[1], Taruna Ikrar[2], Xiangmin Xu[2], Aaron McGee[3]
[1]University of Southern California, Los Angeles, CA, USA, [2]University of California - Irvine, Irvine, CA, USA, [3]University of Louisville, Louisville, KY, USA

Perturbing sensory experience can disrupt developing neural circuitry. In primary visual cortex (V1), depriving one eye of vision (monocular deprivation, MD) during a developmental 'critical-period' permanently degrades cortical responsiveness to that eye, a phenomenon termed ocular dominance (OD) plasticity. Yet where and how this experience-dependent visual plasticity emerges and propagates within the laminar circuitry of V1 is controversial. Here we explored how OD plasticity is governed with a conditional mutant of *nogo receptor 1 (ngr1)*, a gene required to close the critical period. Deleting *ngr1* selectively in the thalamorecipient layer 4 (L4), but not L2/3, L5, or L6, prevented the critical period from closing and was accompanied by a sustained capacity for disinhibition by parvalbumin-positive (PV) interneurons with MD. After only 2 days of MD, responses in L4 had shifted significantly more than L2/3 or L5 in both adult mice lacking *ngr1* selectively in L4 and critical-period WT mice. We propose that extracellular factors from myelin and peri-neuronal nets signal through NgR1 in L4 excitatory neurons to limit disinhibition and close of the critical period for feed-forward visual plasticity.

2

Learning changes the selectivity and interactions of GABAergic interneuron classes in visual cortex

Adil Khan[1], Jasper Poort[2], Antonin Blot[1], Thomas Mrsic-Flogel[1], Sonja Hofer[1]
[1]Biozentrum, Basel, Switzerland, [2]University College London, London, UK

Neural representations of sensory stimuli can be modified by experience. In the mouse primary visual cortex (V1), responses become increasingly selective when animals learn the behavioural relevance of visual stimuli. However, it is unclear how learning reorganises the activity of different cell types, including excitatory pyramidal (PYR) neurons and different classes of GABAergic interneurons that are thought to play distinct computational roles in cortical networks. We used two-photon calcium imaging of GCaMP6f signals to record responses of neuronal populations in layer 2/3 of V1 as mice learned to discriminate two visual patterns. After the behavioural experiments we co-registered immunostained brain sections with in-vivo recording sites to identify simultaneously imaged parvalbumin (PV), somatostatin (SOM) and vasoactive intestinal peptide (VIP) positive interneurons.
Within and across cell classes, neurons exhibited a large degree of heterogeneity in responses to the task-relevant stimuli, as well as in how the amplitude of their responses changed with learning. Learning increased stimulus selectivity in PYR but also in PV cells, that became as selective as PYR cells. Response correlations decreased over learning not only between cells belonging to the same class, but more strikingly, between cells from different classes. SOM cells in particular exhibited marked reduction in correlations with all other cell classes, and a subset of SOM cells that negatively correlated with VIP cells were linked to selectivity increases in PYR cells. These results demonstrate how learning the behavioural relevance of visual stimuli leads to concerted changes in the selectivity and co-activation patterns across multiple cell classes.

3

Direct presynaptic and indirect astrocyte-mediated mechanisms both contribute to endocannabinoid signaling in the pedunculopontine nucleus of mice

Adrienn Kovács, Csilla Bordás, Péter Szücs, Zoltán Hegyi, Miklós Antal, Balázs Pál
University of Debrecen, Debrecen, Hungary

The pedunculopontine nucleus (PPN), a cholinergic nucleus of the reticular activating system, is known to be involved in the regulation of sleep and wakefulness. Endogenous and exogenous cannabinoids, either by systemic or local administration to the pedunculopontine nucleus can both influence sleep. We previously demonstrated that activation of astrocytes by cannabinoid type 1 (CB1) receptor agonists was able to modulate the membrane potential of PPN neurons, even in the presence of blockers of fast synaptic neurotransmission. In the present work we provide evidence that synaptic inputs of PPN neurons are also affected by activation of presynaptic and astrocytic CB1 receptors.

Using slice electrophysiology combined with calcium imaging, optogenetics and immunohistochemistry, we revealed a direct presynaptic inhibitory action on inhibitory postsynaptic currents, along with a mild increase of excitatory postsynaptic currents during CB1 receptor stimulation. Besides inhibition of excitatory and inhibitory neurotransmission through stimulation of presynaptic CB1 receptors, astrocyte- and mGluR-dependent tonic inhibition and excitation also developed. The mild stimulatory action of CB1 receptor activation on excitatory neurotransmission is the combination of astrocyte-dependent tonic excitation on excitatory neurons and the canonical presynaptic CB1 receptor activation and consequential inhibition of excitatory synaptic neurotransmission, whereas the astrocyte-dependent stimulatory action was not observed on inhibitory neurotransmission within the PPN.

Our findings demonstrate that endocannabinoids act in the PPN via a dual pathway, consisting of a direct presynaptic and an indirect, astrocyte-mediated component, regulating synaptic strength and neuronal activity via independent mechanisms.

4

A web based meta-analysis of microdosing of psychedelic drugs as a form of nootropics

Ahnjili ZhuParris
Radboud University, Nijmegen, Germany

OBJECTIVE: Testimonials dating back to the 1960s have described the microdosing of LSD to have nootropic properties such as cognitive enhancement, physical boost, increased creativity and mindfulness. Microdosing refers to ingesting subperceptual amounts of psychedelic drugs.
RESEARCH DESIGN AND METHODS: This paper catalogued 600 reports from microdosing users from Reddit and Erowid. The drugs examined were Tryptamines (5-methoxy-N,N-dimethyltryptamine, Psilocybin),Ergolines, Phenethylamines (Mescaline, The 2C family, NBOMe derivative, 2,5-dimethoxy, 4-substituted amphetamines), Cannabinoids and Empathogens (Substituted methylenedioxy-phenthylamines). Self-reports of microdosing with prescribed nootropic drugs such as, psychostimulants (methylphenidate and amphetamine) and wakefulness-promoting agents (modafinil) were also collected. The data is composed of the methodology of the microdosing, which includes dosage, form of administration, tolerance and tolerance duration. Furthermore, the physiological and cognitive differs have been achieved, this encompasses sleep, side effects, appetite, motivation, concentration, memory, physical energy.
RESULTS: 56% of the users choose Ergolines for microdosing, 32% with Tryptamines, and 12% with Phenetylamines, Empathogens and Psychostimulants. Users experienced a variety of effects such as emotional clarity, enhanced senses, increased concentration and stamina. However there were several reports of reduced appetite, excessive sweating, reduced sleep, and digestive and warped time perception.

5

Network model of interictal and recurrent ictal activity in epilepsy

Alexander V. Goltsev[1], Marinho A. Lopes[2], KyoungEun Lee[1], Jose F. F. Mendes[1]
[1]Department of Physics & I3N, University of Aveiro, 3810-193 Aveiro, Portugal, [2]Wellcome Trust Centre for Biomedical Modelling and Analysis & College of Engineering, Mathematics and Physical Sciences, University of Exeter, Exeter, UK

We present a description of interictal and ictal activity based on a neuronal network model representing two networks of interacting excitatory and inhibitory neurons. This model allows us to reproduce recurrent seizures and analyze experimental data. In the interictal state of this model, interictal spikes emerge sporadically from a low background activity. These paroxysmal-like spikes are strongly nonlinear events that comprise nearly all neurons (about 90%) in synchronized activity. Although interictal spikes are collective events of the whole network, they can be elicit by a small perturbation applied to a small group of neurons (it is about or less than 1% of the whole neurons). There is an effective threshold which tends to zero as the neuronal network approaches a critical point above which ictal-like activity emerges in the form of high-amplitude low-frequency sustained network oscillations. The transition between these two dynamical states corresponds to a saddle-node bifurcation that is the mechanism of a second-order phase transition from the normal (interictal) state into the ictal state. We show that when the neuronal network approaches the bifurcation point, the power of the low-frequency spectrum of the neuronal activity increases and, thus, it is the precursor of the transition. Based on the proposed model we discuss recent electroencephalogram (EEG) and magnetoencephalography recordings of spike wave discharges in human absence epilepsy.

6

Postingestive mechanisms in instrumental reinforcement learning

Ana B. Fernandes[1], Joana Almeida[1], Rui M. Costa[1, 2], Albino Oliveira Maia[1, 2, 3]
[1] Champalimaud Centre for the Unknown, Lisbon, Portugal
[2] Nova Medical School, Universidade Nova de Lisboa, Lisboa, Portugal
[3] Department of Psychiatry and Mental Health, Centro Hospitalar de Lisboa Ocidental, Lisboa, Portugal.

While palatability is typically thought to be the main reinforcing property of food, recent findings, obtained in food preference assays, have demonstrated the importance of caloric content. Here, we proposed to determine the role of postingestive feedback in an instrumental reinforcement-learning task. To isolate postingestive stimulation, sucrose or a non-caloric sweetener (sucralose) was injected in Bl6 mice through an intragastric catheter, contingent upon lever pressing. Mice significantly increased lever pressing to obtain intragastric sucrose, but not sucralose. Consistently, in a simultaneous 2-lever choice task, mice showed a preference for the lever associated to intragastric sucrose over another lever associated to intragastric delivery of sucralose. Furthermore, Trpm5-/- mice, where sweet orosensory feedback is abolished, showed increased lever pressing to obtain access to sucrose, but not sucralose, confirming that postingestive mechanisms are sufficient to sustain instrumental behaviours. To explore the importance of dopaminergic neuronal activity for these behaviors, the single-lever instrumental task was repeated in mice with absent NMDA receptors in ventral tegmental area (VTA) dopamine-producing neurons. As expected, both control and KO mice increased lever pressing to obtain access to sucrose for oral consumption. However, only control, but not KO mice, increased lever pressing to obtain intragastric injection of sucrose, indicating that functional VTA dopaminergic neurons are fundamental to sustain instrumental behaviours through postingestive feedback. Thus, we have demonstrated that mice can learn a reinforcement learning task based exclusively in postingestive reinforcement, and that dopamine-producing neurons in the ventral tegmental area are necessary for these postingestive-dependent behavior to be acquired.

7

The CCU Fish Platform: supporting Neuroscience Zebrafish Research through continuous development of husbandry and health programs, and advanced services

Ana Catarina Certal, Sandra Martins, Joana Monteiro, Telma Costa
Champalimaud Centre for the Unknown, Lisbon, Portugal

The Champalimaud Centre for the Unknown (CCU) Fish Platform oversees a fish facility that houses, breeds and maintains wild-type, mutant and transgenic zebrafish with the most rigorous international health and welfare standards essential for biomedical research. The Platform also provides advanced supporting services to researchers such as fish crosses, complex maintenance of fish lines by phenotyping and genotyping, genetic screens, embryo microinjection, in vitro fertilization, advanced training, database management and continuous development of husbandry protocols. It is also the fish coordinator of a recently formed consortium (CONGENTO – Consortium for Genetically Tractable Organisms) aiming to provide external zebrafish services to the scientific community such as fish production, generation of transgenic and mutant fish (e.g. via Tol2 and CRISPR), genetic and drug screens and advanced training.

Here we present an integrated view of our facility management program focusing on relevant husbandry protocol development enabling a life cycle of 60 days at a density of 10 fish/L and optimal survival and breeding performance*. We also disclose our rigorous health program as well as some of the most useful services offered to our neuroscience researchers.

* S. Martins, J.F. Monteiro, M. Vito, D. Weintraub, J. Almeida, A.C. Certal (2016) Toward an Integrated Zebrafish Health Management Program Supporting Cancer and Neuroscience Research. Zebrafish 13(1):S47-S55; DOI: 10.1089/zeb.2015.1198

8

Optogenetic manipulation of distinct deep cerebellar nuclei differentially effects coordinated locomotion in mice

Ana S. Machado, Megan R. Carey
Champalimaud Centre for the Unknown, Lisbon, Portugal

Smooth and efficient walking requires the coordination of movement across different parts of the body. The cerebellum plays an important role in this process, yet the specific neural circuit mechanisms of whole-body coordination are poorly understood. We have recently described LocoMouse, a system for high resolution tracking of locomotion, and used it to establish a quantitative framework for whole-body locomotor coordination in mice (Machado, Darmohray et al. elife 2015). We are now combining this approach with optogenetics to ask how different output regions of the cerebellum differentially contribute to locomotor coordination. We expressed ChR2 in Purkinje cells and stimulated their terminals in the medial, interposed, and lateral cerebellar nuclei of freely walking mice. Here, we identify locomotor parameters that were specifically related to the manipulation of each nucleus. Acute disruption of neural activity in medial and interposed nuclei immediately perturbed ongoing locomotion. In contrast, similar manipulation of Purkinje cell inputs to the lateral nucleus had no observable effect on ongoing locomotor behavior. These results are broadly consistent with previous anatomical and lesion studies suggesting a medial-to-lateral functional organization of cerebellar outputs.

9

Why use benzodiazepines in alcohol withdrawal treatment?

A. Ponte, H. Prata Ribeiro, M. Duarte, L. Carvalhão Gil, M. Lázaro, S. Henriques, J. Teixeira
Psychiatry, Centro Hospitalar Psiquiátrico de Lisboa, Lisbon, Portugal

Introduction: Alcohol withdrawal syndrome (AWS) occurs when alcohol consumption is suddenly reduced or stopped after a period of high and regular intake. Typical symptoms include agitation, tremor and tachycardia, and, sometimes, seizures and altered consciousness.

Objectives: We reviewed the literature to ascertain why benzodiazepines are still recommended as first-line treatment for AWS and what other alternatives there are.

Methods: We conducted a search on PubMed, using "alcohol withdrawal" and "benzodiazepines" as keywords.

Results: Alcohol's inhibitory effects in the brain are primarily achieved via the neurotransmitter GABA. Alcohol causes an increased release of the GABA neurotransmitter and enhances the sensitivity of GABA-A receptor subtypes, resulting in an increase of inhibitory neurotransmission. Alcohol also inhibits the binding of glycine to the NMDA receptors, preventing the excitatory action of glutamate on the NMDA receptors. With chronic alcohol ingestion, the brain undergoes functional adaptations that result in tolerance. Sudden alcohol reduction exposes the inappropriately upregulated glutamate neurotransmission and suppressed GABA activity, resulting alcohol withdrawal. Benzodiazepines are the most commonly used compounds for managing alcohol withdrawal. They act as positive allosteric modulators of GABA-A receptors, augmenting the inhibitory activity. Nonbenzodiazepine anticonvulsants may be effective for the treatment of mild-to-moderate cases, as an adjunctive treatment and/or in mild-to-moderate withdrawal of low-risk patients in outpatient settings.

Conclusions: A greater understading of how our intervention in the AWS affects patients is important and will lead to better outcomes. Benzodiazepines are still the mainstay of treatment in alcohol withdrawal but nonbenzodiazepine anticonvulsants may serve a helpful adjunct role.

10

Midbrain structures control extremes in fear and anxiety

A. Genewsky, N. Scheithauer, S.A. Bura, M. Nussbaumer, P. Kaplick, S.F. Kaltwasser, C.J. Riebe, M. Engel, B.T. Bedenk, M. Czisch, C.T. Wotjak
Max-Planck Institute of Psychiatry, Munich, Germany

The neuronal circuits that mediate the perception and evaluation of threatening stimuli, are essential for survival. They allow an animal to evade an approaching predator quickly, by triggering fear reactions. Changes in these circuits can generate maladaptive responses to fearful stimuli, resulting in either an exaggerated or blunted behavioral repertoire. Thus we were interested if extremes in trait-anxiety in a mouse model of anxiety-related behavior, lead to alterations in threat detection. Upon the confrontation with a Robocat, high anxiety-related behavior (HAB) mice displayed escape and flight responses, even if they were not directly approached, whereas low anxiety-related behavior (LAB) mice where entirely tolerant to movements of the Robocat and also frequently collided, indicative of threat negligence. Analysis of tonic brain activity changes by manganese-enhanced MRI (MEMRI) pointed to decreased neural activity at primary centers of threat detection (superior colliculus, periaqueductal gray). Therefore we studied consequences of chemogenetic enhancement of neuronal activity on threat detection in LAB mice. Activation of hM3Dq by clozapine-*N*-oxide within the superior colliculus, leads to an increase in anxiety-related behavior and threat detection. Pharmacological inactivation of the dorsolateral subdivision of the periaqueductal gray in LAB mice, drastically decreased anxiety-related behavior as well as sonic distress calls, indicative of a switch from passive to active fear-coping strategies. Taken together, this demonstrates the power of combined in vivo imaging, chemogenetics and refined ethobehavioral studies, in elucidating the neural basis in pathologically altered responses to real or potential threats.

II

Serum Response Factor: regulator of dendritic spines' maturation.

Anna Krysiak, Anna Suska, Szymon Leski, Leszek Kaczmarek, Katarzyna Kalita
Nencki Institute of Experimental Biology PAS, Warsaw, Poland

Dendritic spines are morphologically heterogeneous and there is a relationship between spine structure and function. During brain development, dendritic spines' shapes change from thin elongated filopodia-like structures to stable mushroom forms. These changes play a critical role in proper synaptic transmission and neural circuit formation. In our study we investigate potential new role of SRF (Serum Response Factor), one of the major transcription factors in neurons, in regulation of structural plasticity during brain development. We found that SRF expression alters within the course of postnatal development of mouse hippocampus in vivo. Next, we examined results of SRF depletion during dendritic spines formation in primary rat hippocampal culture. Neurons with low level of SRF have greater number of filopodia-like protrusions and lesser number of mushroom spines with the lack of changes in the overall density of dendritic spines. Moreover, spines of SRF-depleted neurons exhibit altered morphology, determined by increased length and area of filopodia-like spines. To study whether observed morphological changes influence number of functional synapses and their activity we analyzed AMPAR-mediated miniature excitatory postsynaptic currents (mEPSCs). The analysis revealed reduction in the frequency and amplitude of mEPSCs in SRF-depleted cells. Obtained results are in agreement with our observation that SRF depleted neurons have lower level of surface AMPAR GluR1 and GluR2 subunits. Our results support the notion concept that SRF regulates transcription of genes essential for spine development maturation and synapse formation during hippocampal development.

I2

Early life social environment in larval zebrafish affects behavior in social and non-social contexts

Antonia H Groneberg, João C Marques, Michael B Orger, Gonzalo G Polavieja
Champalimaud Centre for the Unknown, Lisbon, Portugal

Early social experience can have long lasting effects on social behavior and development. Zebrafish are a shoaling species with oviparous development and transparent bodies in the larval stage, allowing for non-invasive imaging of neural activity as well as very controlled manipulation of the environment during very early development. Here we set up to test how the social environment during early development affects the development of social and non-social behavior. We reared wild-type zebrafish in isolation or in groups until 6 days post fertilization and subsequently measured spontaneous locomotion at high temporal resolution, allowing for the analysis of single tail beats. Our results show that when swimming in groups or pairs, isolatedly raised larvae avoid each other at a larger distance than group raised larvae. This difference was absent when the same test was performed in darkness, suggesting that this increased avoidance is visually mediated. Further, we noticed several differences in morphology, as well as general locomotion kinetic parameters irrespective of the social context during testing when comparing isolated and group raised larvae. In summary, we here characterized a model of social isolation during early development in larval zebrafish. Further molecular, behavioral and neural circuit experiments will allow us to study how the developing brain is altered when exposed to social deprivation early in life.

13

Behind and beyond the brain. Against a conceptual distinction between practical and philosophical neuroethics.

António Jácomo, Carlos Gomes, Susana Magalhães
Institute of Bioethics, Porto, Portugal

Recent advances in neurosciences promote a neuroethical debate, often shrouded in skepticism and lack of concern. The nature of the brain has attracted philosophers and scientists for thousands of years. However, can modern neuroscience ever hope to crack this mysterious secret?
The purpose of this reflection is to contest the classical distinction synthetized by the slogan "brain of the ethics" and the "ethics of the brain".
In our perspective, this traditional split is harmful to the main goal of neuroethics and its social impact on society.
For a sustainability of this new proposal we launch a vision and a method with three avenues: research interaction; both side training and join publishing policy.
As a conclusion, faced with the brain complexity, neuroscience leads us to a kind of humility. The real triumph of neuroscience would be to make us aware of "how" we can discover: using correct methods, and relying on the structure of science as a basis of knowledge, we can understand not only the world but also the experience of ourselves. This is the framework within which we could fit Neuroethics; which is not knowledge, but gives "meaning to learn" through a set of proposals for the integration of scientific advances in the context of a genuine humanity.
What is the practical impact of this change? The deepening neuroscience expertise of many neuroethicists and the migration of neuroscientists to the field of neuroethics.

I4

Modulation of PMv activity during social interactions in female mice

António Dias, Susana Lima
Champalimaud Centre for the Unknown, Lisbon, Portugal

Choosing a suitable partner with whom to mate is one of the most important decisions an animal has to make during its lifetime. In most species, females are the choosier sex and their decision is influenced by a variety of elements. These include the female's own reproductive state, e.g. whether she is sexually receptive or not, and cues from potential mating partners, e.g. vocalizations and pheromones. In rodents, the activity of several brain areas is modulated during sociosexual behavior. However, the role of each one of those areas and especially how they work together to orchestrate complex behavioral decisions is still largely unknown. Our lab has previously shown that neurons in the ventrolateral region of the ventromedial hypothalamus (VMHvl) of female mice, a region fundamental for the execution of female sexual behavior, are activated during social interactions between conspecifics, with a preference for male-associated stimuli. One of the major input areas to the VMHvl is the ventral portion of the Premammillary Nucleus (PMv). Previous work using immediate early genes has shown that the PMv increases its firing when animals are exposed to soiled-bedding from conspecifics. This suggests that the PMv could play an important role in the neuronal circuitry processing olfactory cues relevant for sexual behavior. Using fiber photometry to measure calcium transients in PMv neurons, we are investigating the activity of this brain region during social and sexual interactions with conspecifics. Preliminary results show that the activity of female PMv neurons is modulated by male, but not female, stimuli.

I5

Role of chronic ghrelin in memory and synaptic plasticity enhancement in hippocampal CA2: restoration of long-term potentiation following amyloid -induced Alzheimer's disease

Bahman Sadeghi
Shahid Beheshti University of Medical Sciences, Department of Physiology, Tehran, Iran

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by memory loss and cognitive deficits following cerebrovascular deposits of amyloid. Ghrelin is a hormone which has been associated with neuromodulation, neuroprotection, memory and learning processes. This study investigated the effects of ghrelin-induced memory retention on amelioration of cognitive deficits via restoration of long-term potentiation and induction of synaptic plasticity in hippocampal CA2, using a rat model of AD induced by amyloid-β (1-42) injection. Five groups of male rats (n=40, 230-270 g) including control (intact), sham-operated, ghrelin-treated (200 ng /rat, intracerebroventricular (ICV), daily for two weeks), Aβ1-42 injected (5 µl/rat) and Aβ1-42 plus ghrelin-treated animals were designed. Ghrelin was administered after an ICV injection of Aβ1-42. To assess cognitive performance and the motor dysfunction, passive avoidance tests and open-field were performed, respectively. Step-through latency (STL) was evaluated as learning and memory index. Intrahippocampal field potential recordings were done and LTP were used to detect the electrophysiology changes. Results showed that following Aβ1-42 injection, STL and induction of LTP were significantly decreased whereas ICV injection of ghrelin significantly enhanced memory retention by improvement of STL and restitution of LTP in CA2 with increased EPSP slope and PS amplitude, suggesting the involvement of ghrelin in postsynaptic mechanisms of hippocampal LTP. It was revealed that neuroprotective effects of chronic ghrelin not only can enhance but also can restore LTP in CA2 area in Aβ-induced AD. Therefore, ghrelin may be considered as a promising therapeutic agent to alleviate cognitive deficits of AD.

