Intravital imaging of brain development reveals the spatio-temporal dynamics of axonal selection during neuronal circuit wiring in individuals

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While adult brains present stereotypical wiring diagrams, there is still significant variation between individuals. We have previously shown that intrinsically stochastic developmental processes (Langen et al., 2013) can lead to individuality in visual response behavior (Linneweber et al., 2020). However, **How and when individualized wiring patterns emerge and become stable during development** remains largely unknown.
To address this question, we use the *Drosophila* Dorsal Clustered Neurons (DCNs), a well-defined model that has a stereotypical axonal projection with stochastic developmental variations between the left and right hemispheres of the same individual. DCNs are commissural neurons located in both hemispheres of the central brain. While their axons target two alternative areas of the optic lobe - proximal (Lobula) and distal (Medulla), the number of distal targeting axons differs between left and right hemispheres, and among individuals. Thus, understanding **when and how this targeting choice is made during development** is fundamental to decipher mechanisms behind these developmental variations in DCN wiring diagram.

Using long-term live imaging in intact individuals, we accessed deeper brain regions and tracked targeting events from development to the final adult pattern from the same individual. We uncovered a previously unknown phenomenon of transient axonal fiber amplification during target selection, followed by resorption of all but one axonal fiber, which becomes stabilized as the future axon in the distal target area.

This type of "intra-axonal" fiber selection follows an initial phase of Notch-based cell-cell competition whereby "winner" cells amplify their axonal fibers into what we term an "axonal bundle" and grow towards more distal targets. In contrast, "loser" cells retain a classic single axonal fiber, which explores locally and innervates more proximal targets. Turning all cells into "losers" by ectopic activation of Notch signalling abolishes bundle formation, while increasing the number of "winner" cells by Notch inactivation enhances bundle formation.

The multiple fibers of an axonal bundle are all Actin-rich during their initial growth phase, followed by the entry of a microtubule into one of these fibers, the stabilization of that fiber and the retraction of all the others. This event, which requires the interaction between Actin and

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Tubulin, predicts precisely which individual fiber will become the axon that innervates the distal target area.

Finally, selected axons remain stable during adult life, supporting the idea that variability in adult DCN wiring pattern is a consequence of a developmentally stochastic competition process. In summary, deep intravital imaging identifies the precise spatio-temporal sequence of events that underlies the individualization of neuronal circuit architecture during brain development.

Counting flies: Evidence of numerical discrimination in Drosophila melanogaster

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Numerical competence is a cognitive trait that benefits animal fitness and survival by reducing costly behaviours and increasing mating success. Very diverse species of the animal kingdom have been shown to be able to discriminate numbers. However, the mechanisms of numerical skill at evolutionary and neuronal level remain poorly understood. In the present work we show that *Drosophila melanogaster* discriminates against different sets of objects depending on the number of items they contain. Freely moving flies show a systematic preference for more objects in a two-choice assay independently of non-numerical continuous variables. Moreover, by using a novel visual conditioning paradigm we show that flies are capable of associating reward with numerical quantities. We establish the first genetically tractable model to study numerical skills. Using the well-known genetic toolkit that fruit flies offer, future studies will unravel the brain areas and neuronal circuits related to insect number cognition. The findings presented here provide a new framework to study number-based judgement crucial to the understanding of the evolutionarily conserved number computation.

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Spatio-temporal regulation of neuronal RNA granules in mature neurons.

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Neuronal cells rely on macro- and micro-cellular compartmentalization to rapidly process information, and locally respond to external stimuli. By transporting RNAs to axons or dendrites, and by tightly regulating their translation in space and time, neuronal ribonucleoprotein (RNP) granules play a crucial role in such a sub-cellular organization. How these membrane-less organelles enriched in RNA molecules and associated regulatory proteins respond to physiological stimuli on both short- and long timescales has however remained unclear. I will present recent work we have performed to address this question in the adult *Drosophila* brain.

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sNPF modulates appetitive learning in honey bees (Apis mellifera)

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In mammals, feeding behavior is modulated by several neuropeptides such as the neuropeptide Y (NPY), which in higher concentrations enhances food intake. In the honey bee (*Apis mellifera*), two independent homologs of NPY, the neuropeptide F (NPF) and the short neuropeptide F (sNPF), have been identified but only the latter has a coupled receptor (sNPFR). A functional link exists between sNPF signaling and feeding behavior under conditions of starvation: a reduction of the transcript levels of sNPFR by dsRNA is sufficient to alter the perception of the satiation state in starved bees, which then behave like their fed counterparts. Conversely, sNPF topical application is sufficient to trigger food intake in fed bees. Besides, sNPF also modulates sensory perception prior to ingestion. Topical application of sNPF increases, therefore, sucrose responsiveness and spontaneous responses to appetitive odors. Given the enhancing effect of sNPF on sucrose responsiveness, we studied if this effect translates to the differential visual learning, an operant conditioning in which bees learn to discriminate a color that is rewarded with a sucrose solution from another color that is not. Starved or fed bees were used. Fed bees were treated either with solvent or with sNPF. All groups were conditioned to discriminate a rewarded VS a non-rewarded color. Within each group, two subgroups were conditioned in parallel, each with a different rewarded color (Yellow+ or Blue+). Bees were then tested for mid-term memory retention 1 h after conditioning by completing a last trial without the reward. Starved bees showed better learning and mid-term memory performances than fed bees but only when conditioned on the yellow color. Yet, treating fed bees with sNPF improved retention performances one hour after conditioning for both colors. These results indicate that sNPF has the potential to modulate memory retention in an appetitive context.

