# Unidade de Curricular Optativa

**Designação da Unidade Curricular: Neurociências Experimentais**

**(*Translational Neuroscience*)**

**Ano letivo 2020 – 2021**

**Tipologia da Unidade Curricular**

○ disciplina optativa

**Esta Unidade Curricular pode ser frequentada por estudantes do 3º, 4º e 5º anos**

*Esta Unidade Curricular funciona no 2º Semestre.*

**Número de vagas – 12**

**Idioma: Inglês**

**Breve descrição da Unidade Curricular**

(Explicar a relevância do tema e indicar objetivos gerais e específicos)

**The rationale**

The prevalence of neurological and psychiatric disorders is increasing worldwide due to recent extensions in lifespan and the consequent ageing of the human population. At the same time, there are significant gaps in our current understanding of the molecular basis of these disorders, resulting in severe **unmet medical needs, especially concerning treatment and diagnosis**[17]

Despite the substantial commercial opportunities, discovery and development of effective medications have proven to be challenging[18]. This is, in part, related with the complexity of the nervous system with the scientific challenges related to target identification and validation and limited understanding of the value of animal models, which leads to poor design in preclinical validation trials.

An explosion of new methods to reveal brain structure and function from cellular to organ system levels has emerged. Since the origins of Neuroscience, the development of new techniques for cell visualization, such as the Golgi method, has contributed to revealing the beauty of the central nervous system. However, there have been groundbreaking advances and a revolution in the technology with which we study the nervous system, and, in its potential to translate new therapies to humans.

*The field of neurosciences is now in a very privileged position to translate recent discoveries into real applications.*

**Our ability to record and stimulate neural circuits based on advances in neuroengineering and bioengineering** has yielded novel insights into the fundamental nature of neural circuit assembly during the course of normal learning and memory[1] and in the setting of dysfunction associated with neurodegenerative disorders or such diseases as epilepsy[2]. A new generation of therapies has emerged from this work, from chronically implanted stimulators for Parkinson's disease[3] and dystonia[4] to brain–machine interface after nervous system injury[5].

Imaging has also advanced dramatically, from the level of novel microscopes that can image the single cells and subcellular structures repeatedly over time periods of months[6] to whole-brain quantitative MRI[7]. **Novel PET scan markers such as PIB imaging[15] and tau imaging[16]** in Alzheimer's disease are enabling the clinical testing of potential therapies even before symptom onset[8]. Structural MRI may emerge as a biomarker of disease progression and response to therapy[9]. Functional MRI of the actively behaving brain has provided a wealth of information regarding the role of brain regions in behavior[10], which in turn may contribute to the identification of mechanisms of disease[11], and from there to therapies.

**Several of the preceding advances have been utilized to explore the existence and utility of biomarkers for better disease diagnosis and monitors of treatment in blood and CSF[12]**. Neural stem cell technologies have advanced to a breathtaking degree in the last 20 years, from the initial discovery that self-renewing cells exist in all the adult mammalian nervous system[13] to the current ability to generate an individual adult's own stem cells and their derivatives using specified sets of transcription factors[14]. Indeed, the technology for directly generating neural

stem cells and specific neural cells from “terminally” differentiated adult cells has rapidly advanced to neural transdifferentiation, in which even the induced pluripotent stem cell stages of cells can be bypassed[15].

**Aim**

The aim of this optional *‘**Translational Neuroscience’** Course* is to provide basic background and updated information in preclinical methods and animal models that intend to recapitulate human brain disease, in order to advance knowledge and inform therapeutics.

On completion of the course, students should understand the basic applied aspects of research in the field of neuroscience and a range of transferable skills. The skills acquired will also be of value for those wishing to pursue pre-clinical investigation in the field.

This course should be adequately integrated and contribute to the establishment of a solid molecular psychiatry and experimental neurology programs at the Medical School, in a strong coordination and connection to the clinical program, particularly, but not limited, to the Neurology, Neurosurgery, Neuropathology and Psychiatry research groups.

