Special Information on Corona:

All F1/F2 practical courses will be held as single practical training in our lab subject to a hygiene plan. This means that you can apply directly to the person in charge mentioned below to agree on a starting date for your course.

WG Wegener (4 Projects)

1. The timing of eclosion in *Drosophila melanogaster*

Drosophila melanogaster's eclosion can be used as a model to study the relationship between the master clock and peripheral clocks (here: prothoracic gland). The rhythmicity of the eclosion behaviour is the direct result of neuroendocrine pathways that synchronise these clocks and only allow it to happen at a certain time of the day.

Sub-Project 1: The role of TD neurons in the timing of eclosion

It is evident that shortly before eclosion the tracheal system of the fly collapses and the fly undergoes a phase of hypoxia. The tracheal dendrite (TD) neurons are CO_2 sensitive and may function as hypoxia sensors responsible for relaying this information to the brain. The aim of this study is to understand the role of these neurons in timing of eclosion. Thus, we are going to investigate that by optogenetical activation of these neurons and searching for premature eclosion patterns.

Sub-Project 2: The activity pattern of the PTTH neurons

Our lab has shown before that the prothoracicotropic hormone (PTTH) signalling is the core mechanism that couples the central clock and the periperhal clock in the prothoracic gland. Interfering with PTTH signalling renders eclosion arrhythmic. Also, we could show that this signalling is important at the final stages of pupation. Now the goal is to understand the activity pattern of these neurons during the course day and obtain a better temporal resolution by calcium imaging.

1.

Literature: Selcho M *et al.* 2017 Central and peripheral clocks are coupled by a neuropeptide pathway in Drosophila. *Nature Communications* **8**, 15563. (doi:10.1038/ncomms15563)

Sub-Project 3 Testing synaptic connections between the clock neurons and the VM neurons

The ventromedial (VM) neurons that produce eclosion hormone are important for the timing of eclosion. The aim of this research is to identify potential synaptic connections between the central clock neurons and the VM neurons in pharate Drosophila using an advanced genetic (syb-GRASP) technique, immunostainings and confocal microscopy.

More information:

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Phone: +49 931 31-80746

2. The role of synaptic active zones in neuropeptide release

Project1:

The role of synaptic active zones for the release of neuropeptides in the brain remains elusive. To get an idea of localization of active zones in a neurosecrotory context, a genetic screen for endogenous expression of active zone proteins will be performed in neuropeptidergic cells in the Drosophila brain. The methods in this project will mainly include immunostaining and confocal/SIM microscopy.

Sub-Project2:

Reconstruction and annotation of single clock neurons plus their postsynaptic partners in the whole adult electron microscopy volume.

Recently, a complete electron-microscopic stack of the Drosophila adult brain became available – a historic moment. This project is primarily computer work and will be based on a software package called CATMAID. Our main goal is to reconstruct (from the electron microscopic slices) part of the neural circuitry that underlies the circadian control of behaviour and to define in- and output sites (synapses, dense core vesicle release sites) of clock neurons in these reconstructions. The project can/will nevertheless also include wet lab work (for example immunostainings, SIM microscopy).

More information:

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3. Circadian control of anxiety (centrophocitiy)

Drosophila shows a similar centrophobia behavior as mammals. Using an open field test to measure anxiety, we can investigate the psychological mysteries with powerful genetic tools available in a basic and simpler animal model, Drosophila *melanogaster.*

We observed that anxiety levels follow a daily rhythm driven by the circadian clock. The next step is to understand how the endogenous clock regulates or modulates the anxious level. The project will genetically interfere with output signals from the circadian clock, and then test effects on the circadian pattern of anxiety (centrophobia).

More information:

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4. Bioinformatic and molecular analysis of the N/E carboxypeptidase complement of insect genomes

Neuropeptides are important signalling molecules used in interneuronal communication, but also in the neuroendocrine communication of the nervous system to the rest of the body. Neuropeptides are produced from larger precursors (preproproteins) which are post-translationally cleaved by a dedicated set of proteases. One important enzyme class in preproprotein processing are N/E carboxypeptidases. In mammals, the most important enzyme is carboxypeptidase E (CPE). Mice with a loss-of-function mutation in the CPE gene show severe phenotypes, including extreme obesity. Yet, they are vital since carboxypeptidase D (CPD) can partially compensate CPE action.