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An atypical pacemaker mechanism drives spontaneous and irregular feeding patterns in Aplysia

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Motivated behaviors, such as food-seeking actions, are generated by internal drives from the CNS and are regulated by external stimuli through learning processes. In the marine mollusk *Aplysia*, the neuronal and network computations responsible for adapting the type, frequency and regularity of biting and consummatory movements of the radula by external stimuli and learning procedures have been the focus of intense investigation. However, little is known about the intrinsic releasing mechanism(s) that are responsible for spontaneously triggering the emission of the motivated action itself. Using *in vitro* buccal ganglia preparations that contain the central pattern generating circuit for food-seeking behavior, we analyzed the functional properties of an identified pair of interneurons (B63) whose plateau potential-driven impulse bursts are both necessary and sufficient to trigger the motor pattern for each bite cycle. We found that these neurons express a spontaneous and synchronous membrane potential oscillation that persists after functional synaptic isolation. This voltage oscillation, due to its variable amplitude, irregularly triggers B63's plateau potentials. Its expression occurs independently of the neuron's voltage-sensitive membrane channels, but relies critically on an organelle-derived intracellular calcium dynamic that activates voltage-independent membrane conductances. Moreover the oscillation is gated by the second messenger inositol triphosphate (IP3) and is propagated from B63 to other gap junction-coupled neurons in the buccal CPG network. Thus, our study provides the first example of a spontaneous and rhythmic organelle-derived calcium signal serving as a primary oscillator mechanism for driving neuronal bursting that underlies the highly variable expression of a motivated behavior.

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Establishing a Drosophila model of BPAN disease

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The Beta-Propeller protein Associated with Neurodegeneration (BPAN) disease was identified in 2012 and is responsible for severe neurodegeneration. The BPAN is a rare human genetic disease resulting from the mutation of the *wdr45* gene. It leads to static encephalopathy of childhood with neurodegeneration in adulthood (SENDA), which has been established as a subtype of neurodegeneration with brain iron accumulation (NBIA) Previous studies have shown that WDR45 mutant cells have both a dysregulated autophagy and ER stress response. We hypothesize that WDR45 is involved in autophagy induction upon specific response to ER stress.
We have established a *Drosophila* model of BPAN disease using RNAi and CRISPR-Cas9 strategies to, respectively, knock-down and knock-out CG11975, the *Drosophila* WDR45 putative homolog.
We demonstrated that knock-down or knock-out of CG11975 in *Drosophila* provoke a locomotor disorder shown by climbing assays. Furthermore, knock-down of CG11975 decreased the number of photoreceptor neurons, induced a dysregulation of autophagy and ER stress pathways. Our results suggest that abnormal autophagic and ER stress may be responsible for neuronal death. Thus, we provide evidence of a novel *Drosophila* model of BPAN disease that mimics specific phenotypes observed in BPAN disease in Human and mouse model.

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Axon-secreted CX3C chemokine-like Orion induces astrocyte infiltration and engulfment during mushroom body neuronal remodeling

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Neuronal remodeling is a widely used developmental mechanism, across the animal kingdom, to refine dendrite and axon targeting necessary for the maturation of neural circuits. Importantly, similar molecular and cellular events can occur during neurodevelopmental disorders or after nervous system injury. Astrocytes can clear neuronal debris and they have an active role in neuronal remodeling. Developmental axon pruning of *Drosophila* memory center neurons occurs via a degenerative process mediated by infiltrating astrocytes. However, how astrocytes are recruited to the axons during brain development is unclear. Using an unbiased screen, we identify the gene requirement of *orion*, encoding for a CX3C chemokine-like protein, in the developing mushroom bodies. Functional analysis shows that Orion is necessary for the removal of the axonal debris and for the pruning of some axons. Orion performs its functions extracellularly and bears some features common to chemokines, a family of chemoattractant cytokines, e.g. a CX3C motif and 3 glycosaminoglycan binding consensus sequences that are required for its function. We propose that Orion is a neuronal signal that elicits astrocyte infiltration and astrocyte-driven axonal engulfment required during neuronal remodeling in the *Drosophila* developing brain. This hypothesis contains an implicit role for an as-yet-undefined Orion receptor on the surface of the glial cells.
Thus, we have uncovered a neuronally-secreted chemokine-like protein acting as a "find-me/eat-me" signal involved in the neuron-glia crosstalk required for axon pruning during developmental neuron remodeling. It is considered that chemokines first appeared in a common ancestor of the vertebrate lineage and, although chemotaxis has been described in invertebrate cells, analogs of the chemokine system do not appear to exist in *Drosophila* or even in insects. Therefore, it is possible that chemokine involvement in neuron/glial cell interaction is an evolutionarily ancient mechanism.

