



Program of the 22nd meeting of the Club of Invertebrate Neurobiology

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Parmentier

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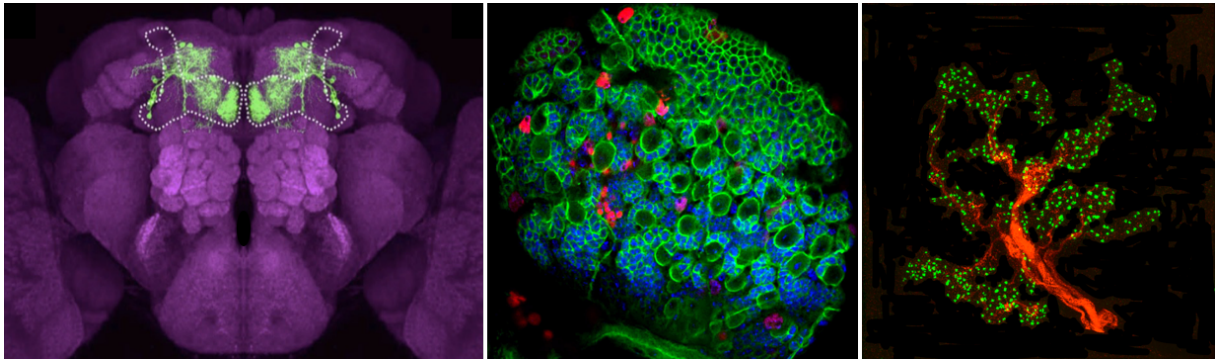
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Program of the 22nd meeting of the Club of Invertebrate Neurobiology

Montpellier, 19-20th of May 2022

Keynote speakers :

Christelle JOSET-ALVEZ, EthoS, Caen
Bérangère PINAN-LUCARRE, MeLIS / INMG, Lyon
Thomas PREAT, ESPCI, Paris

Organizers
Jean-Maurice DURA
Christelle LASBLEIZ
Emmanuel PERISSE
Marie-Laure PARMENTIER



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Program of the 22nd meeting of the Club of Invertebrate Neurobiology

Thursday, 19th May 2022

Welcome of participants (13h30-14h)

Conference 1: introduced by Jean-Maurice Dura

14h-15h: **Thomas Pr  at**, ESPCI, Paris

Building a metabolic code of memory

Session 1: Chairperson Maheva Andriatsilavo

T1 - 15h-15h20 : **Jean-Marc Devaud**, CRCA, Toulouse: Olfactory learning performance correlate with head size and is impacted by exposure to a heavy metal

T2 - 15h20-15h40: **Laurent Seugnet**, CRN de Lyon: Notch signaling in different glial cells of the *Drosophila* brain and its impact on learning, sleep and mitochondria.

15h40-15h45: **Jean-Ren   Martin** will present the next Neurofly meeting (September 6th to 10th, 2022) that will be held in Saint-Malo, France.

Coffee/Tea break – Poster Session 1 (15h45-17h)

Session 2: Chairperson Jean-Charles Lievens

T3 - 17h- 17h20: **Marion Celle**, LBMC, ENS de Lyon: Establishing a *Drosophila* model of BPAN disease

T4 - 17h20-17h40: **Jeanne Urban**, CSGA, Dijon: Exploration of CYP27A1 function in eye cholesterol signaling between glia and neurons in *Drosophila*.

T5 - 17h0-18h: **Guillaume Isabel**, CRCA, Toulouse: Images of copulating conspecifics elicit mate copying in fruit flies.

Assembl  e G  n  rale du Club (18h-18h30)

18h30-19h: **Free time - informal discussion.** Please note that we have to leave the venue by 19h sharp.

20h: **Club dinner** at H  tel Oceania Le M  tropole – 3, rue du clos Ren   34000 Montpellier (20h Aperitif in the lobby – 20h30 Dinner).



Friday, 20th May 2022

9h-9h30: Coffee/Tea/Juices/Mini-cakes and Pancakes

Conference 2: introduced by Emmanuel Périssé

9h30-10h30: **Christelle Jozet-Alves**, Ethos, Caen

Brain and behavioral asymmetries in cuttlefish

Coffee/Tea break (10h30-11h)

Session 3: Chairperson Serge Birman

T6 - 11h-11h20: **Martin Giurfa**, CRCA, Toulouse: An insect brain organizes numbers on a left-to-right mental number line.

T7 - 11h20-11h40: **Mercedes Bengochea**, ICM, Paris: Numerical discrimination in *Drosophila melanogaster*

T8 - 11h40-12h: **Maxime Lehman**, NeuroPSI, Saclay: Neural circuitry underlying sensorimotor decisions

Lunch (12h-13h30)

Conference 3: introduced by Marie-Laure Parmentier

13h30-14h30: **Bérangère Pinan-Lucarré**, INMG, Lyon

Control of synapse formation by novel extracellular interactions in *C. elegans*

Coffee/Tea break – Poster Session 2 (14h30-15h30)

Session 4: Chairperson Cécile Bellanger

T9 - 15h30-15h50: **Julie Delescluse**, CSGA, Dijon: Role of Minidiscs, a SLC7A amino-acid transporter, on glutamatergic activity in *Drosophila melanogaster* mushroom bodies.