*Therefore it can and will be adapted according to the first year appraisal and evaluation.*

The main objectives of the discipline are:

**1) Acquisition of the fundamentals in preclinical methods to recapitulate human brain disease**

**2) To develop the critical sense of the main methodologies used to access brain function and dysfunction, and thus,**

**3) To be equipped with the core concepts required for an informed reading of scientific papers in the field.**

During the course participants will be exposed to all relevant in vivo or in vitro experimental models and approaches to study brain disorders. A major focus lies on the understanding of the differential validity and limitations of the various models and their outcome parameters. In addition, all models will be discussed in the context of their clinical relevance. Special emphasis will be put on quality issues, including standard operating procedures. The most relevant models

will be demonstrated by experienced faculty members, however, hands on exercises by the participants are not possible due to ethical as well as practical issues.

*(Note for reference: comparable courses currently taught in European Medical Schools: Imperial College London (Experimental Neuroscience); Trinity College Dublin (Biological Psychiatry); University of Oxford (Research in Psychiatry); University Medizin Berlin Charité (Experimental Neurology))*

**Literature cited:**


1. Buzsaki G, Stark E, Berenyi A, et al. Tools for probing local circuits: high-density silicon probes combined with optogenetics. Neuron. 2015;86(1):92–105.
2. Stacey WC, Litt B. Technology insight: neuroengineering and epilepsy-designing devices for seizure control. Nature clinical practice. Neurology. 2008;4(4):190–201.
3. Kalia SK, Sankar T, Lozano AM. Deep brain stimulation for Parkinson's disease and other movement disorders. Curr Opin Neurol. 2013;26(4):374–80.
4. Fox MD, Alterman RL. Brain stimulation for torsion dystonia. JAMA Neurol. 2015 Apr 20.
5. Hochberg LR, Bacher D, Jarosiewicz B, et al. Reach and grasp by people with tetraplegia using a neurally controlled robotic arm. Nature. 2012;485(7398):372–5.
6. Trachtenberg JT, Chen BE, Knott GW, et al. Long-term in vivo imaging of experience- dependent synaptic plasticity in adult cortex. Nature. 2002;420(6917):788–94.
7. McEvoy LK, Fennema-Notestine C, Roddey JC, et al. Alzheimer disease: quantitative structural neuroimaging for detection and prediction of clinical and structural changes in mild cognitive impairment. Radiology. 2009;251(1):195–205.
8. Johnson KA, Fox NC, Sperling RA, Klunk WE. Brain imaging in Alzheimer disease. Cold Spring Harb Perspect Med. 2012;2(4):a006213.
9. Okamura N, Furumoto S, Fodero-Tavoletti MT, et al. Non-invasive assessment of Alzheimer's disease neurofibrillary pathology using 18F-THK5105 PET. Brain. 2014;137(Pt 6):1762–71.
10. Sperling RA, Rentz DM, Johnson KA, et al. The A4 study: stopping AD before symptoms begin? Sci Transl Med. 2014;6(228):228fs21
11. Fox MD, Raichle ME. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nat Rev Neurosci. 2007;8(9):700–11.
12. Matthews PM, Honey GD, Bullmore ET. Applications of fMRI in translational medicine and clinical practice. Nat Rev Neurosci. 2006;7(9):732–44.
13. Lleo A, Cavedo E, Parnetti L, et al. Cerebrospinal fluid biomarkers in trials for Alzheimer and Parkinson diseases. Nat Rev Neurol. 2015;11(1):41–55.
14. Kaplan MS, Hinds JW. Neurogenesis in the adult rat: electron microscopic analysis of light radioautographs. Science. 1977;197(4308):1092–4.
15. Okita K, Ichisaka T, Yamanaka S. Generation of germline-competent induced pluripotent stem cells. Nature. 2007;448(7151):313–7.
16. Kim J, Efe JA, Zhu S, et al. Direct reprogramming of mouse fibroblasts to neural progenitors. Proc Natl Acad Sci U S A. 2011;108(19):7838–43.
17. Insel, T. R. Next-generation treatments for mental disorders. Sci. Transl. Med. 4, 155ps19 (2012).
18. Paul, S. M. et al. How to improve R&D productivity: the pharmaceutical industry's grand challenge. Nat. Rev. Drug Discov. 9, 203–214 (2010).