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Sex-specific anaesthesia via olfactory receptor inhibition in Drosophila

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Odours have a wide range of vital actions for survival. They convey information to select a sex partner, to find a food source, or to detect a danger. They can also affect the vigilance of any organism. Among those some volatile molecules have been shown to cause a reversible anaesthesia. However, their mode of action on vigilant state appears to be still largely mysterious. Here we describe a novel property of Olfactory Receptor 47b (OR47b), a member of the insect 7-transmembrane chemosensory receptor family, in olfactory sensory neurons (OSNs) expressing the male-specific transcription factor FruM. We identified the effect of one of its ligands, propanoic acid, which is a fermentation product that can be present on food sources and oviposition sites for Drosophilid species. We show that OR47b neurons projecting to VA1v glomerulus can be directly inhibited by propanoic acid perception, and that this inhibition influences *Drosophila* behaviour causing a reversible anaesthesia. Strikingly, males are more sensitive than females to this acid. This effect is also adult specific, since larvae are never anaesthetized by the propanoic acid, in contrary to carboxylic acid (CO2) or nitric oxide (NO). Furthermore, we observed that the anaesthetic sex-specific effect of propanoic acid is not displayed in a closely related species, *Drosophila suzukii*. These findings reveal a spectacular stage-dependent sensitivity to some odours through a specific sensory pathway, which might be differently conserved in other organisms.

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How do muscles and motoneurons meet for life?

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Locomotion is a stereotyped behavior used by animals to find food, mates, or escape from predators. The precise pattern of locomotion is linked to the sophisticated architecture of the locomotor system. Each motoneuron (MN) axon terminal innervates specific muscle fibers and displays a unique architecture defined by their shape and number of synaptic boutons. The unique wiring and architecture of MN axon terminals ensures the proper contraction of muscles allowing correct movements.
The wiring between an axon and its muscle partner is built during development and under the control of transcriptional programs during development. The cellular mechanism and the effector genes of this transcriptional program are unknown. My project seeks to understand the development of muscle innervation by discovering the genetic and cellular mechanisms that control the crosstalk between motoneurons (MNs) and muscles in *Drosophila melanogaster*. We hypothesis that MNs and muscles express proteins differentially to establish the unique architecture of the innervation during development.

MNs innervating fly leg or vertebrate limb muscles send axons out of the CNS during development to meet its muscle partner localized in the fly imaginal leg disc or the vertebrate limb bud. In Fly, the immature leg of wondering larvae is crossed by a single nerve. MN axons defasciculate from this nerve very early during leg metamorphosis suggesting that axons could recognize myoblasts before the process of fusion.

First, I will determine if an axon recognizes a muscle before or after muscle fusion by imaging axons and developing muscles at different time points or by performing live imaging experiments. Second, I will discover the gene networks expressed differentially in each immature MN and myoblasts and enabling their communications by performing transcriptomic profiling of single immature MNs and myoblasts. Preliminary data show that MN axons are dynamic structures that begins to make their first muscle connections at 5h after pupa formation before fusion. Moreover, I recently obtained preliminary data on myoblasts at 5h, and this first sequencing allows to already define 10 cell clusters and identify good candidates like secreted molecules expressed in only sub-population of myoblasts. I will next perform sequencing at different time points.
This project will reveal for the first time the early dynamic of axon-muscle recognition specificity in appendages and the molecular pathways controlling it.

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Morphological analysis of Dacini antennae (Diptera:Tephritidae) suggests an improved olfactory sensitivity of Cucurbitaceae pests

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Physical and metabolic constraints limit the size of body parts of an organism. A positive allometric relationship, defined as parts scaling supralinearly with body size, is rarely observed and usually suggests an evolutionary benefice. The family Tephritidae includes many pests of fruits across the world and their olfactory systems adapted to their various host-ranges. I measured the antennal dimensions in a collection of Tephritidae specimens, including 105 species of the tribe Dacini, 59 species of the tribe Ceratitidini and 11 species of the tribe Gastrozonini. Suprisingly, I observed a significant positive allometry of antenna length in Dacini but not the other two tribes. More specifically, both the olfactory funiculus and the mechanosensory pedicel were proportionally longer in larger species, suggesting a developmental synergy between the two antennal parts. Finally, length of the funiculus but not the pedicel correlated with the host-range. Longer funiculus resulted in larger surface of the olfactory epithelium and higher number olfactory sensory neurons only in specialist species of Cucurbitaceae. Microscopic analysis revealed that the additional olfactory sensilla in Cucurbitaceae specialists were mostly basiconic sensilla, but not trichoid sensilla, strongly suggesting a functional implication of these morphological traits.

*Intervenant

A comprehensive series of temporal transcription factors in the fly visual system