In contrast, the fruit fly *Drosophila* has no gene for CPE. We recently showed that instead, CPD is the major preproprotein processing CP in the fly (Pauls et al. 2019). We performed a rather superficial search for CPE/CPD genes across insects genomes. The results suggest that all insect taxa have a gene for each CPE and CPD, except for Diptera (flies, mosquitoes and allies) and Hymenoptera (bees, wasps, ants and allies). Astonishingly, one single tephritid fly species seems to have regained a CPE gene.

The aim of this project is to develop a bioinformatic pipeline that allows a comprehensive in-depth search for N/E carboxypeptidase genes across all available insect genomes to confirm the loss of CPE in Diptera and Hymenoptera, and to test whether regain or single loss of CPE has occurred also in other insect taxa. Another aim is to confirm the presence of a CPE gene in the tephritid species in question by genomic polymerase chain reaction (PCR) and sequencing.

Literature:

Pauls D, Chen J, Reiher W, Vanselow JT, Schlosser A, Kahnt J, Wegener C. 2014 Peptidomics and processing of regulatory peptides in the fruit fly Drosophila. EuPA Open Proteomics 3, 114–127. (doi:10.1016/j.euprot.2014.02.007)

Pauls D, Hamarat Y, Trufasu L, Schendzielorz TM, Gramlich G, Kahnt J, Vanselow JT, Schlosser A, Wegener C. 2019 Drosophila carboxypeptidase D (SILVER) is a key enzyme in neuropeptide processing required to maintain locomotor activity levels and survival rate. European Journal of Neuroscience (doi:10.1111/ejn.14516)

More information:

Email: christian.wegener@biozentrum. uni-wuerzburg.de

WG Rieger / WG Senthilan (2Projects)

1. Characterization of a rhythm mutation in *Drosophila*

You are going to characterize a clock mutation in *Drosophila melanogaster* using neurogenetic methods. The mutation has a dramatic effect on the morphology of the endogenous clock of *Drosophila*, has an effect on the expression of the core clock genes and can therefore be studied very well via behavioral rhythms.

We have sequenced the genome of the mutant and the sequence data serve as clues for further investigation. You can build on preliminary work from diploma and master theses.

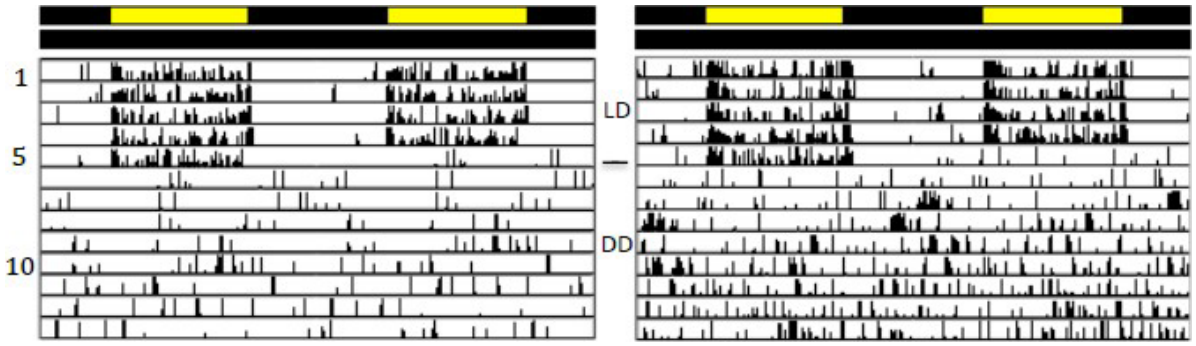


Fig.1: Mutant activity rhythm in light dark (day1-5) and constant dark (day6-13)