T10 - 15h50-16h10: **Maria Capovilla**, IPMC, Valbonne: New insights into the pathophysiology of the Fragile X Syndrome using a *Drosophila* model

T11 - 16h10-16h30: **Ana Boulanger**, IGH, Montpellier: Neuron secreted Orion is involved in the transformation of glial cells into phagocytes during neuronal remodeling

Final words and meeting closure (16h30-16h45)



Conference and Talk abstracts

Conference 1

Building a metabolic code of memory

Thomas PREAT

ESPCI Energy & memory, Paris

T1

Olfactory learning performance correlate with head size and is impacted by exposure to a heavy metal

Coline Monchanin, Mathieu Lihoreau, Jean-Marc Devaud

Centre de Recherches sur la Cognition Animale, Toulouse, France

Pollutants can have severe detrimental effects on insects, even at sublethal doses. Agrochemicals have been identified as important causes of pollinator declines, but the impacts of other anthropogenic compounds, such as metallic trace elements, have received considerably less attention. We exposed honey bee colonies to chronic field-realistic concentrations of lead in food and demonstrate that consumption of this single trace element impaired bee cognition and morphological development. Honey bees exposed to the highest lead concentration had reduced olfactory learning performances. They also developed smaller heads, which may have constrained their cognitive functions.

Indeed, we have also shown that brain and head size correlate with learning performance, even in unexposed bees. Based on morphological data (obtained from 3D-reconstructed brains from micro computed tomography scans) and behavioural results (from 1,600 honey bees tested in various standard cognitive assays), we found that bees with larger heads showed higher olfactory learning and memory performance in different tasks (absolute, differential and reversal conditioning). In addition, bees that performed better also had larger brains, and specifically larger antennal lobes (olfactory centers). Importantly, no correlation was found with the size of other brain areas or sensory organs. Overall, these results reveal unsuspected cognitive differences among workers and suggests possible neural underpinnings of inter-individual behavioural variability, that are impacted by exposure to sublethal stressors.

Notch signaling in different glial cells of the *Drosophila* brain and its impact on learning, sleep, and mitochondria

Elodie Guichon, Dylan Girard, Laurent Seugnet

Physiologie intégrée du système d'éveil (WAKING), Bron, France

We have shown that the trans-membrane receptor Notch mediates a neuro-glial signaling pathway linked to sleep/wake regulation and learning in *Drosophila*. When this pathway is constitutively activated in glial cells, flies display an attenuated sleep homeostatic response to sleep deprivation and no impairment in aversive phototaxis suppression, a short term memory assay that is sensitive to sleep loss and requires dopamine signaling through D1-like receptors. Notch signaling is activated in a subset of glial cells and downregulated by sleep deprivation, whereas its ligand Delta is broadly expressed in neurons. Here, we present evidence that Notch is required in several different glial cell types for learning, including surface glia, cortex glia and ensheathing glia. We show that Notch activation is correlated with mitochondrial volume and activity as well as glucose levels in those cells.

Establishing a *Drosophila* model of BPAN disease

Marion Celle¹, Sahra Anierte¹, Marion Falabregue², Tereza Coman³, Francine Côté³, Gaetan Lesca⁴, Ludivine Walter¹, Bertrand Mollereau¹

¹ Laboratory of Biology and Modelling of the Cell – CNRS : UMR5239, INSERM U2110, Université de Lyon, ENS de Lyon, UMS344 Biosciences Lyon Gerland - France

² Institut Cochin, INSERM U1016, CNRS UMR 8104, Paris, France.

³ Service d'Hématologie, Institut Gustave-Roussy -, Villejuif, France.

⁴ Department of Medical Genetics – University Hospital of Lyon – France

The Beta-Propeller protein Associated with Neurodegeneration (BPAN) is associated with a rare neurodegenerative genetic disease characterized by iron brain accumulation. The BPAN disease is caused by the mutation of the *wdr45* gene, which has been identified in 2012. WDR45 is known to be involved in autophagy process, which is deregulated in various BPAN disease models. Moreover, iron metabolism and ER stress response are also perturbed in some models of BPAN disease. The molecular events that lead to neurodegeneration in *wdr45* mutants are still largely unknown. We have established a *Drosophila melanogaster* BPAN disease model using RNAi and CRISPR-Cas9 strategies targeting CG11975, the *Drosophila* WDR45 homolog. We have demonstrated that flies harboring CG11975 mutation mimic characteristics of the BPAN disease such as locomotor disorder, neuronal loss and increased sensitivity to iron that are also associated with autophagy and ER stress response dysregulations. Therefore, I have established a *Drosophila* BPAN disease model that will be a precious tool to investigate the molecular roles of WDR45 and its importance to maintain neuronal health.

Exploration of CYP27A1 function in eye cholesterol signaling between glia and neurons in *Drosophila*.

J. Urban, Y. Grosjean, N. Acar, E. Masson, G. Alves

*Centre for Taste and Feeding Behaviour, CNRS, INRAE, Institut Agro, University of Burgundy-Franche-Comté 9E
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Cholesterol is essential to maintain the integrity of cell membranes and plays important roles in neuron viability and transmission of nervous signals. In mammalian brain, a fine regulation of its metabolism is associated with the communication between glial cells and neurons. The dysregulation of cholesterol homeostasis is associated with many neurodegenerative disorders [1]. In particular, cholesterol accumulation in the retina is implicated in age-related macular degeneration, the leading cause of vision loss in western countries [2]. In normal condition, cholesterol elimination from the retina could rely on its conversion into oxysterols via the action of several cholesterol hydroxylases, including the CYP27A1 enzyme [3][4].