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The brain consists of thousands of different neuronal types that are generated through multiple divisions of neuronal stem cells. These stem cells have the capacity to generate different neuronal types at different stages of their development. In *Drosophila*, this temporal patterning is driven by the successive expression of temporal transcription factors (tTFs). While a number of tTFs are known in different animals and across various parts of the nervous system, these have been mostly identified by informed guesses and antibody availability. We used single-cell mRNA sequencing to identify the complete series of tTFs that specify most *Drosophila*medulla neurons in the optic lobe. We tested the genetic interactions among these tTFs. While we verify the general principle that tTFs regulate the progression of the series by activating the next tTFs in the series and repressing the previous ones, we also identify more complex regulations. Two of the tTFs, Eyeless and Dichaete, act as hubs integrating the input of several upstream tTFs before allowing the series to progress and in turn regulating the expression of several downstream tTFs. Moreover, we show that tTFs specify neuronal identity by controlling the expression of cell type-specific genes. Finally, we describe the very first steps of neuronal differentiation and find that terminal differentiation genes, such as neurotransmitter-related genes, are present as transcripts, but not as proteins, in immature larval neurons days before they are being used in functioning neurons; we show that these mechanisms are conserved in humans. Our results offer a comprehensive description of a temporal series of tTFs in a neuronal system, offering mechanistic insights into the regulation of the progression of the series and the regulation of neuronal diversity. This represents a proof-of-principle for the use of single-cell mRNA sequencing for the comparison of temporal patterning across phyla that can lead to an understanding of how the brain develops and how it has evolved.

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Isoform-dependent neurotoxicity of the Alzheimer's disease genetic risk factor BIN1

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Alzheimer's disease (AD) is the most common form of dementia with a strong genetic component estimated around 60-80%. For the last decade, our understanding of this genetic component has strongly progressed with the identification of 76 loci associated with the disease.
Among these loci, BIN1 is the second susceptibility gene after APOE in terms of association but little is known about its physiological functions. Moreover, BIN1 has more than 10 isoforms with BIN1 isoform1 (BIN1iso1) and isoform8 (BIN1iso8) respectively expressed in the brain and skeletal muscles whereas isoform9 (BIN1iso9) is ubiquitously expressed. The presence of these isoforms expressed in different cerebral cell types makes the deciphering of BIN1 pathophysiological role difficult.

Here we took advantage of a drosophila model to assess in vivo the impact of different BIN1 isoforms on neuronal toxicity. We have shown that the expression of the brain-specific isoform (BIN1-1) specifically induces photoreceptor neuron degeneration with age in the Drosophila eye. In order to know why the degeneration was present only for the isoform 1, we investigated the role of its exon 7 and its CLAP domain that are not in the isoforms 8 and 9. We have shown that truncation of the CLAP domain abolished BIN1-1-induced degeneration, indicating that this domain is necessary for the BIN1-1 induced toxicity. This domain is involved in endocytosis, a process related to the endosome-lysosome pathway. In addition, the degeneration was also characterized by endosome-positive large vesicles. We decided to assess if an alteration of the endosome lysosome pathway could be a cause of the degeneration, we tested the effect of the modulation of this pathway on BIN1-1 associated degeneration. We found that modulators of the early and recycling endosomes, Rab5 and Rab11 respectively, abrogated photoreceptor degeneration.
Altogether, these results suggest that BIN1 isoform 1 impair the endosome-lysosome pathway at the level of early and/or recycling endosomes, leading to neuronal death and thus could contribute

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to Alzheimer's disease.

Neural circuitry underlying sensorimotor decisions

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From finding nearby food to escaping a predator, animals must respond to sensory cues with appropriate motor actions in order to survive. The neural circuit mechanisms underlying the transformation of sensory information into appropriate motor output remain incompletely understood. It is for instance unclear how one action is selected among several possible responses to a single stimulus. In addition, how the selected action is specified by motor circuits depending on stimulus characteristics is not known either at the cellular and synaptic level. To understand these mechanisms better, it would be important to map the entire neural circuitry from the sensory to the motor side in a model organism allowing functional testing of such circuits. Thanks to recent progress in connectomics, allowing the mapping of entire neural circuits in electron microscopy (EM) with synaptic resolution and to the genetic toolbox for cell-specific neuronal manipulations and monitoring, Drosophila larva presents itself as such a model. We will here present the progress we made on the investigation of the neural circuitry underlying larval responses to an aversive mechanosensory stimulus, the air puff. Drosophila larvae typically respond with either startle or escape behaviours to the air-puff (Jovanic et al, 2016). Startle responses are for example Hunching (head-retraction), and Stopping. Escape responses include bending (i.e. headcasting and turning) and crawling. The selection of one action implies the inhibition of other, mutually exclusive, actions. Competitive interactions between the neural modules underlying startle and escape behaviors thus could exist in order to enable the selection between the two. Using cell-specific inactivation and optogenetic activation of neuronal activity in behaving larvae combined with high-speed video tracking and automated behavioral detection (Masson et al., 2020), we determined the role of interneurons at different stages of the sensorimotor pathways and found they are differentially involved in startle and escape behaviors. Some of these neurons promote one response and repress another suggesting they are involved in competitive interactions. Using EM-based reconstruction of neurons and of their synaptic connections, we are now mapping the sensorimotor pathway underlying the startle (hunch) response with synaptic resolution and investigating where and how it could interact with the escape pathway. Neurons involved in competitive interactions should make connections with the two pathways, that would allow them to promote escape behaviors and repress startle behaviors for example. Determining where competitive interactions take place in the nervous system and what the involved neural circuit mechanisms are in a model system where we can trace all connections at synaptic resolution across the entire nervous system and manipulate single neurons may bring insights into the neural circuit mechanisms of sensorimotor decisions in general.