I6

Fast 3D imaging of spine, dendritic, and neuronal assemblies in behaving animals

Gergely Szalay[1*], Linda Judák[1*], Gergely Katona[1,3*], Pál Maák[4], Katalin Ócsai[3], Máté Veress[4], Zoltán Szadai[1,2], Tamás Tompa[2], Balázs Chiovini[1,2], Balázs Rózsa[1,2]

1. Two-Photon Imaging Center, Institute of Experimental Medicine, Hungarian Academy of Sciences, Budapest-1083, Hungary.
2. The Faculty of Information Technology, Pázmány Péter Catholic University, Budapest-1083, Hungary.
3. MTA-PPKE ITK-NAP B – 2p measurement technology group, The Faculty of Information Technology, Pázmány Péter Catholic University, Budapest-1083, Hungary.
*4. Department of Atomic Physics, Budapest University of Technology and Economics, Budapest-1111, Hungary.**
corresponding address: rozsabal@koki.hu

Understanding neural computation requires methods such as three-dimensional (3D) random-access point scanning that can simultaneously read out neural activity on both the somatic and dendritic scales. This method can increase measurement speed and signal-to-noise ratio (SNR) by several orders of magnitude, but suffers from one main disadvantage: fluorescence information is lost during brain movement. In this work we present a novel technology, 3D DRIFT acousto-optical scanning, which can extend each scanning point to small 3D lines or surface or volume elements, preserving fluorescence information for motion correction. Our method effectively eliminates *in vivo* motion artifacts, allowing fast 3D measurement of over 150 dendritic spines with 3D lines, over 100 somata with squares and cubes, or multiple spiny dendritic segments with surface and volume elements in behaving animals. Finally, a four-fold improvement in total excitation efficiency resulted in about 500 µm × 500 µm × 650 µm, scanning volume with GECIs.

I7

MMP-9 in Traumatic Brain Injury: friend or foe?

Barbara Pijet, Marzena Stefaniuk, Emilia Rejmak-Kozicka, Leszek Kaczmarek
Institute of Experimental Biology PAN, Warsaw, Poland

Epilepsy in 20% of cases, develops as an effect of traumatic brain injury (TBI). Recent evidences indicate important role of extracellular **matrix metalloproteinase-9** (MMP-9) in neuronal synaptic plasticity. **The aim of the present study** was to establish and characterize the experimental model of TBI and evaluate the MMP-9 activity changes and dendritic spines reshaping after brain injury. As an animal model of TBI we used Controlled Cortical Impact CCI. After different time points we analyzed: lesion volume, MMP-9 activity, changes in dendritic spines parameters. Progressive cortex degeneration and structural changes in the hippocampus were observed during 30d after CCI. This effect was MMP-9 expression level dependent. In mice with deficiency of MMP-9 the degeneration volume degree was significantly lower, compared to wild type and overexpression mice. The gel zymography analysis showed time-associated elevation of MMP-9 activity in ipsilateral Cx, Hp and Thalamus within 30d after CCI. Density of the spines labeled with fluorescent dye, measured after 7&14d after CCI was significantly decreased in ipsilateral Cx and CA1 field of Hp. We aimed also at characterizing variations in dendritic spines shape related with its function. Length to width ratio of spines was decreased in ipsilateral Cx and CA1. Moreover we observed increase of spine head width in ipsilateral CA1 and Cx. We described the correlation between TBI and MMP-9 activity and indicated that MMP-9 might be important for major dendritic spine reshaping, observed after brain injury, which in consequence may lead to altered sensibility of neuronal circuits to trigger seizures.

I8

Task engagement predicted by global dopaminergic activity during temporal judgements

Bassam V Atallah, Sofia Soares, Joseph J Paton
Champalimaud Centre for the Unknown, Lisbon, Portugal

Moment-to-moment variability in the accuracy of our judgements is a ubiquitous feature of our experience. This variability is thought to be largely related to changes in our motivation and ability to engage with a task in a particular instant. Here we study this variability in task engagement in the context of temporal judgements. Midbrain dopamine (DA) neurons have been implicated in time estimation as well as motivation and attention. Indeed we establish a direct link between dopamine neurons and temporal judgements: pharmacogenetic inhibition of these neurons decreased mice's sensitivity to time while performing a freely-moving temporal categorization task.
We then use fiber photometry to measure dopaminergic activity in either the SNc or the VTA both while subjects: 1) chose to initiate and engage in the task and 2) during the execution of temporal judgments (see our sister poster: Midbrain dopamine neurons modulate judgment of time). Here we focus on the former and observed substantial variability in dopaminergic activity 2 seconds before a subject engaged in the task by initiating a trial. This variability in dopaminergic tone was predictive of the subjects engagement: performance on trials preceded by high levels of dopaminergic activity was systematically impaired relative to performance following lower dopaminergic activity. Furthermore, this was a global feature of dopaminergic activity as we observed it both in VTA and the SNc neurons. These data demonstrate that moment-to-moment fluctuation in task performance can be predicted by dopaminergic activity levels long before judgments are executed.

I9

Vesicular Trafficking of Cholinergic Machinery in Acetylcholine Signaling Requires Scaffold Protein BNIP-H (Caytaxin) working in Concert with Kinesin Motor, Rab GTPases and Secretory Proteins

Jichao Sun[1], Catherine Qiurong Pan[1], Tiweng Chew[1], Fengyi Liang[2], Margit Burmeister[3], Boon Chuan Low[1]

[1]Department of Biological Sciences and Mechanobiology Institute, National University of Singapore, Singapore, Singapore, [2]Department of Anatomy, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore, [3]Department of Human Genetics, Department of Psychiatry and The Molecular and Behavioral Neuroscience Institute, University of Michigan, Ann Arbor, USA

The neurotransmitter acetylcholine (ACh) is essential for neuronal development, memory, learning and motor movement. It is synthesized from choline and acetyl-CoA by choline acetyltransferase (ChAT). ATP citrate lyase (ACL) is a key metabolic enzyme that produces the acetyl-CoA for this process. However, the precise spatial disposition of this cholinergic machinery for both morphogenesis and neurotransmission remain largely unknown.

Mutations in the *ATCAY/Atcay* gene, which encodes BNIP-H (also known as Caytaxin), lead to ataxia and mental retardation in humans (Cayman ataxia), as well as ataxia and dystonia in several rodent models. Recently, we used molecular genetics, biochemical and imaging methods and revealed that BNIP-H recruits the cholinergic machinery to neurite terminal to regulate cholinergic signaling (*Developmental Cell, 2015*). BNIP-H links kinesin-1 (KLC1) motor protein to ACL and transports ACL towards neurite terminal. There, the BNIP-H/ACL complex synergistically recruits ChAT, leading to enhanced secretion of Ach which then activates MAPK/ERK via muscarinic receptors to promote neuritogenesis. In mice deficient in BNIP-H, ACL fails to interact with KLC1, and formation of the ACL/ChAT complex is prevented. Significantly, Bnip-h knockdown in zebrafish causes axon defect of motor neuron through impaired cholinergic pathway, leading to motor disorder. We further show that BNIP-H specifically engages Rab11 GTPases and Sec15, a component of the actin-based exocyst complex, to regulate its dynamic disposition and neurologic function. Our results provide the first molecular evidence that precise spatial regulation of the cholinergic machinery is crucial in neuronal differentiation and neurotransmission, the significance of which will be further discussed.

20

Circuit principles of neuronal processing in larval drosophila melanogaster thermotaxis

Bruno Afonso[1], Mason Klein[2], Matthew Berck[3], Marc Gershow[4], James Truman[1], Simon Sprecher[5], Albert Cardona[1], Aravinthan Samuel[2], Marta Zlatic[1]
[1]HHMI Janelia, Ashburn, VA, USA, [2]University of Miami, Coral Gables, FL, USA, [3]Harvard University, Cambridge, MA, USA, [4]NYU, New York City, NY, USA, [5]Université de Fribourg, Fribourg, Switzerland

An important goal of systems neuroscience is to understand the computational process by which neural circuits use sensory information to generate adaptive behaviors. Drosophila larvae avoid excessively cool temperatures using a small set of sensorimotor transformations regulating the frequency and outcome of navigational decisions. During each navigational decision, larvae sweep their head from side to side, gathering thermal information that informs the choice of a new direction for forward movement.

Automated trajectory and posture analysis of individual animals navigating temperature gradients enables us to quantify navigational decisions of each animal. We have identified two distinct groups of projection neurons that when inactivated exclusively modulate individual navigational decisions, such "which way to turn" and "when to turn". We mapped the "hits" from the behaviorally screen using EM reconstruction and found they receive direct synaptic inputs from cold sensing neurons. We then mapped all of their downstream partners using EM reconstruction identifying key candidate descending neurons that project to nerve cord.

We are currently characterizing the computational dynamics of these elements of larval navigation circuits by measuring and manipulating neuronal activity in freely moving and/or restrained animals using novel methods in optical neurophysiology.

21

$GABA_B$ receptors tune cortical feedback to the olfactory bulb

Camille Mazo, Gabriel Lepousez, Antoine Nissant, Matthew T. Valley, Pierre-Marie Lledo
Institut Pasteur, Paris, France

Sensory perception emerges from the confluence of sensory inputs that encode the composition of external environment, and top-down feedback that conveys information from higher brain centers. In olfaction, sensory inputs activity is initially processed in the olfactory bulb (OB), serving as the first central relay, before being transferred to the olfactory cortex. In addition, the OB receives dense connectivity from feedback projections, thus the OB has the capacity to implement a wide array of sensory neuronal computation. However, little is known about the impact and the regulation of this cortical feedback. Here we describe a novel mechanism to selectively gate glutamatergic feedback from the anterior olfactory cortex (AOC) to the OB. Combining in vitro and in vivo electrophysiological recordings, optogenetics and fiber photometry-based calcium imaging, applied to wild-type and conditional transgenic mice, we explore the functional consequences of circuit-specific GABA type-B receptors ($GABA_B$Rs) manipulation. We found that activation of presynaptic GABABRs specifically depresses synaptic transmission from the AOC to OB inhibitory interneurons but spares direct excitation to principal neuron. As a consequence, feedforward inhibition of spontaneous and odor-evoked principal neuron activity is diminished. We also show that tunable cortico-bulbar feedback is critical for generating beta but not gamma OB oscillations. Together, these results indicate that $GABA_B$Rs on cortico-bulbar afferents gate excitatory transmission in a target specific manner and as such, shape how the OB integrate sensory inputs and top-down information.

22

PyControl-GUI, a graphical software tool to control and analyse behavioural experiments.

Carlos Mão de Ferro, Ricardo Ribeiro, Thomas Akam
Champalimaud Centre for the Unknown, Lisbon, Portugal

Setting up experiments to collect and study data from animals' behaviours can be technically demanding, specially when hardware and software are required for the automation of tasks with low latency responses. Often, to overcome these challenges, researchers make use of generic purpose open-source electronics platforms and try to adapt them to their specific needs. The current state of the art includes popular frameworks like Arduino, Raspberry Pi, or Micropython that, although abstracting the hardware and offering a high-level language development, still require advanced computer science skills. Besides these frameworks were not designed with behavioural experiments in mind, they focus on the data acquisition and researchers have to use alternative software tools to visualize and monitor the experiments results.

To address these issues, we developed PyControl-GUI, a graphical and cross platform tool to control and analyse behavioural experiments. Built on top of the Pycontrol framework, it offers specific features that alleviate the researchers work such as simplified planning of the experiments, real-time plotting of running behaviour tasks, hardware setup is much simplified and experiments data format is standardized. Furthermore, through the installation of plugins, the application can be easily extended with extra functionalities. Already developed plugins include the control of experiments from remote computers or macros that can be triggered depending on the state machine events.

The PyControl-GUI has been tested with the pyboard hardware (which uses Micropython) but other devices can be used in the future.

23

Locomotor activity modulates performance in delay eyeblink conditioning in mice

Catarina Albergaria, N. Tatiana Silva, Dominique Pritchett, Megan R. Carey
Champalimaud Centre for the Unknown, Lisbon, Portugal

In mice, locomotor activity modulates sensory responses across visual, auditory and somatosensory cortices. Here we show that locomotion also modulates behavioral performance in delay eyelid conditioning, a cerebellum-dependent form of classical conditioning. In head-fixed mice that were running voluntarily on a running wheel, we monitored both eyelid responses and running speed. We found that increased locomotion was associated with earlier onset of learning and more frequent and larger amplitude conditioned responses. The correlation between running and learning was specific to conditioned (vs. unconditioned) responses. It held across animals, sessions, and trials, and for conditioned stimuli of various modalities. In contrast to the previously described modulation of sensory cortical processing, we found that the influence of locomotion on conditioned responses was dissociable from effects of arousal as measured by changes in pupil size. Locomotor activity on a motorized treadmill also modulated learning in a speed-dependent manner, further suggesting that locomotor activity per se, rather than arousal, mediates the effect. To investigate the underlying neural circuit mechanisms, we used direct optogenetic stimulation of cerebellar mossy fibers as a conditioned stimulus. Conditioned responses elicited by optogenetic stimulation within the cerebellar cortex were also positively modulated by locomotor activity, indicating that enhanced sensory processing of the conditioned stimulus cannot account for the modulation of the behavioral response. We conclude that locomotor activity modulates learned performance in delay eyelid conditioning through mechanisms that are distinct from those underlying modulation of sensory cortical responses and that act downstream of mossy fiber inputs to the cerebellar cortex.

24

Exploring input-output relations of neurons in vivo

Christopher Roome, Bernd Kuhn
Okinawa Institute of Science and Technology, Okinawa, Japan

Measuring input-output relations of single neurons in vivo is very important for understanding how the brain works. So far, the most complete input-output relations were measured in brain slices, which lack physiological input to dendrites and soma. Here we combine two-photon microscopy and electrophysiology to simultaneously measure dendritic voltage and calcium signals (inputs) and somatic output from Purkinje cells (PC) in vivo. To record dendritic voltage optically we labelled single PCs with the voltage sensitive dye ANNINE-6plus, using a chronic cranial window with access port (Roome and Kuhn, 2014). For dendritic calcium recording, adeno-associated viruses delivering the gene of the genetically encoded calcium indicator GCaMP6f, was injected prior to ANNINE-6plus labelling. Extracellular electrophysiology was also performed at the labelled PC soma to record their somatic activity. Combing techniques allows measurement of voltage and calcium changes in the PC dendrite and simultaneous electrical recording from the PC soma in the cerebellum of awake mice. By dissecting input-output relations at a single cell level within the intact brain, we aim to address important questions concerning neuronal computations in vivo. Here we show how coincident input to the PC dendrite by climbing fibres and its ongoing background activity permits spatial modulation of dendritic spiking and thus creates 'hotspots' for dendritic integration.

25

Retrieving a context tree from EEG data

Aline Duarte[1], Ricardo Fraiman[2], Antonio Galves[1], Guilherme Ost[1], Claudia D. Vargas[3]
[1]Instituto de Matemática e Estatistica da Universidade de São Paulo, Sao Paulo, Brazil, [2]Centro de Matematica da Universidade de la Repúbica, Montevideo, Uruguay, [3]Instituto de Biofísica Carlos Chagas Filho, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil

Since the pioneer work of von Helmholtz (1867) it has been widely conjectured that the brain does statistical model selection by assigning probabilistic models to samples of stimuli. Here we present a novel approach based on the introduction of a new class of stochastic processes driven by context tree models allowing addressing this conjecture. Using this class of stochastic processes, it is possible to establish a formal relationship between structured sequences of random stimuli and the processing of the stimuli in the brain. This framework associates to an experimental protocol that can be summarized as follows: a volunteer is exposed to sequences of auditory stimuli whose sequences are generated step by step by a random source whose structure is defined by an algorithm that sets the probabilities of occurrence of each next unit. Electroencephalographic (EEG) signals are recorded during the exposure to the sequence of stimuli. The conjecture is that the volunteers' brain automatically identifies the context tree characterizing the source. If this is the case, a signature of the structure of the source should be encoded in the brain activity. The question whether this signature can be identified in the EEG data recorded during the experiment is faced here by the introduction of a new model selection procedure for functional data driven by a context tree model. Applied to samples of electrophysiological trajectories collected during structured auditory stimuli presentation, this procedure produces results supporting the conjecture that the brain effectively identifies the context tree characterizing the source. NeuroMat/FAPESP (2013/07699-0)

26

Cerebellum-dependent locomotor adaptation on a split-belt treadmill in mice

Dana Darmohray, Jovin Jacobs, and Megan R. Carey
Champalimaud Centre for the Unknown, Lisbon, Portugal

Locomotor patterns are constantly adapted for changing environments but the neural mechanisms underlying this basic form of learning are not well understood. Locomotor adaptation has been extensively studied in humans, using a split-belt treadmill that controls the speeds of opposite body sides independently (Reisman et al, 2005). Here, we describe split-belt adaptation in mice, using high-speed videography and 3D whole body tracking (Machado, Darmohray et al, 2015). We find that mice learn to adapt their locomotor patterns to achieve a more symmetrical gait in a way that is remarkably similar to human adaptation: measures of interlimb coordination adapt to become more symmetrical over several minutes of split-belt walking. A stable walking pattern is learned, in which each side of the body matches the speed of its belt, while interlimb and whole-body coordination improves to enable a more symmetrical gait. To investigate the neural substrate of this adaptation, we tested two cerebellar mutants (pcd and reeler) on the split-belt treadmill. While these ataxic mutants were able to respond appropriately to the changes in belt speed, they showed no evidence of learning. Interlimb coordination did not adapt over the course of split-belt walking, and there were no aftereffects observed post-adaptation. Thus, split-belt locomotor adaptation in mice, as in humans, appears to be a cerebellum-dependent form of learning. Our results suggest that the neural mechanisms of locomotor adaptation may be conserved across species, opening up the possibility of using genetic manipulations to dissect the neural circuit mechanisms underlying this form of motor learning.

27

Hypothalamic inflammatory makers and POMC are differentially regulated in response to dietary fats in obese prone as compared to obese resistant mice.

Daniela Soares Razolli, Licio Augusto Velloso
State University of Campinas, Campinas, São Paulo, Brazil

Hypothalamic dysfunction has emerged as an important determinant of diet-induced obesity (DIO). However, it is unknown what mechanism is the trigger of this process. Here, we employed obese prone (OP) and obese resistant (OR) mice to evaluate three hypotheses. The first hypothesis was that consumption of dietary fats (HF) would promote early changes in gut microbiota leading to increased gut permeability to LPS and/or fatty acid (FA) that could trigger hypothalamic dysfunction. Sequencing of the 16S rRNA revealed no differences in gut bacterial communities between OP and OR prior or one day after HF. The second hypothesis was that HF or systemic infusion of FAs would lead to an early differential increase of blood free FAs. Non-esterified FA determination revealed that after one-day treatment, systemic FAs were similar in OP and OR submitted to either treatment. Finally, the third hypothesis was that FAs would promote different regulations of either inflammation or neuropeptide expression in hypothalamus. Upon continuous infusion of palmitate, OP mice presented an early (24h) increase in the expression of POMC, TNFa, F4/80, CD11b and CX3CL1 as compared to OR. Increased expression of POMC was accompanied by a lower increment in the hypothalamic a-MSH levels following FA infusion and different proconvartase 1/3 expression between OP and OR mice. Thus, inflammatory markers and POMC are differently regulated in OP as compared to OR mice following the systemic treatment with FA. This data places early defective hypothalamic responsiveness to dietary fats as a mechanism potentially involved in the predisposition to DIO.

28

Single fly behavioral responses to odor blends

Danielle Mersch, Gregory Jefferis
MRC - Laboratory of Molecular Biology, Cambridge, UK

Integration of sensory signals is central for perception and crucial for steering behavior. Combining information within and across senses enables more robust behavioral decisions.When we face a bowl of fruit, it is the combination of color, shape and smell that enables us to select the ripest of our preferred fruit.Although this seems a simple task, little is known about how multiple inputs are combined by single neurons to guide our behavior.Here, we tackle the question by asking how a fruit fly integrates blends of male pheromone and food odor. Male pheromone by itself elicits little attraction, but strongly enhances the attractiveness of food in groups of flies.To investigate the mechanism of this synergy at the neuronal level, we first need to ensure that the blend of food odor and male pheromone reliably triggers enhanced attraction in individual flies. Male pheromone is a monomolecular odor that activates only two olfactory channels for which the downstream pathways are well identified.In contrast food odors, such as vinegar and yeast, that are attractive to the fly, are composed of many monomolecular odors and activate a multitude of olfactory channels simultaneously; it is therefore likely that these signals are integrated at numerous sites in different pathways.To limit the number and complexity of possible integration sites, we aim to identify a monomolecular food odor that triggers a strong synergistic behavioral response in individual flies. Here we present the first results of our behavioral screen that assesses a fly's attraction to blends of male pheromone and monomolecular food odors

29

Novel peptidomimetic MMP-9 inhibitors as potential anti-epileptogenic therapeutics

Danylo Khomiak[1], Emilia Rejmak[1], Sandra Bertran[2], Leszek Kaczmarek[1]
[1]Nencki Institute of Experimental Biology, Warsaw/Masovian, Poland, [2]Iproteos, Barcelona/Catalonia, Spain

Epilepsy is the most widespread neurological disorder (prevalence - 50 million). Existing treatments rather focus on symptoms, and 30 % of patients are still resistant to them. While conventional approaches to study epileptogenesis have concentrated on modifications occurring to neurotransmitters, channels and receptors, the recent discoveries suggest that remodelling of the brain extracellular matrix may play a fundamental role in the pathogenesis of epilepsy. These changes are executed by extracellularly operating proteases. One of them, MMP-9 has been particularly linked to epileptogenesis. It has been demonstrated the functional involvement of MMP-9 in kainic acid and pentylenetetrazole-kindling models of temporal lobe epilepsy.
Inhibitors of peptidomimetic nature were obtained from our commercial partner and their ability to inhibit cleavage of β-dystroglycan and nectin-3 (confirmed MMP-9 substrates) has been estimated. In hippocampal and cortical cell culture (derived from Wistar rats (P7)), pre-treated with compounds IPR-179 and IPR-181 (3 mg/kg and 6 mg/kg) for 15 min and stimulated by glutamic acid (50 μM) the inhibition at concentrations 10 μM and 50 μM, respectively, was observed. Following in vivo experiments, in which IPR-179 was given intraperitoneally to mice 25 min before seizure-evoking agent administration (pentylenetetrazol 50 mg/kg and kainic acid 20 mg/kg), also showed the decrease in β-dystroglycan and nectin-3 cleavage. Futhermore, the delay in seizure onset was observed. Hence, IPR-179 and IPR-181 proved effective and can be further tested in advanced models of epileptogenesis. Supported by EU Horizon 2020, Marie Sklodowska-Curie grant agreement No 642881.

30

Improved control of movement initiation underlies the development of balance in zebrafish

David Ehrlich, David Schoppik
New York University, New York, NY, USA

Balance arises from the interplay of external forces acting on the body and internally generated movements. Most animals possess bodies that are inherently unstable and must therefore initiate corrective movements to maintain stability. Balance is particularly difficult for growing animals, given changes to morphology and underdevelopment of movement control. Here we dissociate morphological and sensorimotor contributions to balance across early development by studying swimming in larval zebrafish. Using this model, we identify that sensitivity to stability emerges with age and comes to determine movement initiation. We first model the physical forces that challenge underwater balance and confirm experimentally the presence of constant destabilization due to nose-down torque. We find that larvae propel in corrective swim bouts that, due to larval morphology, tend to stabilize the body. Intriguingly, developing zebrafish acquire control of the initiation of stabilizing bouts, preferentially generating movements when unstable to facilitate the rapid restoration of preferred postures. To test the sufficiency of locomotor-driven stabilization and the developing control of movement timing, we incorporate both into a generative model of swimming. Simulated larvae recapitulate observed postures and movement timing across early development, but only when locomotor-driven stabilization and control of movement initiation are both utilized. We conclude that the ability to move when unstable is the key developmental improvement to balance in larval zebrafish. Our work informs how emerging sensorimotor ability comes to impact how and why animals move when they do.

31

Why do only some patients recover their arm motor function? Role of mirror neurons in BA44.