The aim of the present study is to determine the mechanisms underlying cholesterol elimination in the visual system as well as neuron-glia interactions. The *Drosophila* genetic model has been chosen for its efficiency in exploring neuronal signaling pathways. We have started to screen the down-expression of a series of CYP27A1 orthologs using RNA interference in specific neurons or glial cells in the visual system. We first used the neuron specific driver, *gmr-Gal4*, to inactivate CYP27A1 orthologs in the eye. In parallel, we started to perform immunostaining experiments to determine whether down-regulation of CYP27A1 orthologs can induce neurodegeneration in the eye during aging. Cholesterol accumulation in fly heads will also be evaluated using gas/liquid chromatography to determine the role of CYP27A1 orthologs in cholesterol metabolism in *Drosophila*.

A better understanding of the role of retinal cells in cholesterol homeostasis should help in the development of effective retinal degeneration therapies.

References

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Images of copulating conspecifics elicit mate copying in fruit flies

Sabine Nöbel, Magdalena Monier, David Villa, Etienne Danchin, Guillaume Isabel

Centre de Recherches sur la Cognition Animale, Toulouse, France

Humans are highly sensitive to two-dimensional images, particularly in the domain of sex. However, little is known on the perception of flat images in non-human animals despite the use of artificial stimuli is widespread. Mate copying occurs when naïve females observe the mating success of potential mates and use that social information to build their own mating preference. In fruit flies mate-copying experiments involve a demonstration during which virgin observer females can watch demonstrator females choosing for copulation between two males of contrasting phenotypes. Then, in a mate-choice test, observer females freely choose to copulate with one of the two male phenotypes. We developed a new approach to study mate copying in the fruit fly by using photos or simplified images of copulating conspecifics instead of real flies during the demonstration phase. We show that these demonstrations still elicit efficient mate copying, suggesting that females perceived them as actual sexual intercourse. Furthermore, specific traits in demonstrator images, such as wings and eyes, are necessary to promote copying. This suggests that sensitivity to sex images also exists in insects, and thus potentially in many organisms. The new approach of using images instead of real flies as stimuli offers countless new opportunities to study mate choice or social learning in general in *D. melanogaster*. Furthermore, using photos helps to reduce the number of animals used in experiments and should increase reproducibility as they allow full control over the stimuli.

Conference 2

Brain and behavioural asymmetries in cuttlefish

Christelle Jozet-Alves

Laboratoire EthoS – Equipe NECC, Caen, France

Brain and behavioural asymmetries seem ubiquitous in the animal kingdom. While a general pattern of hemispheric specialisation has been described in vertebrates, how environmental information are asymmetrically processed in invertebrates remains poorly understood. Indeed, although the list of species showing asymmetries is continuously extending over the years, few species have been thoroughly studied from a mechanistic, developmental and functional point of view. Since several years, the cuttlefish, a cephalopod mollusc, has been the focus of a range of studies aiming at understanding the nature and the function of these asymmetries (i.e. which information is preferentially processed *via* which hemibrain), their development (how genes and environment interact during ontogenesis), and how these asymmetries bestow favourable selective advantages. In cuttlefish, behavioural symmetries suggest a preferential use of the right hemibrain for routine behaviour and of the left hemibrain for emergency responses, as in vertebrates. Going further in the study of the

attributes shared or not between species will be helpful in the future to better depict the complexity of laterality and its evolutionary roots.

T6

An insect brain organizes numbers on a left-to-right mental number line

Martin Giurfa(1), Claire Marcout(1), Catherine Thevenot(2) and Rosa Rugani(3)

(1) Centre de Recherches sur la Cognition Animale, Centre de Biologie Intégrative (CBI), University of Toulouse, CNRS, UPS, 31062 Toulouse cedex 9, France (2) Institute of Psychology, University of Lausanne, CH-1015, Lausanne, Switzerland. (3) Department of General Psychology, University of Padova, 35100 Padova, Italy

The ‘mental number line’ (MNL) is a form of spatial numeric representation that associates small and large numbers with the left and right space, respectively. This spatial-numerical organization can be found in adult humans and has been related to cultural factors such as writing and reading habits. Yet, both human newborns and birds order numbers consistently with a mental number line, thus questioning culture as a main explanation for MNL. Here we explored the numeric sense of honey bees and show that after being trained to associate numbers with sucrose reward, they order novel numbers from left to right according to their magnitude. Importantly, the location of a number on that scale varies with the reference number previously trained and does not depend on low-level cues present on numeric stimuli. We provide a series of neural explanations for this effect based on the extensive knowledge accumulated on the neural underpinnings of visual processing in honey bees and conclude that the MNL is a form of numeric representation that is evolutionary conserved across nervous systems endowed with a sense of number, irrespective of their neural complexity.

