Theoretical and Applied Neuroscience

# Research Program

Cycle 38°

Academic year 2022-2023

# List of the Research Topics

| Curriculum | Research Project | Host Institution | Number of fellowships |
|---|---|---|---|
| **Curriculum 1: Cognitive and Behavioral Neuroscience** | | | |
| 1.4 | Behavioral neurophysiology in macaques | University of Parma | 1 |
| 1.7 | Neural mechanisms underlying higher cognitive functions | SISSA | 1 |
| **Curriculum 3: Preclinical Clinical and Translational Neuroscience** | | | |
| 3.4 | To study the cellular and molecular mechanisms of neurodegeneration and neuroinflammation in vivo and in vitro | University of Modena and Reggio Emilia | 1 |
| 3.6 | Psycho-biological and psychometric correlates of the effects of meditative practices | University of Pisa | 1 |
| 3.8 | Role of sleep in shaping neural circuits and behavior | University of Camerino | 1 |
| 3.10 | To study individual vulnerability in substance use disorders: A genetic, molecular and neurocircuitry level approach in rodents. | University of Camerino | 1 |
| 3.17 | The brain renin angiotensin system as a target for intervention in Alzheimer's disease | University of Cagliari | 1 |
| **Curriculum 4: Computational and System Neuroscience** | | | |
| 4.8 | Bio-signals analysis and imaging in epilepsy | University of Messina | 1 |

**Curriculum 1: Cognitive and Behavioral Neuroscience**

**Code 1.4**

**ERC Field: LS5_2**

**Project title:** To study the neuronal correlates of perceptual and cognitive processes in non-human primates

**Key words:** single neurons, macaque, neurophysiology, multielectrode recording, perception, behavior.

**Host Institution:** University of Parma

**Reference person/supervisor:** Luca Bonini **luca.bonini@unipr.it**

**Research topic description**
The research will involve the recording of single neuron activity with state-of-the-art multielectrode systems from different brain areas, to dissect the neuronal circuitries underlying perceptual and behavioral functions. Details on the research activities and publications of the lab can be found here: https://boninilab.unipr.it/index.php/publications/

**Research team and environment**
The team benefits from funding from the European Research Council and the Italian Ministry of University and Research that can cover all the needs to support the research activities. It includes, in addition to the PI (full professor), 2 researchers and a group of ~15 PhD students and post-doc/research fellows, see https://boninilab.unipr.it/index.php/lab-members/

**Preferred Research Skills and Competences**
Sound background in neurophysiology and neuroscience, availability to work with non-human primates; competences in statistics and programming and previous experience with non-human primates are a plus

**Curriculum 1: Cognitive and Behavioral Neuroscience**

**Code 1.7**

**ERC Field: SH4 / LS5**

**Project title:** Neural mechanisms underlying higher cognitive functions

**Key words:** Language, psycholinguistics, time perception, tactile perception, visual perception, memory, intelligence.

**Host Institution:** SISSA

**Reference person/supervisor:** Davide CREPALDI (Domenica Bueti, Mathew Diamond, Eugenio Piasini, Raffaella I. Rumiati, Alessandro Treves, Davide F. Zoccolan) **rumiati@sissa.it**

**Research topic description**
The project will focus on the mechanisms underlying higher cognitive functions such as language, perception, memory or intelligence. The topic that the candidate will develop during her/his doctorate will fall within one of these research domains and will be defined together with the candidate. The projects that the faculty is currently carrying out fall within the following areas: statistical learning, lexical and semantic processing, time perception, tactile perception, visual perception, space and memory. The project will contain original experimental or/and neural computational research. Ideally, the candidate is expected to complete 2-3 manuscripts during the doctorate.