Deanna Anderlini, Guy Wallis
University of Queensland, Brisbane, Australia

Cortex and cortical function can be regarded as modular, with separate areas involved in processing sensory information and the initiation of motor movement. The blood supply supporting cortex is, like the brain itself, modular. Disruption in blood flow leads to a multiplicity of dysfunctions like the frequent co-occurrence of aphasia and right upper limb hemiparesis.
A review of the stroke literature reveals a correlation between Broca's aphasia and upper limb motor recovery. The precise reason for the correlation is not known but this paper proposes one.Our argument is that speech impairment is indicative of damage to Brodmann area BA45 but that the motor deficits are due to damage to the proximal, but functionally discrete area BA44. BA44 is a multisensory area. But experiments on tone-deafs or stutters, radiological tools like fMRI and DWI, studies of the neuro-ontogeny and development in babies, findings of genetic, epigenetic and embryology, all point to BA44 playing a central role in visuo-motor integration.
Intact BA44 offers a source of unimpaired input to a damaged motor system from primary visual pathways and the cortico basal-ganglia thalamic loop. However, when damaged, the motor system is starved of one important source of signal for effective retraining and recovery.

32

Development of new tools to measure social hierarchy in the home-cage.

Diana Costa, Marta Moita, Cristina Márquez
Champalimaud Centre for the Unknown, Lisbon, Portugal

Most animals that live in groups establish hierarchies where the dominant individual has priority access to limited resources, such as water, food, space, or females. These hierarchies eliminate fighting within a group minimising energy costs. Available standardised protocols to access social status in laboratory rats evaluate the establishment of dominance, and require the introduction of a new environment, restriction of resources, and often social isolation. There are no available protocols to crystallise an already stablished hierarchy between cage mates in the context of the home-cage. Here we present data where we measured social hierarchy between non-deprived dyads of cage-mates in their home-cage in the context of a competition for positive reinforcers (1% sucrose or palatable pellets) and compare it to adaptations of the standard tests available (food or water competition and tube test). We performed a detailed characterisation of the social behaviour displayed in each type of interactions and studied reliability of social rank between tests.

33

Natural low molecular weight compounds, modulating the acid-sensing ion channel 3

Dmitry Osmakov, Sergey Koshelev, Maxim Dubinnyi, Yaroslav Andreev, Sergey Kozlov
Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry of the Russian Academy of Sciences, Moscow, Russia

Acid- sensing ion channels (ASICs) are trimeric membrane proteins belonging to the family of degenerin/epithelial Na+-channels. ASIC3 channel, which is one of the types of these channels, is widely expressed in neurons of the peripheral nervous system and plays an important role in the perception of painful stimuli in various physiological and pathological processes. The use of natural low molecular weight ligands is one of the most effective research methods of functioning of these channels not only in fundamental terms but also in practice as allows the development of new drugs with target action. Medicinal plants are known for a long time as a rich source of various biologically active compounds - ligands of certain receptors or enzymes. From the plants Thymus armeniacus and Laurus nobilis we isolated two low molecular weight compounds that modulate the ASIC3 channels functioning. In the first case, it is a brand new compound (named sevanol) that in micromolar concentrations inhibits the ASIC3 channels and has, as a consequence, anti-inflammatory and analgesic effect in in vivo tests on mice. Structure-functional analysis, conducted on sevanol and its structural analogues (produced by chemical synthesis), showed the influence of certain groups of molecules on the activity to the channel. In the case of L. nobilis we isolated the compound that in micromolar concentrations potentiate only human ASIC3 in more than two times, while not exerting this effect on rodents ASIC3, despite their high percent of their identity.

34

Geometry and state-dependence of sound representations in rat auditory cortex

Dmitry Kobak, Jose Pardo-Vazquez, Mafalda Valente, Christian Machens, Alfonso Renart
Champalimaud Centre for the Unknown, Lisbon, Portugal

There is a large body of theoretical work on how the structure of neural variability shapes the accuracy of representations. The standard view is that noise correlations can severely limit the amount of stimulus information that the neural population is able to encode. However, not all noise correlations are information-limiting and experimental evidence of the impact of variability on population encoding is scarce. Here we perform a systematic empirical investigation of this problem by analyzing the structure of variability in large, simultaneously recorded cortical populations across different brain states.

We used silicon probes to record population spiking activity in the primary auditory cortex of urethane-anesthetized rats. Animals were repeatedly presented with stationary noise stimuli delivered bilaterally through custom-made headphones. The stimuli differed in the overall intensity and in the perceived lateralization. As typical under urethane, different recording sessions span different levels of cortical activation, ranging from very active to very inactive.

Analysis of the N-dimensional structure of population responses suggests that the geometry of stimulus representation strongly depends on the brain state. Not only the noise correlations differ, but the signal subspace is changing as well. During the active states, the signal and noise subspaces are largely orthogonal, leading to high signal-to-noise ratio and good stimulus encoding. In contrast, during inactive states the noise is primarily lying in the subspace corresponding to up-down fluctuations of the network; however, the signal space turns itself to become largely aligned with the same subspace, thus reducing signal-to-noise ratio and making noise correlations information-limiting.

35

Dissecting stored variables underlying reinforcement learning in *Drosophila*

Eduardo Dias-Ferreira, Gaby Maimon
The Rockefeller University, New York, New York, USA

Learning is a capacity that is critical for many species because it allows organisms to change their behavior based on previous experience. Which environmental variables does an organism use when learning the relation between two or more events has been a matter of debate. Predominant theories, mostly based on behavioral data, propose that associative learning depends on several potential variables such as the time interval between two paired events (contiguity), the time interval between two paired events normalized to the time interval between each pairing, or the probability that one event follows another rather than the two occurring independently (contingency). Because of *Drosophila's* numerically simple brain, and the genetic and physiological methods available, we developed a positive-reinforcement learning paradigm in tethered flies that should allow us to ultimately monitor neural activity in a fly as it learns. In this learning paradigm, small drops of sugar water are delivered to the fly's proboscis in coordination with the presentation of simple visual stimuli on a panoramic visual display. This paradigm allows us to follow the dynamics of learning on a trial-by-trial basis, for hundreds of trials, by monitoring reflexive movements of the proboscis in anticipation of the sugar reward. We observe strong conditioning to the visual stimuli after tens of trials. Preliminary experiments suggest that contiguity and the time-interval between each pairing do not strongly alter the dynamics by which conditioning develops. We are currently examining the role of contingency on learning dynamics alongside other environmental variables that could underlie associative learning.

36

Algorithms underlying olfactory navigation in walking fruit flies

Efrén Álvarez-Salvado, Katherine Nagel
New York University, New York, NY, USA

In order to locate food sources in complex environments, fruit flies rely on multi-sensory integration, using odors and wind cues simultaneously. This combined use of environmental information applies beyond the olfactory system, and it is important for many other organisms. We want to understand how the brain performs those computations necessary to turn complex sensory input into a goal-directed, successful behavior. To achieve this goal, we have developed a high-throughput assay to monitor olfactory-driven behavior in walking flies, while precisely controlling wind and odor stimuli. Using this apparatus we have identified two major behaviors that underlie approach to an attractive odor. In the presence of odor, flies turn and run upwind, and following odor offset, they engage in a downwind-biased local search. We show that these two behaviors depend differently on odor and wind, suggesting they are under control of different neuronal computations or even different circuits. Based on our experimental measurements, we developed a computational model that is capable of reproducing the behavior of real flies. We use this model to show that the algorithms that we have described are capable of solving more complex tasks. Furthermore, our model provides insight into the specific roles played by each of the different components of the flies' behavior. Together, our data and model provide a template for understanding the computations taking place in the fly brain during olfactory search behavior, and represent a first step towards dissecting the neuronal substrates of these computations.

37

Septum responds to elementary motion cues related to the perception of animacy in visually naïve chicks

Elena Lorenzi, Uwe Mayer, Orsola Rosa Salva, Giorgio Vallortigara
University, Trento, Italy

The septum among vertebrates is an evolutionarily well-conserved part of the limbic system. It contains sex steroid hormone receptors, a defining feature for the nodes of the social behavior network. The detection of animate creatures is fundamental for survival and social interaction. Simple shapes moving in a self-propelled fashion (implying the presence of an internal energy source), are spontaneously perceived as animated and engage attention since infancy. Autonomous changes in speed are one of the cues associated with animacy perception. We were able to demonstrate that newly hatched visually naïve chicks prefer a simple object that changes its speed (accelerating-decelerating) to an identical object that moves at constant speed, suggesting that these mechanisms are predisposed and active at birth. To study the neuronal basis of this phenomenon, we exposed two groups of visually naïve chicks to either one of the two stimuli and visualized brain activity by an immunohistochemical staining of the immediate early gene product c-Fos. Results suggest a differential involvement of the right septum between the two groups. Subjects exposed to speed changes showed higher activation, implying the involvement of this social brain area in processing of elementary visual cues to animacy. We also measured activity in the intermediate medial mesopallium (an area involved in filial imprinting in chicks), arcopallium and nucleus taeniae (avian homologues to the mammalian amygdala). The activity in these areas was not different between the two groups, suggesting that the difference found in septum is region specific.

38

Cleavage of nectin-3 is blocked by MMP-9 specific inhibitor in the hippocampus upon neuronal stimulation

Emilia Rejmak, Magdalena Dziembowska, Katarzyna Kalita, Leszek Kaczmarek
Nencki Institute of Experimental Biology Polish Academy of Sciences, Warsaw, Poland

Structural changes of dendritic spines occurring in response to synaptic activity are accompanied by changes in the connections between pre- and postsynaptic membrane. The strengthening and weakening of these contacts can be modulated by nectin-3 that is postsynaptic Cell Adhesion Molecule (CAM), which role to interact with presynaptic nectin-1 is well known. Previously we described that the increased nectin-3 proteolysis under chronic stress conditions correlates with the elevated MMP-9 activity in the rat hippocampal CA1 fragment. Proteolytic cleavage of the nectin-3 results in the appearance of a 20 kDa nectin-3 derived fragment. The cleavage was inhibited by the MMP-9 inhibitor (inhibitor I). Moreover, taking into account the possibility of non-specific activity of the applied inhibitor we experimentally demonstrated its specific activity towards MMP-9 by conjugating inhibitor I with biotin with following purification on the magnetic streptavidin beads. We analyzed the binding capacity of inhibitor I to the endogenous and exogenous MMP-9 by gel zymography. Due to the MMP-9 low brain expression level and its secretion on the synapse upon neuronal stimulation we decided to use the hippocampi from rats injected with kainic acid (10h after injection, 10 mg/kg) for our experiments. The activity of MMP-9 in the inhibitor-bound probe was detected. The inhibitor's specificity towards MMP-9 was supported by the absence of MMP-2 activity in this probe, which is another abundant in the brain metalloproteinase showing gelatynase activity. This results strongly confirm that inhibitor I is specific towards MMP-9. Supported by National Science Centre grant 2013/09/N/NZ3/00108.

39

Development of sex-specific connectivity in Drosophila

Erika Dona[1], Ben Sutcliffe[1], Darren Logan[2], Gregory Jefferis[1]
[1]MRC Laboratory of Molecular Biology, Cambridge, Cambridgeshire, UK, [2]Wellcome Trust Sanger Institute (WTSI), Hinxton, Cambridgeshire, UK

In Drosophila, sexual differentiation of the central nervous system is controlled by two master regulatory transcription factors, fruitless (fru) and doublesex (dsx), but how these regulate downstream transcriptional targets through development to produce circuit specificity remains poorly understood.
A powerful entry point to this question is provided by the olfactory circuit processing 11-cis-vaccenyl acetate (cVA), a male pheromone eliciting sex-specific behaviours in flies. Our lab identified a tri-partite functional switch along this circuit, where the same input is connected to two different outputs depending on sex. At the cellular level, the switch is implemented by sexually dimorphic dendritic projections of two classes of lateral horn (LH) interneurons, aSP-f and aSP-g. Remarkably, manipulation of fru function in these neurons, but not their pre-synaptic partners, is sufficient to sex-reverse their morphology and odour responses. It is therefore likely that dimorphic dendritic projections emerge as a consequence of sex-specific expression of dendritic guidance factors during development mediated by fru; aSP-f and aSP-g are therefore an excellent experimental system to address how differential regulation of effector molecules controls the development of circuit specificity.
We address transcriptional differences between males and females in these neuronal populations through RNAseq. To help selecting meaningful developmental stages to harvest the cells, we have analysed aSP-f and aSP-g neuroanatomy through development and described when dimorphic features are established. The analysis of sex-specific gene expression during development should allow us to identify candidate guidance factors controlling sexually dimorphic wiring of these pheromone responsive neurons.

40

Correlative morphological and electrophysiological study of proenkephalin (PENK) expressing neurons in the spinal dorsal horn

Éva Kókai[1], Miklós Sivadó[1], Angelika Varga[1], Zita Puskár[2], Péter Szücs[1]
[1]MTA-DE-NAP B-Pain Control Research Group, Debrecen, Hungary, [2]Szentágothai János Laboratory, Semmelweis University, Budapest, Hungary

Cutaneous primary afferents transmitting nociceptive stimuli project to laminae I, II, and V of the spinal dorsal horn. Electron microscopy studies showed that many of these central sensory axons in the spinal cord participate in the formation of synaptic glomeruli structures, in which the sensory afferent terminal receives axo-axonic and dendro-axonic inputs. A recent virus-based transneuronal tracing study revealed that while most of these contacts are from GABAergic neurons, some of them originate from enkephalinergic neurons residing in superficial spinal laminae and in the rostral ventromedial medulla.
In order to reveal the identity and function of spinal enkephalinergic neurons we used an in vitro intact spinal cord preparation with attached dorsal roots from mice expressing either tdTomato or channelrhodopsin (ChR2) in a proenkephalin (PENK) dependent manner. We performed multiple immunfluorescent labelling, whole-cell patch-clamp recordings and biocytin labelling in PENK neurons.
We revealed that PENK positive neurons in the spinal dorsal horn are mostly excitatory, express known excitatory markers and their axons extend for 1-2 segments. Activation of spinal PENK neurons increased the frequency of spontaneous postsynaptic currents and facilitated primary afferent evoked bisynaptic inhibition targeting lamina II neurons and projection neurons in lamina I.
Our results demonstrate that spinal PENK neurons are involved in direct modulation of primary afferent transmission and indicate that this effect may extend beyond the segment where they are located.
The work was supported by the KTIA_NAP_13-2-2014-0005 grant of the Hungarian Government (PSz), the János Bolyai Research Scholarship of the Hungarian Academy of Sciences (PSz)

41

Methylphenidate Induces Neurons and Astrocytes Loss in Hippocampus and Behavior Changes in Juvenile Rat

Felipe Schmitz[1], Paula Pierozan[1], André Rodrigues[1], Helena Biasibetti[1], Matheus Grunevald[1], Letícia Pettenuzzo[1], Giselli Scaini[2], Emilio Streck[2], Carlos Netto[1], Angela Wyse[1]

[1]Laboratório de Neuroproteção e Doenças Metabólicas, Departamento de Bioquímica, Instituto de Ciências Básicas da Saúde, Universidade Federal do Rio Grande do Sul, Porto Alegre, Rio Grande do Sul, Brazil, [2]Laboratório de Bioenergética e Núcleo de Excelência em Neurociências Aplicadas de Santa Catarina, Programa de Pós-Graduação em Ciências da Saúde, Universidade do Extremo Sul Catarinense, Criciúma, Santa Catarina, Brazil

In the present study, we investigate biochemical and histochemical alterations in the hippocampus, as well as assessment the performance of juvenile rats chronically treated with methylphenidate (MPH) in behavioral tasks. In this study, Wistar rats received intraperitoneal injections of MPH (2.0 mg/kg) or an equivalent volume of 0.9% saline solution (controls), once a day, from the 15th to the 45th day of age. Twenty-four hours after the last administration of MPH the rats were decapitated (for biochemical studies), or perfused (for histochemical studies) or subjected to the behavioral tasks. Student's t test was used to evaluate the different parameters after the dates presented a normal distribution in Shapiro-Wilk test. We showed that chronic MPH treatment promoted a loss of astrocytes and neurons in hippocampus of juvenile rats. BDNF and pTrkB immunocontents, and NGF levels were decreased; while TNF-α and IL-6 levels, Iba-1 and caspase 3 cleaved immunocontents (active microglia marker and active apoptosis marker, respectively) were increased. ERK and PKCaMII signaling pathways, but not Akt and GSK-3β were decreased. We also observed that SNAP-25 was decreased by MPH treatment, while GAP-43 and synaptophisyn were not altered. Exploratory activity and memory of object recognition were impaired by MPH treatment. These findings provide additional evidence that early-life exposure to MPH can have complex effects, as well as provide new basis for understanding of the biochemical and behavioral consequences associated with chronic use of MPH during the development of central nervous system.

42

Neural circuits controlling Prolactin release during sexual behavior

Francisco F. Esteves, Nadja Oellrich, Susana Q. Lima
Champalimaud Centre for the Unknown, Lisbon, Portugal

Prolactin (PRL) is a pleiotropic hormone released from the pituitary gland in numerous social behaviors. Originally identified in the context of parental care, PRL is also released during/after orgasm in humans and ejaculation in other mammals. Different hypothalamic neuroendocrine dopaminergic (NEDA) neuronal populations can influence PRL release. However, the neural circuits underlying PRL discharge and function during social and sexual behaviors are largely uncharacterized: Which higher brain areas are controlling PRL release? To answer this question we need an entry point into the circuits governing PRL release. Therefore, we mapped whole-brain synaptic NEDA inputs to allow subsequent identification of inputs involved in specific behaviors. To map whole-brain inputs into NEDA we employed a Rabies Virus based monosynaptic tracing system capable of retrograde mapping inputs into genetically defined neuronal populations. Having identified synaptic inputs into NEDA, we ask which ones are involved in sexual behavior. We hypothesize that brain regions specifically activated by ejaculation must directly or indirectly modulate NEDA and thus PRL release during/after ejaculation. To this end, we have compared immediate early gene (c-fos) expression by immunohistochemistry between male mice receiving different types of social/sexual stimulation: no contact, social contact, intromissions without ejaculation, and ejaculation. We have identified brain regions specifically active during ejaculation in behaving mice and investigated whether these intersect with regions providing inputs into NEDA.

23 fri

Posters
43 to 83

43

A brainstem circuit consolidating NREM sleep

Franz Weber, Johnny Do, Shinjae Chung, Yang Dan
University of California, Berkeley, Berkeley, CA, USA

Lesion and pharmacological experiments identified brain regions involved in the control of sleep. However, how these brain regions induce sleep or how they maintain a specific sleep stage is largely unknown.
Previously, we reported that optogenetic activation of GABAergic neurons in the ventrolateral periaqueductal gray (vlPAG), located in the midbrain, strongly suppresses REM sleep, while increasing NREM sleep. Here, we demonstrate that GABAergic vlPAG neurons maintain NREM sleep through an interaction with wake/REM promoting neurons in the dorsal pons.
To further elucidate the mechanisms how the vlPAG promotes NREM sleep, we first anatomically identified postsynaptic projection targets of these neurons using anterograde viral tracing techniques. To functionally test the identified projections, we activated them using optogenetics. Stimulation of projections from the vlPAG to the dorsolateral pons was sufficient to maintain NREM sleep.
Furthermore, state-dependent stimulation during NREM sleep demonstrated that activation of GABAergic vlPAG neurons maintains and consolidates NREM sleep by increasing EEG power in the delta range (0-4 Hz). In contrast, pharmacogenetic inhibition of GABAergic vlPAG neurons suppressed sleep.
To further characterize the activity patterns of GABAergic vlPAG neurons we perform in vivo Calcium imaging and optetrode recordings in freely moving mice.
These experiments identify a brainstem pathway that is crucially involved in maintaining NREM sleep and thus elucidate mechanisms how sleep is consolidated in the brain.

44

Bayesian estimation and logarithmic-like representation lead to geometric mean optimal averaging in group estimation tasks

Gabriel Madirolas, Gonzalo G. de Polavieja
Champalimaud Centre for the Unknown, Lisbon, Portugal

Collective estimations have been shown to improve upon the estimates of most individuals of the group in several different contexts, an effect popularly known as Wisdom of Crowds. We studied under which circumstances allowing for social interactions improves the average accuracy of the group. To do this, we modeled how individuals in groups integrate private and public information. A model that employs Bayesian estimation and a logarithmic-like representation of numbers lead to the geometric mean as the optimal aggregation strategy. We verified this prediction analyzing a simple consensus estimation task, and found that groups of three subjects (ages from 11 to 17) were more likely to be using a geometric mean aggregation rule than other simple strategies, including the arithmetic mean. We also analyzed data from an estimation task where subjects were asked to reconsider their initial opinion after receiving information about the group estimates. When the group was already biased, social interactions made subjects agree upon values far from the truth. We developed further our model to find a method that improves group accuracy, by extracting the subgroups resisting social influence.

45

Flavor-nutrient conditioning is disrupted by weight-loss surgery

Gabriela Ribeiro[1, 2,] Ana Fernandes[1], Marta Camacho[1], Maria Manuela Oliveira[3], João Sequeira Duarte[3], Rui M. Costa[1, 4], Albino J. Oliveira-Maia[1, 4, 5]
1 Champalimaud Centre for the Unknown, Lisbon, Portugal
2 Lisbon Academic Medical Center, Faculdade de Medicina de Lisboa, Lisboa, Portugal.
3 Department of Endocrinology, Diabetes and Metabolism, Centro Hospitalar de Lisboa Ocidental
4 Nova Medical School, Universidade Nova de Lisboa, Lisboa, Portugal
5 Department of Psychiatry and Mental Health, Centro Hospitalar de Lisboa Ocidental, Lisboa, Portugal

Flavor-nutrient conditioning (FNC) is the process whereby the preference for a particular flavor is altered by multiple pairings of that flavor with the postingestive consequences of a nutrient. FNC has been extensively demonstrated in rodents but there is significant variability regarding methods and findings in humans. Also, its relevance in the context of obesity and weight-loss surgery has not been explored. We hypothesized that weight-loss surgery reduces postingestive food reward and, to test this hypothesis, developed a novel method for controlled FNC in humans. Our FNC protocol was developed and optimized in a control sample of healthy non-obese volunteers (n=55). In a pre-conditioning day, two flavors with similar novelty and pleasantness ratings were selected for each participant. In the following days, subjects drank one of the flavors, enriched with maltodextrin (MD), an insipid carbohydrate, in alternate days. Intake and pleasantness measurements were taken daily.
The optimized protocol was applied in a cohort of 26 patients either prior to or after weight-loss surgery, specifically, gastric bypass or gastric sleeve. We did not find, in either sample, significant conditioning-induced differences of flavor pleasantness, for any flavor (conditioned/control). However, regarding intake, in the control sample, FNC induced increased consumption of the flavor paired with MD. In the clinical sample, only the obese group, but not the post-surgery patients, had a significant increase in the intake of the conditioned flavor. Our findings suggest that flavor-nutrient conditioning contributes towards feeding behavior in humans and that such mechanisms are altered after weight-loss surgery.

46

A high-dimensional interface to study complex decisions

Gautam Agarwal, Tiago Quendera, Marta Ferreira, Zachary Mainen
Champalimaud Centre for the Unknown, Lisbon, Portugal

We routinely integrate multiple sources of evidence to make choices that have long-term consequences. While seemingly simple, solving such problems optimally depends on searching a potentially large space of possibilities. Our goal is to understand how humans solve such problems. To this end, we have designed a game in which subjects must quickly plan a path in order to capture multiple moving targets at suitable times. We record the timing and quality of subjects' actions, as well as physiological correlates of their internal state. We find that each subject solves the task, and displays a variety of physiological changes, in a distinct yet stereotyped manner. We seek to model each subject's behavior in order to identify the cognitive and physiological processes underlying individual differences in complex, goal-directed behavior.