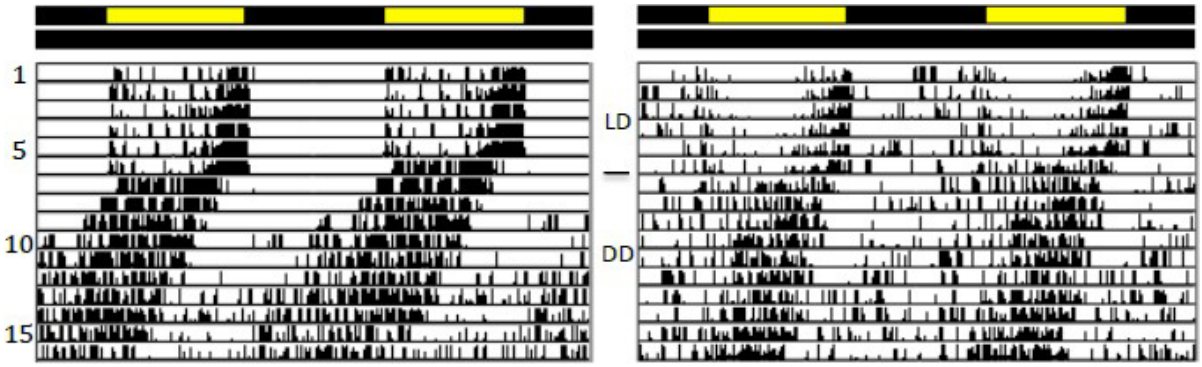


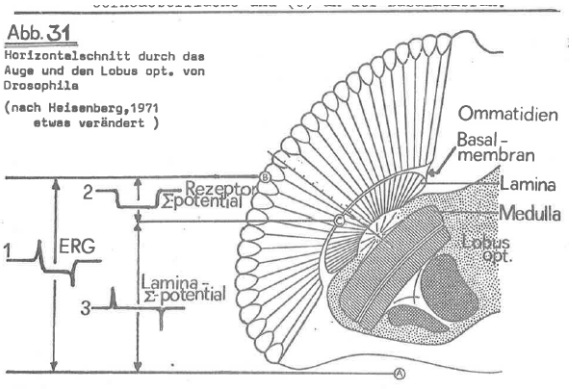
Fig.2: Wildtype activity rhythm in light dark (day1-6) and constant dark (day7-16)

Methods: Fly work, Drosophila behavior, Gene knockdown and rescue experiments, recording daily activity rhythms, statistics, and molecular biology: RNA extraction and qPCR.

2. Functional investigation of rhosopsin7 by electroretinogram

You are investigating the function of Rhodopsin7 (Rh7), which has recently been characterized in *Drosophila melanogaster*. You perform direct electrophysiological measurements on the fly eye. By stimulating the compund eyes with monochromatic light of different wavelengths, light pulses and intensity curves, the function of Rhodopsin7 in the compund eye of *Drosophila* will be investigated. The experiments will be flanked by

investigations of the daily activity rhythm. You will continue the research work for which the chair has laid the foundation with numerous research projects.



Literature:

Senthilan, P. R., Grebler, R., Reinhard, N., Rieger, D., and Helfrich-Förster, C. (2019) Role of Rhodopsins as Circadian Photoreceptors in the Drosophila melanogaster, Biology 8, 6

Grebler, R., Kistenpfennig, C., Rieger, D., Bentrop, J., Schneuwly, S., Senthilan, P. R., and Helfrich-Förster, C. (2017) Drosophila Rhodopsin 7 can partially replace the structural role of Rhodopsin 1, but not its physiological function, Journal of Comparative Physiology A 1—11

Methods: Fly work, Drosophila behavior, Gene knockdown and rescue experiments, statistics

More information:

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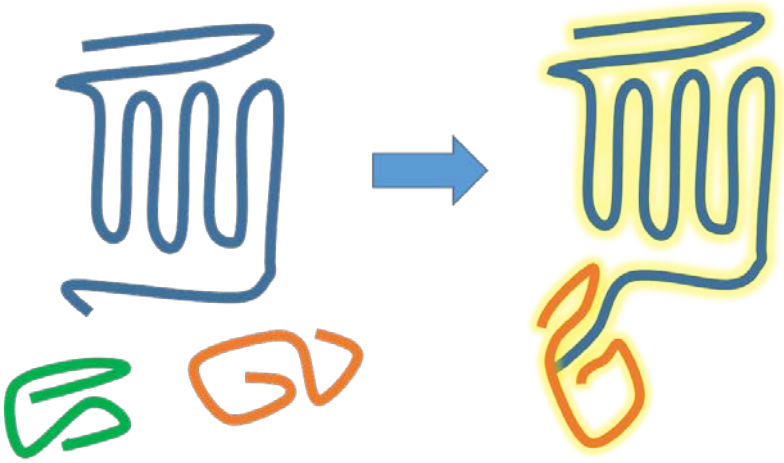
WG Senthilan (2 Projects)

1. Finding the signaling pathway of Rhodopsin 7 (Rh7) in *Drosophila melanogaster*

Rhodopsins are light-sensitive, retinal-binding, membrane proteins that play an important role in phototransduction. To have a broad and sensitive visual system, many animals express more than one Rhodopsin molecule. The fruit fly Drosophila melanogaster expresses seven different Rhodopsins. Rhodopsin 7 (Rh7) was discovered in 2000 when the fly genome was completely sequenced. Although Rh7 shares many important properties with other rhodopsins, it also has fundamental differences to these. As an example, Rh7 lacks the highly conserved QAKK domain in its cytoplasmic loop, which is important for G-protein binding and the subsequent activation of the known phototransduction pathway. Since Rh7 cannot activate the phototransduction pathway via G-proteins, it requires other potential interaction partners and/or signaling pathways in order to transmit its signal.

In this F1 project, we aim to identify potential interaction partners of Rh7 by performing protein interaction assays. Therefore, we will express potential Rh7 interaction sites and potential interaction partners in vitro and perform Far-Western blots. In the further course of a master's thesis, we will perform additional experiments such as Yeast-Two hybrids and mutagenesis.



Methods: Molecular biology: molecular cloning (PCR, restriction digestion, ligation, bacterial expression), protease reactions, heterologous protein expression and purification, protein-protein interaction, SDS-PAGE, Western blots, etc.)

2. Rhodopsin 7's (Rh7) contribution to the lights-off-startle response in *Drosophila melanogaster*

Rhodopsins are light sensitive, membrane proteins that play an important role in phototransduction. The fruit fly *Drosophila melanogaster* has seven different *Rhodopsin* genes in its genome. Although the seventh Rhodopsin, Rh7 has almost all important features of a functional Rhodopsin, it differs from other Rhodopsins in its genomic, structural, and expressional properties. In order to examine the circadian clock of the flies, flies are usually

monitored under an artificial day with 12h dark and 12h light phase. Fruit flies show increased activity when the light suddenly turns on or out. Mutants lacking the Rh7 gene show no hyperactivity when the light is suddenly turned off.

Since the exact function and the expression site of Rh7 are not yet clear, we want to investigate the exact role of Rh7 in this F1 course. First, we want to rescue Rh7 in different cells and check the lights-off response. In addition, we want to downregulate Rh7 with the help of RNAi in different cell types and test for the lights-off reaction. With these experiments, we want to learn more about the expression site, about the function of Rh7, as well as about the origin of the startle response.

Methods: Fly work, Drosophila behavior, Gene knockdown and rescue experiments, recording daily activity rhythms, statistics, and molecular biology: RNA extraction and qPCR.

