Champalimaud Research Groups

Champalimaud Research accepts internship applications via a designated <u>form.</u> Applicants choose up to 5 labs to apply to and, if accepted for an internship, will design their own project with the PI. Therefore, the details requested here will only be decided when the PI and the intern agree on a project.

Ribeiro Lab

Nutrition is a key determinant of health, wellbeing and aging. We want to understand how animals decide what to eat and how these decisions affect the fitness of the animal. To achieve a mechanistic, integrated, whole-animal understanding of nutritional decision-making we work at the interface of behavior, metabolism and physiology in the adult fruitfly. The powerful neurogenetic tools available in model organisms allow us to identify molecular as well as circuit mechanisms involved in producing the appropriate behavioral response to a specific need of the fly. We also dedicate a significant effort to the development of novel, automated and quantitative behavioral assays to understand the behavioral strategies used by the fly to make the right nutritional decisions. The combination of powerful molecular circuit manipulations, sophisticated behavioral analyses, and imaging approaches allows for a mechanistic understanding of how neuronal circuits control nutritional decisions to regulate important traits such as aging and reproduction.

Moita Lab

Living in a group has an adaptive value for a number of reasons. In the lab we focus on social interactions in different contexts, namely when individuals perceive a threat or when they are foraging for food. The neural mechanisms by which animals use social information to detect impending danger are largely unknown. We are studying how animals use defence behaviours of con-specifics as alarm cues. In addition, we study how the social context modulates defence behaviours. For example, we are studying how the presence of offspring affects defence behaviours displayed by mothers. We are also studying prosocial behaviour of rats using food foraging tasks. Here we would like to understand what drives an animal to coordinate with another or to perform an action that benefits another in the absence of self-benefit. To understand the mechanisms by which social interactions shape behaviour we use a combination of behavioural, pharmacological and optogenetic tools in rats and fruit flies.

Sánchez Danés Lab

Most tumours are heterogeneous at the cellular and (epi)genetic levels. This heterogeneity has been proposed to be responsible for tumour progression, metastasis and resistance to therapy. Our goal is to understand the contribution of the different tumour cell populations and genetic alterations to cancer progression and response to therapy. We do that by combining genetic lineage tracing, clonal analysis, imaging techniques, tumour organoid cultures and functional experiments in vivo and in vitro. We use the most frequent human cancer – basal cell carcinoma – and one of the most common pediatric cancers – medulloblastoma – as the models for our studies. Both types of cancer arise upon the constitutive activation of the Hedgehog signalling pathway.

Moreno Lab

Humans are able to detect fitness decay in colleagues by looking at the graying of the hair or the wrinkles in their faces. Work from my laboratory in the last few years has shown that cells can also detect fitness levels of neighboring cells using a molecular code. Those "fitness fingerprints" (Rhiner et al., Dev.Cell, 2010; Merino et al., Curr. Biol., 2013) can be used to mediate cell selection by recognizing and eliminating less fit cells during ageing (Merino et al., Cell, 2015), regeneration (Moreno et al., Curr. Biol., 2015) and cancer (Levayer et al., Nature 2015).

Renart Lab

We are interested in identifying generic principles governing the dynamics of cortical circuits and the way in which they produce function. Our current work evolves around two lines of research: sensory perception in the auditory modality – with an emphasis on the relationship between the response variability of sensory neurons and the accuracy of perceptual discriminations – and working memory, with a focus on the mechanisms underlying the maintenance of information across time in the prefrontal cortex. Our research strategy relies both on identifying characteristic signatures of population organization – through recordings of the simultaneous activity of neuronal populations during controlled behavioral tasks – as well as on developing a mechanistic understanding of how these patterns of population activity emerge – which we investigate by developing mathematical models of the underlying neuronal circuits.

de Polavieja Lab

Our decisions, learning experiences and emotions depend on other people, and conversely the patterns in collectives result from interacting individuals. What are the rules of interaction? Which patterns can emerge?

Our aim is to reach a quantitative understanding of individual and collective behavior, including collective coordination, collective decisions and collective intelligence. We approach this problem using a variety of techniques, including behavior, mathematical modelling, machine learning and artificial intelligence, virtual reality, neurobiology, and molecular biology. We chose to implement this approach in zebrafish and humans.

Petreanu Lab

Our brain is constantly interpreting the environment around us to plan and guide our actions. This requires combining often noisy and contradictory sensory inputs with internal models of the world. We study how this process emerges from networks of neurons in the mouse brain. We focus on the neocortex, a seemingly simple sheet of neurons located at the outermost part of the brain that endows us with our advanced cognitive abilities. Despite its uniform appearance, the neocortex is a complex network of specialized areas. We use the latest techniques to study how these areas interact to combine sensory stimuli and internal factors and give rise to perception.