**Research team and environment**
In addition to Davide Crepaldi SISSA's Cognitive Neuroscience faculty is constituted of Domenica Bueti, Mathew Diamond, Eugenio Piasini, Raffaella Rumiati, Alessandro Treves, Davide Zoccolan, principal investigators of heads of different labs. This is a very stimulating environment **providing students with the fundamental knowledge and skills for conducting cutting-edge research** in the field. The faculty is strongly **research oriented** and offers **exceptional tutorship**. This substantial investment in research is reflected in the faculty's ability to attract **highly competitive funding**, develop **strong research ties**, both locally and internationally; and publish in **leading journals**. **The official language of the doctorate program is English**, thus speaking Italian is not a requirement. The faculty provides its students with a **vibrant research environment**. In addition to frontal and hands-on learning, a journal club series takes place weekly; post-docs offer research talks every other week; a summer school is offered yearly, bringing to SISSA both a cohort of brilliant external students and established scholars in the field; national and international visitors come regularly to SISSA offering cutting-edge talks. Facilities for **human and animal research** at SISSA span virtually all state-of-the-art techniques in the field. As to the former, SISSA offers a number of **behavioural testing** booths, different **eye tracking** systems, Biosemi **EEG** systems, a **neuronavigation-guided TMS** system and a Biopac system for **electromyography**. An **olfactometer, movement tracking systems,** and a **mirror stereoscope are also available**. Our department has access to **3T fMRI**, entirely maintained by School funds. **Animal research** also takes advantage of unique facilities and equipment.

**Preferred Research Skills and Competences**
The research theme is suitable for students with backgrounds in experimental psychology, computer science, math, medicine, theoretical physics, biology and linguistics, as well as neuroscience proper, or equivalent fields. In addition to the generic software in Windows and Linux, a strong expertise in scripting and scientific programming with Python, MatLab, and similar languages is preferred as well as command of quantitative data analysis and statistics and a high proficiency in written and spoken English.

**Curriculum 3: Preclinical Clinical and Translational Neuroscience**

**Code 3.4**

**Project Title:** To study the cellular and molecular mechanisms of neurodegeneration and neuroinflammation in vivo and in vitro

**Key words:** neuroinflammation, microglia, neuroimaging, RNA/protein quality control

**Host Institution:** University of Modena and Reggio Emilia

**Reference person/supervisor:** Michele Zoli **michele.zoli@unimore.it**

**Research project description**
Specific research projects include:
- Role of non-neuronal cells in the pathophysiology and treatment of psychiatric and neurodegenerative disorders
- Pathophysiology of neuronal nicotinic receptors of neuronal and non-neuronal cells in neurodegeneration, inflammation and drug dependence
- Role of molecular chaperones in regulating the properties and functions of membraneless organelles, thus enabling dynamic cellular compartmentalization in response to physiological and external stimuli, and preventing age-related neurodegenerative and neuromuscular diseases.
- Understanding how mutations in genes encoding for several small heat shock proteins and co-chaperone BAG3 cause neurodegenerative and muscular diseases and to what extent pathogenesis is linked to PQC failure.
- 2-photon microscopy live imaging of neuronal circuits, microglia and astrocytes in pathophysiological conditions and reconstruction of their functioning through computational approaches
- Kynurenine pathway dysregulation in the pathophysiology and treatment of psychiatric disorders

**Research team and environment**
The Molecular and cellular neurobiology environment at UNIMORE shares facilities (SPF and conventional animal facility, Large instrument Center [https://www.cigs.unimore.it/index.php], Advanced laboratory for bioimages, iPSC facility, Cell culture facility [http://www.cell-lab.unimore.it/site/home.html]) and multiple research collaborations and projects and comprises several PIs including Dr. Silvia Alboni, Johan Blom, Serena Carra, Giulia Curia, Jonathan Mapelli, Luca Pani, Fabio Tascedda, Antonietta Vilella (see the UNIMORE website for details on CV).

**Research skills and competences**
Basic cell and molecular biology, confocal (live, STED) imaging, in vitro and in vivo 2-photon imaging, proteomics, analysis of RNA and protein quality control mechanisms, production and analysis of iPSC differentiated to neural and muscular cells, quantitative neurohistology, stereotaxic neurosurgery, small rodent behavioral analysis, neural circuit modelling.