More information:

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https://www.biozentrum.uni-wuerzburg.de/neurogenetics/forschung/ag-zandawala/

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WIR
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Master's Thesis Project available to decipher the neural circuitry regulating feeding in *Drosophila*

Overview of the working group
The nervous systems of animals control a wide range of essential behavioral and physiological processes including development, feeding, metabolism, stress, reproduction, aggression, sleep, and locomotion. Many of these processes are governed by neural circuits that are based on synaptic transmission. The complete neural circuitry (a brain connectome) of the vinegar fly *Drosophila melanogaster* is now available. Thus, we have a basic underlying framework that governs a wide array of complex behaviors in these animals. Our working group focuses on deciphering the neural circuitry regulating feeding and metabolism in *Drosophila*.

Project
The aim of this project is to gain insight into the neurons regulating feeding behavior using the *Drosophila* connectome. You will be responsible for using computational methods to 3D reconstruct neurons and analyzing connectivity between neurons of interest. Previous experience with Python or R would be preferred, but not necessary so long as there is to learn coding during the course of the project. Following successful training, you will have the option to work on this project remotely.

You will work in a highly motivated team working on various aspects of this project using diverse approaches including bioinformatics, anatomical mapping, genetics and behavior.

If you enjoy working with complex data and would like to work at the intersection of neuroscience, connectomics and genetics, please get in touch!

Recent publications:
https://doi.org/10.1371/journal.pgen.1009425
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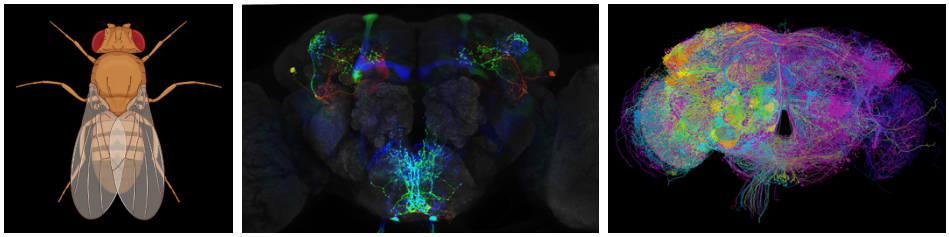

Lab website: https://lab.zandawala.com/

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WIR
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Master's Thesis Projects available to investigate the neuronal regulation of glucose homeostasis

Overview of the working group

The nervous systems of animals utilize a wide variety of chemicals for neuronal communication. These include amino acids, biogenic amines, and neuropeptides amongst others. Neuropeptides are by far the most diverse, and control a range of essential physiological processes including feeding, metabolism, sleep, stress, reproduction, development and locomotion. Our working group is interested in understanding how neuropeptides mediate their effects. Specifically, we are interested in discovering and characterizing novel neuropeptides that regulate insulin signaling and glucose homeostasis in the fruit fly *Drosophila melanogaster.* Unraveling these pathways in *Drosophila* by utilizing the power of relatively simpler nervous and endocrine systems will provide a framework for understanding dysregulation of glucose homeostasis in humans which is linked to diabetes, obesity and other metabolic disorders. We utilize multiple approaches in our lab including standard molecular techniques, CRISPR/Cas9, *Drosophila* genetics, behavioral analyses, optogenetics and calcium imaging. We are also developing cutting-edge genetic tools to study neuropeptide function in *Drosophila*.

Project

We have several on-going projects in the lab and the student will have the flexibility to learn different techniques depending on their interest and future goals. Examples of projects include generating CRISPR/Cas9 mutants for different neuropeptides, recording and analyzing the behavior of mutant flies, labelling and imaging neurons using conventional light microscopy, and developing new genetic tools using molecular techniques.