Veiga-Fernandes Lab

The interplay between diet, immune cells and intestinal microbes ensures vital functions of the organism, such as energy and micronutrient extraction from the diet, protection from pathogenic microbes and maintenance of a healthy epithelial barrier. These complex networks are of vital importance to organismic homeostasis, while inadequate relationships can lead to cancer and chronic inflammatory diseases, which are major Public Health concerns.

Adaptive immune lymphocytes express recombining antigen-specific receptors. These lymphocytes are activated by defined antigens and require a differentiation phase before exerting their effector function. In contrast, innate lymphocytes display rapid effector functions despite their set of limited germ-line encoded receptors. A mounting body of evidence indicates that in addition to their well-established developmentally regulated program, immune cells are also controlled by dietary signals and neuronal inputs. Thus, although there is tangible evidence suggesting that immune cells possess unexpected sensing strategies, how lymphoid cells perceive, integrate and respond to environmental cues remains poorly understood and vastly unexplored.

We centre our efforts on defining lymphocyte sensory mechanisms in health and

disease. We use an integrative across-level approach aiming to elucidate the tenets of lymphocyte sensing and communication, within, across and beyond the organism.

Vasconcelos Lab

Animals exhibit behavioral repertoires that are often innate and result in stereotyped sexual and social responses to their environment. Innate behaviors do not require learning or experience and are likely to reflect the activation of developmentally programmed neural circuits. We are interested in the nature of defined neural circuits: how activation of circuits elicits specific behaviors.

It has been extremely difficult in complex organisms to study a circuit beyond the early stages of sensory processing. *Drosophila melanogaster* is an attractive model system to understand a circuit because flies exhibit complex behaviors that are controlled by a nervous system that is numerically five orders of magnitude simpler than that of vertebrates.

We use a combined behavioral, genetic, imaging and electrophysiological approach to determine how defined neural circuits and their activation elicit specific behaviors.

Paton Lab

Learning to adaptively respond to cues in the environment that predict behaviourally relevant events is critical for survival. However, in the natural world, where animals are exposed to myriad sensory stimuli, learning the predictive value of cues is non-trivial. How do animals figure out which cues are predictive, and of what? This is called the credit assignment problem. Conceiving of this problem as statistical inference in the time domain offers a parsimonious account of animals' learning abilities. In other words, when cues occur relative to meaningful events is what determines their information content, their usefulness, and thus, whether they warrant learning about. However, we still do not understand how the brain might keep track of

times. We aim to reveal neural mechanisms for time by observing and manipulating neurophysiology in behaving rodents performing tasks that lead them to estimate intervals.

Carey Lab

Understanding how cellular and synaptic mechanisms interact within neural circuits to control behavior is a fundamental goal of neuroscience. To achieve that goal, we need a thorough understanding of behavior as well as a detailed knowledge of the underlying neural circuit. With this in mind, we focus our research on the cerebellum, a brain area that is critical for coordinated motor control and motor learning and whose circuitry is relatively simple and well understood. Many of the neuron types in the cerebellum are molecularly identifiable, and existing technologies allow us to target transgenes to specific neuronal populations. By comparing specific aspects of behavior and neural activity across mice in which we have targeted genetic perturbations to different cell types, we hope to determine links between cellular function, circuit activity, and behavior.

Costa Lab

To study actions is to study the way we do things, which is different than studying how we remember stimuli, or facts and events. Some actions are innate or pre-wired (like swallowing or breathing). Others are learned anew throughout life, likely through a process of trial and feedback. We currently focus on understanding the processes mediating the latter.

A growing body of evidence suggests that cortico-basal ganglia circuits are involved in action generation and selection, in skill learning, and in learning goal-directed actions and habits. We center our efforts on investigating the cortico-basal ganglia mechanisms underlying these processes using an across-level approach, from molecules to circuits.

We chose to implement this integrative approach in mice because they combine the power of genetics, a mammalian brain with canonical cortico-basal ganglia loops that can generate and propagate oscillatory activity, and the possibility of accurately quantifying simple behaviors like action initiation (with EMG recordings or using inertial sensors) and stereotypic skill learning, and more elaborate behaviors like goal-directed actions.