**Curriculum 3: Preclinical Clinical and Translational Neuroscience**

**Code 3.6**

**ERC Field: SH4_3, SH4_5**

**Project title:** Psycho-biological and psychometric correlates of the effects of meditative practices

**Key words:** slow breathing, pranayama, sensory processing, sleep, perception attention, decision making, emotions, sleep
**Host Institution:** University of Pisa

**Reference person/supervisor:** Angelo Gemignani **angelo.gemignani@unipi.it**

**Research topic description**
Approaches based on meditative practices have recently shown their influence in the psychological treatment of various psychopathological conditions and there is scientific evidence to suggest that some of the effects of meditative practices may be based on the synchronizing effect that slow breathing has on brain rhythms and activities mediated by olfactory bulb. On this basis, the project aims to study how simple and complex behaviours, from sensation, perception to decision making and emotion processing and regulation, can be altered by meditative practice and which psychophysiological correlates could sustain the putative behavioural changes. Also sleep functions as modified by meditative practice would be the object of investigation.

**Research team and environment**
Research team will involve psychologists and bioengineering profiles. The PhD student could benefit from facilities resident at University of Pisa for the psychophysiological investigation in humans, from high-density EEG to high field MRI. Also perturbational approaches such as TMS/tDCS protocols could be implemented.

**Preferred Research Skills and Competences**
Ideal profiles for the project should express expertise in cognitive neuroscience combined with fundamentals of biological signal analysis and modelling.

**Curriculum 3: Preclinical Clinical and Translational Neuroscience**

**Host University/Research Institution:** University of Camerino

**Code 3.8**

**ERC Field:** LS5_6 (Neural bases of behaviour), LS5_1 (Neural cell function, communication and signalling, neurotransmission in neuronal and/or glial cells)

**Project title:** Role of sleep in shaping neural circuits and behavior

**Key words:** neurodevelopment, sleep loss, rodent, neuroinflammation, optogenetics, EEG, calcium imaging, glia

**Host Institution:** University of Camerino

**Reference person/supervisor:** Luisa de Vivo **luisa.devivo@unicam.it**

**Research topic description**

Sleep is essential to ensure correct brain functioning and, in the long term, to maintain mental health. Sleep is involved in ameliorating a variety of cognitive processes including emotional regulation and motivated behaviour, but the biological mechanisms linking sleep to maturation of neuronal circuits are still unclear.

The aim of this project is to understand how sleep regulates neuronal activity of key brain regions involved in emotion regulation and motivation. Specifically, the candidate will probe the role of sleep in shaping the structure and function of mesocortical limbic connectivity by using in vivo electrophysiology, calcium imaging and optogenetics in freely behavior rodents. In these brain regions, the candidate will further dissect the cellular pathways modulated by sleep at the molecular level by using single-cell omics techniques to identify potential targetable mechanisms at the basis of behavioral disorders and poor mental health induced by poor sleep during neurodevelopment.

**Research team and environment**

The lab aims at understanding the functions and mechanisms of sleep in health and disease. Our research combines morphological and functional methods of analysis in both animals and humans to investigate why sleep is beneficial for the brain at the molecular, circuit and behavioral level.

One main line of research wants to address the consequences of sleep impairment across the lifecycle and to characterize the interaction between sleep disruption and other environmental and genetic factors. Another research topic is to study the therapeutic potential of sleep enhancement to improve health and cognition at different levels. The lab explores also scientific questions linking sleep to glial cells, gut microbiome, cellular metabolism, adipose tissue, torpor, etc., thanks to the collaboration with other research groups within the University of Camerino and outside. Relevant publications and key interests of the research group can be found at https://www.bsr-laboratory.org/

**Preferred Research Skills and Competences**

The ideal candidate has a genuine interest for neuroscience and sleep research, a proactive attitude in studying relevant literature, formulate plausible hypothesis and experiments to test them. Self-motivation and ability to work both alone and in team are essential characteristics. Background in neurophysiology is desirable. An interest in assembling circuits and other electronic components (e.g. Arduino), and basic knowledge of Matlab or Python could be of advantage.

**Curriculum 3: Preclinical Clinical and Translational Neuroscience**

**Code 3.10**

**Project title:** To study individual vulnerability in substance use disorders: A genetic, molecular and neurocircuitry level approach in rodents.