# Equipa docente

*The Faculty is composed of teachers and researchers experienced in implementation and analysis of preclinical studies applied to brain disorders.*

**Coordination: Prof. Luisa Lopes *(Regente)***

Luisa Lopes is a Group Leader at IMM since 2013 and a guest Associate Professor at FML since 2018; **https://imm.medicina.ulisboa.pt/en/investigacao/labs/lopes-lab/)** , whose research program is aims at understanding the mechanisms inducing the "early-aging" of cognitive function, focusing on hippocampal circuitry and related behavior, using rodent models. Her team has pinpointed circadian disorders as a trigger for accelerated cognitive loss (**Mol. Psychiatry, 2013; Scientific Reports, 2016**)), established one of the underlying mechanisms for early synaptic degeneration in the hippocampus (**Nature Neuroscience, 2017**); and most recently, collaborated in the evidence of a neuro-immune link in short-term memory (**Sci Immunol, 2019**) with Bruno Silva Santos lab. The group is currently focused on implementing novel ageing-equivalent models to study human synaptic function (**Mol. Psychiatry 2018; Cell Rep 2019**).
Since starting her own lab in 2008, she has coordinated several national and international projects, mentored 6 PhD, 9 MSc students and 3 postdocs, published more than 60 papers in international peer-reviewed journals with over 2000 citations. Luisa has been teaching the Neuroscience module at the LisbonBiomed Program since its foundation, collaborates in several national and international PhD programs; coordinates the Neuroscience module and acts as a member of the coordination committee of the Biomedical Research Master Course (IMM; FML).

**Faculty: Alexandre de Mendonça, MD, PhD**

Alexandre de Mendonça, MD, PhD, Principal Investigator @FML, neurologist and clinical researcher, coordinator of the dementia group, with>30 years experience in treating patients and involvement in AD clinical trials. He has developed a translational program pursuing early detection of dementia and Alzheimer's diagnosis. (>150 papers; JAD, 2013; JAMA Psychiatry, 2018). He has an established track record of advancing laboratory findings into the clinic; illustrated by participation in several multicentric trials: BIOMARKAPD (JPND 2012-15) – Biomarkers for AD and PD (B. Winblad, coordinator; A. de Mendonça, PI, national coordinator); RHAPSODY (JPND 2014-17) - Research to Assess Policies and Strategies for Dementia in the Young (A. Kurz, coordinator; A. de Mendonça, PI, national coordinator), GENFI - GENetic Frontotemporal dementia Initiative (J. Rohrer, coordinator; A. de Mendonça, PI, national coordinator.

**Faculty: Miguel Remondes, DVM, PhD**

Miguel Remondes is a Guest Assistant Professor at FML and a Group Leader @IMM. He received his DVM from the Technical University of Lisbon in 1993, worked as a Veterinarian for 5 years, and was then selected for the VI Gulbenkian PhD Program in Biology and Medicine. He worked with Dr. Erin Schuman at Caltech where he investigated the synapses directly connecting the hippocampus with the neocortex, and found that they exert a strong modulatory influence over neural activity and plasticity in the hippocampal network (Nature, 2002), and that they are necessary for the consolidation of long-term spatial memory (Nature, 2004). He joined the lab of Dr. Matthew Wilson at MIT and found that cingulate and hippocampal populations oscillate at the same rhythm, while increasing choice-coding accuracy (Neuron, 2013). In 2015

he formed his own lab at iMM-JLA, discovered a population of CG neurons that respond to hippocampal memory replay (Cell Reports, 2015), developed an implant to record neural activity in rodents (Frontiers in Neural Circuits, 2017) and provided a functional characterization of the connections between the hippocampus with the medial mesocortex (Cell Reports, 2019).