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Pallidin in Drosophila surface glia modulates sleep via essential amino acid availability

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The Pallidin protein is a component of a multimeric complex named the Biogenesis of Lysosome-related Organelles Complex-1 (BLOC1) that regulates lysosome function. In a gene profiling study, we have found pallidin mRNA to be strongly upregulated in somnolent mice with the defective histaminergic transmission, suggesting a link between the cellular and molecular mechanisms controlled by the pallidin gene and sleep/wake regulation. To investigate this question, we used a genetic knockdown strategy in Drosophila and demonstrated that down-regulation of pallidin in the surface glia, the Drosophila equivalent of the blood-brain barrier, is sufficient to reduce, fragment, and delay nighttime sleep at the adult stage and in a circadian clock dependent manner. Other members of the BLOC1 complex appear to be involved in this pallidin-dependent sleep regulation. Interestingly, in agreement with pallidin's involvement in amino acid transport, down-regulation of the Large Neutral Amino acid Transporter 1 (LAT1)-like transporters JhI-21 and minidiscs, as well as the TOR amino acid signaling, phenocopy the down-regulation of pallidin. In addition, supplementing food with essential amino acids normalized the sleep/wake phenotypes of pallidin and JhI-21 down-regulation. Furthermore, we identify a role for pallidin in the subcellular trafficking of JhI-21 in surface glial cells. Finally, we provide evidence that pallidin function in surface glia is required for GABAergic neurons activation involved in promoting sleep. Taken together, these data identify a novel role for pallidin that, through LAT1-like transporters subcellular trafficking modulates essential amino acid availability and GABAergic sleep/wake regulation.

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ninaD regulates cholesterol homeostasis from the midgut which protects against neurodegeneration

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Cholesterol homeostasis is required to maintain normal cellular function. Recently, we have reported the genetic and molecular characterization of a small nucleolar RNA (*jouvence*) required in the enterocytes, the main epithelial cells of the gut. The loss of *jouvence* shortens lifespan and leads to intestinal hyperplasia, and consequently to defects in metabolic parameters. Inversely, targeted expression of *jouvence* in enterocytes (overexpression) increases lifespan, and prevents hyperplasia in aged flies gut. A transcriptomic analysis of *jouvence* deleted adults gut revealed a deregulation in expression level of several genes. Among them, *ninaD (neither inactivation nor afterpotential D)*, which encodes a mammalian homolog to class B Scavenger receptor-like membrane protein, is importantly upregulated. In *Drosophila*, *ninaD* is known to be required for the uptake and storage of the dietary carotenoid and consequently for the formation of rhodopsin. Here, we show that the targeted expression of a *UAS-ninaD-RNAi* specifically in the gut restores the mRNA level of *ninaD* and consequently results in lifespan extension. We also demonstrate that *ninaD*, required in enterocytes, is essential for cholesterol homeostasis. Indeed, *jouvence*-deleted flies accumulate an excess of free cholesterol, but a striking decrease of cholesterol-ester. In addition, at the organismal level, *jouvence*-deleted old flies present neurodegenerative lesions. Restoring *ninaD* mRNA level in the gut with a targeted *ninaD-RNAi* extends lifespan, restore metabolic homeostasis and prevents neurodegeneration. Our studies identifies a new aspect of *ninaD* as a central regulator of cholesterol homeostasis as well as a longevity-promoting factor.

*Intervenant

Studying multisensory external context and internal state integration for the modulation of neuronal circuit activity in Drosophila larva

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In a given external context, the internal state of the individual modulates decisions so that behavior that best meets its current needs is promoted. Neuropeptides represent a wide family of molecules that are known to act as modulators of neuronal activity. Their expression patterns are various and may change in multiple conditions. For one, neuropeptide Y (NPY) enhances feeding-related behaviors in starved mammals. However, its role in non-feeding related behaviors is poorly documented. In flies, short neuropeptide F (sNPF) - a member of NPY family – and its receptor (sNPF-R) are widely expressed in the nervous system and might thus modulate various behaviors depending on the internal state. To define sNPF impact on internal state-dependent choices, we use genetic manipulations combined with high-throughput behavior tracking in *Drosophila melanogaster* larva. We exploit one decision-making circuit we have previously characterized in detail (Jovanic et al., 2016) to determine whether sNPF could affect its activity according to the internal state.
To this aim, we downregulate sNPF-R expression in specific neurons of the described decision circuit, that we found positive to sNPF-R immunostaining, to study the impact of sNPF signaling in larvae in different feeding states. We then quantify the impact of downregulating sNPF-R on the behavioral output of the circuit (in response to a mechanical stimulus) using an automated behavior classification algorithm.

Our preliminary results thus show that sNPF signaling modulates neuronal response to mechanical stimuli as well as the final behavioral output of the circuit differently depending on the feeding state. We aim to develop a model of the internal-state dependent modulation of the behavioral output of the decision-making circuit, taking into account the effect that sNPF signaling exerts on intrinsic properties of each neuron in the circuit.

In addition, connectome electron-microscopy data of air-puff sensing mechanosensory neurons suggest they receive olfactory and gustatory information from long-range descending neurons which may participate in the modulation of mechanosensory neurons depending on the feeding state.
In order to study how appetitive odors may modulate the activity in a mechanosensory network depending on the feeding state, we are developing a setup for automated delivery of odors and air-puff combined to the larvae under our behavior tracking apparatus, allowing us to impose a conflicting choice to the larvae: either move away from a noxious air puff or move towards an appetitive odor source. The ultimate aim of this study is to determine how internal-state information and external multisensory context are integrated at the level of neuronal circuits in order to select the appropriate behavior.