Lima Lab

The main goal of our laboratory is to gain mechanistic insights into the neuronal processes underlying fundamental behaviors in females: the choice of a suitable mate and how to initiate and terminate sexual behavior. To do so, we use mice as model system and a combination of approaches that include physiological, anatomical and molecular tools to dissect the contribution of candidate brain areas to the emergence of these natural behaviors. Our long-term goal is to test the hypothesis that mate choice has an impact on the regulation of sexual behavior.

Shemesh Lab

Modulations in neural circuit dynamics and microstructures can translate to functional enhancements (e.g., upon plasticity), or, conversely, to severe functional deficits (e.g., upon neurodegeneration). We are interested in identifying and investigating the links between such longitudinal functional modulations, their underlying microarchitectural modifications, and the ensuing behavioral responses in vivo. To this end, we harness ultrahigh field Magnetic Resonance Imaging (MRI) coupled to specificityendowing modalities such as optogenetics and optical microscopy. These offer the opportunity of eliciting activity in circuits of interest, and concomitantly monitoring the ensuing activity in 3D. We further develop and apply novel methodologies based on nonBOLD mechanisms, which can potentially provide much insight into the nature of the activity, as well as probe rather fast dynamics. Microstructures are unraveled via MR methodologies tailored to probe cellular-scale size distributions (in white matter) as well as highly heterogeneous morphologies (in gray matter). These measurements are performed in vivo using state of the art 9.4T and 16.4T scanners, in both anesthetized and behaving rodents, as well as in animal models of neurodegeneration and plasticity. Our long term goals are to understand the mechanisms by which modifications in the tissue's microstructure transcend globally and modulate function and behavior, and to explore the potential of these as early disease biomarkers.

Chiappe Lab

Our goal is to understand the fundamental principles for the function and organization of neural circuits involved in estimating an animal's own movement, especially in the context of visually guided locomotion. Many basic functions of our brain, from motor control, to more cognitive operations such as navigation, critically depend on selfmovement estimation. We investigate which circuits are involved in this representation, and what computations these circuits perform. In addition, we aim to identify the activity dynamics and mechanisms by which these computations are generated.

Our strategy focuses on connecting neural activity dynamics to the locomotive behavior of the fruitfly, *Drosophila melanogaster*. We employ multiple methods to record and reversible perturb neural activity in behaving flies, to analyze the structure of interconnected neurons, to quantify different aspects of the fly's locomotive behavior, and to model functional networks. This multidisciplinary approach, together with the ever-expanding genetic toolkit of the fruitfly, allows us to find mechanistic explanations for how multisensory and sensorimotor integration processes in the brain are used to guide adaptive behavior.

Rhiner Lab

Many tissues including the brain contain quiescent stem cell populations, which are activated upon damage. We study recently discovered damage-responsive neural stem cells in the fruit fly, which start proliferating after traumatic brain injury and efficiently produce new neurons in the injured brain region. We want to uncover the injury signals and molecular mechanisms that activate neural stem cells and control regenerative neurogenesis. We are also interested in understanding how altered stem cell plasticity (hyperactivation or adult neural stem cell loss) impacts on tissue regeneration, aging and cancer.

To uncover regulators of stem cell activation and neural differentiation, we use highly sensitive lineage tracing tools, in combination with whole genome expression profiling, functional genetics and high-end confocal microscopy.

Moreover, we complement current efforts to understand brain regeneration at the cellular level with behavioral assays to answer fundamental questions such as how adult-born neurons integrate into pre-existing circuits and how they may contribute to recovery of impaired brain functions after injury. This setup allows us to interrogate brain restorative processes in a holistic fashion.

Mainen Lab

We do not perceive the world directly. Rather, our brains must decipher what is out there using the window of information we receive from our senses. The result of this process is referred to as a 'model' of the world. Understanding how brains construct and use internal models is a central problem in neuroscience. This problem can be approached by thinking of the brain as a kind of an intuitive scientist, collecting and analysing data, constructing and testing hypotheses based on those data, and revising them in light of new data. Each brain gets different data and produces a different model, making the beliefs that guide our actions subjective and sometimes wrong. Fortunately, like a good scientist, our brains can and do evaluate the quality of the data. This gives us a sense of confidence in our beliefs and decisions, helping us to know when our subjective reality is worth acting on and when to question it. Understanding how all this works in terms of neural circuits is the long-term goal of research in the Systems Neuroscience lab.