**Faculty: Bruno Miranda, MD, PhD**

Bruno Miranda is a neurologist, Clinical Researcher@IMM and Assistant Professor at FML, obtained is Medical degree (2006) at the University of Lisbon and his PhD degree (2016) in Neuroscience at the University College of London. His graduation work was on the computational models and neural signatures for different reinforcement learning strategies which can be used to guide decision-making. His current research work is focused on how the basic principles of human goal-directed behaviour and decision-making models can provide mechanistic explanations for neuropsychiatric manifestations – characterized by failures to learn or act based on models of the environment.

**Faculty: Joana Coelho, PhD**

Joana Coelho, PhD is a senior Postdoc fellow@IMM, with track record in celular mechanisms of neurodegeneration with >20 papers in top journals (Nat Neuro; J Neuro; Human Mol Genetics), very experienced in implementing and evaluating animal models of brain disorders. She acted as consultant regularly for either academia or private companies in neuroscience preclinical studies' implementation. She is regularly invited to give talks and workshops on the subject of animal models and preclinical studies, in various master courses, and in the last years at the AIMS meeting for medical students. As manager of the rodent behavior facility at IMM, she also provides consulting and training in animal behavior experimental design.

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**Invited Faculty: João Peça, PhD (1 hr contact)**
**João Peça** is an Assistant Professor and Group Leader at the CNC (University of Coimbra). After completing his PhD work at Duke University in 2011, he moved to MIT for postdoctoral research. In 2014 he started setting up his laboratory at the University of Coimbra with focus on understanding how neuronal circuits process information in the healthy and the diseased brain. A main topic of research is in understanding developmental disorders; autism, schizophrenia and the underlying molecular cellular and circuit basis of social behavior.

**Invited Faculty: Teresa Summavielle, PhD (1 hr contact)**
Teresa Summavielle has a degree in Biochemistry and a PhD in development of the nervous system under exposure to psychostimulant drugs. She heads the Addiction Biology Group (I3S, Porto), which explores the mechanisms of neurotoxicity induced by drug abuse and addiction. She coordinates courses in "Neurobiology of Addiction" in two doctoral programs (University of Porto) and she is an invited Professor at the Allied School oh Health in Porto (ESTSP-IPP).

## Conteúdo programático

**Contents:**

### Module I - Animal models in neuroscience

- *Modelling Psychiatric disorders*
- *Addiction models*
- *Developmental disorders*
- *Neurodegeneration*
- *Stroke*
- *Movement disorders*
- *Quantification of behavioral: pain, locomotion, memory: anxiety, stress, depression,*

### Module II – Technologies of outcome quantification

- *NeuroImaging PET; MRI*
- *Cell Imaging and NeuroPathology*
- *Brain function (circuit and synapse) and EEG*
- *Sleep*
- *Biomarkers (CSF, Plasma)*

### Module III - Neurobiology of CNS therapies

- *Gene Therapy of CNS Disorders (viral, antisense)*
- *Stem cell therapies*
- *Activity-Dependent Plasticity and Neurorehabilitation*
- *Immunological approaches*
- *Novel Pharmacological Approaches*

## Metodologia de ensino

The course will include theoretical lectures and debate/discussion modules.

Each Module will have one theoretical course per subject with a duration of 60-90 min in a total of 5 hours/Module. These can be delivered either in a face-to-face or in an online format, allowing to have invited faculty external to the Medical School. This will be followed by a 90 min-Journal club per Module in which students in groups (of 2) analyze and discuss original scientific papers that will be presented to the class and subject to evaluation. The latter intends to consolidate the concepts but more importantly to encourage a critical mind.