*Intervenant

ERASTIN-INDUCED FERROPTOSIS ENHANCES LOSS-OF FRATAXIN PHENOTYPES IN A DROSOPHILA MODEL OF FRIEDREICH ATAXIA

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Friedreich's Ataxia (FRDA) is the most prevalent autosomal recessive ataxia in the European population (1:50000). The disease is caused by the reduced expression of frataxin, a mitochondrial protein involved in iron–sulfur cluster biogenesis. Deficiency of frataxin leads to a drastic reduction in the cellular energy production (1). Remarkably, the characterization of the type of cell death that affects the cells deficient for frataxin still remains unsolved. Several studies in cell culture models point towards apoptosis (2-4). However, no marker of apoptotic cell death has been observed in *in vivo* models (5). A very attractive possibility is a new type of cell death named as ferroptosis. Deregulation of iron metabolism, depletion of glutathione and accumulation of lipid peroxides are the major hallmarks of ferroptosis (6). Remarkably, these three molecular signatures have been detected in samples from FRDA patients as well as in disease models including *Drosophila melanogaster*, suggesting that loss of frataxin recapitulates ferroptotic cell death (7). We have used 3 different known inducers of ferroptosis (buthionine sulfoximine (BSO), Erastin and Tert-Butyl Hydroperoxide) to analyse whether frataxin-deficient flies display increased sensitivity towards this stressor. Our results indicate that flies seem to react differently to all three chemicals. Erastin but not BSO and Tert-Butyl reduced locomotion of frataxin-deficient flies, affected heart function, boosted the production of lipoperoxides and impaired mitochondrial function (monitored as aconitase activity and ATP production) without enhancing longevity defects. Similar results were obtained when the fly ortholog of Glutathione Peroxidase 4 (GPTx1) was downregulated in frataxin-deficient flies. We are now assessing whether inhibitors of ferroptosis or upregulation of GTPx1 are able to alleviate frataxin-deficient phenotypes.

*Intervenant

Recruitment during honeybee colony defence

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Honeybees defend their nest against large predators thanks to a collective effort to harass and sting the intruder. Typically the threat is detected by a few bees, which then need to quickly mobilize their nestmates into a defensive response. At the core of this recruitment is the sting alarm pheromone (SAP), a complex odour blend released when the bees' stinger is exposed. The SAP attracts and primes nearby workers for attack, thus providing a seemingly simple communication channel during defensive events. However, when taking a closer look at this system we found that the behaviour of bees receiving this signal was dependent on a number of factors, both internal and external. We show that the likelihood for a bee to sting is linked to the concentration of alarm pheromone in a non-linear way, whereby responsiveness increases in the lower range of concentrations but decreases for very high concentrations. Such a dose-response curve could be important to prevent recruitment from getting out of control and depleting the colony of its workforce. We also found that the social context plays a major role in regulating stinging behaviour and responsiveness to SAP. Finally, honeybees responded differentially to SAP as a function of their age: young ($<$ 10 days) and old ($>$ 30 days) bees had an increased likelihood to sting in the presence of SAP, while middle-aged (11-29 days) bees did not. Honeybees perform different tasks for the colony as they age, and this likely reflects this division of labour. Overall, our results suggest that recruitment by SAP is a finely-tuned mechanism. Our next challenge will be to understand the neurobiological processes underlying these modulations of SAP responsiveness.

*Intervenant

Ants detect cancer cells through volatile organic compounds

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Cancer cells possess specific features such as a deregulated cellular energetic metabolism, the ability to self-sustain themselves with proliferating signals or the formation of tumour-promoting inflammation factors. Their metabolism produces volatile organic compounds (VOCs) that can act as biomarkers for cancer diagnosis. Animals, especially dogs, have been used to detect human VOCs via olfactory associative learning. However, training dogs is costly and time-consuming. Other animals, such as insects, have a refined sense of smell and can be easily trained with olfactory conditioning. Here, we show that individual ants need only a few training trials to learn, memorize and reliably detect cancer cells. Using ovarian cancer cells (IGROV-1), we first found that ants can learn to detect VOCs from IGROV-1, when compared to culture medium alone. In addition, by comparing normal mammary cells (MCF-10A) to breast cancer (MCF-7, MDA-MD-231) cell lines, we demonstrated that ants are able to distinguish cancer from normal cells, as well as to discriminate between the two breast cancer cell lines. These performances are due to cell line-specific VOC patterns, as shown by headspace chemical analysis via gas-chromatography/mass-spectrometry. Our findings demonstrate that using ants as living tools to detect biomarkers of human cancer is feasible, fast, and less laborious and expensive than using other animals.