47

Functional Asymmetries in *Drosophila* Motion Vision

Georg Ammer, Aljoscha Leonhardt, Armin Bahl, Alexander Borst
Max Planck Institute of Neurobiology, 82152 Martinsried, Germany

Detecting the direction of visual movement is fundamental for every sighted animal. In *Drosophila* motion is computed in parallel pathways for brightness increments (ON) and decrements (OFF). Detailed characterization of their functional tuning properties through in vivo physiology and behavioral analyses revealed stark differences in temporal tuning between ON and OFF channels. We trained an in silico motion estimation model on natural scenes and discovered that our optimized detector exhibited differences similar to those of the biological system.
Furthermore, we investigated how presynaptic cells shape the specific temporal tuning properties in downstream direction-selective cells. We focused on the ON pathway where recent connectomic data has suggested a candidate neural circuit for the motion detection with medulla cells Mi1 and Tm3 providing the majority of input to direction-selective T4 cells. By genetically silencing either Mi1 or Tm3 cells and using electrophysiological recordings and behavioral responses of flies as a readout, we show that Mi1 is a necessary element of the ON pathway under all stimulus conditions. In contrast, Tm3 is specifically required only for the detection of fast ON motion in the preferred direction. These results argue against a recently proposed role for these two cell types but rather suggest that additional, yet unidentified cells or circuit mechanisms are involved as well.
In summary, we discovered an asymmetric temporal tuning of ON and OFF motion pathways and provide evidence for a differential contribution of specific cell types to these tuning properties.

48

Physiological, behaviorally relevant targets of amyloid beta sleep regulation in vivo

Guliz Ozcan, Jason Rihel
UCL, London, UK

Recent studies have highlighted links between Alzheimer's disease (AD) and sleep. In particular, sleep is disrupted in AD patients, often years before cognitive deficits. Furthermore, amyloid beta (Aβ) is most strongly secreted during waking, which leads to a daily rhythm of extra-neuronal Aβ. Therefore, worsening sleep may exacerbate Aβ plaque formation and AD progression. While most studies have concentrated on sleep's contribution to disease pathology, Aβ's physiological function (which has remained elusive) may be to regulate sleep.
Our experiments indicate that physiological and temporary upregulation of Aβ levels promotes zebrafish wakefulness and activates discrete subpopulations of neurons. We propose that one physiological function of Aβ is to modulate sleep via the direct regulation of neuronal activity by binding to specific receptors. Basic knowledge of the mechanistic link between Aβ and sleep may help identify novel early biomarkers of AD progression, and the zebrafish model is especially well suited to future drug discovery efforts.

49

Kir channel upregulation in the heart of PTZ induced epileptic rats

Hayrullah Köse[1], Ramazan Kozan[2], Fahri Akbas[1], Enes Akyüz[1], Harun Basoglu[1], Merve Beker[1]

[1]Bezmialem Vakif University, istanbul, Turkey, [2]Istanbul Medeniyet University, istanbul, Turkey

In previous studies, inward rectifier potassium (Kir) channel upregulation was reported in the brain tissue of epileptic animals. In order to explain heart comorbidity in epilepsy, we examined Kir channel protein and gene expression in heart tissue of epileptic rats. In addition we also performed blood pressure measurement and electrocardiographic (ECG) recordings during seizure.

Animals were divided into four groups including control and experimental groups of male and female rats. Intraperitoneal (ip) 0.5 ml of saline was administered to the control groups and 35 mg/kg i.p. pentylenetetrazole (PTZ) was applied to the experimental groups, three times a week for 4 weeks.

At the end of the four weeks, under anesthesia, 0.5 ml of saline and 50 mg/kg PTZ was administered to the control and experimental group respectively then ECG and blood pressure were recorded. Kir channel protein and gene expression were studied from the heart.

Western blot results indicated that the upregulation of cardiac Kir2.1, Kir2.2 and Kir4.1 protein expression were seen in male epileptic rats and upregulation of Kir4.1 gene expression was observed in the same group. Significant decrements were seen in blood pressure of female rats at the onset of epileptic seizure. In the analysis of ECG recordings, RR interval, ST and QT interval were significantly changed in female rats.

As a result, decrease in blood pressure of female experimental group during epileptic seizure, significant upregulation of both gene and protein expressions of Kir4.1 and upregulation of Kir2.1and Kir2.2 protein expressions were seen in epileptic male rats only.

50

Dopamine, glutamate and biotypes in the future of schizophrenia

H. Prata-Ribeiro, A. Ponte, Luisa Gil
Psychiatry, Centro Hospitalar Psiquiátrico de Lisboa, Lisbon, Portugal

Introduction Approximately a third of patients with schizophrenia show limited response to antipsychotic medication (1). As several studies have been suggesting new classifications to schizophrenia, our aim is to review different hypothesis and seek a new way of approaching patient´s treatment in day-to-day practice.

Methods The methods we used consisted on reviewing several papers that have recently been published on the area of classification and treatment of schizophrenia, considering an approach to the findings that enables a practical and clinical advantage in the area.

Discussion New studies suggest that neuroimaging measures of dopamine and glutamate function might provide a means of stratifying patients with psychosis according to their response to treatment (2). Some of those studies associate treatment response with the anterior cingulate level of glutamate (2, 3, 4) and striatal dopamine synthesis capacity (2, 5). Other study identified three biotypes with different outcomes to psychosis, reaching a stronger association between biotypes as predictors of illness severity than the DSM-V classification (6). If a correlation between these studies was found, we would be able, in theory, to predict the response to treatment using simple and affordable neurobiological measures.

Conclusion Associating the anterior cingulate glutamate levels, the striatal dopamine synthesis capacity and the biotypes hypothesis in schizophrenia, one can expect to be possible to predict the degree of response to treatment, based on more affordable methods to day-to-day clinicians than the measure of neurotransmitter levels, enabling the regular clinicians to narrow their pharmacological options for patients, achieving better results in the approach to schizophrenia.

References

(1) Lindenmayer JP (2000): Treatment refractory schizophrenia. Psychiatr Q 71:373–384.
(2) Demjaha A et al, Antipsychotic Treatment Resistance in Schizophrenia Associated with Elevated Glutamate Levels but Normal Dopamine Function DOI: 10.1016/j.biopsych.2013.06.011

(3) Egerton A et al, Anterior Cingulate Glutamate Levels Related to Clinical Status Following Treatment in First-Episode Schizophrenia; DOI: 10.1038/npp.2012.113
(4) Elias Mouchlianitis et al, Treatment-Resistant Schizophrenia Patients Show Elevated Anterior Cingulate Cortex Glutamate Compared to Treatment-Responsive; doi:10.1093/schbul/sbv151
(5) Egerton A et al, Presynaptic Striatal Dopamine Dysfunction in People at Ultra-high Risk for Psychosis: Findings in a Second Cohort, DOI: 10.1016/j.biopsych.2012.11.017
(6) Brett A. Clementz et al, Identification of Distinct Psychosis Biotypes Using Brain-Based Biomarkers; DOI: 10.1176/appi.ajp.2015.14091200

51

Neuronal correlates of auditory implicit learning in the mammalian midbrain

Hugo Cruces-Solis[1], Olga Babaev[1], Zhizi Jing[3], Nicola Strenzke[3], Livia de Hoz[1]
[1]Max Planck Institutte of Experimental Medicine, Göttingen, Germany, [2]Auditory Systems Physiology Group, InnerEarLab, University Medical Center, Göttingen, Germany, [3]International Max Planck Research School for Neurosciences. Graduate School for Neurosciences and Molecular Biosciences, Göttingen, Germany

Our brain filters incoming auditory information according to its relevance. In real life the relevance of many sounds is learned without explicit feedback (implicit auditory learning). The extent to which this process involves subcortical structures is unknown. Our aim was to test whether auditory experience, in the form of implicit learning, affects sound processing at subcortical level. Therefore, we investigated the plastic changes in the inferior colliculus (IC) elicited by relevant auditory experience.
We used the Audiobox that allows continuous monitoring of individual behavior and consists of a homecage and a corner with water access. Adult mice were divided into three groups: exposed group- in which visits to the corner were accompanied by fixed tone pips; silent group- no pips were presented; and random group -pips were not paired with visits to the corner. The mice lived in the Audiobox for 7-11 days, following which we characterized the tuning curves of the IC by performing acute in vivo recordings. The exposed group showed an increase in evoked and spontaneous multiunit activity, wider tuning curves and an increase in the area that responded to the exposed sound. This effect did not appear in the random group and hence was specifically produced by exposure to a behaviorally relevant sound. Implicit learning was later tested using the latent inhibition paradigm. We conclude that plastic changes in sound processing take place at subcortical levels, specifically in the IC, where they might contribute to the filtering of auditory information according to previous experience.

52

Dreammist, a novel peptide implicated in Zebrafish sleep

Ida Barlow[1], Emily Wheater[1], Steve Zimmerman[2], Alex Schier[2], Jason Rihel[1]
[1]University College London, London, UK, [2]Harvard University, Cambridge, MA, USA

Genetic and neuronal regulation of sleep is highly conserved from zebrafish to humans. However, our understanding of the molecular and neurobiological mechanisms that regulate sleep onset, length, and function remain relatively limited. A high-throughput locomotor tracking system to monitor zebrafish larvae sleep has identified a novel gene, *dreammist* (*dmist*), implicated in regulating vertebrate sleep. Homozygous viral disruption to dmist significantly decreases total sleep during both the day and night compared to WT. Computationally predicted to encode a small (<70aa) transmembrane peptide, dmist gene structure and synteny is highly conserved among vertebrates, including fish, birds, mice, and humans. Furthermore, in situ hybridisation shows localised expression of *dmist* from 1dpf in the eye, ventral telencephalon, diencephalon, and hindbrain, with expression becoming more widespread in the brain at later stages of development (5dpf). A split-ubiquitin yeast two-hybrid screen to find Dmist-interacting partners has identified several candidate transmembrane proteins implicated in regulating the hearing, vision, and neurite outgrowth. On-going experiments are validating candidate interactions using a combination of in vitro techniques and in vivo phenotypic analysis on dmist mutant and transgenic animals, as well as investigating in detail Dmist's subcellular localisation in early zebrafish embryos. Thus, by investigating Dmist's function and role at the cellular, neuroanatomical, and behavioural level, this work will provide a deeper understanding of Dmist's role in regulating sleep and wake, and possibly other biological processes.

53

The neurobiology of social behavior: Characterization of the oxytocin/vasopressin system in ants

Ingrid Fetter-Pruneda, Zachary Coto, Ni-Chen Chang, Margaret Ebert, Leonora Olivos-Cisneros, Peter Oxley, Waring Trible, Yuko Ulrich, Cornelia Bargmann, Daniel Kronauer
The Rockefeller University, New York, NY, USA

One of the major challenges of neuroscience is to unravel the mechanisms underlying complex behaviors, such as an animal's ability to communicate and maintain social relationships. With recent advances in DNA sequencing, behavioral tracking and genome editing, social insects have great potential to advance our knowledge in this field. The ant *Cerapachys biroi* constitutes a powerful new model system to study complex social behavior. All individuals in a colony are clonal, lack morphologically distinct castes, and undergo synchronized behavioral and reproductive cycles, alternating between a "queen-like" reproductive phase and a "worker-like" foraging and brood care phase. These traits allow for experimental control of age, genetic background and social environment, which cannot be easily standardized in other social insect species. The neuropeptides oxytocin and vasopressin are known to influence a number of important social and reproductive behaviors in animals, and ants have an ortholog of these peptides called inotocin. The main goal of my research is to elucidate the molecular/cellular mechanisms underlying social behavior in ants, with a focus on the possible role of inotocin. My results show a correlation between the number of inotocinergic cells in the brain and both behavior (i.e. propensity to forage) and age, which also correlates with foraging propensity. To establish causality between the neuronal staining pattern of inotocin and social behavior, I have developed pharmacological strategies to manipulate the inotocin signaling system in individual ants, and we are currently developing techniques for generating stable germline knockouts in *C. biroi*.

54

Transient Competitive Amplification during states of cortical activation

Jacques Bourg[1], Nivaldo Vasconcelos[2], Peter Barthó[3], Alfonso Renart[1]
[1] Champalimaud Centre for the Unknown, Lisbon, Portugal
[2] ICVS, Universidade do Minho, Braga, Portugal
[3] Hungarian Academy of Sciences, Budapest, Hungary

The temporal structure of spontaneous activity in cortical circuits is strongly affected by brain state. Recently, Okun et al. (Nature, 2015) found that during synchronized states cortical activity is close to one-dimensional, so that temporal correlations between cells can be almost fully accounted for by the way in which each neuron couples to the strong fluctuations in population firing rate – PFR. Using recordings from rats under urethane (Layer 5, A1, S1), we study the temporal structure of cortical circuits during desynchronized states, during which fluctuations in PFR are very small (Renart et al., Science 2010). We find that the activity during desynchronized states is also close to one-dimensional, but the activity pattern which organizes these fluctuations is approximately orthogonal to the PFR, revealing two populations of neurons with graded anti-correlated activity. This type of "competitive" dynamics, occurs at a large range of time-scales and is strongest among locally recorded populations. We then investigate which kind of circuits might generate competitive activity. We first show that standard randomly connected balanced networks do not show competitive dynamics. We then identify a novel circuit motif in a 3-population network (two excitatory, one inhibitory), which produces competition through non-normal amplification. Fluctuations generated by this motif can be strong but short-lived (transient), so we refer to this phenomenon as transient competitive amplification – TCA. We show that TCA predicts parsimoniously many features of the data, such as asymmetry in the magnitude as well as in the temporal delay of correlations during desynchronized states.

55

Motor coordination impairment and autistic like traits in Purkinje cell specific TSC1 knockout mouse

Jan Wiaderkiewicz[3], Marta Przybyla[1], Marta Nowacka-Chmielewska[4], Marta Glowacka[1], Domimika Chojnacka[1], Anna Slugocka[1], Jaroslaw J. Barski[1]
[1]Center for Experimental Medicine, Medical University of Silesia, Katowice, Poland, [2]Department of Physiology, School of Medicine in Katowice, Medical University of Silesia, Katowice, Poland, [3]Department of Pharmacology & Physiology, The George Washington University, Washington, USA, [4]Laboratory of Molecular Biology, Faculty of Physiotherapy, The Jerzy Kukuczka Academy of Physical Education, Katowice, Poland

Tuberous Sclerosis Complex (TSC) is an multi-organ disease resulting from hyperactivation of the mTOR signaling pathway, which in turn is caused by mutations in *TSC1* or/and *TSC2* genes, coding two inhibitors of mTOR: hamartin and tuberin. Hyperactivation of the mTOR pathway results in formation of nonmalignant tumors - hamartomas, which can develop in many organs including brain, where subependymal nodules or subependymal giant cell astrocytomas (SEGA) can be also observed. These malformations are responsible for various neurological and psychiatric manifestations including autistic like traits present in about 20-60% of patients suffering from TSC. Study results published recently indicate, that one of the brain parts responsible for the autistic like behaviors is cerebellum. This evolutionary old part of the central nervous system seems to be involved not only in pure motor functions, but also in cognition and control of emotions**.** Many studies showed, that in patients with malfunctions in cerebellum additionally cognitive deficits were stated.
To check this hypothesis we generated a Purkinje cell specific *TCS1* knockout mouse line, and subjected the animals to motor and behavioral tests. Obtained results suggest, that at least in our model, motor impairment is accompanied by some autistic like behaviors.

56

The first step to filial imprinting: a neurobiological investigation of c-Fos expression in dopamine neurons and substance P effects during the first visual experience of newly hatched chicks (*Gallus gallus*)

Jasmine Loveland, Giorgio Vallortigara
University of Trento, Trento, Italy

In precocial birds, filial imprinting is the process by which chicks form a strong memory of, and attachment to, their mother and conspecifics. This phenomenon is influenced by two main factors: an experience-independent predisposition to approach objects that resemble conspecifics and a robust ability to learn the distinguishing features of these objects. In a preference test, visually naïve chicks will preferentially approach a stuffed-hen over a less naturalistic version of a hen (e.g. box-shaped hen), and the existence of an innate predisposition is thought to underlie this experience-independent approach response. While there has been extensive behavioral research on the topic of social predispositions in chicks, very little is known about the neuronal and physiological mechanisms underlying this response. Because the stuffed-hen is a social stimulus with positive valence and dopaminergic transmission can regulate motivation in social contexts, we expected a reward-associated response in chicks that approached the hen. Therefore, in a first experiment, we predicted that chicks that show a preference for the stuffed-hen would have a greater proportion of c-Fos positive dopamine neurons compared to controls, and we were particularly interested in examining whether only a subset of dopamine neuron subpopulations showed this pattern. In a second experiment, extending from the notion that substance P (SP) decreases social approach as part of a vasotocin-induced primitive social circuit, we tested whether SP injections decreased preference scores for the stuffed hen. We found that SP had a sexually dimorphic effect on preference scores for the stuffed hen.

57

Functional characterisation of human melanopsin variants, P10L and T394I, using targeted AAV delivery *in vivo*.

Jessica Rodgers, Steven Hughes, Carina Pothecary, Laurence Brown, Doron Hickey, Michelle McClements, Russell Foster, Stuart Peirson, Mark Hankins
University of Oxford, Oxford, UK

Melanopsin is an opsin photopigment found in intrinsically photosensitive retinal ganglion cells (ipRGCs) involved in non-image forming responses to light. Recently, two single nucleotide polymorphisms (SNPs) in human melanopsin (hOpn4), P10L and T394I, have been associated with seasonal affective disorder and abnormal pupil constriction. In this study, ipRGC-specific delivery of hOpn4 wildtype (WT), P10L or T394I adeno-associated virus (AAV) in melanopsin knockout mice (*Opn4*$^{-/-}$) was used to determine the functional consequences of hOpn4 SNPs on melanopsin-associated behaviour. Immunohistochemistry and qPCR confirmed that hOpn4 AAV was successfully transduced and expressed exclusively in mouse ipRGCs. Behavioural assays of *Opn4*$^{-/-}$ mice before and after injection also showed hOpn4 AAV restored a range of non-image forming behaviours to normal physiological levels, including pupil constriction and circadian photoentrainment. This validated the AAV technique for modelling hOpn4 SNPs *in vivo*. The pupil and circadian phenotypes of *Opn4*$^{-/-}$ mice treated with hOpn4 P10L or T394I AAV were found to be comparable with hOpn4 WT AAV, suggesting both SNPs have limited effects on whole-animal physiology. However, multi-electrode array recordings of ipRGC spike firing in hOpn4 T394I AAV-treated retina revealed significantly attenuated sensitivity and faster offset kinetics compared to hOpn4 WT AAV treated-ipRGCs. This implies T394I may be a functionally significant site for melanopsin activity. In comparison, introduction of the P10L mutation had no effect on ipRGC responses, indicating this amino acid is not critical for melanopsin function. These findings represent the first attempt to establish a causal role for hOpn4 SNPs in abnormal non-image forming behaviour *in vivo*.

58

The effect of morphine on beta-adrenergic signaling in rat cerebral cortex

Jitka Skrabalova, Lucie Hejnova, Jiri Novotny
Charles University in Prague, Faculty of Science, Department of Physiology, Prague, Czech Republic

Morphine exerts its effects through stimulation of opioid receptors. However, other receptors may also participate in the processes of tolerance and dependence. Interestingly, chronic morphine treatment failed to cause tolerance in β2-adrenic receptor (AR) knockout mice. Previous studies have shown that administration of morphine lead to stimulation of the adrenergic system. Here we investigated whether morphine treatment affects β-AR signaling in cerebral cortex.
Morphine was administered to adult male Whistar rats for 10 consecutive days (10 mg/kg/day). β-ARs were determined by radioligand binding with nonselective antagonist [3H]CGP12177. Activity of adenylyl cyclase (AC) was measured by assessment of cAMP production. Relative expression of selected key components of the β-AR signaling system was detected using Western blotting.
The total amount of β-ARs was significantly increased after chronic morphine treatment (from 42 to 49 fmol/mg protein), while their affinity was unchanged. Results of competition binding experiments with β2-AR selective antagonist ICI 11855 indicated that the ratio of β-AR subtypes was not affected by morphine. Western blot analysis did not reveal any changes in the amount of G proteins, but some AC isoforms were increased (ACI by 19%, ACII by 40% and ACIII by 27%). Whereas basal, NaF- or forskolin-stimulated AC activity did not change, AC activity stimulated by the β-AR agonist isoprenaline was significantly increased (by about 20%).
Conclusion: Chronic administration of morphine may significantly affect β-AR signaling in cerebral cortex of rats. Total amount of beta-AR grows up and isoprenaline-stimulated activity of AC is increased.

59

Premotor population codes controlling elementary motor behaviours

Joanna Lau, Isaac Bianco
University College London, London, UK

Our goal is to understand how neural networks in the vertebrate brain control behaviour. We use larval zebrafish as a vertebrate model with a tiny, optically transparent brain to study the functional organisation of the reticulospinal (RS) pathway which provides the main source of descending control to the spinal cord. We can image the activity of the entire reticulospinal population during visually-evoked behaviour to examine the structural and functional organisation of premotor supraspinal circuits underlying motor output.
Regression-based methods allow us to identify groups of reticulospinal neurons whose activity correlates with specific characteristics of swimming. The contribution of these groups on behaviour can be tested by loss and gain of function experiments. Overall, we hope to determine how different reticulospinal circuits interact to modulate swimming during complex, adaptive routines.

60

Channelrhodopsin engineering and characterization of novel optogenetic tools designed in silico

João Calmeiro[1], Bruce F. Milne[2], Gladys L. Caldeira[1], Gladys L. Caldeira[3], Gladys L. Caldeira[4], Joana Fernandes[1], Ana Luísa Carvalho[1], Ana Luísa Carvalho[5], Fernando M. S. Nogueira[2], João Peça[1], João Peça[4]

[1]Center for Neuroscience and Cell Biology, University of Coimbra, Coimbra, Portugal, [2]CFisUC, Department of Physics, University of Coimbra, Coimbra, Portugal, [3]PhD Program in Experimental Biology and Biomedicine (PDBEB), Coimbra, Portugal, [4]Institute for Interdisciplinary Research, University of Coimbra, Coimbra, Portugal, [5]Department of Life Sciences, University of Coimbra, Coimbra, Portugal

Optogenetics confers the ability to hyperpolarize or depolarize specific populations of neurons using light. Channelrhodopsin-2 (ChR2) is a light-gated cation channel derived from Chlamydomonas reinhardtii that has been used as a main tool in optogenetics. The optogenetic toolbox is under continuous update with contributions from protein engineering strategies such as site-directed mutagenesis and chimeric constructs. However, some aspects of the wild-type form of ChR2 require further attention; these include the optimization of its action spectra, channel kinetics, expression levels, inactivation time, conductance and absorption peak sharpness. In terms of spectral properties, only a few variants of the protein have been successfully generated and fully characterized. ChR2 is optimally excited by blue light (470nm), which limits its use in high light-scattering biologic material such as the brain. Therefore, adjusting the ChR2 spectra towards red-shifted activation and sharpening the absorption peak are two of the most sought after properties. In this project, we performed ab-initio design to propose four new ChR2 variants with tuned absorption using site-directed mutagenesis on key residues in the chromophore region. The mutations were selected with the application of Time Dependent – Density Functional Theory (TDDFT) to predict the absorption spectra of selected mutants. We also expressed and purified wild type ChR2 and four novel variants using a eukaryotic heterologous expression system. We are also performing additional electrophysiological protein characterization and assessing membrane trafficking in nerurons and HEK293 cells for the new variants.

61

LocoMouse: A 3D Markerless Video Tracker for Mice

João Fayad, Ana S. Machado, Megan R. Carey
Champalimaud Centre for the Unknown, Lisbon, Portugal

We built a custom 3D video tracking system for measuring and analysing locomotion in mice. The LocoMouse System uses no markers, being instead trained using machine learning algorithms to detect the paws snout and tail on each image of a video stream. Robustness to false positive detections is achieved by imposing temporal coherence of appearance and dynamics using a bayesian network framework. The system performs under three different scenarios – simple overground locomotion, walking on a split-belt treadmill, or on a horizontal ladder – with a spatiotemporal resolution of 0.2mm and 2.5ms. Our software is open-source and available at https://github.com/careylab.