T7

Numerical discrimination in *Drosophila melanogaster*

Mercedes Bengochea¹, Jacobo D. Sitt¹, Veronique Izard², Thomas Preat³, Laurent Cohen^{1,4}, Bassem A. Hassan¹

¹Institut du Cerveau-Paris Brain Institute (ICM), Sorbonne Université, Inserm, CNRS, Hôpital Pitié-Salpêtrière, Paris, France.

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Sensitivity to numbers is a crucial cognitive ability that is widespread across the animal kingdom. The lack of experimental models amenable to systematic genetic and neural manipulation has precluded discovering neural circuits required for numerical cognition. Here, we demonstrate that, when provided with a choice, *Drosophila* flies spontaneously prefer sets



containing larger numbers of objects. This preference is determined by the ratio between the two numerical quantities tested, a characteristic signature of numerical cognition across species. Individual flies maintained their numerical choice over consecutive days. Using a numerical visual conditioning paradigm, we found that flies are capable of associating sucrose with numerical quantities and can be trained to reverse their spontaneous preference for large quantities. Finally, we show that silencing LC11 neurons reduces the preference for more objects, thus identifying a neuronal substrate for numerical cognition in invertebrates. This discovery paves the way for the systematic analysis of the behavioral and neural mechanisms underlying the evolutionary conserved sensitivity to numerosity.

T8

Neural circuitry underlying sensorimotor decisions

Maxime Lehman¹, Chloé Barre², Sandra Autran¹, Tihana Jovanic¹

1 : Neuro-PSI, CNRS UMR 9197, Neural circuits and behavior, Gif-sur-Yvette

2 : Decision and Bayesian Computation, USR 3756 & Neuroscience Department, Institut Pasteur & CNRS, Paris.

The neural circuit mechanisms underlying the transformation of sensory information into appropriate motor output remain incompletely understood. Thanks to recent progress in connectomics and to its powerful genetic toolbox, *Drosophila* larva presents itself as a powerful model for mapping and functionally testing of complete sensorimotor circuits. We investigated the neural circuitry underlying larval responses to an aversive mechanical stimulus, the air puff. *Drosophila* larvae typically respond to air puff with either startle or escape mutually exclusive behaviors. We have previously identified neural circuits underlying competitive interactions underlying startle and escape behaviors at the early sensory processing center. Using inactivation and optogenetic activation we identified a second order interneuron repressing Hunching, a head-retraction startle response, and promoting Escape:A19c. The optogenetic activation of A19c triggers escape sequences that are modulated by the sensory context. Surprisingly, the inactivation of A19c during optogenetic activation of different subsets of its pre-synaptic partners, first order projections neurons that also trigger escape responses, resulted in increase in the strongest escape response type. Thus, A19c an inhibitory neuron, appears to inhibit Hunching and regulate Escape. Using EM-based connectomics, we are now mapping its downstream targets. We found A19c synapses onto a pre-motor target of a group of second order excitatory neurons we found were required for Hunching. Determining the neural circuit mechanisms underlying competitive interactions in a model system where we can trace synaptic connectivity and manipulate single neurons may bring insights into the neural circuit mechanisms of sensorimotor decisions in general.

Conference 3

Control of synapse formation by novel extracellular interactions in *C. elegans*

Bérangère Pinan-Lucarré

MeLIS / INMG / Université Claude Bernard Lyon I, Lyon

Chemical synapses are evolutionarily ancient structures. The diversity and specificity of synapses rely upon core organizing Cell Adhesion Molecules (CAM) that regulate contact initiation, synapse formation, maturation, maintenance and functional plasticity. Using the roundworm *Caenorhabditis elegans*, we seek to elucidate new molecular mechanisms sustaining synapse biology. We recently identified newly trackable neuron-to-neuron synapses using a fluorescent reporter of the ACR-16 acetylcholine receptor, ortholog of the human acetylcholine alpha7 receptor. First we identified the neuron types forming these specific synapses, using leading edge technologies and data available in the field. These neurons take part in the locomotory circuit. Second we performed a visual screen upon random mutagenesis, to identify mutants of ACR-16 positive synapses. One mutant caught our attention because, in this mutant, the ACR-16 acetylcholine receptor was no longer synaptic and appeared diffuse at the neuronal surface. This phenotype is typical of a mutation in a core synaptic organizer. The mutated gene encodes a CAM of the Immunoglobulin superfamily. This CAM shows a strikingly specific localization at ACR-16 positive synapses. Moreover, we found that a known *in vitro* binding partner of this CAM is also very specific of ACR-16 positive synapses. Overall, our data suggest that we identified two novel synaptic molecules that might form a bridge across neurons and control synapse formation and/or maintenance in *C. elegans*. Interestingly, orthologs of this CAM are associated with a wide spectrum of human neurodevelopmental and neuropsychiatric disorders, and might control synaptogenesis in mammals.

T9

Role of MINIDISCS, a SLC7A amino-acid transporter, on glutamatergic activity in *Drosophila melanogaster* mushroom bodies.

Julie Delescluse, Mégane Simonnet, Kevin Piffarretti, Yaël Grosjean and Gérard Manière.

Centre des Sciences du Goût et de l'Alimentation, CNRS, Institut Agro, Université de Bourgogne Franche-Comté Dijon

The SLC7A heterodimeric amino acid transporter family plays a crucial role in cell and tissue physiology and metabolism in mammals, and is a key factor in some human cancers. Five potential SLC7A orthologs -*minidiscs*, *genderblind*, *Jhl-21*, *sobremesa* and CG1607- have been identified in *Drosophila*.