*Intervenant

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

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Immediate early genes (IEGs) are genes which are expressed rapidly and transiently in brain neurons in response to various stimuli. They are commonly used as a tool to study neural structures activation, especially in learning and memory tasks. Recent behavioural studies indicate how proficient common cuttlefish are in these aforementioned tasks, but the neural substrates associated to these capabilities have yet to be fully explored. Thus, this study aims to identify suitable IEGs and appropriate *in situ* hybridization techniques to perform functional studies of the cuttlefish brain. Three genes (cFos, Uch and Egr1) were selected as potential IEG candidates to test. Their orthologs were searched in *Sepia officinalis* transcriptomes and found as confirmed by phylogenetic analyses and comparisons with sequences of other model species. We conducted two studies to validate functional homology. In the first study, we stimulated a group of one-week-old cuttlefish *via* multiple sensory modalities, using light flashes, algae, shrimps, snails, crabs, cuttlefish ink, water movement and tactile stimulation, whereas the control group stayed in the dark without stimulation. In the second study, we stimulated only one eye of cuttlefish with light flashes whereas the other eye was kept in the dark. After euthanasia, cuttlefish's brains were studied using *in situ* hybridization, looking for the transcripts of the three IEGs of interest. 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 shows the greatest differences in neural activation between test and control individuals, making it the best candidate for our upcoming studies on neural substrates of cuttlefish memory.

*Intervenant

Glial glucose fuels the neuronal pentose phosphate pathway for long-term memory

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Brain function relies almost solely on glucose as an energy substrate. At the cellular level, mammalian glial cells are thought to provide metabolic support to neurons. Particularly, it was proposed that glucose is taken up and converted into lactate by astrocytes to fuel energy-demanding neuronal activity underlying plasticity and memory. But whether direct neuronal glucose uptake is required for memory formation remains elusive. Using a combination of behavioral experiments and *in vivo* imaging in the Drosophila melanogaster model, we first uncovered a specific need for glucose consumption by mushroom body (MB) neurons upon formation of olfactory long-term memory (LTM). We deciphered a mechanism of glucose shuttling to MB neurons from cortex glia, an exclusively perisomatic glial subtype. We showed that downstream of cholinergic activation of cortex glia, autocrine insulin signaling increases glucose concentration in glia. After olfactory conditioning, this activation cascade enabled glucose transfer from glia to neuronal somata in the MB, to fuel the pentose phosphate pathway and allow LTM formation. Our results reveal the critical role of increased neuronal glucose metabolism for LTM.

*Intervenant

Shared volatile compounds among the various host-fruits shape Tephritidae olfactory system

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Evolutionary constraints shape the sensory systems of insects. Thus to understand the origin of chemical selectivity of insect olfactory systems, it is necessary to study their chemical environment. For this purpose, Tephritidae is relevant insect family model because, in addition to their economic importance, they have a wide range of host-fruits that partially overlap between species. We aim at studying if, for several tephritid species, the olfactory sensitivity is tuned to compounds that are shared between different hosts and informative on fruit phylogeny. We analyzed the volatilomes of 193 intact and 176 sliced fruits from 28 species with gas chromatography coupled mass spectrometry (GC-MS). We quantified respectively 511 and 665 volatile compounds in intact and sliced fruit emissions. Phylogenetic Principal Component Analysis showed common volatile compounds to all hosts of the generalist species *Bactrocera dorsalis*, specific compounds to Cucurbitaceae infested by *Zeugodacus cucurbitae*, and specific compounds to Solanaceae infested by *Neoceratitis cyanescens*. This quantifies the selection pressure that each compound exerts on the flies in the choice of the egg-laying site. Then, we analyze the emission of mango by gas chromatography coupled electroantennogram detector (GC-EAD) on eight tephritid species. Although mango is host for five of these species, some compounds were detected by all species while other were not. It suggests that different olfactory strategies are suited to detect the same host. Further investigation is required to test if these differences are related to the selection pressure. **Keywords:** Evolution; GC-EAD; GC-MS; Host-range; Tephritidae; Volatilome

*Intervenant

Quantifying insect olfactory sensitivity with multipoint electroantennography

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Electroantennography (EAG) is widely used to estimate the olfactory sensitivity of non-model insect species to putative semiochemicals. However, such recordings mostly sample the activity of a subset of the olfactory receptor neurons on an antenna. This is especially problematic in species, such as flies with bulbous antenna, with an inhomogeneous distribution of receptors on the antennal surface. Here, after discussing the neuronal origin of the EAG signal, we demonstrate that multipoint recording is necessary to exhaustively infer the olfactory sensitivity of insects. Accordingly, we built a novel experimental setup composed of three simultaneous EAG recordings dispersed on an insect antenna. Maximized spacing between the microelectrodes enhances mechanical stability and ensures covering the activity of most antennal olfactory receptors. Data are analyzed through an adapted model of current source density. The setup is coupled with a gas chromatograph through a system chopping the effluent gas at a frequency of 1 Hz. Recordings were successfully performed in several Tephritidae and Drosophila species with various antennal size and shape. The chemical specificity depended on the recording position, confirming an improved scanning of antennal responsiveness with this tool. This new setup allows quantitatively determining the olfactory sensitivity of an insect antenna and roughly localizing the activated neurons. It will be an asset in future research on flies Chemical Ecology and Evolution. **Keywords:** Chopper stabilization; electroantennogram; fruit flies; GC-EAD; Olfactory Receptor Neurons

*Intervenant

Exploring potential links between the gut and the brain in Parkinson's disease using Drosophila.