62

Magnetoresistive sensors integrated in bendable probes for local field detection in neurosciences

J. Valadeiro, M. Silva, J. Gaspar, S. Cardoso and P.P. Freitas
INESC-MN, Lisboa

Recently a wide range of customized spintronic devices has been developed for biomedical applications [1]. In particular, the detection of neuronal activity has been pointed as a key application where the use of magnetoresistive sensors can offer unmatched advantages for local field detection [2], combined with small footprint, portability and room temperature operation [3]. The probe's design can be adapted to match the requirements of a neurological experiment, where the substrate flexibility allows a more adaptable tool able to reach further within the signal sources and thus provide in-situ detection of ultra-small local magnetic fields (pTesla range).
Giant magnetoresist ive (GMR) sensors based on Ni80Fe20 3.5/Co80Fe20 2.3/Cu 2.3/Co80Fe20 2.3/Mn76Ir24 8.0 stacks and tunneling magnetoresistive (TMR) sensors Ir20Mn80 7.5/Co70Fe30 2/Ru 0.85/Co40Fe40B20 2.6/MgO>1/Co40Fe40B20 3/Ta 0.21/Ni80Fe20 16 (thickness in nm; alloy compositions in %) were used. These structures were incorporated in micromachined Si probes with different thicknesses (700m to 50m), allowing tunable flexibility. Si-probes were designed with two different tip configurations: (i) sharp tip (18o) for *in-vivo* experiments, to penetrate the brain and place the sensors near field sources; (ii) flat tip (104o) for *in-vitro* measurements, to place sensors on top of a brain slice without damage. To make the probes a full flexible tool, magnetoresistive sensors were also incorporated in polyimide substrates, being able to bend and conform to non-planar surfaces.
Several golden pads can also be included during the fabrication process, allowing an electrical measurement of the interest signals. To merge the recording probe with the electrical stimulus (*in-vitro* experiments), excitation micro coils are being developed for a local neural stimulation.

The Si-probes with a single TMR element and integrated flux guides (Co93Zr3Nb4) displayed TMR=179% and sensitivity of 264%/mT. Also, a detection level of 30pT/Hz1/2 at 1kHz was demonstrated in partially bendable Si-probes competing with rigid technologies. The bending impact on sensor performance was evaluated, under controlled bending tests. The sensor characteristics (sensitivity, noise levels) was correlated with the Si-probe mechanical robustness. The results can provide guiding lines while selecting the optimum probe thickness for *in-vivo/in-vitro* experiments.

[1]P.P.Freitas et al.,LoC 12(2012) 546 [2]J.Amaral et al.,JAP 09(2011) 07B308 [3]J.Amaral et al.,IEEE Trans. Magn.49(2013) 3512

63

Neural circuits underlying visuomotor integration in Drosophila

Johannes Seelig[1], Vivek Jayaraman[2]
[1]Max Planck Society, caesar, Bonn, Germany, [2]Janelia Research Campus, Ashburn, USA

Head direction cells integrate visual and self motion cues for representing an animal's heading. Using two-photon calcium imaging in *Drosophila melanogaster* walking in a virtual reality arena we demonstrate that visual and self motion cues are combined in neurons whose dendrites tile the ellipsoid body, a toroidal structure in the center of the fly brain. This neural population encodes the fly's walking direction relative to its environment, tracking visual landmarks when available and relying on self-motion cues in darkness. When the animal is stationary, a representation of its orientation is maintained through persistent activity, a potential substrate for short-term orientation memory. Several structural and functional features of these neurons are suggestive of ring attractors, network structures that have been proposed to support the function of navigational brain circuits. The confluence of visual and motor signals in this system allows us to dissect neural circuits and computations underlying visumotor integration in a genetically accessible system.

64

A circuit architecture for angular integration in *Drosophila*

Jonathan Green, Atsuko Adachi, Kunal Shah, Jonathan Hirokawa, Pablo Magani, Gaby Maimon
The Rockefeller University, New York, USA

While navigating their environment, many animals keep track of their position and orientation over time, even without visual landmarks. For example, in the *Drosophila* central complex, *heading neurons* track the fly's orientation, similar to head direction cells in rodents. However, the circuit architecture that gives rise to these orientation tracking properties remains largely unknown in any species. Here we describe a neural shifting mechanism in the *Drosophila* central complex that allows heading neurons to quantitatively integrate the fly's orientation over time. Specifically, we highlight an anatomically defined set of *shifting neurons* whose wiring provides a path to rotate an activity peak in heading neurons clockwise or counterclockwise around a circular neuropil called the ellipsoid body. Using two-photon calcium imaging, we reveal that the balance of activity between clockwise- and counterclockwise-shifting neurons quantitatively matches the fly's turning velocity. We further show that clockwise- and counterclockwise-shifting neurons each exist in two subtypes, whose timing and spatial activity patterns suggest that the first subtype helps to initiate the rotation of the heading-neuron activity peak, while the second subtype helps to terminate its rotation. When we inhibit synaptic output in either subtype of shifting neurons, the heading system no longer updates accurately during turns. This work describes how turning velocity can be integrated into angular position in a neural circuit. The central features of this circuit are analogous to models proposed for head-direction cells in rodents, and may inform how neural systems, in general, perform addition.

65

Level-invariant accuracy through level-dependent speed in a sound lateralization task

Jose L. Pardo-Vazquez, Ana Mafalda Valente. Alfonso Renart
Champalimaud Centre for the Unknown, Lisbon, Portugal

Understanding the correlation between neural fluctuations and perceptual variability requires recording neural activity during a task in which: 1) behavioral choices reliably represent what the subject perceives, with little influence of non-sensory factors; and 2) the physical features of the stimulation delivered to the brain are strictly controlled. We have recently developed a 2AFC sound lateralization task aimed at satisfying both requirements. On the one hand, the task capitalizes on the ethological relevance of sound localization and on the fact that the threshold for detection of lateralization (the midline) is hardwired, which facilitates training and makes the task less susceptible to non-sensory factors. On the other hand, given that rodents only use interaural level differences (ILDs) to localize sound in the horizontal axis, it is possible to create a percept of lateralization by presenting different sound intensities to each ear over custom-made detachable headphones, which allow highly controlled stimulation. Behavior shows that performance depends mostly on sensory evidence, since motivation and history effects have weak or none influence on rats' choices. Interestingly, we observed two different speed-accuracy trade-offs. For different average binaural levels (ABLs), rats manage to reach similar accuracy levels by spending more time sampling the sensory evidence at low ABLs. For different ILDs, rats spend more time to decide at low ILDs, but this does not translate in equalizing accuracy with that obtained at high ILDs.

66

Decision making under sensory uncertainty by stochastic optimal agents

Juan R. Castiñeiras, Alfonso Renart
Champalimaud Centre for the Unknown, Lisbon, Portugal

How should agents make decisions? Normative approaches assume that they try to make the best use of available evidence in order to minimize long-term costs (or equivalently maximize rewards). Sensory uncertainty complicates the problem, because while the cost function depends on the true state of the world, the agent only has access to noisy observations. Partially Observable Markov Decision Processes (POMDPs) provide a useful formalism to solve this kind of problems and to find the optimal strategy. For an agent trying to determine the sign of a constant stimulus in the presence of Gaussian noise in a 2AFC task, this translates into a drift diffusion process with a deterministic bound that depends on the prior belief, the cost of accumulating evidence and the amount of reward. Here, we generalize Todorov's Linear Markov Decision Processes to be problems with sensory uncertainty (POMDPs). While not linear, our framework allows us to find directly the optimal control law, which becomes stochastic. Instead of the hard bound on belief used by the POMDP agent, our agent has a certain belief-dependent probability of choosing per unit time (a difference similar to the one between a standard integrate-and-fire neuron and one with a Poisson escape rate). This enables the possibility of early decisions with low confidence, and predicts that correct decisions tend to take longer to make than incorrect ones. Remarkably, preliminary data from rats performing a 2AFC sound lateralization task supports both predictions from the model of the stochastic optimal agent.

67

Interplay of GABAergic neurons and hypothalamic stem cells in the ageing process

JM Reichel, Y Tang, Y Zhang, D Cai
Albert Einstein College of Medicine; Department of Molecular Pharmacology; NYC, USA

In today's fast ageing society neurodegenerative diseases and metabolic malfunction are major health and economic burdens. One of the most devastating consequences of aging is cognitive decline, which has been ascribed to deteriorating function of distinct neuronal populations, as for instance GABAergic interneurons. Our immunohistochemistry and qPCR data show that the number of GABAergic neurons in the mammalian hypothalamus, in particular the Arcuate Nucleus, decreases with age. The mammalian hypothalamus in turn has been shown to play a major part in instigating and controlling the aging process. Moreover, hypothalamic neural stem cells (htNSC) are mechanistically involved in a variety of (aging-related) disease processes. While the decrease of hippocampal neural stem cells in age has been shown previously, using Sox-2 and BrdU stainings we were now also able to show the same trend for htNSC in the aging mouse brain.

There are a number of genetic mutations that result in age-related disease phenotypes, e.g. mutations in proteins related to the nuclear envelope (e.g. $lmna^{-/-}$ mice), or for artificially shortened telomerase ends as in $terc^{-/-}$ mice. Both diseases and mouse models have been associated with stem cell and metabolic abnormalities. Therefore we investigated whether age-related decline of htNSC and GABAergic interneurons in the mammalian hypothalamus are mechanistically connected. Furthermore we postulated that replenishing htNSC will increase GABAergic interneurons in the hypothalamus and subsequently slow down the aging phenotype, including cognitive decline. Finally, we hypothesize that aging-related transgenic mouse models present with a decreased number of htNSC, and replenishing these will significantly ameliorate their disease phenotype.

68

Adult deletion of SRF regulates structural plasticity in neurons

Karolina Nader, Anna Suska, Anna Krysiak, Leszek Kaczmarek, Katarzyna Kalita
Nencki Institute of Experimental Biology of Polish Academy of Sciences, Warsaw, Poland

Serum Response Factor (SRF), one of the major transcription factors in the brain, plays an important role in regulating transcription of activity-induced genes. Our recent results indicate that the lack of SRF leads to prominent changes of basal excitatory synaptic transmission and spines morphology during neuronal development. The aim of this study was to investigate whether SRF depletion in adult neurons may affect neuronal plasticity. We found that adult deletion of SRF results in altered spines morphology in dentate gyrus, manifested by increased spines length compared to control neurons. No differences in the density of dendritic spines and in the number of spines classified to long, mushroom and stubby categories were observed. Morphological alteration of neurons observed in DG was accompanied by the lack of differences in the frequency and amplitude of miniature excitatory postsynaptic currents. This result was further confirmed by the analysis of the level of AMPA receptors subunits on synapses. We have found no differences in the level of GluR1 and GluR2 receptors in synaptoneurosomal fraction isolated from hippocampus of control and SRF KO animals. These findings indicate that SRF regulates spines morphology in the adult hippocampal neurons, but not the number of synapses and their activity in contrast to results observed during neuronal development.
Supported by Polish National Science Center grant (SONATA BIS 2) DEC-2012/07/E/NZ3/01814.

69

Identification of chemosensory neurons that mediate yeast and amino acid feeding in Drosophila melanogaster

Kathrin Steck, Samuel James Walker, Pavel Itskov, Célia Baltazar, Ana Paula Elias, Gabriela Fioreze, Ricardo Leitão-Gonçalves, Carlos Ribeiro
Champalimaud Centre for the Unknown, Lisbon, Portugal

Olfaction and taste play a major role in the selection of the appropriate food sources needed to satisfy the metabolic requirements of an animal. These requirements vary a lot depending on the current needs. The molecular and neuronal mechanisms the brain uses to detect these specific metabolic requirements and modify the chemosensory input to prioritize among the different available feeding possibilities are currently largely unknown. Despite being key nutrients the identity of the chemosensory channels insects use to decide to ingest amino acid rich food remain to be identified. This is also the case in Drosophila melanogaster where the chemosensory basis for the ingestion of yeast, its main source of amino acids, or pure amino acids remain elusive. We used a combination of two choice feeding assays, internal state manipulations, neuronal silencing approaches and neuranatomy to identify and characterize a subset of chemosensory neurons that is required for ingestion of yeast and amino acid rich food. The identified neurons are part of the gustatory system of the fly. This work thus provides important novel insights into the gustatory basis of yeast and amino acid feeding, one of the elementary gustatory modalities promoting the fitness of the animal.

70

The role of PGR-expressing neurons in the ventromedial hypothalamus on female sociosexual behavior

Kensaku Nomoto, Susana Q. Lima
Champalimaud Centre for the Unknown, Lisbon, Portugal

Female mice behave adaptively in response to males depending on their reproductive state. While female mice copulate with males when they are fertile, they reject males' mounting attempts during the rest of the reproductive cycle.

The ventrolateral region of the ventromedial hypothalamus (VMHvl) has been implicated in the control of female sociosexual behavior. In particular, the VMHvl is thought to have facilitatory effects on lordosis behavior, the sexually receptive posture of female rodents. However, little is known about how VMHvl neurons respond to sociosexual stimuli in behaving females. Previously, we have shown that, by using in vivo electrophysiology recording methods, most VMHvl neurons are activated by social stimuli and that male-evoked VMHvl responses are enhanced during the sexually receptive period (Nomoto and Lima, 2015).

To gain more insight into the neural circuitry underlying socially evoked VMHvl responses, we performed fiber photometry experiments to monitor the activity of VMHvl neurons expressing progesterone receptor (PGR). We found that PGR+ VMHvl neurons respond greatly to male stimuli irrespective of the reproductive state. We also observed modulation of PGR+ VMHvl activity during copulation as well as when females showed rejection behaviors. These results suggest that, in contrast to the dominant current model where the VMHvl has facilitatory roles on lordosis, the VMHvl might be involved in several aspects of female sociosexual behavior, including opposing behavioral decisions such as mating with or rejecting the male. We are currently testing this hypothesis by using optogenetics and in vivo microendoscopic calcium imaging.

71

Effects of autism-related genetic modifications in zebrafish on social behavior and neural activity

Kuo-Hua Huang[1], Kyohei Kitamura[2], Michael Schebesta[3], Fabrizio Serluca[3], Peixin Zhu[3], Tewis Bouwmeester[3], Rainer Friedrich[1]
[1]Friedrich Miescher Institute, Basel, Switzerland, [2]Kyoto University, Kyoto, Japan, [3]Novartis Institutes for Biomedical Research, Basel, Switzerland

Many autism spectrum disorders (ASDs) have a genetic basis but it remains unclear how genetic modifications cause disease phenotypes such as social deficits and repetitive behaviors. We examined effects of mutations in ASD-linked genes on social behaviors of adult zebrafish. We focused on shoaling, a social behavior that can be elicited by visual stimuli. Using systematically modified movies, we found that attraction to shoals is modulated by skin pigmentation patterns, body size and aspect ratio. Wild-type fish and various mutants showed similar behavioral response profiles to modified fish movies. However, fish carrying mutations in shank3B and fish expressing a dominant-negative shank3B construct exhibited a sustained behavioral response to repeated stimuli, while responses of wild-type fish attenuated. To investigate the neuronal correlates of normal and abnormal social behaviors we have established a 3D virtual-reality environment for head-fixed adult zebrafish, which exhibit attractive and repulsive navigational behavior in the virtual world. Two-photon microscopy allows for imaging fish homologs of the hippocampus, the amygdala and part of the isocortext at a single-cell resolution in the behaving animal.

72

Win or Lose – Behavior, cellular and molecular characterization of social subordinance

Lara Franco[1, 2, 3], Renato Sousa[1], Joana Fernandes[1], Ana Luísa Cardoso[1], João Peça[1, 2]
[1]Center for Neuroscience and Cell Biology, University of Coimbra, Coimbra, Portugal, [2]Institute for Interdisciplinary Research, University of Coimbra, Coimbra, Portugal, [3]PhD Program in Experimental Biology and Biomedicine (PDBEB), Coimbra, Portugal

Animals in social groups display dominant-submissive relationships that culminate in the formation of a social hierarchy. This stratification is critical for group dynamics and group fitness, as it reduces the number of intra-group conflicts through the formation of a "pecking order". Higher-ranking, dominant individuals have priority access to food, nesting places and mate selection. In humans, it has also been shown that the perceived socioeconomic status very strongly correlates with risk for respiratory, cardiovascular, inflammatory, and psychiatric illness. Still, while genetic elements, environmental factors and prior experience all play a role in establishing social dominance, the discrete elements that predict the future rank of an individual remain conspicuously unexplored.

Mice subjected to early life deprivation and adversity (EDA) display a submissive phenotype in adulthood. These animals rank lower when compared to controls, and are more easily defeated in dominance tests. To help identify the underlying molecular targets linked to this phenotype, a RNA-sequencing was performed and 180 genes showed altered expression levels in the prefrontal cortex of EDA mice. From these, 20 genes seemingly correlate to the dominance index of the animals. On-going work centres on exploring early life adversity and its role in shaping dominance behaviour in adulthood. Based on the RNA-sequencing data, target pharmacological and genetic experiments are being conducted to manipulate established hierarchies. Furthermore the molecular and cellular correlates of social hierarchy are being explored in the context of synaptic and neuronal circuitry activity.

73

The encoding of future reward by dopamine release is shaped by action initiation and is implicated in action selection.

Laura Grima, Emilie Syed, Masud Husain, Mark Walton
University of Oxford, Oxford, UK

Dopamine release in the nucleus accumbens has been hypothesized to encode a reward prediction error signal, indicating the difference between a predicted reward and its actual properties, such as its magnitude and timing. Yet dopaminergic manipulations suggest that dopamine transmission is also essential for acting upon such predictions to obtain reward.

To investigate the differing contributions of reward prediction and movement on mesolimbic dopamine, we recorded phasic dopamine release in the nucleus accumbens core using fast-scan cyclic voltammetry in a task where cues instructed whether an action had to be made ('Go') or withheld ('No-Go') to gain either a small or large reward. While dopamine release rapidly increased on correctly performed 'Go' trials, it was significantly attenuated when withholding a response for reward until movement was initiated, demonstrating that dopamine release in the nucleus accumbens is contingent on correct action initiation.

To probe the role of dopamine transmission in selection or suppression of goal-directed actions, we next conducted a systemic pharmacology experiment. Stimulation of D1 receptors reduced rats' ability to withhold responses for reward. In contrast, stimulation of both D1 or D2 receptors reduced correct 'Go' responses: D2 receptor stimulation increased the number of 'Go' trials with no response, whereas D1 receptor stimulation increased incorrect selection of the large 'Go' option when the cue instructed a small reward lever response. D1 receptor blockade also increased incorrect lever presses. This suggests that, while rapid dopamine transmission facilitates movement initiation, its imbalance can cause impulsive action and selection of contextually inappropriate responses.

74

A Parvalbumine-expressing Cell Population in the Lateral Habenula Promotes Anxiety-Related Behaviors

Laura Pozzi, Irene Pallucchi, Iskra Dorocic Pollak, Konstantinos Meletis
Karolinska Institutet, Stockholm, Sweden

Compelling evidence indicate that increased activity of the lateral habenula (LHb), an epithalamic nucleus, contributes to promote negative emotions such as aversion, anxiety and pain. Despite increasing interest in the LHb, basic research aimed to characterise its cellular populations has been limited. In part because of the lack of reliable genetic tools by which to target and classify habenular neurons, the majority of studies assume that the LHb comprises a single, homogeneous population of glutamatergic excitatory neurons that control the activity of dopaminergic and serotonergic regions trough long-range projections. Here we used genetic and optogenetic tools in a Cre-driven rodent line (PVCre) to show that the LHb contains a unique inhibitory population of neurons expressing parvalbumine (PV^{LHb}) that promotes anxiety-like behavior. Our results show that i) the PV^{LHb} neurons express both the vescicular glutamate (Vglut2) and the GABA (vGat) transporter, ii) that the PV^{LHb} are long-range projections that directly contact DAergic cells in the VTA and serotonergic cells in the DR and, iii) that optogenetic activation of PV^{LHb} neurons promotes anxiety and hyperactivity but it is not involved in aversive-like behavior in mice.

75

Quantitative predictions orchestrate visual signaling in *Drosophila*

Lisa Fenk*, Anmo Kim*, Cheng Lyu, Gaby Maimon
The Rockefeller University, New York, New York, USA

Consider a hovering, flying fly. Her head might rotate to the left due to a gust of wind or due to an active head movement, commanded by the brain. In the former case, an optomotor response should kick in to turn the head to the right, thus stabilizing gaze. In the latter case, to allow for the intended head movement, the optomotor responses must be suppressed. One proposed mechanism for achieving this suppression is for the brain to send a copy of the motor command, an *efference copy*, to the visual system to transiently silence the optomotor response. Consistent with this idea, we recently described motor-related inputs to visual-lobe output neurons in *Drosophila* during intended flight turns. However, what is the exact function of these visual neurons and thus their motor-related modulations? Through behavioral genetics, we argue that these neurons regulate head optomotor responses. An analysis of head movements suggests that the head's optomotor response about one rotational axis must be abrogated during flight turns. Comprehensive electrophysiological recordings from these neurons shows that the magnitude of their motor-related inputs covaries with each cell's sensitivity to visual motion about this axis. We posit that these visual neurons control rotational head movements and their motor-related inputs function to abrogate a specific axis of head rotation during intended flight turns. This work reveals how quantitatively precise, cell-type-specific modulations can nullify one specific sensory signal in a population of neurons that carries multiple related signals.

76

The chemoreflex as an animal model of panic attack: pharmacological validity and modulation by the endocannabinoid system

Luara Augusta Batista, Andrea Haibara, Fabricio Moreira
Federal University of Minas Gerais, Belo Horizonte, Minas Gerais, Brazil

The chemoreflex induced by potassium cyanide (KCN) comprises a sympathetic, a parasympathetic, and an escape response. We tested the hypothesis that enhancement of endocannabinoid signaling attenuates escape duration. Male Wistar rats (250-330g) received iv injections of KCN (80 µg/0.1mL) 30 minutes after receiving the following drugs: an inhibitor of anandamide hydrolysis, URB597 (0.1, 0.3, 1 mg/kg); a CB1/CB2 agonist, WIN552122 (0.1, 0.3, 1 mg/kg); a dual blocker of TRPV1 channels/anandamide hydrolysis, AA-5-HT (1, 2.5, 5 mg/kg); an inhibitor of anandamide hydrolysis/agonist of 5-HT1A receptors, cannabidiol (5, 10, 20, 40 mg/kg); and alprazolam (1, 2, 4 mg/kg). Duration of escape reaction induced by one infusion of KCN after the treatment with the drugs was measured, whereas the cardiovascular responses induced by KCN were evaluated before and 30 minutes after the injection of alprazolam (4 mg/kg). Responses were analyzed by one-way ANOVA or Two-way ANOVA. URB597 and WIN552122 failed to attenuate the escape duration: n=10-12 [$F(3,39)=1.21$; $p=0.31$], n=9-12 [$F(3,37)=1.45$; $p=0.24$]. AA-5-HT and cannabidiol also failed to change escape duration: n=9-14 [$F(3,39)=1.07$; $p=0.37$], n=9-13 [$F(4,48)=2.23$; $p=0.07$]. Alprazolam decreased escape duration without altering locomotion at all doses: n=9-14 [$F(3,38)=5.30$; $p=0.003$]; for locomotion: n=6 [$F(3,20)=2.62$; $p=0.07$]. Alprazolam (4 mg/kg) decreased the pressor response induced by KCN: n=7, interaction [$F(1,12=5.27)$; $p=0.04$]; treatment [$F(1,12)=9.17$]; $p=0.01$]; trial [$F(1,12)=8.84$; $p=0.01$]; this drug did not alter bradycardia: interaction [$F(1,12)=5.78$; $p=0.03$]; treatment [$F(1,12)=4.68$; $p=0.4$]; trial [$F(1,12)=0.04$; $p=0.83$]. Alprazolam inhibited KCN-induced responses, reinforcing the pharmacological validity of this model. Contrary to our hypothesis, cannabinoid-related compounds failed to mimic alprazolam effects.