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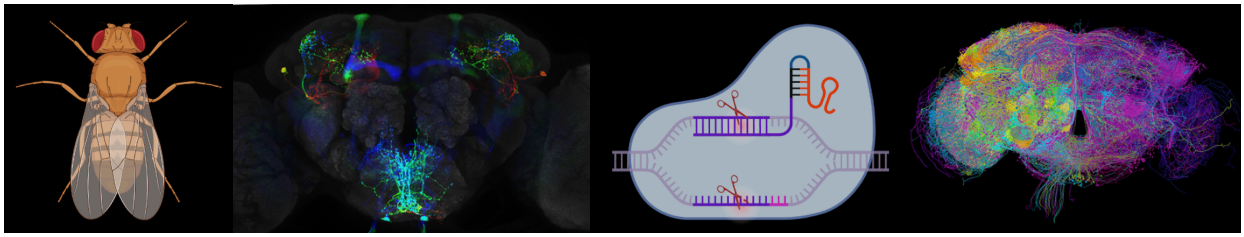

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17. 10. 2023

Molecular Biology / Behavioral Project

Identifying a potential new mutation in the *Drosophila* clock factor CRYPTOCHROME (CRY)

Supervision: Peter Deppisch, Prof. Dr. Charlotte Förster (LS Neurobiology and Genetics, Uni Würzburg)

Suitable for: Bachelorthesis, Master F1 or accompanying internship

Start: from now on

Supervision: Peter Deppisch, Prof. Dr. Charlotte Förster

Languages: German, English

Contact: peter.deppisch@uni-wuerzburg.de

Outline:

Constant light disrupts the circadian clock of wild-type fruit flies (*Drosophila melanogaster*) and thus generates arrhythmic activity. This phenotype can be explained on the molecular level, where the constantly active circadian photoreceptor CRYPTOCHROME (CRY) causes an enduring degradation of the core clock genes PERIOD (PER) and TIMELESS (TIM).

From a wild-type African *Drosophila* population we now isolated a strain that displays robust rhythmic behavior in constant light. We observed that CRY is not expressed in the clock neurons of these flies. Subsequently, we could exclude a contamination with an existing *cry*-mutant, leading us to the conclusion that we are dealing with a new type of mutation. Our task is now to identify the mutation, which might be located in the *cry*-gene or its upstream regulatory sequence. Eventually, this could give us new hints about the expression regulation of CRY.

Therefore, we are looking for a highly motivated student who is interested in molecular and behavioral work with *D. melanogaster*.

Main Methods:

- *Molecular Biology (DNA-extraction, PCR, Cloning, Sequencing, …)*
- *Activity recording with the DAM-TriKinetics-system in different conditions (light-dark cycles, constant light, etc.)*
- *Sequence analysis*

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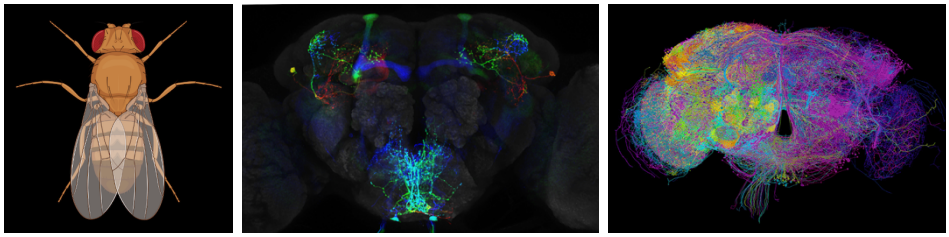

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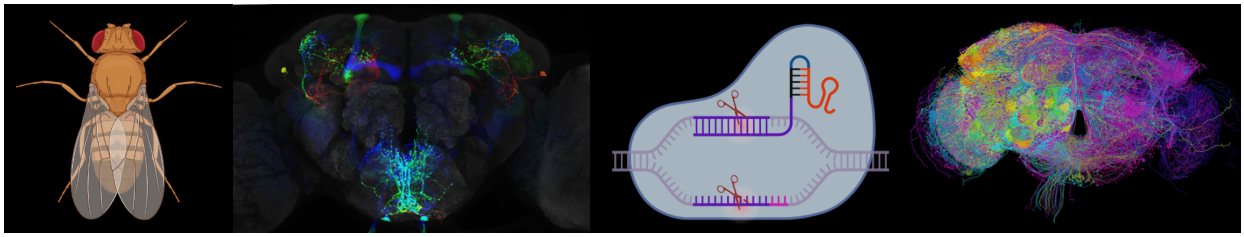

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