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Parkinson's disease (PD) is the most common neurodegenerative disorder that affects the motor system, which is characterized by typical symptoms such as resting tremor, rigidity and bradykinesia. However, some non-motor symptoms, constipation for instance, generally appear many years before the motor defects. Recently, a growing number of articles reported that patients with PD have intestinal inflammation and altered gut microbiota, and that gut-brain interactions may play an important role in the development of the disease. However, how neurons and gut cells interact in PD pathogenesis is still a matter of investigation. The protein α-synuclein is known to be involved in PD, as its aberrant accumulation and subsequent aggregation can cause both familial and sporadic cases of the disease. Here we expressed a mutant isoform of human α-synuclein (α-synA30P) in the *Drosophila* model, either in neurons or gut cells (enterocytes), or both in neurons and gut, respectively, in order to investigate the potential links between the nervous and intestinal tissues in PD pathogenesis. Our results showed that the expression of α-synA30P both in neurons and gut decreased flies' spontaneous activity and oxidative stress resistance, and increased reactive oxygen species accumulation in the gut of young and aged flies. Such effects were not observed when α-synA30P was expressed only in neurons or gut. Furthermore, the expression of α-synA30P both in neurons and gut altered the expression of antimicrobial peptides in young flies and the gut microbiota composition of aged flies. Our results, therefore, suggest that α-synuclein accumulation in the gut and brain can induce significant disturbances in intestinal redox homeostasis and gut microbiota. Similar defects could occur in humans and contribute to accelerate PD pathogenesis.

*Intervenant

Multi-scale approach to investigate neural circuit dysfunction: From synaptic changes to probabilistic behavior

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Currently, the available treatments for Alzheimer's Disease (AD) are limited and address only physiological symptoms instead of the exact cause of pathogenesis because the neurobiological bases of AD are poorly understood at the neural circuit level. *Drosophila melanogaster* is an advantageous, cost-effective animal model for making rapid progress in elucidating circuit mechanisms underlying neurodegenerative diseases. In the larvae, electron microscopy (EM) images of the entire nervous system have been generated, and circuits can be mapped with synaptic resolution. In addition, larval behavior can be quantitatively characterized, correlated with neural activity, and modeled with machine learning. By combining synaptic, functional, and behavioral analyses of a previously mapped larval mechanosensory circuit, we plan to build a comprehensive circuit model of AD to investigate neural circuitdysfunction in AD and to automate data processing for rapid diagnostic/drug discovery. Here I will present early results on how induction of AD related trans-genes can impact larval startle and escape behavior.

*Intervenant

The role of neuronal lipid production on morphology, function, and maintenance

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Around 60 % of the brain consists of lipids and changes in the lipid homeostasis are linked to the onset and progression of neurological disorders such as epilepsy, Alzheimer's disease, Parkinson's disease and many more. However, the function of specific lipids and lipid homeostasis regulators within neurons are not yet sufficiently understood. Using the complex, *Drosophila* dendritic arborization (da) neurons we study the role of lipid metabolism key regulators on neuronal morphology, function, and maintenance.
We recently identified that neurite expansion in morphologically complex neurons, such as the c4da neurons, relies on the up-regulation of cell-autonomous fatty acid production via the transcription factor SREBP. In *srebp* mutant c4da neurons, dendritic structures are correctly established at early developmental stages, but fail to scale with the animal's growth. As a consequence dendritic trees are severely simplified at late larval stages. Additionally, we observed length-dependent, progressive axon loss. The dendrite simplification in mutant c4da neurons was accompanied by hypersensitivity to the neuron's stimuli.

Another very recently described regulators of lipid metabolism are (dihydro)Ceramide Synthases (CerS). Those have a dual role as they harbor a catalytic domain involved in dihydroceramide production. Ceramides are the precursors for complex sphingolipids and act as lipid second messenger molecules. Lack of CerS enzymatic activity leads to reduced dendritic complexity in various neurons including *Drosophila* c4da neurons. However, in contrast to *srebp*, this phenotype seems to result from degeneration rather than from developmental defects. Additionally, most CerS carry a homeodomain by which they regulate lipid catabolic pathways in peripheral tissues. Selective loss of the homeodomain function in da neurons results in reduced dendritic complexity. In contrast to *srebp* mutants, *cerS* mutant neurons are less excitable than control cells.
Taken together, our data are in support of a clear cell-autonomous control for lipid production in neurons and help to gain detailed insights into the consequences of a lipid unbalance on neuronal morphology and function.

*Intervenant

From connectome to function: connectivity features underlying neuronal population dynamics in the nematode C. elegans

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The field of neuroscience is currently undergoing enormous efforts to map synapse-resolution connectomes of entire brains, e.g. from fruit flies and mice. These endeavours bear the potential of uncovering fundamental principles in brain-architecture that are linked to brain-function. The connectome of the nematode *C. elegans*, composed of just 302 neuronal nodes, has been mapped decades ago. However, a solution to the structure-function problem was still pending. We therefore systematically compared pairwise correlations in neuronal population activity data obtained from single cell resolution whole brain imaging with connectivity measures obtained from graph-theory. Surprisingly, direct connection strength can only weakly predict neuronal interactions, but higher order connectivity features such as connectivity motifs, input symmetries and the rich club architecture of the connectome seem crucial for establishing globally correlated neuronal dynamics.

*Intervenant