77

Life-long genetic access to neural circuits using Self-inactivating Rabies virus

Ernesto Ciabatti, Ana González-Rueda, Letizia Mariotti, Fabio Morgese, Marco Tripodi
MRC Laboratory of Molecualr Biology, Cambridge, UK

The understanding of the physical implementation of information processing in the brain and, ultimately, of the neuronal underpinnings of behaviour relies on understanding how neurons operate within specific network configurations. During the last few years new methods have emerged that facilitate the mapping neuronal connectivity as well as monitoring and manipulating neural activity. Yet, our ability to combine the two and target specific nodes of a neural network for functional or genetic manipulations remains limited. The recent development of monosynaptically restricted Rabies viruses offers the possibility to bridge the structural and functional investigation of neural circuits in a systematic manner. However, a major limiting factor for the implementation of Rabies based methods to gain genetic access to neural circuit elements lies with their inherent cytotoxicity. In order to overcome this limitation, we developed a transiently expressed **S**elf **i**nactivating ΔG-**R**abies virus (SiR) that transcriptionally disappears from the cell shortly after the primary infection. We show that SiR allows mapping of neuronal connectivity and provide a virtually unlimited temporal window for the genetic and functional manipulation of topologically defined network nodes. We show that neurons within SiR mapped networks maintain normal electrophysiological properties up to several months following the infection and, potentially, for the entire life of the animal. The development of **S**elf **i**nactivating **R**abies (SiR) opens new possibilities for linking neural network function to behaviour by allowing permanent, life-long, genetic access to topologically defined network elements without adverse effects on neuronal physiology and circuit function.

78

Effects of changes in ownership and agency on human behavioral variability, a virtual reality study.

Victòria Brugada-Ramentol, Ivar Clemens, Ángel-Carlos Roman, Gonzalo G de Polavieja
Champalimaud Research, Lisbon, Portugal

Behavioral individuality is a remarkable property in the understanding of cognitive processes. However, individual responses have been overlooked in the study of self-representation, as most of them measure averaged instead of individual responses.
In this study, we have developed a setup to study human behavioral individuality in self-representation using state of the art techniques, such as virtual reality and action tracking systems. In a custom made virtual reality environment, we have quantitatively analyzed individuality in a reaching-like task in which we modulated the subcomponents of the representation of the self (i.e. sense of ownership and sense of agency).
First, we show that our paradigm allows us to modulate individual levels of sense of ownership and agency. Secondly, we explore individual behavioral responses to the modulation of self-representation in terms of performance and plasticity. Finally, we address the relevance of our results in the context of the individual variability.

79

Population receptive field size and cortical magnification factor changes across polar angle in human early visual cortex

Maria Loureiro Silva[1], Jan Brascamp[3], Sónia Ferreira[1], Miguel Castelo-Branco[1], Serge Dumoulin[2], Ben Harvey[4]
[1]Visual Neuroscience Laboratory, Institute for Biomedical Imaging and Life Sciences (IBILI), Coimbra, Portugal, [2]Experimental Psychology, Helmholtz Institute, Utrecht University, Utrecht, The Netherlands, [3]3Department of Psychology, Michigan State University, Michigan, USA, [4]Faculty of Psychology and Education Sciences, Coimbra, Portugal

The whole visual field is not represented with the same detail in the human visual cortex. Changes in neural properties with eccentricity, such as, in receptive field/population receptive field (pRF) size and cortical magnification factor (CMF) are well established, and associated with changes in visual acuity. Indeed, visual acuity falls away from the center of vision, while RFs become larger and CMFs become smaller, implying a coarser representation of visual space. However, it remains unclear how these proprieties change across polar angle. Here, we use pRF modeling of human fMRI data to examine differences in pRF size and CMF properties across polar angle in V1 to V3. We find smaller pRFs and larger CMFs in horizontal (left and right combined) than vertical (upper and lower combined) visual field quadrants. Differences increase with eccentricity, approximately in proportion to average pRF size and CMF. Similarly, we find larger CMFs in the lower than upper quadrant, and again differences increase with eccentricity. PRF size differences between lower/upper quadrants change direction with eccentricity. Finally, we find slightly smaller pRFs in the left than right visual field quadrants in V2 and V3, though no differences in CMF. Overall, there were small but highly significant differences in pRF size and CMF with polar angle Thus, the early human visual cortex seems to have radially asymmetrical visual field representations, which may underlie consistent reports of asymmetries in perceptual abilities.

This work was supported by Foundation for Science and Technology (COMPETE POCI-01-0145-FEDER-007440) and Netherlands Organization for Scientific Research.

80

Single Nucleotide polymorphisms in the OXTR gene associated with social phenotypes: a review

Maria Leonor Godinho[1], Raquel Pedrosa[2], Margarida Figueiredo[3]
[1]Faculdade de Medicina da Universidade do Porto, Porto, Portugal, [2]Clínica de Psiquiatria e Saúde Mental do Centro Hospital de S. João, Porto, Portugal, [3]Departamento de Neurociências Clínicas e Saúde Mental da Faculdade de Medicina do Porto, Porto, Portugal

The peptide oxytocin is highly conserved throughout the mammalian evolution and has been implicated in the regulation of complex social behavior. During the last decade, several studies have supported the hypothesis that exogenous administration of oxytocin favors the processing of social stimuli and promotes empathy, attachment and trust behavior, besides inducing an anxiolytic effect. However, the neurological mechanisms responsible for these effects are not completely understood. Research in molecular genetics suggests that genotype might modulate the interaction between oxytocin levels and social behavior. Amongst several candidates, the oxytocin receptor gene (OXTR) is the one that has received more attention in the literature. In this work we systematize the SNPs (single Nucleotide polymorphisms) in the OXTR gene associated with 6 social phenotypes: prosocial and antisocial behaviors, parenting, social cognition, reaction to stress and psychopathology, which were assessed with experimental tests, questionnaires, neurophysiological measures or neuroimaging. We conclude that polymorphisms rs1042778, rs2254298, rs237887 and rs53576 are the most consistently involved in human social behavior. Furthermore, combinations of SNP alleles set genotypes that are more or less favorable to social adaptation, and this genetic variability is related to age, gender and ethnicity of the participants.

81

Eye movement behavior in the early detection of Alzheimer's disease: the impact of time and cognitive effort

Marina Camargo, Marta Pereira, Ariella Belan, Bernardo Santos, Orestes Forlenza
University of Sao Paulo, Sao Paulo, Brazil

Background: Research has been showing that oculomotor measurements can accurately detect higher-order cognitive deficits, namely in memory and visuospatial processing deficits (Garbutt et al., 2008; Crutcher et al., 2009). Literature has still failed to analyze the impact of the cognitive effort on the oculomotor parameters used to distinguish healthy subjects from those with cognitive decline due to Alzheimer's disease.
Methods: 26 participants divided into 3 groups: 6 AD, 10 MCI and 10 NC. Computerized task: familiarization phase (5 seconds)/ time delay (5 seconds or 2 minutes) / test phase: two images were presented one previously seen, one new). The subject was instructed to select the novel image. The experiment consisted of four blocks of five trials (2 minutes/similar; 2 minutes/non-similar; 5 seconds/similar; 5 seconds/non-similar). The following parameters were analysed within predefined regions of interest (ROI) for each group: fixation count (FC) and visit duration (VD).
Results: Both time and cognitive effort discriminated between groups. Cognitive effort was effective in discrimination between groups in all the selected parameters. Longer time delay showed was effective in discriminating between groups, only in association with cognitive effort.
Conclusion: Cognitive effort and time delay discriminated between groups, suggesting they represent a difficulty level increment on cognitive tasks. AD showed a lower number of fixations and time spent on the familiar stimuli, when the images required cognitive effort. AD tend to analyze the images more superficially, even when the task demands a more detailed analysis.

82

Organization of central amygdala circuits controlling feeding and appetitive behaviours

Marion Ponserre[1], Amelia Douglass[1], Hakan Kucukdereli[1], Milica Markovic[2], Jan Gründemann[2], Cornelia Strobel[1], Pilar Lucia Alcala Morales[1], Klaus Conzelmann[3], Andreas Lüthi[2], Rüdiger Klein[1]

[1]Max Planck Institute of Neurobiologie, Martinsried, Bavaria, Germany, [2]Friedrich Miescher Institute for Biomedical Research, Basel, Switzerland, [3]Max von Pettenkofer-Institute & Gene Center, Munich, Bavaria, Germany

The central amygdala (CeA) has been extensively described as a brain region involved in controlling aversive behaviours such as fear, anxiety, and appetite suppression. Neurons within the mouse CeA that express protein kinase C-δ (PKCδ) are for instance known to mediate the anorexigenic effects of malaise. We have now identified a population of PKCδ negative neurons that express the serotonin receptor Htr2a. Functional manipulation of these neurons demonstrated that they exert a net positive influence on feeding and encode appetitive and reward-related behaviours. Using in vivo calcium imaging, we showed that a subpopulation of CeA^{Htr2a} neurons is active during feeding, corroborating a role for these neurons in food consumption. Recombinant rabies virus technology and ChR2-assisted circuit mapping revealed a reciprocal and asymmetrical inhibitory interaction between CeA^{Htr2a} and CeA^{PKC}δ neurons. We also found that CeA^{Htr2a} and CeA^{PKC}δ neurons sit within a large network of connected brain regions that have described roles in processing food intake and reward related information. Among those, insula cortex, ventral posteromedial thalamic nucleus (VPMPc), lateral parabrachial nucleus (lPBN), paraventricular hypothalamus (PVH) and paraventricular thalamus (PVT) unequally project onto CeA^{PKC}δ or CeA^{Htr2a} cells. Finally, we showed that CeA^{Htr2a} neurons send axons to the PBN and demonstrated that the reward-seeking function of CeA^{Htr2a} neurons is mediated through inhibition of neurons in the PBN. Our study highlights that not only is the CeA important for the control of aversive behaviours but subpopulations of CeA neurons signal positive valence to promote reward-related behaviours.

24 sat

Posters
84 to 124

83

A novel navigation task for studying planning in the rodent brain

Michael Pereira, Christian K. Machens, Rui M. Costa, Thomas Akam
Champalimaud Centre for the Unknown, Lisbon, Portugal

Planning mechanisms are thought to coexist in the brain with other decision making strategies, including those based on trial-and-error learning and heuristics. Though many decision problems can only be solved optimally through planning, action recommendations generated by different strategies often coincide, making it hard to disambiguate them.

We developed a novel navigation task which quantitatively isolates the contribution of planning to rodent navigation. Mice navigate a tortuous elevated maze to collect reward. On each trial, 1 out of 36 possible goal locations is cued with a stimulus light, the mouse navigates to the cued goal to receive a reward. Another randomly selected goal location is then cued to start the next trial.

The non-repeating sequences of reward locations minimize the utility of habitual strategies, while the tortuous maze structure causes planning and directional heuristic to give different recommendations, and rewards planning with shorter routes to goal. The modular design of the apparatus yields a large space of possible maze configurations, from which those which optimally dissociate planning from heuristic strategies can be chosen.

Mice perform hundreds of trials in a single session and that their trajectories decrease in length with training. Analysis of choice behaviour at decision points reveals mice tend to more often choose actions preferred by planning than actions preferred by a directional heuristic. A mixture of strategies model fit to the data also indicates a significant component of planning. Both measures of planning are found to increase over the course of training.

84

Eye movement behavior predictive of cognitive decline in Alzheimer's disease

Marta Pereira, Marina Camargo, Ariella Belan, Bernardo Santos, Orestes Forlenza
University of Sao Paulo, Sao Paulo, Brazil

Background: Eye movement analysis has proved to be a valuable method to explore higher-order cognitive processes (Rizzo et al., 2004). Also, eye movement impairments may have some diagnostic value in the early identification of MCI due to AD (Crutcher et al., 2009; Lagun et al. 2011).
Methods: 90 participants were divided into 3 groups, 22 subjects diagnosed with AD (M= 72,73 / SD= 5,22), 41 subjects with MCI (M= 69,45 / SD= 8,59) and 27 normal subjects (NC) (M= 69,26 / SD=7,68). They performed a set of computerized cognitive tasks, while their eye movement was measured. The following oculomotor parameters were analysed within predefined regions of interest (ROI): time to first fixation (TFF), fixation duration (FD), fixation count (FC), visit duration (VD) and visit count (VC). Eye movement behaviors were compared in order to determine if they can effectively discriminate between groups.
Results: (1) Selected ROIs has shown to be sensitive in distinguishing the different groups throughout the oculomotor parameters: MCIxNC groups (FC: 47.06%; TFF: 45.45%; FB:42.86%; VD: 38.10%), ADxMCI groups (TFF: 42,42%; VD: 40.48%; FC: 41.18%; FB: 39.28%) and with a significantly higher discrimination between ADxNC (TFF, VD: 66.67%; FB: 60.71%; FC: 50%); (2) when comparing new ROI vs. familiar ROI, approximately 88% of the discriminating ROI using TFF, VD and FC parameters referred to new stimuli.
Conclusions: Eye movement can accurately distinguish between groups. Regarding FC, MCI and AD presented a similar oculomotor behavior, suggesting that MCI may present a similar profile to the one associated with AD.

85

Neural correlates of a visual motion detector in *Drosophila*

Matthias Meier, Etienne Serbe, Alexander Borst
Max Planck Institute for Neuroscience, Martinsried, Germany

Estimating motion is a fundamental task for the visual system of any sighted animal. In *Drosophila melanogaster*, direction-selective T4 and T5 cells respond to moving brightness increments (ON) and decrements (OFF), respectively. Current algorithmic models of the circuit are based on the interaction of two differentially filtered signals. However, electron microscopy studies have shown that T5 cells receive their major input from four classes of neurons: Tm1, Tm2, Tm4, and Tm9. Using two-photon calcium imaging, we demonstrate that T5 is the first direction-selective stage within the OFF pathway. Notably, the four cells provide a wide array of spatio-temporal filters to T5. Silencing their synaptic output in various combinations, we find that all input elements are involved in OFF motion detection to varying degrees. Our comprehensive survey challenges the simplified view of how neural systems compute the direction of motion and suggests that an intricate interplay of many signals results in direction selectivity.

86

Roles of chemical and electrical synaptic connections in sensory-to-interneuron communication in a C. elegans chemotaxis circuit

May Dobosiewicz, Cori Bargmann
The Rockefeller University/HHMI, New York, NY, USA

Neurons communicate through chemical synapses that release neurotransmitters, and through electrical synapses that allow direct passage of current and small molecules between neurons. The complete anatomical wiring diagram of the C. elegans nervous system contains 7000 chemical synapses and 600 predicted electrical synapses. Most neurons have both connection types, and mutant analyses indicate that both electrical and chemical synapses contribute to behavior. However, their relative contributions to circuit activity are poorly understood.
C. elegans senses attractive odors using the sensory neuron AWA, which forms chemical and electrical synapses onto several interconnected sensory neurons and interneurons that signal downstream to drive the animal's chemotaxis toward odor. One of AWA's target neurons is the AIA interneuron, which it connects to only by electrical synapses. We used direct optogenetic activation of AWA to probe the AWA-to-AIA connection, which we monitored using calcium imaging. We find that AWA-to-AIA communication is regulated by synaptic input from surrounding neurons. Wild-type AIA responses to diacetyl odor are strong and reliable, but they have altered dynamics and reduced frequency in animals lacking chemical synapses. This suggests that a second neuron, likely AWC, detects diacetyl and activates AIA through chemical synapses. In contrast, wild-type AIA responses to direct AWA depolarization are unreliable and delayed, but are reliable, time-locked, and extended in animals lacking chemical synapses. This indicates that chemical synapses have a net inhibitory effect on AWA-to-AIA signaling. We hypothesize that multiple sensory neurons work together to drive interneuron activity, collaborating or competing with each other depending on context.

87

Diversity of medial septal neurons: State-dependent activity in awake mice and axonal target regions

Minas Salib, Abhilasha Joshi, Kristina Wagner, Peter Somogyi, Tim Viney
Medical Research Council Brain Network Dynamics Unit, Department of Pharmacology, University of Oxford, Oxford OX1 3TH, UK.

The medial septum is part of the basal forebrain and provides cholinergic, glutamatergic GABAergic input to the cortex, including the hippocampal formation. Much of the neuronal activity in the cortex and medial septum is rhythmic, and this activity is governed by behaviour-dependent network oscillations, including 5-12 Hz theta oscillations. The contribution of the hippocampus to learning and memory is influenced by subcortical inputs, including those from the medial septum, but the cellular and synaptic mechanisms of how these inputs influence the network remain to be defined. We have explored the role of GABAergic neuron to the networks and analysed how inhibition shapes network activity. Medial septal GABAergic neurons selectively target GABAergic neurons in the dentate gyrus, CA3, CA2, CA1, subiculum, the entorhinal and other cortical areas (Unal et al., 2015), but the relationship between the firing patterns of single medial septal neurons and their postsynaptic targets is unknown. Using in vivo extracellular recordings in awake mice and juxtacellular labelling of single medial septal cells, we have (1) revealed single theta-rhythmic GABAergic septal neurons targeting the temporal lobe, (2) their activity in relation to different network and behavioural states and (3) the molecular profiles of neurons postsynaptic to well-labelled septal neurons. We have discovered that single medial septal theta-rhythmic GABAergic cells innervate multiple, functionally-related cortical areas, including the hippocampus and the entorhinal cortex. Septo-cortically innervated postsynaptic interneurons showed four different molecular profiles, selectively targeted within the pre-subiculum. In addition, we have observed and identified rhythmic and non-rhythmic burst firing medial septal cells as well as behaviour-related changes in firing rates of medial septal cells. Overall, single septal GABAergic cells show a high degree of specialisation and are likely to contribute to the generation of cortical theta oscillations via their GABAergic cortical target cells and to co-ordinating neuronal activity across functionally-related cortical areas required for learning and memory.

Unal G, Joshi A, Viney TJ, Kis V, Somogyi P (2015) Synaptic targets of medial septal projections in the hippocampus and extrahippocampal cortices of the mouse. J Neurosci 35:15812–15826.

88

The role of mGluR signaling and associated network proteins in the regulation of neuronal morphology and spine maturation

Mohamed Edfawy[1, 2, 3], Ana Luísa Carvalho[1, 4], João Peça[1, 2]
[1]Center for Neuroscience and Cell Biology, University of Coimbra, Coimbra, Portugal, [2]Institute for Interdisciplinary Research, University of Coimbra, Coimbra, Portugal, [3]PhD Program in Experimental Biology and Biomedicine (PDBEB), Coimbra, Portugal, [4]Department of Life Science, University of Coimbra, Coimbra, Portugal

Autism and autism spectrum disorders (ASDs) are neurodevelopmental disorders diagnosed based on a triad of criteria: deficits in communication, impaired social interactions, and repetitive or restricted interests and behaviours. ASDs pose an immense burden to society and are currently thought to afflict 1 out of each 68 children. Recent genetic and genomic studies have identified a large number of candidate genes for ASDs, many encoding synaptic proteins, indicating synaptic dysfunction may play a critical role in ASDs. Disease susceptibility proteins, such as those in the Neurexin/ Neuroligin/PSD-95/SAPAP/SHANK macromolecular complex, converge on ionotropic and metabotropic glutamate signaling. Dysfunction in these genes has been shown to disrupt neuronal morphology, dendritic complexity and synaptic communication. Presently, several lines of evidence suggest that metabotropic glutamate receptors (mGluRs) play an important role in ASD pathophysiology. Nevertheless, research work centering on the proteins that directly regulate the trafficking and surface availability of mGluRs has not been widely explored.
Our data suggests that the perturbation of the mGluR network of proteins has an impact in the regulation of neuronal complexity, spine density and spine maturation. We are now using mouse molecular genetics to understand the functional, cellular and behavioral consequences of disrupting candidate genes that display a vital role in the physiological regulation of metabotropic glutamate receptor signaling.

89

Taking the pulse of flies during defensive behavior.

Natalia Barrios, Marta Moita
Champalimaud Centre for the Unknown, Lisbon, Portugal

The detection of a threat and consequent modification of behavior are adaptive crucial features to the survival of organisms. In vertebrates, such behavioral responses are paralleled by physiological adaptations such as changes in heart rate, blood pressure or respiration and determine the arousal state of the animal. However, little is known about how invertebrates modulate their physiological response to threatening stimuli. In Drosophila, looming stimulation is perceived as a threat and flies respond showing characteristic defensive behaviors: running, jumping and freezing (S. de Vris and T.R. Cladinin, 2012; R. Zacarias and M. Moita, unpublished). We will focus on the modulation of the cardiac function in response to looming stimulation. We will measure heart rate in Drosophila of freely moving flies by using the Calcium indicator RGECO expressed in the heart chambers of living animals. Currently, we have been able to image fluorescence from cardiomyocites through the cuticle of intact flies, using RGECO under the control of tin-Gal4 driver. If we detect changes in heart rate triggered by looming stimuli, we will determine the neuropeptides and circuitry that mediate the modulation of the heart beating during defensive behaviors.

90

Diminished Network Sparseness in V1 Encodes Correct Performance Following Reward-based Associative Learning

Nicholas D. Olivas[1], Dario L. Ringach[1,2], and Joshua T. Trachtenberg[1]
[1]*Department of Neurobiology, David Geffen School of Medicine, University of California, Los Angeles, California 90095, and*
[2]*Department of Psychology, University of California, Los Angeles, California 90095*

Sparse network coding by pyramidal neurons represents naturalistic scenes in primary visual cortex (V1). Whether sparse network representations provide optimal conditions for sensory coding remain unclear. To test whether alterations in network sparsity correlate with improved performance, we longitudinally surveyed cortical activity with GCaMP6 in V1 as mice learned to discriminate between visual stimuli in a go, no-go task. We demonstrate that correct performance drives increased cortical activity as non-sparse network codes whereas incorrect performance retains a sparse representation. We propose that reward-based associative learning recruits additional neurons encoding the conditional stimulus to increase network coding density.

Motor cortex-directed movement of the mystacial vibrissae through pre-motor neurons in the spinal trigeminal nuclei

Nicole Mercer Lindsay[1], Per M. Knutsen[2], Dan Gibbs[1], Harvey J. Karten[1], David Kleinfeld[1]
[1]University of California, San Diego, La Jolla, CA, USA, [2]University of Oslo, Oslo, Norway

The coordination of orofacial motor actions into context dependent behavior requires a convergence of reflexive circuits, sensory feedback, and motor commands in brainstem pre-motor circuits. The spinal trigeminal nuclei (SpV) receive primary sensory input and contain pre-motor neurons that project onto facial motor neurons (Takatoh et al. Neuron 2013; Matthews et al. J Comp Neurol 2015). Here, we investigate descending projections from vibrissa motor cortex (vMCx) onto SpV pre-motor neurons and their role in controlling movement of the mystacial vibrissae and filtering of sensory information.
Using a combination of modern viral techniques, we show that vMCx projections target the region of SpV containing pre-motor neurons. Ongoing experiments utilizing glycoprotein (G)-deleted rabies virus in combination with cre dependent G in pre-motor populations preliminarily show that vMCx projects directly to SpV pre-motor neurons. Small, focal injections in vMCx of a synapse-labeling virus show preliminary evidence that this cortical innervation is somatotopic within SpV. We use a retrograde lentivirus to optogenetically activate SpV-projecting vMCx neurons. Laser stimulation of these cortical neurons evokes vibrissa protraction. Further analysis will determine if protraction is evoked uniformly across vMCx.
We conclude that SpV pre-motor neurons integrate inputs from vMCx and primary trigeminal afferents, along with those from the extensively studied vibrissa primary somatosensory cortex (Matyas et al. Science 2010). vMCx inputs to SpV likely modulate whisking behavior through control of the set-point of vibrissa position.