**ERC Field:** LS5_3 Neurochemistry and neuropharmacology; LS7_3 Pharmacology, pharmacogenomics, drug discovery and design, drug therapy;LS5_12 Psychiatric disorders

**Key words:** Reward and Motivation, Genetics, Environment, Neurocircuitry, Pharmacology, Electrophysiology,

**Host Institution:** University of Camerino

**Reference person/supervisor:** Nazzareno Cannella **nazzareno.cannella@unicam.it**

**Research topic description**

Substance Use Disorder (SUD) is a psychiatric condition associated with increased health risks and social harm with dramatic impact to the global disease burden. In humans addictive behavior is characterized by a shift from recreational to compulsive drug seeking as described in the DSM-IV. Long-term consumption of substances of abuse induces neuroadaptations that are associated with loss of control, compulsive drug taking and negative emotional states (i.e. anxiety, depression). However, not all subjects develop SUD in response to prolonged exposure to drugs. Inter-individual vulnerability to lose control of drug consumption and develop addiction depends upon genetics, environment, personality traits, psychiatric comorbidities and the interplay of all these factors. Two projects in our laboratory are aimed at investigating the mechanisms through which these factors (and their interaction), contribute to SUD vulnerability. Protective factors conveying resilience to SUD will be also scrutinised. To exploit these projects, in addition to classical pharmacological manipulations, in vivo optogenetic, chemogenetic and neurophysiological approaches will be used. Viral mediated upregulation and downreulation of specific receptors in selected brain areas are used to determine the role of specific neurocircuitry in encoding vulnerability to SUD. *Ex vivo* brain slice electrophysiology will be also used to support the study.

**Research team and environment**

This research project will be carried out in the School of Pharmacy, University of Camerino, Italy. Nazzareno Cannella and Esi Domi, researchers in the Laboratory of Neuropsychopharmacology, headed by Roberto Ciccocioppo, are responsible of coordinating these projects. The laboratory is conceived as a multidisciplinary environment to investigate complex questions in neuroscience. The main research focus of the laboratory is on the study of the neurobiological basis of abnormal behavior and brain functions relevant to human psychopathology with emphasis on motivation and reward-related disorders. The majority of this work is directed at the understanding the neurological mechanisms responsible for these aberrant behaviours and at identifying innovative pharmacological targets to aid the development of new more effective treatments. Attention to the study of neurocircuitry and molecular mechanisms controlling emotional and cognitive disturbances associated with protracted exposure to drugs of abuse or chronic stress is also an important area of research. Over the years this research team contributed to the preclinical development of at least 3 compounds that reached various clinical development stages. The team consists of several researchers, post-doctoral fellows and PhD students with different backgrounds including biology, pharmacology, philosophy, psychology and physics. Researchers have access to 1500 $m^2$ of animal facility equipped with 50 operant self-administration chambers, EPM equipments, Porsolt swimming tubes, open field arenas for social interaction, Noldus Etovision system for behavioral monitoring, and areas dedicated to surgical procedures etc. Fully equipped lab for immunohistochemistry, light, confocal and scanning electron microscopes are also available. One laboratory is equipped an Electrophysiological setup for patch-clamp recordings in slices. Finally, equipment for molecular and cellular studies is available.

**Preferred Research Skills and Competences**

The doctoral candidate will receive training in the techniques most commonly used in basic neuroscience, including brain activity recording, imaging, electrophysiology, proteomics, behavioural testing, molecular

biology, histology and data analysis. Pharmacological, chemogenetic and optogenetic approaches will be also experienced. Candidates with training backgrounds in life sciences, behavioral pharmacology, electrophysiology, pharmaceutical sciences, molecular genetics, are preferentially considered for this position.

**Curriculum 3: Preclinical Clinical and Translational Neuroscience**

**Code 3.17**

**ERC Field:** LS - Life Sciences

**Project title:** The brain renin angiotensin system as a target for intervention in Alzheimer's disease

**Key words:** renin angiotensin, Alzheimer's disease, ACE/MasR/AT1R, transgenic mice

**Host Institution:** University of Cagliari

**Reference person/supervisor:** Paola Fadda **pfadda@unica.it**

**Research topic description**

The PhD program through in vitro and in vivo studies has as main objective to study the role of the renin-angiotensin system (RAS), expressed in the brain where it intervenes in the control of physiological processes, in inflammatory processes and in endothelial problems typical of Alzheimer's disease (AD), to identify new molecular targets.