To unravel the role of SLC7A transporters in the amino acid signalling in the adult central nervous system (CNS) we focused on MINIDISCS (MND) transporter. MND is expressed in various cells in the CNS. We already highlighted the role of MND in IPCs as a crucial factor for DILP secretion and



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sugar metabolism. Here we show that MND is also expressed in some neurons forming the α/β and γ lobes of the mushroom bodies (MB). Downexpression of *mnd* in these neurons impairs the role of various amino-acids on MB activity using live calcium imaging. Surprisingly, we found that MND is an important glutamatergic actor in these neurons. We investigated the genetic co-expression of MND with various glutamatergic receptors, and we found that ionotropic (NMDAR, KAINATE, GLUCL α) and metabotropic (dmGLUR) receptors are co-expressed in the MB. We also found that downstream effectors of MND, such as Glutamate Deshydrogenase (GDH) and TOR are also involved in glutamatergic response in these kenyon cells.

These results strongly support a key role played by MND in glutamatergic activity control in *Drosophila melanogaster*. This information opens fascinating new field of investigations, which could allow a better understanding of how nutrients and simple molecules, such as glutamate, can influence neuronal activity.

T10

New insights into the pathophysiology of the Fragile X Syndrome using a *Drosophila* model

Maria Capovilla, Delphine Debayle, Lucile Fleuriot, Anne Sophie Gay, Asma Boulksibat, Barbara Bardon, Takeshi Harayama, and Carole Gwizdeck

Intitut de Pharmacologie Moléculaire et Cellulaire, Valbonne, France

Fragile X syndrome (FXS) is the most common form of inherited Intellectual Disability and the leading monogenetic cause of Autism Spectrum Disorder. FXS is due to the silencing of the highly conserved FMR1 gene resulting in the absence of FMRP, an RNA binding protein modulating the abundance of a large set of neuronal proteins. Mutation of the *Drosophila* FMR1 ortholog (dFMR1) recapitulates the main phenotypes associated with FXS patients. dFMR1 mutants present a starvation phenotype that is partially corrected by metformin, a drug shown to rescue the memory phenotypes of dFMR1 mutants. Since this drug has an impact on lipid metabolism, we undertook lipidomic studies in *Drosophila* heads to have a global overview of the differences in lipids between wild-type flies and flies mutant for dFMR1 in the presence and in the absence of metformin in seven days old females and males and 72-hour-old pupae, a stage at which synaptogenesis is intense. Our preliminary results reveal an imbalance in lipid composition in the *Drosophila* FXS model. Proteomic data sets obtained between WT and mutant flies suggest that anomaly in lipid composition may result from an unbalance in the levels of key enzymes involved in lipid biogenesis, mitochondrial function and stress. No effective and validated treatments are available for FXS. Our study allowing a better understanding of its pathophysiology may result into the identification of therapies for this disease.

The chemokine-like neuron secreted Orion is involved in the transformation of glial cells into phagocytes in different neuronal remodeling and apoptosis paradigms

Ana Boulanger, Clarisse Perron, Salomé Ruiz Demoulin, Eva Minnaert, Pascal Carme, Héloïse Szczkowski and Jean-Maurice Dura

Institut de Génétique Humaine, Montpellier, France

During nervous system development, neurons undergo a remodeling process necessary for their normal function. A critical crosstalk between glia and neurons is required for neuronal remodeling. At metamorphosis, the mushroom body (MB) larval-specific dendrites and axons of early γ neurons are pruned and replaced by adult-specific processes. We recently isolated Orion, a MB secreted protein that bears some mammalian chemokine-associated motifs and which is required in a non-cell autonomous way for MB γ axon astrocytic infiltration and engulfment at pruning. We raised the question if Orion was specifically acting on MB-surrounding astrocytes for pruning or if it could have a broader role on other types of phagocytic glial cells. To answer this question, we are investigating the function of Orion in several nervous system remodeling paradigms. Our results show that Orion also activates glia in the central nerve cord by transforming astrocytes into phagocytes for general synapse elimination. This activation results in enlarged astrocytic processes and acquisition of an overall vacuolated appearance. Additionally, in this system we observed Orion was involved in further steps of glia activation such as: engulfment and phagolysosome formation. Moreover, Orion is also essential for both cortex and ensheathing glia activation during cell body apoptosis as well as axon remodeling in both ventral Corazonin and PDF-Tri neurons. These results extend the function of Orion to different types of phagocytic glial cells and suggest that *orion* is involved in the general transformation of glial cells into phagocytes *via* specific Orion glial receptors and partners.