Grants: NIH/NINDS NS090595 and NS058668; NSF EAGER 201490

92

Selective sensory-motor connections determined by dendritic and axonal positioning

Nikolaos Balaskas, Thomas M. Jessell, David Ng
Howard Hughes Medical Institute, Kavli Institute for Brain Science, Zuckerman Mind Brain Behavior Institute, Departments of Neuroscience and Biochemistry and Molecular Biophysics, Columbia University, New York, USA

The selectivity with which pre-synaptic axons form connections with their post-synaptic targets is thought to rely on complementary recognition molecules [1]. The prominence of this view has recently been challenged by emerging evidence that the settling position of neuronal cell bodies is a critical determinant of connection selectivity [1, 2]. This positional perspective, however, leaves open the question of whether the pattern of neuronal dendrites and axonal projections also contributes to the specificity of connections.
To address this issue we focused on spinal motor circuits, mapping the orientation of dendrites in different motor pools as well as the trajectory of sensory axons. We find that lumbar motor pools exhibit diverse dendritic orientations, ranging from simple crescent-like patterns to configurations with radial morphology. We provide genetic evidence that in FoxP1 mutants, in which motor neurons lack pool identities [4, 5], the dendritic diversity of limb-innervating motor neurons reverts to a common bipolar pattern that resembles the organization of hypaxial motor neurons. These results imply that the ground-state assignment of motor neuron dendritic arbors is bipolar and that radial orientation represents the apex of a dendritic hierarchy. The axons of muscle-defined sensory neurons also exhibit distinct angular trajectories en route to their recipient motor pools. Dendritic and axonal orientation accurately predicts the identity of target motor pools, as well as the asymmetric dendritic domain of sensory-motor synapses. These findings argue for a significant role for dendritic and axonal positional cues in defining the assembly of sensory-motor circuits, simplifying the task of recognition.

93

Neuroligin 2 and IgSF9b bi directionally regulate anxiety- related processing

Olga Babaev[1], Elizabeth Meyer[2], Paolo Botta[2], Hannelore Ehrenreich[1], Nils Brose[1], Dilja Krueger- Burg[1]
[1]Max Planck Institute of Experimental Medicine, Goettingen, Germany, [2]Friedrich Miescher Institute for Biomedical Research, Basel, Switzerland

Anxiety is a debilitating condition that affects 3 percent of adult population in the world. While there is a steady advancement in mapping of neural circuits underlying anxiety, the molecular mechanisms that contribute to their pathophysiological function remain largely unknown. Here we investigate the role of two proteins, Neuroligin 2- an inhibitory synaptic protein linked to schizophrenia in humans, and IgSF9b- a novel modulator of inhibitory function, in anxiety- processing brain regions. We show that deletion of Nlgn2 in mice causes robust anxiety- like phenotype which is accompanied by enhanced neural activation of two key components of anxiety processing circuitry, basal amygdala and central medial nucleus, in response to anxiogenic situation. Specifically, deletion of Nlgn2 affects anxiety- induced activation of excitatory neurons that project from basal amygdala to central medial nucleus, thus supporting recently described role of this projection in anxiety. Strikingly, anxiety- related behavior of Nlgn2 KOs is completely rescued by simultaneous deletion of IgSF9b that suppresses the enhanced activation of central medial nucleus in Nlgn2 KOs. In contrast to Nlgn2, lack of IgSF9b enhances the activation of specifically inhibitory interneurons in basal amygdala. We explain these findings by showing that Nlgn2 and IgSF9b each regulate GABA receptors clustering at distinct sub populations of inhibitory synapses in basal amygdala and central medial nucleus, thus leading to differential anxiety induced activation of these structures in mice lacking each, or both, of these proteins. Our findings suggest that Nlgn2 and IgSF9b play an important role in function of anxiety- associated circuitry.

94

Efferent Modulation of Mechanical Information in Zebrafish larvae

Paul Pichler, Leon Lagnado
Sussex Neuroscience, University of Sussex, Brighton, UK

Active locomotion can activate the same sensory channels as external events. One strategy to deal with this self-induced activation is to temporarily supress the sensory system whenever the motor system is active. An example for this is the lateral line system in zebrafish. It senses small pressure changes in the fish's environment, which could be due to external events or self-induced, by locomotion. The lateral line consists of mechanosensory hair cells that are organised in clusters, called neuromasts, each of which is innervated by an afferent neuron, which transmits information centrally and an efferent neuron, which transmits information from the hindbrain. We are investigating how this system works in vivo by using two-photon microscopy in larval zebrafish expressing genetically encoded indicators of calcium and glutamate in Hair Cells, Afferents and Efferents. We simultaneously perform extracellular recordings of the motornerve to monitor the fictive swimming behaviour of the paralysed larvae. Using this preparation, we could confirm that the activity of efferent synapses in the neuromast is tightly correlated with fictive swimming. The sensitivity of the neuromast to a defined mechanical stimulus was monitored by measuring glutamate-release from its afferents in the hindbrain. These measurements were preformed in the absence of motor activity and then repeated during fictive swimming, induced by a visual stimulus. We find that efferent activity reduces the signal from the neuromast by ~50%. These results demonstrate how locomotion can rapidly and reversibly modulate the transmission of mechanical information from the periphery by controlling the sensitivity of the neuromast.

95

Altered AMPARs subunit composition as a result of TDP-43 neuronal depletion

Paulina Koza[1], Anna Suska[1], Anna Konopka[2], Tomasz Górkiewicz[1], Ewelina Knapska[1], Witold Konopka[1], Leszek Kaczmarek[1]
[1]Nencki Institute if Experimental Biology, Warsaw, Poland, [2]Experts' Ctr. for Analytical Chem. Biol. and Chem. Res. Centre, Univ. of Warsaw, Warsaw, Poland

TDP-43 is a predominantly nuclear RNA binding protein that has been identified as a hallmark of a range of neurodegenerative disorders. Despite the wide scale research, neither the mechanism underlying TDP-43-mediated degeneration of neurons nor its physiological role is fully defined.
In order to explore TDP-43 physiological functions, we have developed transgenic rat model characterized by substantially depleted TDP-43 protein level in neurons. Behavioral analysis of those rats revealed enhanced memory of acquired fear. Those alterations were subsequently confirmed by more stable LTP in the CA1 area of hippocampus, one of the regions required for expression of fear related behaviors. At the same time, the basic electrophysiological properties of CA1 pyramidal neurons were unchanged. However, when pentylenetetrazole (PTZ) massive neuronal stimulation was introduced, control animals presented significantly reduced excitability of CA1 neurons. Surprisingly, TDP-43 transgenic rats maintained cell excitability at the same level.
Behavioral and electrophysiological consequences of TDP-43 depletion applied to altered morphology of dendritic spines. However, both control and transgenic animals presented analogous mode of structural changes of spines in response to PTZ, what suggested dominance of molecular over morphological differences. In fact, using label-free UHPLC-ESI MS/MS we verified that TDP-43 depletion led to changed subunit composition of glutamatergic AMPA receptors, regarding FLOP and FLIP splice variants. Alterations of FLOP variant of GluR1 and GluR2 subunits observed under control conditions were further outlined by neuronal stimulation. Proteomic results were subsequently confirmed by electrophysiological whole-cell patch clamp recordings in CA1.

96

A unifying thermodynamics model for voltage-gated and temperature-gated channels

Nahid Taheri[1], Paulo Aguiar[2]
[1]Faculdade de Ciências da Universidade do Porto, Porto, Portugal, [2]INEB - Instituto de Engenharia Biomédica; i3S - Instituto de Investigação e Inovação em Saúde, Porto, Portugal

Neurons are capable of responding to electrical and thermal signals, with different channels of the transient receptor potential (TRP) family playing an important role in temperature transduction. Unfortunately, the mechanisms underlying high-temperature sensitivity and voltage dependence in TRP channels are still not fully understood. Thermodynamic laws provide a unified framework to describe the kinetics of ionic channels subject to distinct gating mechanisms. We investigated therefore the transition state theory for TRP channels by splitting the Gibbs energy (quantized energy for channel activation) into temperature and voltage terms, under the condition of constant pressure and acidity. Temperature has a significant role on the entropy of the system while the effect of voltage is negligible. Enthalpy of the system is also divided into voltage and temperature factors. The activation/inactivation probability of a single channel is described by Van't Hoff's equation. We suggest that voltage-gated and TRP channel kinetics can be described with a unifying expression that includes both temperature and voltage terms. Channels use the easiest way to supply the activation energy to overcome transmembrane voltage. Heat capacity included in temperature term is about eight times larger for TRPs than for voltage-gated channels, reflecting high sensitivity of TRP channel activation to heat. On the other hand, the effective charge in voltage-gated channels is larger than what is calculated for TRPs channels. Therefore, voltage-gated channels are more sensitive to the changes in the membrane potential than TRPs.

97

Automatic high-throughput measurement and manipulation of feeding behaviour.

Pavel Itskov[1], José Maria Moreira[1], Ekaterina Vinnik[1], Gonçalo Lopes[1], Steve Safarik[2], Michael H. Dickinson[2], Carlos Ribeiro[1]
[1] *Champalimaud Centre for the Unknown, Lisbon, Portugal*
[2] *Caltech, Division of Biology and Biological Engineering, Pasadena, USA*

Food ingestion is one of the defining behaviours of all animals, but its quantification and analysis remain challenging. This is especially the case for feeding behaviour in small, genetically tractable animals such as Drosophila melanogaster. Here, we present a method based on capacitive measurements, which allows the detailed, automated and high-throughput quantification of feeding behaviour (the flyPAD). We demonstrate that flies ingest food by rhythmically extending their proboscis with a frequency that is not modulated by the internal state of the animal. Instead, hunger and satiety homeostatically modulate the microstructure of feeding. By performing real time analysis of feeding behaviour we have implemented a closed-loop system for optogenetic manipulation of neuronal ensembles (the optoPAD). Using this system we have demonstrated that rapid closed-loop manipulation of sweet sensitive and bitter sensitive gustatory receptor neurons can dynamically trigger appetitive and aversive behaviour. Together flyPAD and optoPAD open new opportunities to dissect the neuronal and molecular mechanisms controlling feeding behaviour and motor learning.

98

Visual Attention in Zebrafish larvae

Pedro Henriques, Niloy Rahman, Samuel Jackson, Isaac Bianco
University College London, London, UK

Animals use attentional mechanisms to focus computational resources towards behaviorally relevant stimuli, while ignoring less relevant ones. This selection is thought to be mediated by coordinated activity across multiple brain regions, which integrate information about the intrinsic features of the stimulus (salience) and its relevance to behavior. However, the regions that belong to this attentional network and how they're functionally interconnected remains unknown. We are studying attentional mechanisms in the context of larval zebrafish hunting responses, a visually guided, goal-directed behavior. We have developed a virtual-reality assay in which tethered larvae are able to hunt prey-like visual stimuli, while neuronal responses can be simultaneously monitored with 2-photon imaging. We show that hunting is selective for conjunctions of visual features, and that when presented with competing stimuli, larvae are able to discriminate between them and tend to select those with more behaviorally valuable features. We have also begun to characterize a midbrain nucleus, the nucleus isthmus, which is thought to be involved in directing attention to high priority stimuli through feedback connections with the optic tectum. By imaging neuronal activity in these regions while recording behavioral responses to multiple competing stimuli, we hope to uncover a brain-wide network for stimulus selection.

99

Neural correlates of sudden stopping in patients with Parkinson's disease

Petra Fischer, Huiling Tan, Alek Pogosyan, Damian Herz, Binith Cheeran, Peter Brown
University of Oxford, Oxford, UK

The threshold for movement cessation seems pathologically decreased in patients with Parkinson's disease leading to devastating phenomena such as intermittent freezing of gait. Previous studies have described a neuronal stopping network involving frontal and supplementary motor cortical regions, as well as the subthalamic nucleus (STN) that is thought to be hyperactive in Parkinson's disease. To examine the temporal dynamics within this stopping network, we recorded EEG from cortex and LFPs from deep brain stimulation electrodes within the STN in 9 Parkinson's disease patients. Patients were asked to perform rhythmic finger tapping to a metronome and to interrupt this movement abruptly in response to a stop signal sound. The stop signal was delivered after 5-9 metronome sounds and timed such that successful stopping would occur only in ~50% of all trials. Successful stopping was preceded by elevated post-movement beta activity over motor cortex and coincided with increased gamma activity in the contralateral STN. Gamma increased most strongly in trials where participants were able to stop fully instead of interrupting the downward movement halfway. In a control condition, where stopping was not attempted, such gamma increase was not observed. Cortical theta increased in response to the stop signal, however, it was not significantly higher during successful stops. Taken together, sudden stopping was more successful if preceded by a higher cortical beta rebound, possibly reflecting lower cognitive load in line with previous research. Additionally, our data showed that STN gamma activity was associated with successful motor inhibition and is therefore not simply prokinetic.

100

Prefrontal-CA1 interaction supports flexible spatial learning within a CA1-dependent task framework

Philip Avigan, Kate Seip-Cammack, Matthew Shapiro
Icahn School of Medicine at Mount Sinai, New York, NY, USA

We investigated the contributions of medial prefrontal cortex (mPFC) and CA1 to spatial learning within a familiar framework. Rats were trained to a high performance level on a serial spatial reversal task in a plus maze. In each trial, a rat was placed on a start arm (North/South) and entered a goal arm (East/West), only one of which was rewarded. When the rat reliably chose correctly, the contingency reversed. Crucially, the lack of reward in the North/South arms was an invariant task feature. Rats were implanted with cannulae aimed at mPFC bilaterally (prelimbic/infralimbic regions) and either dorsal or ventral CA1 bilaterally. Independent contributions of mPFC and CA1 to spatial learning were reflected by the effects of bilateral inactivations, and the role of mPFC-CA1 interaction was reflected by the relative effects of ipsilateral and contralateral mPFC/CA1 inactivation; if mPFC-CA1 interaction contributes to spatial learning then contralateral, but not ipsilateral, inactivation should impair performance. Bilateral d/vCA1 inactivation impaired choice accuracy and increased the frequency of opposite start arm errors (errors to the North/South arms). Bilateral mPFC inactivation impaired acquisition of reversals more than acquisition of the initial contingency and increased wrong goal arm errors (errors to the East/West arms) only. Contralateral, but not ipsilateral, inactivation of PFC and either dCA1 or vCA1 impaired choice accuracy and increased wrong goal arm errors only. Thus, mPFC and CA1 make independent and joint contributions to spatial learning. Furthermore, CA1 supports memory for task framework and mPFC-CA1 interaction supports flexible spatial learning within the framework.

101

Impaired Episodic memory in William's Syndrome mice models

Rachel Bhushan, Angela Sandri, Sang AH Lee
Cimec, Center of Mind/Brain Sciences, Rovereto, Trento, Italy

Episodic memory records details of a past event. It stores the "what" "where" and "when" components of a precise "episode" in our brain. The hippocampus is one of the main structures of a complex circuit that consolidates memories and underlies episodic memory. Several experiments in humans and animals have shown that damage to the hippocampus causes impaired episodic and spatiotemporal memory.
Hippocampal abnormalities are found in patients affected by Williams-Beuren Syndrome (WBS), a rare genetic disorder caused by a deletion of around 20 genes on chromosome 7 (at locus 7q11.23, also called WBS critical region). Individuals with this disorder have cognitive deficits and impairments in their visuospatial processing and spatial representation. However, it is still unknown how their hippocampal abnormalities affect their episodic memory.
In this experiment, we used two strains of genetically modified mice, each carrying a half-deletion of the WBS region (Gtf2i-Limk1 or Limk1-Trim50). We designed a task to investigate their capacity in recalling objects across a spatiotemporal context. The task was made of three parts: the first investigated their capacity of recalling the position of two identical objects; the second tested their ability to remember the temporal order of presentation of two different objects; and the last combined object identity, spatial location, and temporal order of the objects (episodic memory).

Our preliminary results suggest that WBS mice have an abnormal memory profile and fail to discriminate between objects they saw earlier from the most recent ones, showing impairments in the temporal component of episodic like memory.

102

The effects of hormonal levels on ketamine-induced prepulse inhibition disruption in female rats

Renata Ferreira-Sgobbi[1, 2], Manoel Jorge Nobre[1, 2, 3]
[1]University of São Paulo, Ribeirão Preto, São Paulo, Brazil, [2]Neuroscience and Behavior Institute, Ribeirão Preto, São Paulo, Brazil, [3]Uni-FACEF, Franca, São Paulo, Brazil

Ketamine has potent psychomimetic effects, being able to accentuate the psychotic state of schizophrenic patients and these changes may be modulated by hormonal factors. Attentional disturbances are one of the symptoms present in psychoses and also in drug abuse. The use of prepulse inhibition (PPI) for analysis of this phenomenon made possible the identification of underlying neural systems. We examine the effects of chronic administration and withdrawal of ketamine on attentional processes of female Wistar rats, tested at different stages of the estrous cycle. Saline and ketamine were administered subcutaneously for 14 days. The analysis of chronic and possible symptoms of ketamine withdrawal effects were performed by the PPI test. Our results highlight the protective role of female hormonal levels on the expression of unconditioned fear response. The possible influence on unconditioned fear could be detected by effects on the startle response in rats tested at different hormone levels and treatments. Sex hormones modulate the action of ketamine in rats, although little is known about gender differences or the effect of sex hormones on their potential for abuse. The PPI is a sensory measurement reduced in the psychosis and acute form by treatment with drugs, including ketamine. It varies along the estrous cycle and is enhanced by treatment with estrogen. Our results confirm the hypothesis that estrogen can modulate the PPI, which helps explain the apparent protective effect of estrogen on the psychopathology of schizophrenia and the beneficial effects of estrogen treatment in psychosis. Financial Support: FAPESP (2014/09685-9).

103

Defining new asymmetry markers of the zebrafish habenula.

Renato Martinho, Elena Dreosti, Stephen W. Wilson
University College London, London, UK

The zebrafish habenula is one of the best models of brain lateralization. This paired nuclei structure has both anatomical and functional asymmetries. However, the cellular and signalling mechanisms that underlie these asymmetries are still elusive and forward genetic studies still could have great potential in revealing the genes involved in this process. Furthermore, we need to identify new habenula markers that allow us to study the development of habenula neuronal subpopulations. Given this, we present two approaches that we have taken to characterise the development of habenula's asymmetry. First, we characterised the a66u757 mutant that fails to break symmetry in the dorsal habenula. Second, to find markers of habenula subpopulations, we developed an habenula cell dissociation protocol for RNA single-cell sequencing. With this two approaches we expect to reveal new genes that are differently expressed in the habenula nuclei or involved in the development of its asymmetries.

104

2-AG into the dorsolateral periaqueductal gray of rats reduce the expression of conditioned contextual fear

Rita de Cássia Lima, Daniele Cristina Aguiar
Parmacology Department, ICB-UFMG, Belo Horizonte/ Minas Gerais, Brazil

The 2-arachidonoylglycerol (2-AG) and anandamide (AEA) are the main endocannabinoids and exerts its effects through activation of cannabinoid receptors type 1 (CB1) and type 2 (CB2). The intra-dlPAG facilitation of AEA signalling induces anti-aversive effects in the expression of fear in the contextual fear conditioned model (CFC).The role of2AGon the expression of contextual fear in this region has not yet investigated. Thus we verified whether the administration of 2AG or URB602, an inhibitor of MGL (enzyme responsible for 2AG hydrolysis), will attenuate the fear expression in the CFC test.
Methods: Male Wistar rats (n=8-10/group) with cannulae aimed at the dlPAG, were submitted to Contextual Fear Conditioning (CFC) test. Ten min before the test, they received an intra-dlPAG (0.2 µL) injection of vehicle or 2-AG (5-500pmol), or URB602 (30-1000pmol). The freezing behavior during re-exposure to the context chamber was evaluated.Results: The 2-AG significantly decreased the freezing time (vehicle: 400.5±13.87; 2-AG (50pmol): 212.7±44.20; 2-AG (500pmol): 215.1±31.49-H4 = 15.11, p= 0.001;KruskalWallis followed by Dunn´s post-test), suggesting anti-aversive effects. URB602 did not modify the expression of contextual fear in any doses employed. Discussion: Thefacilitation of 2AG signaling in the dlPAG, through MGL inhibitor, may not be essential to inhibit aversive memories in the dlPAG in the CFC test. However, we cannot exclude the role of this endocannabinoid on the expression of aversive memories in the dlPAG, since it induced anti-aversive effects when injected directly. The mechanism involved in such differences remains to be investigated.
Financial support: CNPQ/CAPES

105

Ontogeny of collective behavior reveals a simple attraction rule

Robert C. Hinz, Gonzalo G. de Polavieja
Champalimaud Centre for the Unknown, Lisbon, Portugal

A variety of individual-based rules has been proposed to explain the motion of animals in collectives. However, extracting these rules directly from experiments has been limited by our ability to obtain large high quality datasets that can better distinguish among models. Here we propose to follow the slow birth of attraction dynamics during animal development as a unique opportunity to obtain a very large dataset of simple interactions. Attraction was found to correspond to motion towards a single animal chosen at random and switching from one animal to another. This very simple interaction rule does not aggregate collective information at any given time yet it produces the effect of aggregative interaction models as an emergent property. We suggest this rule as a basic interaction module in collective behavior.

106

A sleep-like state induced by neuronal hyperactivity

Sabine Reichert, Jason Rihel
University College London, London, UK

The control of sleep and wakefulness is a fundamental biological process that ensures health and cognitive performance across species. The need to sleep (sleep pressure) is determined by two processes: the circadian clock and the sleep homeostat. Compared to the circadian drive for wakefulness, the molecules and neurons regulating sleep homeostasis remain elusive.
In order to dissect the neuronal underpinnings of sleep homeostasis, we developed a novel pharmacological sleep deprivation assay. Immediately following sleep deprivation, zebrafish larvae show sustained increases in rebound sleep, although they recover to normal sleep levels on subsequent days. Interestingly, sleep rebound did not correlate with the extent of physical activity or total wakefulness during the deprivation period. Instead, rebound sleep strongly correlated with the amount of the immediate early gene expression induced by the deprivation protocol. We demonstrate that sleep deprivation engages the sleep homeostat by regulating the expression of the sleep promoting neuropeptide galanin.
To identify potential mediatores and downstream effectors of sleep, homeostasis we performed RNA sequencing. Amongst others, preliminary data indicates a role for EGFR/Stat3 signalling as stat3 expression is robustly increased after exposure to arousing drugs and pharmacological inhibitition of EGFR sugnalling is able to reverse post-drug sleep.
Taken together, our data indicates that sleep pressure is dose-dependently regulated by neuronal activity. We hypothesise that this leads to the accumulation of a not yet identified somnogen, which in turn engages the sleep homeostat and increase sleep drive by inducing the expression of the sleep-promoting neuropeptides such as galanin in hypothalamic neurons.

I07

Misregulation of an activity-dependent splicing network as a common mechanism underlying autism spectrum disorders

Mathieu Vallieres-Quesnel[1], Zahra Dargaei[2], Manuel Irimia[3], Thomas Gonatopoulos-Pournatzis[2], Joanna Ip[4], Tim Sterne-Weiler[2], Shin-Ichi Nakagawa[4], Melanie Woodin[2], Ben Blencowe[2], Sabine Cordes[1]

[1]Lunenfeld-Tanenbaum Research Institute, Mt Sinai Hospital, Toronto, Ontario, Canada, [2]University of Toronto, Toronto, Ontario, Canada, [3]Centre for Genomic Regulation, Barcelona Institute of Science and Technology (BIST), Barcelona, Spain, [4]RIKEN, Wako, Saitama, Japan

A key challenge in understanding and ultimately treating autism spectrum disorder (ASD) is to identify common molecular mechanisms underlying this genetically heterogeneous disorder. Previously, we found that a highly conserved program of 3-27 nucleotide neuronal microexons is disrupted in the brains of more than one third of analyzed ASD subjects. We also found that this pattern of microexon misregulation correlates with reduced levels of expression of the neuronal-specific splicing regulator nSR100/SRRM4. To address a causal role for disruption of the nSR100-microexon regulatory network in autism, we generated heterozygous nSR100 mutant mice expressing reduced levels of this protein and mimic patterns of microexon splicing misregulation seen in ASD subjects. Remarkably, these mice display multiple hallmark features of autism, including altered social behaviors, synaptic density and signaling.