The program would lead to the training of researchers who will be able to contribute to the identification of new molecular targets and pharmacological interventions with important clinical and social consequences, given that AD has a growing incidence all over the world, high unmet needs, and very few therapeutic options.

The PhD student will be directly and conscientiously involved in the research, in the statistical analysis of the data obtained and in the critical interpretation through the analysis of the available scientific literature. An important objective of the doctoral program will be the inclusion of the student in the local, national, and international scientific system.

**Research team and environment**

The Division of Neuroscience of the Dept Biomedical Science is in two modern building, situated inside the Campus “Cittadella Universitaria” of the University of Cagliari. It is well equipped for research activities and among its facilities it includes several research laboratories. Infrastructural arrangements are such that the PhD student will have direct and free of charge access to the arsenal of equipment cumulatively available in the laboratories.

The Laboratory Animal Resources unit maintains a secured, animal facility in the building adjacent to the DiSB. The facility is maintained by a staff of full time animal caretakers.

The PhD student will be coordinated by Professor Paola Fadda who has a broad background in Neuroscience, with high profile expertise in Neuropharmacology. In addition, her laboratories have long-standing experience in behavioral pharmacology and neurochemistry and expertise in molecular and cellular biology techniques.

The members of Prof. Fadda’s team have the multidisciplinary competences needed to support the PhD student. Prof. Fadda will monitor the progression of the experimental procedures and will be responsible for sharing data and for the establishment and maintenance of a constant information flow among the Team components and the PhD student. In-person weekly meetings will be organized, to share and discuss the results, as well as to evaluate the opportunity of possible changes in orientation of the experimental strategies.

**Preferred Research Skills and Competences**

The PhD student must have no problems with animal research activities and a general laboratory background is well accepted. She/he must work in team and possess an attitude to share it experimental and research experiences

**Curriculum 4: Computational and System Neuroscience**

**Code 4.8**

**ERC Field: SH4**

**Project title:** Bio-signals analysis and imaging in epilepsy

**Key words:** imaging, genetics, advanced MRI

**Host Institution:** University of Messina

**Reference person/supervisor:** Angelo LABATE **alabate@unime.it**

**Research topic description**

Predictive biomarkers are becoming increasingly important tools in drug development and clinical research and represent the new frontier for researcher even in epilepsy to definitively improve the individual management of people with epilepsy. A possible method might be to identify robust and validated biomarker cut-points, using innovative and automated instruments. Since 1990s brain imaging techniques, have become routine in the evaluation of patients with epilepsy. Because of the frequent association of imaging abnormalities with epilepsy regardless their drug response, imaging techniques are attractive candidates for diagnostic or prognostic biomarkers. In the last twenty years, a mass of abnormalities has been described in patients with epilepsy, in particular, using routine MRI with specific epileptic protocols as well as morphometric analysis, magnetic resonance relaxometry, diffusion-weighted imaging, MR spectroscopy, volumetry, voxel-based analysis and PET imaging. Many of these abnormalities could, in theory, serve as biomarkers of epilepsy. First of all, the use of an optimal epileptic worldwide imaging protocol represents the background to look for potential and specific biomarkers. Indeed, a typical clinical scanning protocol for a patient with epilepsy must include T1-weighted imaging, T2-weighted imaging, fluid-attenuated inversion recovery (FLAIR) imaging, and 3D volume acquisition sequences. T1-weighted is commonly used to initially define the brain anatomy, T2-weighted and FLAIR images to detect specific brain pathologies such as hippocampal sclerosis; a high resolution 3D volume acquisition provides a useful degree of T1-weighted contrast between grey and white matter, and helps greatly in the identification of subtle abnormalities, such as malformations of cortical development. Moreover, finding a lesion at MRI in a patient with epilepsy does not automatically mean that the lesion is the culprit. Some lesions are epileptogenic, whereas others are not. The identification of neuroanatomical biomarkers, providing essential links between genotype and phenotype, could have a high impact on the diagnostic work-up as well as on therapeutic planning, mainly the surgical therapy, in the majority of epilepsy patients. Likewise, in epilepsy Engel et al already suggested that a first step to identify potential biomarkers for pharmacoresistance may be to classify several well-defined epilepsy syndromes that are associated with drug resistance but in which there are also patients that are well controlled. In this way the cohort of patients with mild mesial temporal lobe epilepsy (MTLE), a common and often unrecognized clinical entity with onset in adulthood and good response to the medications that our group as extensively studied in since many years, suitably symbolizes an ideal epileptic syndrome to be studied with imaging as potential diagnostic/prognostic biomarker.