Poster communications - Abstracts

P1

Impact of a high sugar diet on aversive memory in the fly *Drosophila melanogaster*

Danaë Ajas, Nesrine Merabet and Emmanuel Perisse

Institut de Génomique Fonctionnelle, Montpellier, France

Excess of sugar ingestion is harmful for the metabolism (inducing obesity and/or diabetes) but also on cognition such as learning and memory. High sugar diet (HSD) is known to impacts dopamine signaling and many genes known to play a role in learning and memory. While studies mostly focus on the effect of HSD on appetitive memory, relatively little is known of the impact of HSD on aversive memory capacities, i.e., to encode an absolute aversive value (intensity of bad) and relative aversive value (better or worse than). To study the effect of HSD on aversive memory we chose the fruit fly *Drosophila melanogaster* as a model. We put flies during larval development and/or adulthood on a standard media (corn flour, yeast and agar) supplemented with different concentrations of sugar. We then tested their ability to form and remember different intensities of aversive experiences and their capacity to discriminate between them. Our results surprisingly revealed that only a HSD at 20% during development and adulthood significantly improved fly relative choices but not absolute choices. Flies seem to require a minimum concentration of added sugar in the media during development and adulthood to increase their aversive memory capacities, particularly for relative learning and choice. As the reward dopamine system is involved to encode relative (but not absolute) aversive value, we will then investigate how HSD modulates the reward circuitry to enhance aversive memory capacities.

P2

Spatio-temporal dynamics of stochastic axon targeting during CNS development

Maheva Andriatsilavo^{1,2,3}, Alexandre Dumoulin^{4,5}, Suchetana Dutta^{1,2,3}, Esther Stoeckli^{4,5}, P. Robin Hiesinger^{2,3}, Bassem A. Hassan^{1,2,3}

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While adult brains present stereotypical wiring diagrams, developmental variation in axonal connectivity contributes to non-heritable behavioral individuality (Linneweber et al. 2020).



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The question of how and when these individualized wiring patterns emerge and become stable during development remains unexplored. Using long-term intravital live imaging of axonal growth and targeting of Dorsal Clustered Neurons/LC₁₄ in the developing central nervous system of intact fruit flies, we show that axon selection is a multi-step process with variable outcomes. First, Notch-mediated lateral inhibition defines a subset of neurons with a potential to innervate distal targets. Live imaging and temporal optogenetic activation of Notch signaling reveal that while Notch^{ON} axons stay near proximal targets, Notch^{OFF} axons alter their growth cone morphology to create single-cell bundles of dynamic parallel fibers extending towards distal targets. Live tracking of microtubule dynamics identifies a second selection step, where a subset of Notch^{OFF} axons randomly stabilize one fiber within their bundle structures. In contrast, Notch^{OFF} axons that do not have microtubule stabilization in their bundles retract before reaching distal targets. We observed a similar axonal splitting/selection process in the developing chick spinal cord suggesting a conserved mechanism. Finally, microtubule developmental pattern predicts the adult wiring pattern of an individual and remain stable during adult life, supporting the idea that a temporal succession of stochastic processes explains the emergence of individual variation in robust wiring patterns.

P3

Looking for immediate early genes as neuronal activation markers in the cephalopod mollusc *Sepia officinalis*

Cécile Bellanger², Aude Andouche¹, Sébastien Baratte¹, Lisa Poncet², Tristan Durand², Christelle Jozet-Alves²

1MNHN, Paris, France.

2Unicaen, Caen, France.

Immediate early genes (IEGs) are genes which are expressed rapidly and transiently in brain neurons in response to various stimuli. Imaging IEGs is a commonly used tool to study neuronal activation, especially in learning and memory tasks. Recent behavioural studies indicate how proficient common cuttlefish are in these aforementioned tasks, however the neural substrates associated to these abilities have yet to be fully explored. We aim to validate suitable IEGs and appropriate in situ hybridization (ISH) protocols to perform functional studies of the cuttlefish brain. Three genes (cFos, Uch and Egr1) were selected as potential IEG candidates, their orthologs were identified in *Sepia officinalis* transcriptomes and cloned for RNA probe synthesis. Their expressions were compared both in nervous tissues (by ISH) and quantitatively (by qPCR) between two groups of one-week-old cuttlefish. The stimulated group was exposed to stimulations involving multiple sensory modalities (light flashes, odours, tactile stimulation and handling), whereas the control group was kept in their usual captive conditions under dimmed light and without any stimulations. Our first results indicate that these three IEGs are expressed in the cuttlefish brain and activated by sensory stimulation, showing at minima small differences. Egr1 noticeably produces the greatest differences in neuronal activation between test and control groups. Its expression is found in diverse brain areas, making it the best candidate for our upcoming studies on the neural substrates of cuttlefish memory.



P4

Bernard Victor, no abstract

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P5

CaV4: a new type of Calcium channel identified in Insect

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We have recently cloned a channel homologous to DSC1 (drosophila sodium channel 1) in the honeybee. Despite sequence similarity with voltage-dependent Na⁺ channel, we demonstrate a strong calcium (Ca²⁺) permeation, and suggested that AmSC1 may belong to a new type of voltage-dependent calcium channel (VDCC), now named CaV4.

Identification of a particular sequences for the selectivity filter (DEEA), for inactivation domain (MFL, homologous to the IFM of the NaV channel) and a C-terminus sequence containing a calmodulin (Cam)-binding site led us to analyze the singular permeation and the voltage and calcium-dependent inactivation properties of this new channel.

Its voltage-dependence of activation and deactivation suggest an important role in the Ca influx during action potential.