To investigate the mechanism underlying reduced nSR100 expression and function in autistic brains, we asked whether these changes are linked to altered neuronal activity. Remarkably, upon neuronal depolarization nSR100 levels rapidly decrease and microexons skipped upon neuronal excitation significantly overlap those that are misregulated in nSR100 deficient mice and in the brains of ASD subjects. Moreover the affected microexons are highly enriched in genes functionally associated with synaptic biology and genetically linked to ASD. Collectively, our results provide evidence that misregulation of an nSR100-dependent splicing network controlled by changes in neuronal activity may be causally linked to a significant proportion of autism cases.

I08

The control of protein appetite by neuronal nutrient sensing

Samantha L Herbert, Pavel M Itskov, Carlos Ribeiro
Champalimaud Centre for the Unknown, Lisbon, Portugal

The nervous system plays a key role in coordinating an animal's intake of food, and in matching both the quality and quantity to the organisms needs. However, the molecular mechanisms in neurons underlying the behavioural responses to changing macronutrient availability remain poorly understood. We examined whether the nervous system of adult Drosophila senses amino acid (AA) levels, and whether this information specifically modulates yeast feeding – the main protein source for Drosophila. We show that activity in the highly conserved Target of Rapamycin (TOR) pathway can be modulated in Drosophila heads by dietary AAs. Furthermore, we identify beefeater as a gene required in the nervous system to regulate yeast feeding in adult flies. This gene shows sequence similarity to the Solute Carrier (SLC) family of membrane transporters. beefeater mutants fully recapitulate the changes seen in yeast feeding after dietary AA deprivation; while overexpression has the opposite effect. Finally we have evidence suggesting that Beefeater could be modulating TOR pathway activity. Together these findings outline a molecular mechanism used by the nervous system to read out amino acid levels in order to homeostatically modify feeding behaviour and preserve physiological amino acid levels.

109

State- and experience-dependent modulation of gustatory neurons underlies protein appetite.

Samuel J Walker, Kathrin Steck, Pavel Itskov, Celia Baltazar, Verónica María Corrales-Carvajal, Carlos Ribeiro
Champalimaud Centre for the Unknown, Lisbon, Portugal

Animals must adapt their behaviour to ongoing internal states. Research on how internal states affect neuronal processing has focused on single internal state variables; but in reality, multiple internal states together shape behaviour. In Drosophila, nutrient-specific hungers such as protein and salt appetite are driven by metabolic and reproductive states, but the neuronal mechanisms processing and integrating these states are unknown. We show that reproductive state is detected by neurons in the female reproductive tract, which synapse onto ascending SAG neurons to influence taste processing and nutrition. Specifically, mating silences the activity of these SAG neurons, resulting in increased salt and protein feeding, providing nutrients necessary for egg production.
We further identify a distinct class of gustatory receptor neurons (GRNs) that mediate feeding on yeast, flies' main protein source. Interestingly, the calcium response of these neurons to yeast is enhanced by deprivation from dietary yeast, but, unlike the behavioural response, not by reproductive state. Surprisingly, we find that this sensory enhancement is not driven by a lack of amino acids in the diet. Rather, we hypothesise that exposure to the sensory experience of yeast desensitises yeast GRNs, and this desensitisation suppresses yeast appetite. Lack of dietary amino acids results in a further increase in yeast appetite, which is not dependent on modulation of sensory neurons. The emerging picture is that metabolic and reproductive states act on higher-level processing, while sensory neurons are modulated by the recent history of sensory experience, and these together shape the behavioural output of the animal.

II0

Interactions of vestibular stimulation and locomotor corollary discharge in *Xenopus laevis* tadpoles

Sara Hänzi[1], Hans Straka[2]
[1]Graduate School of Systemic Neurosciences, Munich, Germany, [2]Department Biology II, Ludwig-Maximilians-University, Munich, Germany

Gaze stabilization in tadpoles of *Xenopus laevis* is achieved by multiple mechanisms. The vestibulo-ocular reflex (VOR) stabilizes gaze in response to passive head movements, which are sensed by the vestibular system. In addition, corollary discharge (CD) from the spinal cord causes compensatory eye movements during swimming. Previous studies have shown that the horizontal VOR is suppressed during swimming, indicating that horizontal semicircular canal-related vestibular inputs are cancelled. In contrast, during natural stimulation of the vertical motion-detection system, the VOR is not or only partially suppressed by the locomotor CD. The present experiments aimed at elucidating the details of the interaction between the CD and concurrently evoked vestibular sensory signals. In particular, how spatially specific is the cancellation of vestibular inputs? Electrophysiological experiments were carried out in *in-vitro* preparations of *Xenopus laevis* tadpoles, in which fictive swimming activity as well as extraocular motor commands were recorded. Linear motion was employed to test whether the CD cancels the VOR that originated from an activation of the otolith organs; preliminary results suggest that this is not the case and that the suppression of vestibular signals is specific with respect to their semicircular canal origin. Employing galvanic vestibular stimulation (GVS) allowed stimulation of specific semicircular canals. Here, it appears that the interactions between swimming and vestibular signals are complex: swimming and GVS are not independent factors, since GVS often elicits swimming, and likely facilitates the transmission of the CD. Nevertheless it is likely that the VOR elicited by GVS is largely cancelled.

III

Firing patterns of serotonin neurons underlying cognitive flexibility

Sara Matias[1], Eran Lottem[1], Guillaume P. Dugué[2], Zachary F. Mainen[1]
[1] Champalimaud Centre for the Unknown, Lisbon, Portugal
[2] Institut de Biologie de l'Ecole Normale Supérieure, Centre National de la Recherche Scientifique (CNRS), UMR8197, Institut National de la Santé et de la Recherche Médicale (INSERM) U1024, Paris, France

Serotonin is implicated in mood and affective disorders but growing evidence suggests that its core endogenous role may be to promote flexible adaptation to changes in the causal structure of the environment through behavioral inhibition and increased plasticity. We used long-term photometric recordings in mice to study a population of dorsal raphe serotonin neurons whose activity we could link to normal reversal learning using pharmacogenetics. We found that these neurons are activated by both positive and negative prediction errors, thus reporting the kind of surprise signal proposed to promote learning in conditions of uncertainty. Furthermore, by comparing cue responses of serotonin and dopamine neurons, we found differences in learning rates that could explain the importance of serotonin in inhibiting perseverative responding. Our findings show how the firing patterns of serotonin neurons support a role in cognitive flexibility and suggest a revised model of dopamine-serotonin opponency with potential clinical implications.

II2

Looking beyond the classical areas of speech production: Insights from the case studies

Silky L Arora[1], Priyamvadha K[2], A.K.Singh[3]
1: Neuro-Speech Language Pathologist, Max Institute of Neurosciences, Max Hospital, Dehradun, Uttarkhand, India-248001.
2: Consultant, Neurosurgery, Max Institute of Neurosciences, Max Hospital, Dehradun, Uttarkhand, India-248001.
3: Director, Max Institute of Neurosciences, Max Hospital, Dehradun, Uttarkhand, India-248001.

This case study of two neurosurgical patients investigates the distributed language networks across the brain. The literature generally agrees on two types of language pathway in the brain: the dorsal pathway & the ventral pathway. Concerning the connection between the language-relevant areas, this study tries to delineate the region mainly associated with word retrieval difficulty i.e. anomia. Two cases have been studied following neurological surgery. Language assessment using Western Aphasia Battery revealed similar language difficulty in both the cases. The inability to recall was severely compromised. Furthermore, the correlation was studied with their radiological findings. Magnetic resonance imaging demonstrated the hyperintensity in Left Superior Frontal Gyrus (LSFG). All of them showed improvement in language abilities with similar type of therapeutic intervention. Therefore, it can be proposed that left SFG is the part of ventral language network and plays an important role in the recall & recognition of spoken words.

II3

Investigation into the role of Dopaminergic cells in VTA during sexual behavior in male mice

Silvana C. Araújo, Joaquim A. Silva, Vítor Paixão, Eran Lottem, Rui Costa, Zach Mainen and Susana Q. Lima
Champalimaud Centre for the Unknown, Lisbon, Portugal

The dopaminergic mesoaccumbens system has been suggested to be involved in both appetitive and consummatory phases of sexual behavior. Additionally, pharmacological manipulations of the dopaminergic system in rats have shown that this system is paramount for this particular behavior, although different manipulations can have contradictory effects.

In order to further understand the role of dopamine in sexual behavior we use fiber photometry to investigate the activity of dopaminergic cells in the ventral tegmental area (VTA) during sexual behavior in male mice.

Twelve week old BL6 expressing CRE recombinase under the control of the promoter for the dopamine transporter (DAT-cre) males were injected with a mixture of AAV5-Syn-GCamp6f and AAV5-CAG-tdTomato (to control for movement artifacts) and implanted with an optic fiber in the VTA. After recovery males were presented with a receptive female and engaged in sexual behavior while recording calcium transients in dopaminergic cells.

Results show increased calcium transients when males detect the presence of a receptive female in the behavioral arena. Furthermore during sexual behavior, more specifically before mounting and during intromissions we also detect increased activity in the VTA. Moreover an increase in calcium influx to DAT cells, followed by a longer gradual decay, is observed during an ejaculatory event.

In conclusion our data point out for an involvement of dopaminergic cells of the VTA in both appetitive and consummatory phases of sexual behavior, where the signal is locked with the behavioral events, such as intromissions and with longer transients during ejaculation.

II4

Midbrain dopamine neurons control judgment of time

Sofia Soares, Bassam Atallah, Joseph Paton
Champalimaud Centre for the Unknown, Lisbon, Portugal

Our sense of time is far from constant. For example, time flies when we are having fun, and slows to a trickle when we are bored. This common experience is related to the motivation to approach or engage with a situation, or attention paid to the passage of time. Interestingly, midbrain dopamine neurons have been implicated in motivation and attention, as well as time estimation. However a direct link between signals carried by dopamine neurons and temporal judgments is lacking. Here, we measured and manipulated the activity of dopamine neurons using a combination of pharmacogenetics, fiber photometry, and optogenetics as mice judged the duration of time intervals. First, we found that pharmacogenetic inhibition of dopamine neurons decreased behavioral sensitivity to time, establishing that timing behavior in our task required dopamine neuron activity. Next, we discovered that dopamine neurons encoded information about trial to trial variability in time estimates, exhibiting greater activity when timekeeping appeared slower. Finally, we show that transient optogenetic activation of dopamine neurons was sufficient to slow time estimation, demonstrating that dopamine neurons not only reflect, but can directly control the judgment of time. These data directly link signals carried by dopamine neurons with variability in the sense of time, a finding with broad implications for understanding normal behavior and aberrant behavior associated with disorders and therapeutic treatments affecting the dopaminergic system.

II5

Encoding angular velocity to drive a compass in the *Drosophila* central complex

Stephanie Wegener[1], Romain Franconville[1], Johannes Seelig[2], Daniel B. Turner-Evans[1], Vivek Jayaraman[1]
[1]Janelia Research Campus, Howard Hughes Medical Institute, Ashburn, VA, USA, [2]Research Center CAESAR, Max-Planck, Bonn, Germany

The insect central complex (CX), a set of neuropiles involved in spatial orientation and navigation, is the locus of compass-like neural dynamics reminiscent of rodent head direction cells. These dynamics were first observed using population calcium imaging in a class of columnar neurons that relay information from the ellipsoid body (EB) to the protocerebral bridge (PB), two substructures of the CX. These compass neurons track the fly's heading in darkness using self-motion cues (Seelig & Jayaraman, 2015), making the fly's angular velocity a critical piece of information to update its internal sense of direction. Here we investigate where and how angular velocity is encoded within the central complex. PB-EB-Noduli (PB-EB-No or PEN) neurons seem ideally suited for this task since they: (1) have an inverted neural polarity with respect to the compass neurons (Wolff et al., 2015), (2) appear to make excitatory connections to those neurons, and (3) show calcium responses correlated with angular velocity in their processes that innervate the noduli, a paired structure within the CX. We performed whole-cell patch-clamp recordings in head-fixed flies walking on an air-supported ball to reveal that PB-EB-No neurons are linearly tuned to the fly's angular velocity, with depolarizing and hyperpolarizing responses to turns in the ipsi- and contralateral direction respectively (with respect to the hemisphere in which the neuron's soma is located). We are now investigating the sources of this velocity signal and how it is used to update the fly's internal compass.

II6

mitoLUHMES - an engineered neuronal cell line for the analysis of mitochondrial motility

Tomasz Stępkowski, Marcin Kruszewski
Institute of Nuclear Chemistry and Technology, Warsaw, Mazovia, Poland

Perturbations in mitochondrial transport and quality control in neuronal cells underlie many types of neurological pathologies. Whereas, systems enabling convenient analysis of mitochondrial behavior in cellular models of neurodegenerative diseases are limited. Here in we present a modified version of Lund Human Mesencephalic Cells - mitoLUHMES, expressing GFP and mitochondrially targeted DsRed2 fluorescent proteins, intended for in vitro analysis of mitochondrial trafficking by real-time fluorescence microscopy. This cell line can be easily differentiated into neuronal phenotype and allowed us to observe movements of single mitochondria in single cells grown in high density cultures. We quantified the perturbations in mitochondrial morphology and dynamics in cells treated with model neurotoxins: carbonyl cyanide mchlorophenylhydrazone and 6-hydroxydopamine. For the first time we filmed the processes of mitochondrial fission, fusion, pausing and reversal of movement direction in LUHMES cells. We present a detailed analysis of mitochondria length, velocity and frequency of movement for static, anterograde and retrograde motile mitochondria. The observed neurotoxin treatment mediated decreases in mitochondria morphological and kinetic parameters provide foundation for the future studies exploiting mitoLUHMES as a new model for neurobiology.

II7

Internal states drive nutrient homeostasis by modulating exploration-exploitation trade-off

Verónica María Corrales-Carvajal[1], Aldo A Faisal[2, 3], Carlos Ribeiro[1]
[1] *Champalimaud Centre for the Unknown, Lisbon, Portugal*
[2] *Department of Bioengineering and Department of Computing, Imperial College London, London, United Kingdom.*
[3] *Integrative Biology Division, MRC Clinical Sciences Centre, Hammersmith Hospital Campus, London, United Kingdom.*

Internal states can deeply alter the behavior of animals. Which aspects of behavior change upon metabolic challenges and how these allow the animal to achieve nutrient homeostasis is poorly understood. We used an automated video tracking setup to characterize how amino acid and reproductive states interact to shape exploitation and exploration decisions taken by adult Drosophila melanogaster, to achieve nutritional homeostasis. We find that these two states have specific effects on the decisions to engage and leave proteinaceous food patches. Furthermore, the internal nutrient state defines the exploration-exploitation trade-off: nutrient deprived flies focus on specific patches while satiated flies explore more globally. Finally, we show that olfaction mediates the efficient recognition of yeast as an appropriate protein source and that octopamine is specifically required to mediate homeostatic postmating responses without affecting internal nutrient sensing. Internal states therefore modulate specific aspects of exploitation and exploration to change nutrient selection.

II8

Noradrenergic modulation of reaction time is task dependent

Maria Ribeiro, Miguel Castelo-Branco
IBILI, Faculty of Medicine, University of Coimbra, Coimbra, Portugal

Pharmacological manipulations of the noradrenergic system suggest an impact of noradrenaline on reaction time, impulsiveness, and motor cortex excitability.
In this study, we investigated if noradrenergic activation during motor tasks was associated with enhancement of response speed independent of task requirements. We compared a warned simple reaction time task where fast responses were emphasized, with a warned go/no-go task where, although speed was also emphasized, the requirement for inhibitory control leads to an active slowdown of motor responses. We studied noradrenergic activation non-invasively, in humans, using pupil dilation as a proxy for noradrenergic, locus coeruleus activation.
Participants responded slower in the go/no-go condition than in the simple reaction time condition, as expected. The warning stimuli in both task conditions elicited a preparatory pupillary response. The average amplitude of this pupil dilation response in the simple reaction time condition was not significantly different from the average pupil dilation observed in the go/no-go condition. Yet, the relationship between the single trial amplitude of the preparatory pupil dilation responses and reaction time depended on the task. In the simple reaction time task, stronger pupil dilation responses were associated with faster responses; while in the go/no-go task stronger pupil dilation responses were associated with slower responses.
These findings suggest that pupil dilation does not reflect a straightforward facilitation of motor cortex excitability. This relationship may depend on other factors related to mental state associated with task requirements.
Funded by Fundação para a Ciência e Tecnologia (Grants: SFRH/BPD/102188/2014, and UID/NEU/04539/2013-COMPETE, POCI-01-0145-FEDER-00 7440).

II9

Closed-loop pairing of motor cortex activity and phasic VTA activation reinforces specific spatiotemporal activity patterns

Vivek R. Athalye*[1, 2,] Fernando J. Santos*[1], Jose M. Carmena[2, 3], Rui M. Costa[1]
* co-first author
[1] *Champalimaud Centre for the Unknown, Lisbon, Portugal*
[2] *Department of Electrical Engineering and Computer Sciences, University of California, Berkeley, Berkeley, CA, 94720, USA*
[3] *Helen Wills Neuroscience Institute, University of California, Berkeley, Berkley, CA 94720, USA Joint Graduate Group in Bioengineering UCB/UCSF*

Over skill learning, animals consolidate particular movements and movement-related neural activity patterns, but the neural circuit mechanisms underlying neural spatiotemporal pattern consolidation are not well understood. Because phasic dopaminergic activation promotes behavioral selection, we asked: is pairing arbitrary neural activity patterns in primary motor cortex (M1) with phasic activation of dopaminergic cells in the Ventral Tegmental Area (VTA) sufficient to reinforce the task-relevant patterns?

We combined a mouse operant Brain-Machine Interface (BMI) paradigm (Koralek*,Jin*,et al 2012) with closed-loop optogenetic excitation of VTA. The BMI algorithm translated the activity of two arbitrarily-defined ensembles of 2-4 units from M1 into an auditory tone. When mice produced the rare activity pattern to hit the target audio tone, they received optogenetic stimulation of dopaminergic VTA cells contralateral to the recording site.

We trained TH-Cre mice expressing channelrhodopsin-2 in VTA (ChR2 group, N=10) and YFP in VTA (YFP group, N=6) for 4 days consisting of 20 min daily sessions. Over training, we found that ChR2 animals produced the target audio tone and nearby tones more frequently while there was no change in YFP animals. Finally, we found that increases in neural co-variability predict improvements in BMI performance for the ChR2 animals but not YFP.

These results show that the closed-loop pairing of motor cortex activity with phasic dopaminergic VTA activation leads to the reinforcement of specific spatiotemporal

activity patterns, suggesting a neural circuit mechanism for pattern consolidation during natural skill learning.

I20

Natural antimicrobial peptide potentiates TRPA1 receptor and produces analgesic effects in mice

Yaroslav Andreev[1], Yulia Logashina[1], Klara Stensvåg[2], Yulia Korolkova[1]
[1]Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry, Russian Academy of Sciences, Moscow, Russia, [2]Norwegian College of Fishery Science, University of Tromsø, Tromso, Norway

The transient receptor potential ankyrin-repeat 1 (TRPA1) receptors play significant role in initiation and development of neurogenic inflammatory pain as well as in ischemic neurodegeneration. Novel bioactive peptide named Ueq12-1 was isolated and characterized from the sea anemone Urticina eques. Ueq12-1 showed dual activity, both inhibiting bacterial growth of Corynebacterium glutamicum and Staphylococcus aureus, and potentiating TRPA1 ion channel. 3D structure of Ueq12-1 determined by NMR represents new disulfide-stabilized fold in part similar to defensin-like fold. Ueq12-1 is the unique peptide potentiator of TRPA1 receptor that produce analgesic and anti-inflammatory effect in vivo. Injection of Ue12-1 (50uM solution,10ul) in the hindpaw did not cause pain, paw edema or significant thermal hyperlgesia in 2 h. Pretreatment of mice by intravenous injection of Ueq12-1 (0,2 mg/kg) significantly reduced AITC- induced nocifensive behavior. Moreover, paw edema caused by AITC was significantly reduced in 2, 4and 24 h at 61, 43 and 23%. Ueq12-1 (0.2 mg/kg) reversed thermal hyperalgesia within 30 min after i.v. administration of peptide and reduced paw edema at 27% in 24 h in non-specific inflammation in CFA test. The effect of peptide in behavioral test was not result of sedation of behavior impairment since administration of Ueq12-1 did not change normal behavior of mice in open field test. Antinociceptive properties allow to consider Ueq12-1 as a potential analgesic drug with antibacterial properties.

High Resolution Estimation of the Hemodynamic Response Function across Brain Regions

Yiling Yang[2], Yusuke Murayama[1], Nikos Logothetis[1], Michel Besserve[1]
[1]Department of Physiology of Cognitive Processes, Max Planck Institute for Biological Cybernetics, Tübingen, Germany, [2]Graduate School of Neural & Behavioural Sciences, International Max Planck Research School, Eberhard-Karls University of Tübingen, Tübingen, Germany, [3]Centre for Imaging Sciences, Biomedical Imaging Institute, The University of Manchester, Manchester, UK, [4]Department of Empirical Inference, Max Planck Institute for Intelligent Systems, Tübingen, Germany

Functional magnetic resonance imaging (fMRI) is a widespread neuroimaging technique capturing the changes in local metabolic activity reflected in the blood oxygenation level-dependent (BOLD) signal; however, its relationship to the underlying neural activity remains elusive. In particular, the variability of the neurvascular and neurometabolic coupling across brain regions due to different configurations of neural circuits, glia and blood vessels are largely unknown. Simultaneous in-vivo recording of fMRI and Local Field Potentials (LFP) in a given brain structure using intracranial electrodes offers an exceptional opportunity to characterize this relationship. Here we quantify the LFP-fMRI relationship across structures by fitting a linear convolutive model between these signals. The resulting impulse response of the system provides a structure specific estimate of the hemodynamic response function (HRF). While one major limitation of classical HRF estimation is the low temporal resolution of the fMRI recordings (2 s in our case), we elaborate a new methodology to assess the HRF time course at a much finer scale (.2 s). While low resolution estimation resulted in non-causal and thus unlikely HRFs shapes, preliminary application of our approach to the high frequency band power (80-180Hz) of LFP recordings in the macaque primary visual cortex (V1) and hippocampus resulted in satisfactory, fast and causal, HRFs in both structures, with a time-to-peak of 3.99s in V1 and 3.79 s in hippocampus and a peak 147% larger in V1. These results demonstrate our approach allows a precise estimation of fast HRFs that will allow a better quantification of neurovascular coupling mechanisms

I22

Brain plasticity following physical training in individuals with mild cognitive impairment: Neuroimaging study

Galit Yogev-Seligmann[1], Tamir Eisenstein[2], Elissa Ash[1], Talma Hendler[1], Nir Giladi[1], Yulia Lerner[1]
[1]Tel Aviv Sourasky Medical Center, Tel Aviv, Israel, [2]Tel Aviv University, Tel Aviv, Israel

Mild cognitive impairment (MCI) is a prodromal stage of Alzheimer disease (AD). To date, therapeutic approaches to AD are of modest efficacy. Nonetheless, several modes of evidence in animal models and human populations suggested that physical training results in structural and functional brain changes. However, the extent to which comparable improvement can be found in individuals with amnestic MCI (a-MCI) and the nature of these neuroplastic changes are unknown. Using fMRI experiments, neuropsychological evaluations and physiological markers, our goal is to explore the brain mechanisms mediating the cognitive benefits of aerobic vs. non-aerobic physical training in participants with a-MCI (n=19). Namely, we have evaluated how processing incoming information as well as memory encoding might be modulated by physical training in a-MCI, and whether the impaired pattern of information processing could revert to the common pattern observed in cognitively-intact populations. Additionally, we have assessed the impact of physical training on cognitive performance and on physiological markers associated with brain plasticity (e.g. neurotrophic factor, BDNF). Preliminary results show changes in pattern of information processing following 4 months of intensive individual training. We revealed reliable neural responses in regions that are related to higher order processing of information in cognitively-intact older adults. Moreover, hippocampal activation in memory encoding task increased following 4-months of aerobic intervention. Also, improvement in tests of memory executive functions was found in both physical training groups.The insights gained from the study may have important scientific value and clinical implications for individuals who are at the early stages of AD.