Costa-Silva Lab

The general interest of the Systems Oncology group is to understand how non-tumor cells contribute to tumor initiation, growth and metastasis. More than focusing on specific tumor types, the projects in the group aim in investigating the biological systems that support oncologic disease. For instance, by releasing soluble factors and/or extracellular vesicles, tumor cells can induce phenotypic modifications of stromal cells locally and at future sites of tumor dissemination (also known as pre-metastatic niches), which support tumor growth and metastasis. Extracellular vesicles isolated from liquid biopsies (such as plasma and other body fluids) are emerging as a powerful non-invasive and abundant source of information not only about tumor cells, but also potentially about how non-tumor cells respond/interact with malignant cells. By using animal models of tumor initiation, progression and metastasis, in combination with thorough analysis of extracellular vesicle composition isolated from patients with diverse clinical profiles, we intend to characterize novel cellular and molecular determinants of cancers.

Machens Lab

How does the brain work? What are the kind of computations carried out by neural systems? We try to address these questions by analyzing recordings of neural activity and constructing mathematical models of neural circuits. Our main goal is to link the activity within various brain areas to a computational theory of animal behavior. We

are currently developing methods to summarize the activity of neural populations in useful ways and to compare population activity across areas. In turn, we seek to relate the population activity to behavioral, computational, and mechanistic problems or constraints that organisms are facing. We work in close collaboration with several experimental labs, both within and outside of the CCU.

Orger Lab

Our goal is to understand how the brain integrates sensory information and selects and executes appropriate actions. In particular, we aim to determine the organization and function of neural circuits underlying visually guided behaviors. We use the zebrafish as a model organism because it allows us to visualize and manipulate activity in neural circuits throughout a vertebrate brain. As early as one week post-fertilization, zebrafish display a rich repertoire of innate visual behaviors, following moving patterns, avoiding predators and tracking and capturing live prey. With no skull and transparent skin, the entire volume of the brain can be imaged non-invasively in one field of view, and many neurons are individually identifiable from fish to fish. Our approach has three main themes: 1) Quantitative analysis of behavior. 2) Whole brain imaging of neural activity dynamics in the behaving animal. 3) Perturbation of identified neurons to reveal their role in sensorimotor integration. In parallel, we are developing new genetic tools that allow more specific targeting and manipulation of identified cell types.

Research Associates

Fior Lab

Cancer Development and innate immune evasion

Tumor cells in order to thrive employ mechanisms that circumvent the immune response. This dynamic process is explained by the concept of cancer immunoediting, where some tumor cells variants have the capacity to escape the innate and adaptive immune system recognition, to then expand and hijack the host. However some tumor variants may protect less fit clones enabling immune evasion to then contribute to the whole tumor fitness, generating heterogeneous tumors with clones with different tumor traits. By combining live imaging, genetic and chemical tools we are studying the process of innate immune evasion and intra-tumoral clonal interactions using the zebrafish-larvae xenograft model. Understanding the process of innate immune rejection/ evasion may lead to new avenues of anti-cancer therapies based on modulating conserved innate immune mechanisms.

Zebrafish Avatars, towards personalised medicine

Despite advances in targeted cancer treatments, we still lack methods to predict how a specific cancer in a specific patient will respond to a given therapy. Consequently, patients go through rounds-of-trial-and-error approaches based on guidelines to find the best treatment, often subjected to unnecessary toxicity. We are developing zebrafish Patient Derived Xenografts (PDX) or "Avatars", as sensors for cancer behavior and personalized therapy screening (Fior et al, PNAS 2017). In collaboration with Miguel Godinho Ferreira, IRCAN – Nice, the Champalimaud Clinical Centre and the Hospital Amadora Sintra, we are testing the predictiveness of this assay in CRC and Breast Cancer, by comparing the therapeutic response obtained in patients with their matching zebrafish Avatars.

Diez Del Corral Lab

The nervous system is composed of a large variety of neuronal and glial cell types appropriately connected to reliably perform its functions, such as those sustaining basic survival (e.g. breathing) and behavioural responses to internal and external stimuli. We are currently focusing our work in the understanding of neural circuit formation during development and for this we are using the zebrafish larva as an animal model. We are particularly interested on the intersection of circuit formation and neuronal activity such as the role played by neuronal activity in circuit establishment and selection.

We work in collaboration with the Orger and de Polavieja groups.

Feierstein Lab

How does our brain use information to select an appropriate behavior? I am interested in how brain circuits process and use sensory information from the environment, together with information about the animal's internal state, to choose a suitable motor plan.

To answer this question, I use zebrafish larvae as a model system. Working in close collaboration with the Orger lab, and using custom-built microscopes and high-speed behavior tracking, we can record the neuronal activity of whole brains while monitoring the behavior of the fish larvae. Combining imaging, behavioral analysis, and manipulation of activity, we aim to understand the processing occurring in brain areas and how they contribute to behavior.