P6

A new *in vivo* model to understand the role of Caspases in Tau pathology

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Tau accumulation in neurons, its phosphorylation and the formation of neurofibrillary tangles in the brain of patients with tauopathies correlates with the extent of cell death. Previous studies did show that Tau accumulation can be observed *in vivo* after transient caspase activation¹. Also, Caspase activation can contribute to Tau cleavage, in particular at the D421 cleavage site, leading to aggregation-prone truncated Tau protein. Cleavage of Tau protein is thought to be one early pathophysiological process contributing to Tau pathology². However, the impact of Tau truncation at D421 on Tau phosphorylation remains largely unknown.



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We previously showed that an excess of human Tau (hTau) in dividing cells impaired mitosis and led to cell death³. When studying this process in the developing *Drosophila* wing tissue in presence of an excess of hTau, we could identify a specific area with sustained activation of Caspases. We show that, in this area, Tau protein is cleaved at the D421 cleavage site. This *in vivo* model allows to study early events induced by Tau accumulation, in particular the relationships between caspase activation, Tau cleavage and Tau phosphorylation. Our first results indicate that cleaved Tau is strongly phosphorylated on AT8 and PHF1 sites, early markers of Tau pathology, and this is dependent on Caspase activation. Furthermore, our results indicate that pseudo-phosphorylated S422E Tau mutant, which prevents cleavage of Tau at D421⁴, leads to the appearance of AT100 epitope, a hallmark of late stage of Tau pathology. This suggests that caspase-cleavage of Tau at D421 protects from progression of the Tau pathology.

1. De Calignon et al., 2010 DOI: 10.1038/nature08890

2. Rissman et al., 2004 DOI: 10.1172/JCI20640

3. Bougé and Parmentier, 2016 DOI: 10.1242/dmm.022558

4. Guillozet-Bongaarts, Angela L et al., 2006 DOI: 10.1111/j.1471-4159.2006.03784.x

P7

Bumblebees' cognition: impact of azoxystrobin on memory & learning

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The fungicide Amistar® containing the active agent azoxystrobin is widely used. However, few data exist on possible sub-lethal effects on pollinators such as honeybees and bumblebees. Still, it has been shown to increase the prevalence in antibiotic-resistance genes (ARGs) in nematodes for treated fields by changing the microbiome diversity. Those ARGs can be transmitted horizontally leading to possible sanitary issues at all levels. Concerning bumblebees, azoxystrobin reduced survival-hood by causing gut damages, inducing dysbiosis, but the concentrations used for treatment were much higher than field-realistic ones. In this study we focused on possible sub-lethal effects at field-realistic doses of azoxystrobin on *Bombus terrestris* in laboratory condition. To test possible effects on cognition and memory retention, a 10 colors discrimination task was performed, using field-realistic concentrations for 1-week duration. The results showed no significant effects on both learning and memory retention for female bumblebees. Even though no effect was found, it is likely that the individual fitness could be reduced in very long-term exposure and that our 1-week chronic exposure was not long enough to unveil any effects. But by its action, azoxystrobin could possibly disrupt enough the microbiome to induce decreased immunity, foraging efficiency and overall colony survival throughout winter.

Characterization of the effects of the insecticide deltamethrin on neuronal sodium channels and muscular calcium channels from the honey bee *Apis mellifera*.

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Honey bees are important pollinators and are often described as indicator species for the quality of the environment. Domestic honey bees have suffered significant losses over the last decades and insecticides are clear contributing factors to this decline. Bees intoxicated with deltamethrin, a widely used pyrethroid insecticide, exhibit symptoms of strong neuromuscular alterations. In order to better understand the modes of action of this molecule on bees, we characterized its effects on isolated antennal neurons and skeletal muscle fibers. Using the patch-clamp electrophysiological method, we monitored the effects of deltamethrin on voltage-gated sodium channels (NaVs) and on voltage-gated calcium channels (CaVs), which are responsible for action potentials in neurons and insect muscle fibers, respectively. Under voltage-clamp, deltamethrin clearly impeded neuronal NaVs function by slowing down their closure. The sodium deactivation current was altered in both a use-dependent and a concentration-dependent manner. Conversely, in muscle fibers, preliminary observations suggest that ionic current amplitudes through CaVs are not altered by similar concentrations of deltamethrin. Further analysis of the CaVs biophysical properties are needed to confirm this latter result and in particular to fully describe their voltage-dependency in the presence of the insecticide.

Degradation of an appetitive olfactory memory via devaluation of sugar reward is mediated by 5-HT signaling in the honey bee

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Conditioned food aversion learning induces the devaluation of a preferred food through its pairing with a stimulus inducing internal illness. How this aversive learning further impairs memories of stimuli that were previously associated with the appetitive food subsequently devaluated has not been analyzed in invertebrates. Here we studied this phenomenon in the honey bee and characterized its neural underpinnings. We first trained bees to associate an odorant (conditioned stimulus, CS) with appetitive fructose solution (unconditioned stimulus, US) using a Pavlovian olfactory conditioning. We then subjected the bees that learned the



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association to a conditioned food aversion training during which the fructose solution was contingent or not to the ingestion of quinine solution, which induces malaise few hours after ingestion. Only the group experiencing contingent fructose and quinine-based malaise exhibited a decrease of responses to the fructose and a concomitant decrease of odor-specific retention in tests performed 23 h after the original odor conditioning. The use of antagonists of dopaminergic and serotonergic receptors injected after conditioned food aversion learning revealed that this long-term decrease was mediated by serotonergic signaling so that its blockade rescued responses to fructose and the odor-specific memory 23 h after conditioning. The impairment of a prior CS memory by subsequent aversive food conditioning confirms that bees retrieve a devaluated US representation when presented with the CS. Our findings further highlight the importance of serotonergic signaling in aversive learning in the bee and uncover mechanisms underlying aversive memories induced by internal illness in invertebrates.