Nevertheless, in this context, only prospective epidemiologic studies may allow the identification of early and accurate electro-clinical and imaging biomarkers of a mild course in MTLE. Keeping that in mind, with a mean follow-up of more than 11 years, our group recently showed that mild MTLE remained drug-responsive in about three-fourths of patients and became refractory in the remaining one-fourth. Furthermore, at seizure onset, earlier age at onset, history of febrile convulsions, and the presence of hippocampal sclerosis on MRI, represent prognostic epileptic biomarkers of refractoriness. Using advanced MRI technique, [9,10,11] we further showed a significant reduction of fractional anisotropy along the white matter of the temporal lobes in drug-resistant MTLE, implying it as a valuable biological marker of refractoriness. Afterwards, we extended these findings and showed diffusion abnormalities and reduced cortical thickness of the corpus callosum only in patients with refractory MTLE, suggesting that differences in the distribution of such alterations might represent a biomarker of refractoriness. The other major group of pathologies in which MRI has made massive contributions to epilepsy

throughout imaging is in malformations of cortical development (MCDs). Imaging dramatically helped to identify very subtle and occult lesion cause of epilepsy before considered syndromes with negative MRI. MCDs are usual in children and should be sought in children with epilepsy. MRI can correctly define diffuse malformations such as lissencephaly, periventricular nodular heterotopia, and band heterotopia. It can also define hemimegalencephaly, schizencephaly, and focal subcortical heterotopia. Focal lesions such as focal cortical dysplasia (FCD) are the most common developmental pathologies in children with extratemporal lobe seizures and recognition of these lesions can have an important bearing on the management and prognosis. Despite an overlap of imaging features, each type of FCD can variably exhibit these features. General MRI features of FCD include cortical thickening, blurring of white matter-grey matter junction with abnormal architecture of subcortical layer, T2/FLAIR signal hyperintensity of white matter with or without the transmantle sign, T2/FLAIR signal hyperintensity of grey matter, abnormal sulcal or gyral pattern, segmental and/or lobar hypoplasia/atrophy. Hence, MRI features could differentiate between Taylor's FCD and non-Taylor's FCD in most cases, although there is some overlap. As in TLE, detailed MRI diagnosis may modify the presurgical workup and surgical planning and may have prognostic value in MCDs patients.

**Research team and environment**

The project will be implemented at the BIOMORF Department, Neurophysiopathology and Movement Disorders Clinic of the University of Messina. This Clinic together with the regional center of diagnosis and treatment of Epilepsy have the mission to improve management of epilepsy subjects and to expand knowledge of analysis of bio-signals coming from electroencephalogram (EEG) and magnetic resonance imaging (MRI).

The main research topic will be to look for MRI biomarkers in epilepsy, especially those capable of identifying neuroanatomical epileptogenic abnormalities, because that would be of huge value for choosing proper diagnostic work-up as well as the best therapeutic pharmacological or surgical planning. The environment offers several facilities including clinical expertise in the field of epilepsy, a very complete and deep electrophysiological lab and techniques. Furthermore, the close relationship with the group of neuroradiology will let to use 1.5 and very soon 3 Tesla MRI scans.

**Preferred Research Skills and Competences**

The ideal candidate is a highly motivated physicist or biomedic engineer (or related disciplines) with a solid background in signal analysis, pre and post-processing analysis of imaging signals.