## Bibliografia


- *Specialized Review papers on the relevant topics.*
- Translational Neuroscience - Fundamental Approaches for Neurological Disorders, Editors: Tuszynski, Mark H. (Ed.) Springer
- Nestler, E. J., & Hyman, S. E. (2010). *Animal models of neuropsychiatric disorders. Nature Neuroscience, 13(10), 1161–1169.* doi:10.1038/nn.2647
- Neurologia Fundamental, Princípios, diagnóstico e tratamento (2ª Edição) de José Ferro e José Pimentel. Eds Lidel.


## Local onde as atividades irão decorrer

(aplicável apenas a atividades a decorrer fora da FMUL)

Clique aqui para introduzir texto.

## Carga horária de contacto, duração e distribuição ao longo do ano letivo

(especificar número de horas dedicadas a aulas teóricas, teórico-práticas, práticas, seminários e/ou outras atividades)

20h contact hours (Lectures and journal club) (4h/day, 5 consecutive days), during the 2nd week of 2nd semester plus 36h of individual study time. External faculty may change each year according to the theme or availability.

## Critérios de avaliação

(Adaptar a matriz anexa)

**Intended learning outcomes:**

The students are expected to discuss the main challenges in neurosciences in a critical way so that they may generate new ideas in the field and eventually to integrate those ideas with concepts acquired in other curricular units in a multidisciplinary way. A very interactive environment is expected to be created and discussion heavily encouraged.

**Knowledge and Understanding of:**

- The range of topics and experimental approaches in modern neuroscience
- The research process that enables the student:

(i) to evaluate critically current research

(ii) to evaluate methodologies and develop critiques of them

**Intellectual Skills:**

- A broad understanding of neuroscience
- The ability to critically evaluate the state of knowledge derived from neuroscience research
- The ability to formulate simple hypotheses based on an understanding of neuroscience

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*(A avaliação desta disciplina incluirá duas componentes, de acordo com a matriz "Avaliação da Aprendizagem nas Atividades Optativas" da FMUL:*

*Na componente transversal (comum a todas as atividades optativas), será avaliada a participação / interesse / envolvimento nas aulas. A classificação desta componente será feita com base numa escala de 0 a 4 como recomendado naquela matriz, correspondendo 4 a muito bom, 3 a bom, 2 a suficiente, 1 a insuficiente, 0 a mau.*

*Desta componente transversal resulta uma classificação máxima de 4 valores. Na componente específica desta unidade curricular, será avaliada:*

*No momento de Avaliação #1, os alunos resolverão, individualmente, uma série de problemas hipotéticos (perguntas científicas com abordagem experimental para deteção de erros) dando as suas respostas numa ficha de avaliação online ao longo da semana. O trabalho de cada aluno será avaliado por 2 docentes, ambos usando a escala acima, com intervalos de 0,5 valor, donde resultará uma classificação máxima de 8 valores.*

*No momento de Avaliação #2, os alunos apresentarão e discutirão com os docentes, em grupos de 3, artigos originais do tema, fornecidos no início da semana. O trabalho de cada aluno será avaliado por 2 docentes, ambos usando a escala acima, com intervalos de 0,5 valor, donde resultará uma classificação máxima de 8 valores.*

*Desta componente específica resulta uma classificação máxima de 16 valores. Optou-se por valorizar mais a componente específica, porque o trabalho pedido (em termos de tempo e dificuldade) é substancialmente mais do que para a avaliação da componente transversal.*

*A classificação final da disciplina optativa será dada pela soma das classificações das duas componentes descritas.)*

## Creditação a atribuir: 2 ECTS

(1, 2 ou 3 ECTS de acordo com o seguinte modelo:)

| Tipologia | Carga horária | ECTS |
|---|---|---|
| Disciplinas Optativas | 20h contacto + 36h estudo | **2** |