P10

Similar but different: Delay vs. trace conditioning in honey bees

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Pavlovian conditioning occurs when a neutral conditioned stimulus (CS) is linked to a biologically relevant unconditioned stimulus (US). In the most common form termed 'delay conditioning', the CS and US overlap, which facilitates their association. In a less common form, termed 'trace conditioning', a stimulus-free gap separates the CS and the US, which raises the question of how they are associated given their temporal separation. Moreover, the stimulus gap may render trace conditioning susceptible to distractions occurring during this period. Thus, despite their apparent similarity, delay and trace conditioning may be mediated by different cognitive processes. Here, I investigated these conditioning variants in honey bees using the olfactory conditioning of the proboscis extension response (PER), which allows for fine temporal control of CS and US delivery. I compared the acquisition and retention performances and their sensitivity to different distractors. Although bees learned the CS-US association in both cases, acquisition and retention levels (1h and 24h post conditioning) were lower in trace conditioning. Furthermore, trace learning was vulnerable to distractors (visual and mechanosensory stimulations) whereas delay conditioning was unaffected by them. These results indicate that different cognitive processes underlie trace and delay conditioning. Three hypotheses have been suggested to account for CS maintenance in time in trace learning: working memory, attention and temporal awareness. Distractors could act on these processes, thus leading to differences observed in our work. Thus, the study of trace conditioning opens interesting perspectives for studying higher-order phenomena both at the behavioral and neurobiological levels.

P11

Differential coding of absolute and relative aversive value in the *Drosophila* brain.

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Animals use prior experience to assign absolute (good or bad) and relative (better or worse) value to new experience to enable future appropriate economical decisions. Flies have the capacity to perceive, learn and compare differences in the intensity of punishment and adapt their behavior accordingly. However, the neural circuits and mechanisms underlying the encoding of relative aversive value remain unknown. Here we combined genetic interventions with behavioral analyses, anatomical characterization, and in vivo 2-photon calcium imaging to investigate and identify circuits and mechanisms involved in coding relative aversive value during learning, that allow flies to promote appropriate value-based choices. Our results revealed interactions within the network between mushroom body output neurons (MBON) and dopaminergic neurons (DANs) during learning relative aversive value. Three types of punishment DANs (PPL1- γ 1ped, PPL1- γ 2 α '1 and PPL1 α 2 α '2) and one subtype of reward DANs (PAM- β '2a γ 5n) are central to learn relative aversive value. Through MBON-DAN recurrent network interactions, the rewarding PAM- β '2a γ 5n compare previous with current aversive experiences to assign a relative 'better than' (or 'worse than') value to the lesser (or the worst) of two aversive experiences. This study provides a new model showing how opposing populations of DANs can operate together as a system within the MB network to code and compare sequential aversive experiences to learn relative aversive value.

P12

Formation and neurotoxicity of ADTIQ studied in *Drosophila*

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Parkinsonism-associated protein DJ-1 (also called Park7) is a multifunctional protein involved in oxidative stress responses. It has been recently proposed that this protein can prevent protein and nucleic acid glycation. The glycation process is initiated by a non-enzymatic reaction between sugar-derived aldehydes, such as methylglyoxal (MGO), and nucleophile groups present on biomolecules (amines or thiols). This reaction gives rise to a variety of products known as advanced glycation end-products (AGEs) through a multistep process. Several studies suggest that glycation could play an important role in the pathogenesis of Parkinson's disease (PD). While a lot is currently known about the glycation of



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macromolecules, the processes of glycation of metabolites has been little studied, although these molecules can often be particularly nucleophilic compounds. One of them is a neurotransmitter of specific interest in the context of PD, namely dopamine. Indeed, MGO can react with dopamine to form a tetrahydroisoquinoline called ADTIQ (1-acetyl-6,7-dihydroxyl-1,2,3,4-tetrahydroisoquinoline) that is toxic to neurons and has been found in the brain of PD patients. Our project is to use the *Drosophila* model to better understand the interrelation between ADTIQ and DJ-1, and the respective role of these molecules in PD pathogenesis.

P13

Nociceptive regulation in flies

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Nociception is an alarm signal helping animal to adapt their behaviour and avoid potential danger. Noxious perception is strongly influenced/regulated by descending pathways originating from the central brain to induce hypo/hyper-sensitivity to nociceptive stimuli. A previous nociceptive experience is known to induce hypoalgesia using descending pathways. However, the neural mechanisms underlying nociceptive regulation remain elusive and nonexistent in *Drosophila*. To study this question, we first used behavioral tests to dissect the effect of previous shock experience on future ones. We also investigated the difference between voltage and current electrical stimulation. We revealed that in certain range of shock intensities and temporal window, a previous shock experience strongly affects future shock perception independently of the current delivered to the flies. Thanks to targeted genetics we have access to most single descending neuron and now have the experimental conditions to test the role of fly descending neurons to regulate nociception.

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